Bashar Katirji
Henry J. Kaminski
Robert L. Ruff *Editors*

Neuromuscular Disorders in Clinical Practice

Second Edition

Springer

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To our families, friends, and colleagues without whose support this work could not have been completed.

To my wife Patricia, our children Linda and Michael, my parents Zakaria and Malak, and my brothers Hassan and Ammar.

–BK

To all those dear to me, my father Edmund and mother Janina, my brother Ed, my second mother Louise and her husband Robert, but most of all the source of all that is good in my life, Adam, my boy and Linda, my wife.

–HJK

To daughters Emily and Elizabeth; my wife Suzanne and her children Julia, Daniel, and Antoine; Julia's husband Greg; and Dan's wife Nicole and grandchildren Matthew, Hannah, and Abigail.

–RLR

Preface

Over a decade ago, the editors appreciated a need for a single textbook that would cover comprehensively all aspects of the broad field of neuromuscular disease, which ultimately led to the publication of the first edition of *Neuromuscular Disorders in Clinical Practice*. The book attempts to be comprehensive and clinically oriented with the goal of discussing all disorders of the peripheral nervous system and the techniques used to assess these disorders. It thus parallels other neurology subspecialty texts, such as those for epilepsy or cerebrovascular disease, or internal medicine subspecialty books, such as those for rheumatology, endocrinology, or cardiology.

The second edition mimics the organization of the first. The book is divided into two parts, Part one discusses the approach to neuromuscular disorders followed by Part two dedicated to specific neuromuscular disease. Part one begins with an introduction to the clinical assessment of neuromuscular disorders; though it is not meant to duplicate available monographs on neurological examination, the chapter sets the stage for the evaluation of patients with neuromuscular disease. The second chapter provides concise overview of basic anatomy and physiology of nerves and muscles. The next subsection covers investigative techniques used in evaluating neuromuscular diseases. These include laboratory studies (muscle enzymes, autoantibodies, and exercise testing) and clinical neurophysiology procedures (clinical EMG, single fiber EMG, quantitative EMG analysis, quantitative sensory testing, autonomic testing), as well as nerve and muscle pathology. The new edition adds a chapter in skin biopsy performance and evaluation. The chapter on Molecular Diagnosis and Genetic Testing is updated extensively matching the significant knowledge increase in the last 10 years in this area.

The final subsection of Part one is broad with discussions of assessment and treatment of neuromuscular disorders. Individual chapters include quantitative assessment and outcome measures, rehabilitation, immunotherapy, and critical and respiratory care in the management of patients with neuromuscular diseases.

Part two provides detailed discussions of specific neuromuscular disorders. Most chapters are organized into etiology and pathogenesis, clinical presentation, differential diagnosis, evaluation and diagnosis, treatment and management, and prognosis. This approach was used in order to highlight the clinical emphasis of the book and correlate the clinical, electrodiagnostic, pathological, biochemical, and genetic aspects of neuromuscular disorders. Part two is divided into six subparts. Section one deals with disorders of the motor neuron and dorsal root ganglia (neuronopathies). Section two covers all the peripheral neuropathies including inherited and acquired polyneuropathies, mononeuropathies, radiculopathies, and plexopathies. Section three discusses neuromuscular junction disorders. Section four reviews muscle channelopathies, with a chapter devoted to disorders of muscle membrane excitability, including the periodic paralyses, non-dystrophic myotonias and related disorders, and a separate chapter on malignant hyperthermia. Section five is devoted to the inherited and acquired myopathies. Section six is devoted to the numerous conditions that do not fit neatly into one disorder or cross boundaries to other areas of the nervous system. The section discusses disorders of nerve hyperexcitability, including myokymia, neuromyotonia, muscle cramps, and fasciculations, as well as central nervous system disorders with neuromuscular manifestations, including stiff-man syndrome, and tetanus. Miscellaneous syndromes with neuromuscular presentations are

discussed, including paraneoplastic neuromuscular disorders, weakness in the intensive care unit, the floppy infant, rhabdomyolysis/myoglobinuria, and the fasciitis syndrome. The book ends with a chapter on neuropathic chronic musculoskeletal pain.

The second edition of *Neuromuscular Disorders in Clinical Practice* is intended to serve as a comprehensive text for both novice and experienced practitioners. General neurologists as well as specialists in neuromuscular medicine and trainees in neuromuscular medicine, clinical neurophysiology, and electromyography should find this book inclusive and comprehensive, yet practical and clinically relevant. Additionally, specialists in physical medicine and rehabilitation, rheumatology, neurosurgery, and orthopedics will find the book useful in their practice.

The contributors are an internationally recognized group of clinicians and scientists specializing in neuromuscular disorders, which allows for an appreciation of not only the science but the art of patient care. It is our hope that this text will provide the reader with the true flavor of, the nuances of, and the breadth and depth of the subspecialty field of neuromuscular disorders and thus enhance the care of patients with these conditions.

Cleveland, OH, USA — Bashar Katirji
Washington, DC, USA — Henry J. Kaminski
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Part I

Approach to Neuromuscular Diseases: Principles and Basics

Clinical Assessment in Neuromuscular Disorders

1

Bashar Katirji

Clinical Manifestations in Neuromuscular Disorders

Neuromuscular diseases are conditions that result from disorders or lesions of the peripheral nervous system (PNS). This include disorders of the motor unit or the sensory component including disorders of the motor neurons (anterior horn cells of the spinal cord or motor nuclei of the cranial nerves or both), dorsal root ganglia, spinal roots, cranial nerves, peripheral nerves, neuromuscular junctions, or muscles. These disorders are discussed in details in individual chapters in this textbook.

A systematic neurological evaluation is necessary to accurately localize these disorders and differentiate them from central nervous system (CNS) disorders or other systemic illnesses which do not involve the PNS [1, 2]. In general, neuromuscular disorders manifest with weakness, sensory disturbances, or reflex changes, signs which are shared by CNS disorders. However, other less common manifestations are more specific to neuromuscular disorders, including fasciculations, myokymia, myotonia, muscle cramps, muscle atrophy, or hypertrophy. Careful examination of other organ systems often provides clues to the diagnosis of a specific neuromuscular disease, such as the violaceous rash of dermatomyositis or the posterior subcapsular cataracts ("Christmas tree") seen in myotonic dystrophy.

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Weakness

Weakness is the most common complaint in patients with neuromuscular disorders.

Weakness is also common in CNS lesions including cortical, subcortical, brainstem, or spinal cord lesions. Neuromuscular disorders that are due to disorders of any component of the motor unit often cause weakness. These include anterior horn cell diseases (e.g., amyotrophic lateral sclerosis), root and/or peripheral nerve disorders (e.g., Guillain-Barré syndrome), neuromuscular junction diseases (e.g., myasthenia gravis), muscle membrane disorders (e.g., periodic paralysis), or muscle diseases (e.g., inclusion body myositis). Weakness in neuromuscular disorders is the major cause of disability which, in turn, depends on its severity, distribution, and patient's lifestyle. The variable effect of weakness on disability may result in significant delay in diagnosis due to the long interval between the onset of disease and the time the patient notices the weakness. For example, a patient with shoulder girdle weakness due to facioscapulohumeral (FSH) muscular dystrophy, who has a sedentary lifestyle and profession, may function well for several years before noticing shoulder weakness. In contrast, athletes or individuals with an active lifestyle may notice leg weakness long before it becomes evident to the physician on physical examination.

Proximal weakness in neuromuscular disorders often manifest in the lower extremities before the upper ones. Common complaints of proximal pelvic girdle weakness include difficulty climbing stairs, rising from the floor, arising from a toilet seat, or stepping out of a bathtub. Patients with hip extensor weakness (gluteus maximus) often have difficulty rising from a sitting or supine position without the use of one or both of the upper extremities. Patients with quadriceps weakness more than hip weakness (such as in inclusion body myositis) have more difficulty walking down stairs or down hills than climbing up stairs. This may also result in sudden falls, mimicking drop attacks, due to knee instability. Children with pelvic girdle weakness, such as Duchenne muscular dystrophy or spinal muscular atrophy (SMA), often rise from a

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Table 1.1 Predominant and typical distribution of muscle weakness in generalized neuromuscular disorders

Disorders	Proximal weakness	Distal weakness
Myopathies	Muscular dystrophies (most types)	Myotonic dystrophy I (DM 1)
	Myotonic dystrophy II (DM 2)	Facioscapulohumeral muscular dystrophy[a]
	Polymyositis	Scapuloperoneal syndromes[a]
	Dermatomyositis	Distal myopathies
	Inclusion body myositis[b]	Inclusion body myositis[b]
	Metabolic myopathies (most types)	
	Endocrine myopathies	
	Toxic myopathies	
	Congenital myopathies (most types)	
Neuromuscular junction disorders	Myasthenia gravis	–
	Lambert-Eaton myasthenic syndrome	
	Botulism	
Peripheral polyneuropathies	Acquired demyelinating polyneuropathies[c]	Axonal polyneuropathies (most types)
	Diabetic amyotrophy	Inherited demyelinating polyneuropathies (most types)
Anterior horn cell disorders	Spinal muscular atrophies	Amyotrophic lateral sclerosis[d]
	Amyotrophic lateral sclerosis[d]	

Most muscular dystrophies, including Duchenne, Becker, Emery-Dreifuss, limb-girdle, and oculopharyngeal, cause proximal weakness
[a]Facioscapulohumeral muscular dystrophy and the scapuloperoneal syndromes manifest with shoulder (proximal) girdle weakness and scapular winging with ankle dorsiflexion (distal) weakness
[b]Inclusion body myositis usually presents with quadriceps (proximal) and long finger flexor (distal) weakness
[c]Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy
[d]Amyotrophic lateral sclerosis often presents with unilateral or bilateral asymmetrical distal (hand or foot) weakness but is quite variable and may present with predominantly proximal or generalized weakness

supine position on the floor by first turning over onto the hands and knees, then straightening the legs and arching the back, and finally moving the hands to the knees and gradually extending the trunk by "climbing up" the thighs (*Gowers' sign*). Adults with severe proximal leg weakness rise from a sitting position by utilizing their hands for support against chairs or tables which are adaptive variations of the Gowers' maneuver. Patients with shoulder weakness often complain of difficulty carrying heavy objects or performing tasks above eye level, such as shampooing hair, or removing or placing objects on high shelves. Young patients may be aware that they are unable to shoot a basketball above their head.

Patients with distal leg weakness affecting the anterior compartment muscles often complain that they catch their toes on carpets or curbs and they cannot walk on their heels. When weakness of ankle dorsiflexors is significant resulting in foot drop, such as in peroneal palsy or facioscapulohumeral muscular dystrophy, the patient often excessively flexes the hip and knee to clear the foot, resulting in a "steppage gait." Patients with weakness of calf muscles (plantar flexors), such as with Miyoshi myopathy (Limb girdle muscular dystrophy 2B), cannot walk on their toes and lose the spring associated with normal stepping due to the inability to effectively propel the foot at the end of the stance phase. Patients with distal leg weakness, particularly those with weakness of foot eversion, are often susceptible to ankle sprains, which may be prevented with ankle-foot orthoses. Patients with distal hand weakness complain of difficulty twisting a key, buttoning buttons, or using a nail clipper. When weakness involves the long finger flexors, such as in inclusion body myositis or myotonic dystrophy, patients complain of a weak grip leading to difficulty with opening jars or turning door knobs.

Proximal weakness of hip or shoulder girdles is often due to myopathy or a neuromuscular junction (NMJ) disorder with several exceptions (Table 1.1). In contrast, distal weakness is often, but not always, due to neurogenic causes such as peripheral polyneuropathy or amyotrophic lateral sclerosis (ALS).

Muscle strength in neuromuscular clinics is best evaluated by a combination of manual muscle testing and functional evaluation. Quantitative assessment of muscle strength such as dynamometry and the Tufts Quantitative Neuromuscular Examination (TQNE) are useful tools but usually limited to clinical trials. Functional rating scales are important since they measure functional ability and are discussed in detail in Chap. 15. The most widely used procedure for strength assessment is the manual muscle test (MMT). This test does not require sophisticated equipment and can be performed quickly at the bedside. Various MMT approaches and grading methods are used including the British Medical Research Council (MRC), the most widely and simple used method. This test does not require sophisticated equipment and can be performed quickly at the bedside. The MRC has several modified. However, since grade 4 encompasses a majority of patients with muscle weakness, a modified scale, in which grades 5, 4, and 3 are subdivided, is most popular (Table 1.2) [3, 4]. A composite MRC score, based on examination of ten muscles on each side, may be used in longitudinal follow-up of patients with neuromuscular disease associated with generalized weakness

Table 1.2 Medical Research Council (MRC) grading and a modified MRC grading of muscle power

MRC grading		Modified MRC grading	
5	Normal power	5	Normal power
		5–	Equivocal power, barely detectable weakness (examiner is not truly certain of weakness)
4	Active movement against gravity and resistance	4+	Slight weakness (examiner has to exert considerable effort to overcome the muscle)
		4	Moderate weakness (examiner can overcome the muscle)
		4–	Severe weakness (examiner overcome the muscle with minimal effort)
3	Active movement against gravity	3+	Active movement through full range against gravity with transient resistance with collapse
		3	Active movement through full range against gravity but no resistance
2	Active movement with gravity eliminated	2	Active movement with gravity eliminated
1	Flicker or trace of contraction	1	Flicker or trace of contraction
0	No contraction or movement	0	No contraction or movement

Table 1.3 Composite MRC score useful in longitudinal assessment of neuromuscular disorders associated with generalized weakness

Function	Right	Left	MRC score
Arm abduction	5	5	*Upper extremities 60*
Elbow flexion	5	5	
Elbow extension	5	5	
Wrist extension	5	5	
Fingers abduction	5	5	
Hand grip	5	5	
Total	*30*	*30*	
Hip flexion	5	5	*Lower extremities 40*
Knee extension	5	5	
Knee flexion	5	5	
Ankle dorsiflexion	5	5	
Total	*20*	*20*	
MRC score	*Right*	*Left*	*Total MRC score*
	50	*50*	*100*

MRC score = 0–5 (see Table 1.2). A modified score may be also used (0, 1, 2, 3, 3.5, 4, 4.5, 5)

(Table 1.3) [5]. Such scoring is not useful for examination of patients with mononeuropathy or radiculopathy, or isolated oculobulbar, hand, or foot weakness.

True muscle weakness should be differentiated from "apparent" weakness, which usually occurs when patients are unable to move a joint because of skin, tendon, or joint contractures. For example, a patient with shoulder pain who is unable to abduct his arm may have adhesive capsulitis (frozen shoulder) which limits both active and passive abduction of the shoulder. Pain in limb interferes with their ability to contract a muscle fully. Similarly, nonorganic weakness (malingering or conversion) often produces incomplete muscle contraction. The MMT in patients with limb pain or nonorganic weakness usually shows a collapsing (give-way) weakness. Patients with cachexia due to poor nutrition, malignancy, chronic systemic infection, or inflammatory disease or patients with deconditioning due to inactivity may have functional impairment with walking, climbing stairs, or household- and work-related tasks. Careful questioning of these patients often reveals that activity is limited by shortness of breath, pain, depression, or fatigue.

Contracture

Contracture is the shortening or tightening of skin, fascia, muscle, or joint capsule that prevents normal movement. It commonly develops in patients with muscle weakness, chronic limb pain, and impaired mobility. Measurement of joint range of motion and contracture could be done at the bedside including the use of goniometry. In neuromuscular disorders, the formation of muscle contractures occurs from a combination of (1) intrinsic structural changes of muscle, (2) muscle weakness that causes an inability to achieve active joint mobilization throughout the normal range, (3) imbalance of agonist and antagonist muscle strength, (4) immobility, (5) compensatory postural changes used to biomechanically stabilize joints during standing, and (6) anatomical location of the muscle especially those that cross two joints, such as hamstrings, biceps, and long finger flexors. Frequent areas for soft tissue tightness are neck flexion, shoulder adduction, elbow flexion, forearm pronation, finger adduction and extension, hip flexion and internal rotation, knee flexion, ankle plantar flexion, and foot inversion. Contractures in the lower limbs contribute significantly to the loss of ambulation, while upper extremity contractures add to the restrictions of performance of activities of daily living.

Fatigue

Fatigue that worsens at the end of the day or after exercise is a hallmark of NMJ disorders, particularly myasthenia gravis. An objective sign of fatigue in myasthenia gravis is the progressive worsening of ptosis with sustained upgaze (*curtain*

sign). Less objective signs include fatigue following climbing steps, repeated clenching of the fist, or sustained arm stretch or leg raise.

Weak muscles often fatigue abnormally; thus fatigability is a feature of most neuromuscular disorders, including ALS, muscular dystrophy, and peripheral neuropathy. In metabolic myopathy, patients are normal or slightly weak at rest but become easily fatigued with activity. In general, fatigue occurs in neuromuscular disease when many muscle fibers are damaged, nonfunctional, or denervated. The intact remaining muscle fibers are able to generate force but are often worked at their metabolic limits.

Fatigue due to neuromuscular disease may be difficult to separate from "loss of energy" and asthenia, particularly when there is no fixed weakness at rest. Fatigue is also a common feature of a variety of disorders ranging from anemia, endocrine disorders, heart disease, and multiple sclerosis to chronic fatigue syndrome and fibromyalgia.

Atrophy

Muscle atrophy is second only to weakness in importance and as the presenting complaint in patients with neuromuscular disorders. In general, muscle wasting is appropriate to the degree of weakness in myopathies, while in neurogenic disorders, particularly ALS and SMA, muscle atrophy may be an early manifestation and tends to be proportionally more severe than weakness. However, this sign may be subtle and not always useful. Also, muscle atrophy may be difficult to confirm in obese and thin patients, in women, and in children. In general, muscle wasting is easier to appreciate when it is asymmetric, when it involves the hand and foot intrinsics, and when it occurs near bony prominences (e.g., proximal humerus and scapula).

Atrophy from neuromuscular disorders should be differentiated from disuse muscle wasting which occurs following joint immobilization (such as after fractures), prolonged bed rest, medical conditions that limit movement, or cachexia. In these instances, the contour of the affected muscles, although thinner, is well preserved.

Muscle Hypertrophy

An increase in muscle bulk is common with exercise and is rarely a primary pathological phenomenon. The most striking example of abnormal generalized hypertrophy is seen in patients with myotonia congenita, giving them the appearance of professional weight lifters. These non-dystrophic myotonic disorders have no muscle weakness, and their true hypertrophy of muscle fibers is likely the result of increased spontaneous muscle fiber activity (myotonia). Focal hypertrophy may be seen in calf muscles of patients with Duchenne and Becker's muscular dystrophy as well as in patients with the limb-girdle muscular dystrophies, SMA, and some glycogen storage disorders. In these disorders, the hypertrophy is referred to as *pseudohypertrophy* since it is associated with weakness and there is substantial replacement of muscle by fat and connective tissue as well as true muscle fiber hypertrophy. Focal hypertrophy may also be seen rarely in radiculopathies, cysticercosis, amyloidosis, sarcoidosis, and focal myositis. Palpable masses in muscles may be seen with local cramps, muscle infarct, tumor (such as rhabdomyosarcoma), ruptured tendon, or muscle hernia (where muscle fibers rupture through the perimysial sheath).

Gait Disorder

A keen observation of the gait of patients with neuromuscular disease is extremely helpful in diagnosis. Gait abnormalities may point to a CNS disorder, such as a magnetic gait seen with normal pressure hydrocephalus or a shuffling gait with festination in Parkinson disease.

Typically, proximal weakness results in a *waddling gait* caused by bilateral hip abductor weakness which results in a pelvic tilt toward the swinging leg. A compensatory lumbar lordosis occurs with advanced hip and lumbar paraspinal muscle weakness, during which the upper trunk and shoulders are hyperextended to position the body's center of gravity, behind the hip joints in order to maintain upright posture. In patients with severe quadriceps weakness, such as in IBM, the knee is hyperextended (*back kneeling*) during the stance phase of gait in comparison to the slight flexion at the knee in individuals with normal quadriceps function. The knee hyperextension prevents these patients from falling and helps ambulation. Bilateral foot drop due to weakness of ankle dorsiflexors is associated with a *steppage gait* caused by excessive hip and knee flexion (in order to clear the foot of the floor). When unilateral, this is sometimes referred to as a "slap-foot." In patients with advanced lower extremity weakness (proximal and distal), hip flexion is often replaced by circumduction of a hyperextended knee to clear the toes of the floor. A patient with increased leg muscle tone, such as with spastic hemiparesis, also circumducts his leg due to weak flexors and strong extensors. When spasticity is bilateral, increased muscle tone manifests as a *scissoring gait.*

Patients with loss of position sense due to large-fiber sensory loss or dysfunction of the dorsal column of the spinal cord have a disturbance of equilibrium, often referred to as *sensory ataxia*. Such patients usually stand and walk with a broad base. They may be able to maintain the upright position while the eyes are open but often sway or fall when the eyes are closed (*Positive Romberg sign*).

Reflexes and Tone

The myotatic or deep tendon reflexes (DTRs) are extremely useful tools in the diagnosis of neurological disorders in general and in neuromuscular disorders in particular. This is especially important in the differential diagnosis during the early phases of neuromuscular disorders. In general, the DTRs are preserved in myopathies, and their loss follows closely the degree of weakness (i.e., they are only absent or depressed in severely weakened or atrophied muscles). For example, in patients with Duchenne muscular dystrophy, the knee jerks become absent relatively early, while the ankle jerks are retained well into the nonambulatory phase of the disease. In contrast to the myopathies, the DTRs are usually abolished early even in strong muscles in patients with peripheral polyneuropathy, such as Guillain-Barré syndrome (GBS) or lower motor neuron disorders such as SMA. In patients with a length-dependent polyneuropathy, the DTRs tend to be absent or depressed distally while relatively preserved proximally. Finally, the presence of brisk DTRs in atrophic and weak limbs is highly suggestive of a combined lower and upper motor neuron disorder as seen with ALS or vitamin B12 deficiency.

Apart from spasticity in wasted limbs, as seen with ALS, muscle tone is rarely important in the diagnosis of neuromuscular disorders in adults. In infants, generalized hypotonia may be due to neuromuscular disorders, but it is clear that the "floppy infant syndrome" is a nonspecific syndrome which may be caused by a variety central or peripheral nervous system disorders as well as systemic disorders (such as Ehlers-Danlos syndrome, malnutrition, and metabolic disorders).

Pain and Muscle Cramps

Myalgia is common symptom in patients with neuromuscular disorders. Muscle pain at rest is common in GBS, acute poliomyelitis, polymyositis, and acute viral myositis. Myalgia is a frequent manifestation of polymyalgia rheumatica and rheumatological disorders. It is then often associated with stiffness and arthralgia. Diffuse or focal muscle pain is also common in fibromyalgia and chronic fatigue syndrome. Muscle pain with exertion may occur with muscle ischemia (intermittent claudication with occlusive peripheral vascular disease) but is also common in neurogenic claudication associated with lumbar spinal canal stenosis. Exertional muscular pain, with or without muscle cramps, is a feature of metabolic myopathies such as McArdle's disease and other glycogenosis but may also occur in hypothyroidism and mitochondrial myopathies.

Muscle cramps consist of painful involuntary contractions involving part of or the whole muscle and lasting from seconds to minutes. Often, there is a palpable lump at the site of the contraction which disappears as the cramps ease. On needle electromyography (EMG), cramps are associated with high-frequency and slightly irregular bursts of motor unit action potentials (MUAPs). Muscle cramps are common in healthy individuals and are sometimes referred to as physiologic, benign, or common muscle cramps. They also accompany metabolic disturbances such as hyponatremia, dehydration, or uremia, and are common in pregnancy and hypothyroidism. These cramps tend to be worse in the legs, particularly the calves, and at night. Cramps are often relieved by stretching of the muscle and can be triggered by contraction of a shortened muscle such as forcibly contracting the calf muscles while pointing the toes down. Muscle cramps are common in neuromuscular diseases, particularly neurogenic disorders and metabolic myopathies. For example, patients with ALS often complain of cramps which might predate the onset of weakness. The cramps in metabolic myopathies, such as McArdle's disease, are extremely painful, often brought on by exertion, and may last up to several hours. These cramps are actually *muscle contractures* since they are associated with electrically silent needle EMG.

Neuropathic pain is often caused by damage to the peripheral nerves. Neuropathic pain may be simply divided into two

Table 1.4 Characteristics of major forms of neuropathic pain

	Dysesthetic pain	Nerve trunk pain
Descriptors	Burning, tingling, raw, searing, crawling, drawing	Aching, occasionally knifelike
Recognition	Unfamiliar, never experienced before	Familiar, "like a toothache"
Distribution	(1) Cutaneous or subcutaneous usually	(1) Deep
	(2) Distal	(2) Relatively proximal
Constancy	Variable, may be intermittent, jabbing, lancinating, shooting	Usually continuous but waxes and wanes
Better/worse	Little makes it better; worse following activity	Better with rest or optimal position; worse with movement, nerve stretch, or palpation
Basis of pain (hypothetical)	Increased firing of damaged or abnormally excitable nociceptive fibers, particularly sprouting, regenerating fibers	Increased firing due to physiological stimulation of endings of undamaged afferents from nerve sheaths themselves (nervi nervorum)
Examples	(1) Causalgia	(1) Root compression
	(2) Small-fiber neuropathy	(2) Neuralgic amyotrophy (idiopathic brachial plexitis)

Revised from Asbury and Thomas [5], with permission

types: a dysesthetic and nerve trunk pain (Table 1.4) [6]. Patients with rapidly denervating conditions, such as GBS or acute poliomyelitis, may have muscle pain and tenderness, sometimes mistaken as myalgia due to a primary muscle disorder.

Abnormal Muscle Movements

Inspection of muscle at rest, with contraction, and following percussion, is an important part of the neuromuscular evaluation. In addition to detecting muscle atrophy or hypertrophy, appreciation of abnormal spontaneous movements or abnormal muscle contraction or relaxation is extremely useful.

Fasciculations are brief, asynchronous twitches of groups or bundles of muscle fibers. They are due to involuntary contractions of motor units. Fasciculations should be looked for in muscles at rest and may be difficult to see in infants and obese patients due to subcutaneous fat. As an isolated finding, they are often of no significance since they are common in healthy individuals, particularly after exercise or the consumption of CNS stimulants, such as caffeine. They may also occur in patients receiving cholinesterase inhibitors, with hyperthyroidism, hyperparathyroidism, and hypomagnesemia, as well as with the use of CNS stimulants such as theophylline and lithium. Fasciculations are associated with neurogenic disorders such as ALS, SMA, and, less often, peripheral polyneuropathies and radiculopathies. Although fasciculations do not move large joints, as seen with myoclonus, they may result in low-amplitude asynchronous twitches of the fingers imitating chorea. Fasciculations that are observed during partial muscle contraction ("contraction fasciculations") are less specific but may occur in neurogenic disorders such as in the facial muscles of patients with bulbospinal muscular atrophy (Kennedy's disease). Contraction fasciculations are not true fasciculations but represent rapid firing of large reinnervated motor units.

Myokymia is seen clinically as involuntary, repeated, "wormlike" or writhing contractions of part of a muscle. These are very difficult to differentiate from fasciculations particularly when widespread but are easily distinguished by needle EMG (see Chap. 7). Myokymia is rare and is seen mostly in neurogenic disorders, although facial myokymia may occur in brainstem disease such as multiple sclerosis or pontine glioma. Limb myokymia is a common occurrence following radiation injury to peripheral nerve, such as delayed radiation-induced brachial plexopathy, but may be seen with GBS or nerve entrapment (such as carpal tunnel syndrome).

Myotonia is characterized clinically by failure of muscle to relax immediately after cessation of voluntary contraction. It is caused by spontaneous repetitive depolarization of muscle membrane and has a distinct characteristic appearance and sound on needle EMG (see Chap. 7). Clinical myotonia is common in myotonic dystrophies and in the non-dystrophic myotonias and may be elicited as action myotonia or percussion myotonia. Among *action myotonias*, grip myotonia (elicited by asking the patient to forcefully clench the fist and attempt to release rapidly) is the most common. With this maneuver, there is failure of relaxation which lasts 5–10 s and occasionally as long as 1 min. Lid myotonia is less common and manifests by difficulty opening the eyes after forceful eye closure. Action myotonia tends to improve with repeated contractions (warm-up phenomenon) although in paramyotonia the stiffness may worsen with repeated contractions. *Percussion myotonia* is best elicited by tapping the thenar eminence with a reflex hammer. This results in slow tonic position of the thumb with a gradual relaxation lasting up to 10 s. Less common procedures include tapping the tongue or the forearm extensors which results in contraction with delayed relaxation. With muscle percussion, a dimple (due to contraction of a strip of a muscle) might appear at the sight of the tap which may last up to 10 s.

Neuromyotonia is an extremely rare phenomenon due to continuous motor unit activity resulting in muscle stiffness. In contrast to myotonia, it is of neural origin and disappears after neuromuscular blockade. Neuromyotonia is often seen with myokymia in disorders associated with potassium channel antibodies including Isaac's syndrome (see Chap. 70) but may be encountered in neurogenic disorders such as SMA.

Myoedema is a ridgelike mounding of a portion of a muscle, occurring after percussion of muscle and lasting up to 1–3 s. Myoedema is electrically silent on needle EMG. It is an extremely rare phenomenon and is seen usually in patients with myxedema or cachexia.

Rippling muscle is another rare phenomenon associated with electrical silence on EMG. It manifests as a self-propagating rolling or rippling of muscles that is usually induced by passive muscle stretch. Muscle percussion may result in an exaggerated muscle contraction manifesting as a localized mounding (imitating myoedema) or a prolonged muscle contraction (clinically indistinguishable from myotonia).

Pseudoathetosis comprises undulating and writhing movements of the outstretched fingers, with a combination of flexion, extension, abduction, pronation, and supination. Fine tasks are often clumsy. Pseudoathetosis is more marked when the eyes are closed, which distinguishes it from athetosis. The movements are the result of deafferentation and loss of position sense in the affected limb. They are usually due to severe loss of large sensory fibers, as seen in sensory neuropathies, dorsal root ganglionopathies, and polyradiculopathies as well as in tabes dorsalis and other dorsal column disorders.

A *neuropathic tremor* may accompany peripheral polyneuropathies, particularly the demyelinating polyneuropathies. It is very similar to essential tremor, with a usual frequency of 3–6 Hz and a postural and kinetic component produced by alternating contraction of agonist and antagonist muscles. Its exact mechanism is not well understood though the loss of proprioceptive or muscle spindle inputs may explain for the tremor. The tremor is more common in

demyelinating polyneuropathies than axonal polyneuropathies, such as during the recovery phase of GBS or chronic inflammatory demyelinating polyneuropathy (CIDP) and in anti-MAG polyneuropathy. When tremor is associated with Charcot-Marie-Tooth (CMT) disease type I, it is sometimes referred to as the Roussy-Lévy syndrome.

Sensory Disturbances

Sensory manifestations are features of sensory peripheral nerve disorders or disorders of the dorsal ganglia and consist of a wide spectrum of positive to negative phenomena. *Positive symptoms* include paresthesias (pins and needles sensation and tingling), dysesthesias (uncomfortable sensation particularly to touch with various surfaces), or hyperpathia (painful response to a non-painful stimulus). *Negative symptoms* include numbness, loss of sensation, and imbalance. Sensory manifestations may follow a peripheral nerve (mononeuropathy), single root (radiculopathy or ganglionopathy), or a stocking-glove distribution (peripheral polyneuropathy). Acquaintance with peripheral nerve sensory territories as well as with human dermatomal maps, which may vary among individuals, is essential in distinguishing radiculopathy from mononeuropathy and peripheral polyneuropathy from spinal cord sensory loss (Fig. 1.1a–c).

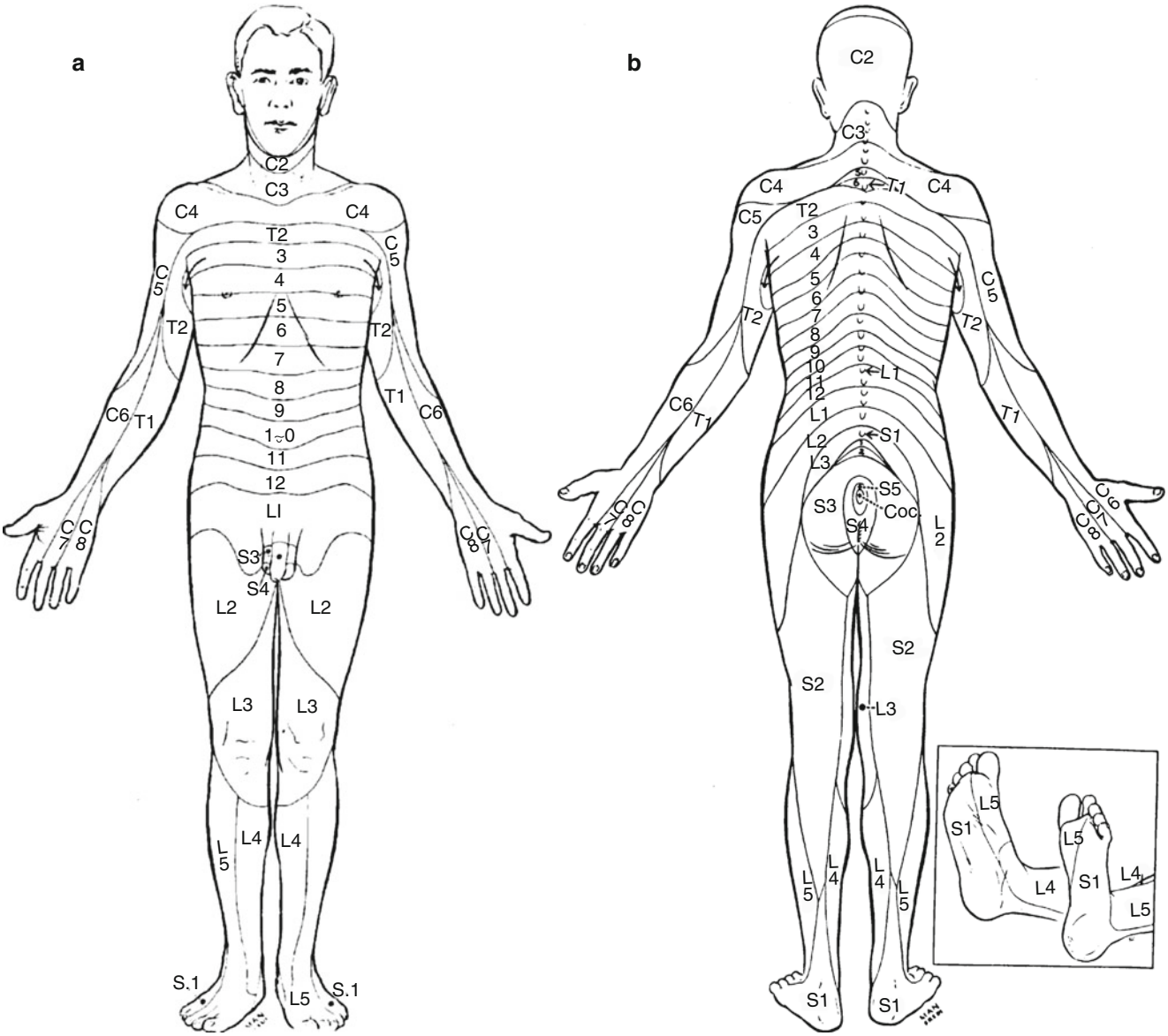

Fig. 1.1 The dermatomes after Foerster [6]). (**a**) Anterior view. (**b**) Posterior view (*inset*: foot). (**c**) Side view. *C* cervical, *T* thoracic, *L* lumbar, *S* sacral (Reprinted with permission from Haymaker and Woodhall [7])

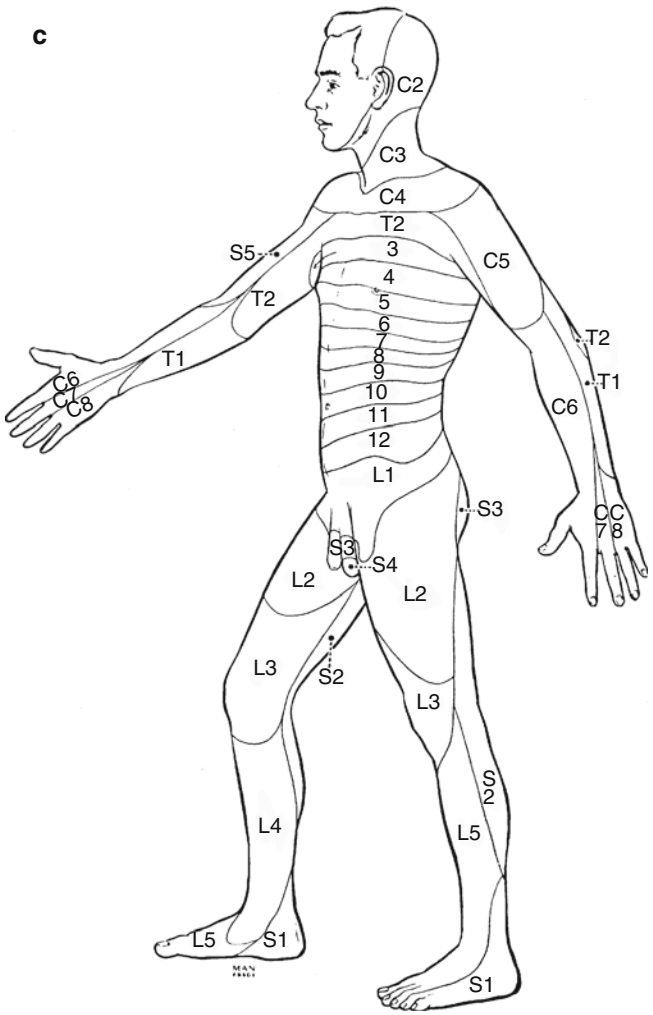

Fig. 1.1 (continued)

Temperature and pain sensation, as well as autonomic functions, are mediated by the small myelinated and unmyelinated fibers, while proprioception and vibration sense, as well as the afferent limb of the muscle stretch reflex, are mediated by the large myelinated fibers. Touch is conducted by both types of fibers. In typical dying back axonal peripheral polyneuropathy, the large fibers, small fibers, or both types of sensory fibers may be affected. In small-fiber neuropathies, there is diminished or loss of pain and temperature sensation, which may be accompanied by dysesthesia, hyperpathia, or dysautonomia. Examples include amyloid neuropathy and small-fiber diabetic neuropathy. In contrast, large-fiber polyneuropathies result in sensory ataxia, areflexia, and loss of position sense. Although tingling and dysesthesia may occur in large-fiber neuropathy, pain is not a common feature of these disorders.

Percussion of peripheral nerves with a reflex hammer or finger may elicit a Tinel's sign, an electrical sensation in the distribution in the percussed nerve. This clinical phenomenon reflects reinnervation of sensory fibers. It is seen at or distal to the site of peripheral nerve damage and may progress distally in regenerating nerves. However, a Tinel's sign may be also elicited in normal individuals with more vigorous percussion of peripheral nerves such as the ulnar nerve at the ulnar groove or the median nerve at the carpal tunnel.

Quantitative measures of sensory functions are useful. These include sensory nerve conduction studies (see Chap. 7), which evaluate the large sensory fibers; autonomic testing which assesses cardiac, sudomotor and vasomotor small nerve fibers (see Chap. 10); and quantitative sensory testing which examines cooling (small-fiber) and vibration (large-fiber) functions (see Chap. 11).

Peripheral Nerve Enlargement

Palpation of peripheral nerves is an important tool in the neuromuscular examination. *Nodular* expansions of peripheral nerves may occur in leprosy or neurofibromatosis, while *diffuse* enlargement of nerves is more common in chronic demyelinative polyneuropathy such as CMT disease type I, Dejerine-Sottas disease, CIDP, or Refsum's disease and in infiltrative polyneuropathy such as in amyloidosis. The following nerves may be easily palpated at the bedside: (1) the greater auricular nerve in the posterior neck, (2) the ulnar nerve in the ulnar groove, (3) the superficial radial sensory nerve as it crosses the extensors to the thumb distal to the wrist, (4) the sural nerve lateral to the Achilles tendon or behind the lateral malleolus, (5) the common peroneal nerve around the fibular neck, and (6) the digital nerves over the dorsum of the fingers.

Common Presentations of Weakness in Neuromuscular Disorders

Rapidly Progressive Quadriparesis

Quadriparesis progressing over days to weeks is a relatively common neurological presentation. Usually, the history is one of an ascending paresis beginning in the lower limbs and progressing cephalad to the trunk and upper limb and often weakening the respiratory, bulbar, and ocular muscles. Descending weakness, progressing in the opposite direction, may occur but is less common.

Causes of rapidly progressive quadriparesis are best discussed using the neuraxis as an anatomical guideline. Disorders presenting with this presentation are usually to spinal cord or peripheral nervous system dysfunction including any element of the lower motor neuron. Hence, it is useful to address the differential diagnosis based on the different elements of the motor unit (Table 1.5). In the western hemisphere with the exception of spine trauma

Table 1.5 Causes of rapidly progressive quadriparesis

Muscle disorders
Polymyositis
Dermatomyositis
Rhabdomyolysis
Critical illness myopathy
Muscle membrane disorders
Familial periodic paralysis
Secondary hypokalemic paralysis
Neuromuscular junction disorders
Myasthenia gravis (myasthenic crisis)
Botulism
Drug-induced neuromuscular blockade
Toxic
Tick paralysis
Organophosphate poisoning
Black widow spider
Snake venoms
Nerve gas
Metabolic
Hypermagnesemia
Hypophosphatemia
Peripheral nerve and/or root disorders
Guillain-Barré syndrome
Acute intermittent porphyria
Diphtheritic polyneuropathy
Critical illness polyneuropathy
Vasculitic neuropathy
Heavy metal acute poisoning (thallium, arsenic)
Diffuse polyradiculopathy (infectious, neoplastic)
Anterior horn cell disorders
Acute poliomyelitis (including West Nile myelitis)
Spinal cord disorders
Transverse myelitis
Cord compression (disc herniation, fracture/dislocation, epidural malignancy)
Cord infarction (anterior spinal artery syndrome)
Brainstem disorders
Central pontine myelinolysis
Pontine infarct (basilar artery thrombosis)

and weakness in the intensive care setting, GBS and transverse myelitis are the most common (Table 1.6). The following is a general guide to the evaluation of patients with rapidly progressive quadriparesis, and the reader should refer to the chapters dealing with specific neuromuscular disorders for a detailed discussion.

Clinical Findings

Distribution and Temporal Progression of Weakness

The neurological examination is most useful in guiding the diagnosis during the early phases of these disorders. The final outcomes of the majority of disorders that lead to generalized weakness are fairly uniform and include severe quadriparesis, hyporeflexia, or areflexia, with or without respiratory failure and bulbar or ocular weakness, thus producing in the later stages of illness. Obtaining a detailed history and/or observing the progression and distribution of the weakness is essential in the formulation of the differential diagnosis. For example, the first symptom of botulism is often asymmetrical ptosis or double vision, followed rapidly by dysphagia, dysarthria, and, finally, respiratory failure and limb weakness. In contrast, in classical GBS, symptoms often begin with symmetrical bilateral leg weakness with imbalance and numbness, followed by trunk and upper limb weakness, which may progress into respiratory failure, and, sometimes, facial diplegia or diplopia.

Deep Tendon Reflexes

Evaluating the deep tendon reflexes (DTRs) is among the most important signs in patients with rapidly progressive quadriparesis. In general, disorders of peripheral nerve are often associated with early hyporeflexia, the DTRs are usually spared in neuromuscular junction disorders and myopathies prior to severe quadriparesis, and they are often absent in any neuromuscular disorder associated with severe weakness. For example, the DTRs in botulism are normal until significant limb weakness develops, while they are often depressed or absent in mildly weak limb(s) early in the course of GBS.

Symmetry of Weakness

Asymmetrical weakness is also an important finding early in the course of illness since most scenarios, if untreated, go on to generalized symmetrical paralysis. In general, subacute polyneuropathies and myopathies are symmetrical from the outset. However, subacute NMJ disorders, polyradiculopathies, and anterior horn cell diseases are often asymmetrical early in the course and sometimes as recovery begins. For example, in GBS, polymyositis, and periodic paralysis, the weakness is often symmetrical from the outset, while in botulism, myasthenia gravis, carcinomatous polyradiculopathy, and acute paralytic poliomyelitis, ocular, bulbar, and limb muscle weakness are often asymmetrical. However, there are many exceptions. For example, the weakness in vasculitic neuropathy is often asymmetrical and may be restricted to peripheral nerve distributions (mononeuropathy multiplex), while tick paralysis typically causes a rapid symmetrical quadriparesis.

Extraocular Muscle Weakness

Extraocular muscle abnormalities are common in neuromuscular junction (NMJ) disorders, particularly botulism and myasthenia gravis. They are rarely found in polyneuropathies and do not occur in subacute myopathies or anterior horn cell disorders. In contrast to ocular findings, bulbar muscle manifestations, particularly dysphagia, are common to most neuromuscular disorders.

Table 1.6 Differential diagnosis of nontraumatic rapidly progressive quadriparesis (listed in anatomical order)

Disorder	Characteristic clinical manifestation	Typical diagnostic findings
Pontine infarction due to basilar artery occlusion	History of transient ischemic attack is common	MRI often reveals brainstem infarct
	Symptoms are sudden in onset, though may be stuttering	MRI often may show basilar artery occlusion or stenosis
	Somnolence is common	
	Brisk reflexes are common but may be delayed	
	Babinski sign(s) is usually present	
	Ocular and bulbar findings are common, often asymmetrical, but vertical eye movements are usually spared	
Central pontine myelinolysis	Alcohol abuse or critical illness (transplantation, severe burn) is common	MRI of brain reveals central tegmental, mostly pontine, T2-weighted signal abnormality
	Rapid correction of hyponatremia is often detected	
	Ocular muscles are usually spared	
	Hyperreflexia and Babinski signs may be delayed	
	Sensory manifestations are rare	
Transverse myelitis	Sphincteric disturbance is common	MRI of spinal cord may reveal abnormal signal or enhancement in cervical or thoracic cord.
	Discrete sensory level on trunk may be evident	CSF pleocytosis and increased IgG production are common
	Brisk reflexes or Babinski signs are common but may be delayed till after spinal shock stage	
	No cranial nerve involvement	
Acute paralytic poliomyelitis	Wild polio virus is extremely rare	CSF lymphocytic pleocytosis is common
	Usually associated with oral polio vaccine or other enteroviruses, coxsackie, and echoviruses	EDX studies reveal asymmetrically low CMAPs with preserved SNAPs, with active denervation in segmental distribution
	Muscle pain and fever are common	Rise in serum antibody titers is common
	Weakness is almost always asymmetrical	Viral culture from CSF or gut is of low yield
	Reflexes are preserved in strong limbs	
	No sensory or sphincteric symptoms	
Neoplastic/infectious polyradiculopathy (leptomeningeal disease)	Radicular pain is common	EDX studies show segmental denervation with intact SNAPs
	Asymmetrical limb weakness, sensory loss, and cranial nerve palsies are the hallmark of disease	MRI of brain or spine may reveal meningeal enhancement
	Deep tendon reflex loss may be patchy	High CSF protein, pleocytosis, and low glucose are often present
	Cognitive changes, headache, or seizures are common	CSF cytology may be detect neoplastic cells
	History of solid tumor, lymphoma, leukemia, HIV, or other immunocompromised state may be present	
Guillain-Barré syndrome	Prodromal flu-like symptoms are common	CSF albuminocytologic dissociation is common
	Areflexia or hyporeflexia in weak limbs is early	Slowing of F waves or motor or sensory NCSs is common but may be delayed
	Sensory manifestations are often subjective only	
	Bilateral facial weakness is not uncommon	
Acute intermittent porphyria	History of abdominal pain, psychiatric disease, or confusion is common	EDX studies reveal subacute axonal sensorimotor polyneuropathy is evident on
	Precipitating factors (drugs, infections) are common	CSF protein is usually normal or mildly elevated
	Autonomic manifestations are very common	Urinary porphobilinogen increases during attack
	Weakness may start in arms	Low-level erythrocyte uroporphyrinogen I synthetase confirms the diagnosis
	Distal sensory loss is usually dense	

Table 1.6 (continued)

Disorder	Characteristic clinical manifestation	Typical diagnostic findings
Vasculitic neuropathy	Onset is often abrupt with stepladder progression	Elevated ESR is common
	Asymmetrical weakness/sensory losses are the usual findings	ANA, RF, and ANCA titers may be elevated
	Findings may be restricted to multiple mononeuropathies	EDX studies often reveal an asymmetrical axonal polyneuropathy or multiple mononeuropathies
	History of connective tissue disorder may be present	Nerve or muscle biopsy often confirms the presence of arterial wall infiltration by inflammatory cells with or without fibrinoid necrosis
	Systemic manifestations (fever, arthralgia, skin rash, etc.) may coexist	
Acute diphtheritic polyneuropathy	Is very rare in developed countries	CSF is similar to GuillainBarré syndrome
	History of fever, severe pharyngitis, membranous exudate over tonsils, and cervical adenopathy few weeks earlier	EDX studies often show signs of demyelinative polyneuropathy similar to Guillain-Barré syndrome
	Palatal weakness and paralysis are always present	
	Quadriparesis is usually descending and may progresses over few months	
Myasthenia gravis (myasthenic crisis)	Oculobulbar weakness is common, often fatigable	Tensilon test may be positive
	Weakness may be descending	Slow repetitive nerve stimulation reveals CMAP decrement, particularly from proximal muscles
	Deep tendon reflexes are usually preserved	Acetylcholine receptor antibody is elevated in the majority
	No sensory loss or bladder involvement	
Tick paralysis	Affects mostly young girls but extremely rare	CSF is normal
	Rapid progression into quadriparesis and areflexia	NCSs show low CMAPs but normal SNAPs and no slowing
	Mimics Guillain-Barré syndrome	Finding and removing the tick (usually near hairline) results in rapid recovery
Botulism (food-borne botulism)	Rapid weakness is almost always descending	Tensilon test may be positive
	Early oculobulbar weakness is the rule	Moderate increment on rapid repetitive nerve stimulation
	Pupillary dilatation is common but may be delayed	Abnormal serum assay is common
	Late ileus and urinary retention are common	
Periodic paralysis	Family history is common	Serum potassium is often abnormal
	The first attack is usually in the first or second decade	EDX studies during paralytic attack show low CMAPs, decrease insertional activity, and short-duration, low-amplitude, and polyphasic MUAPs
	Onset of quadriparesis is rapid, usually overnight	Needle EMG, between attacks, reveals myotonic discharges in hyperkalemic form only
	Cranial nerve involvement and respiratory failure are rare	
Acute rhabdomyolysis (myoglobinuria)	Onset is with severe muscle pain	CK is markedly elevated (up to 1,000 folds)
	Deep tendon reflexes and sensation are normal	Myoglobin is almost always detected in urine
	History of drug or toxin intake, infection, or exercise is often present	Needle EMG may be normal in the acute phase
Polymyositis-dermatomyositis - necrotizing autoimmune myopathy	Myalgia is common	CK is often markedly elevated
	Heliotrope rash in dermatomyositis is characteristic	Short-duration, low-amplitude, and polyphasic MUAPs, with fibrillation potentials, are usually seen on needle EMG
	Neck weakness is common and early	Degenerating and regenerating myofibers with or without inflammatory infiltrate is often seen on muscle biopsy
	Dysphagia is the only cranial involvement	
	Deep tendon reflexes are often preserved	
	May be associated with connective tissue disorder	

CSF cerebrospinal fluid, *EDX* electrodiagnostic, *NCS* nerve conduction study, *EMG* electromyography, *CMAP* compound muscle action potential, *SNAP* sensory nerve action potential, *MUAP* motor unit action potential, *MRI* magnetic resonance imaging, *ESR* erythrocyte sedimentation rate, *ANA* antinuclear antibody, *RF* rheumatoid factor, *ANCA* antinuclear cytoplasmic antibody

Sensory Manifestations

The presence of sensory symptoms or signs excludes all subacute myopathies, NMJ, and anterior horn cell disorders, unless accompanied by a peripheral neuropathy, such as in paraneoplastic disorders. Sensory symptoms and signs are very common in polyneuropathies and polyradiculopathies. They are usually symmetrical in the former and asymmetrical in the latter.

Autonomic Findings

A part from Lambert-Eaton myasthenic syndrome and botulism, where both nicotinic and muscarinic nerve terminals are targeted by the toxin, autonomic findings are a feature of polyneuropathies and polyradiculopathies. These findings include orthostatic hypotension, tachyarrhythmias, ileus, urinary retention or incontinence, and pupillary abnormalities.

Laboratory Investigations

Serum Electrolytes and EKG

Serum electrolytes are easy to measure and may suggest a specific diagnosis. Serum potassium, magnesium, and phosphorus should be obtained promptly in all patients with rapidly progressive quadriparesis. Measuring serum potassium is particularly important in a young patient with a family history of quadriparesis, suggestive of periodic paralysis. Also, secondary hypokalemic periodic paralysis should be considered, if there is a history of thyrotoxicosis, malabsorption, barium salt poisoning, or abuse of diuretics, laxatives, or licorice. The EKG usually is abnormal with hypokalemia (prolonged QT interval, flat T wave, and prominent U wave), with hyperkalemia (peaked T waves), and, sometimes, in hypermagnesemia. The latter may occur in patients with toxemia of pregnancy treated with parenteral magnesium or with the use of magnesium-containing antacids or cathartics, particularly when associated with impaired renal function. Hypophosphatemia is usually associated with parenteral hyperalimentation, the use of phosphate-binding antacids, acute alcohol intoxication, and severe respiratory alkalosis.

Serum Creatine Kinase

Elevated serum creatine kinase (CK) often suggests a primary muscle disorder (see Chap. 3). When acute rhabdomyolysis leads to severe weakness, the CK is markedly elevated, reaching up to 1,000–2,000 folds of the normal level. In polymyositis, dermatomyositis, and, sometimes in critical illness myopathy, the CK is often elevated, reaching usually up to 100–200 folds of the normal value. CK may be elevated modestly in other neuromuscular disorders causing subacute quadriparesis, particularly GBS and acute paralytic poliomyelitis. Caution should be taken in patients with severe quadriparesis and bed confined where CK may be elevated due to muscle crush injury and not due to the primary cause of the weakness.

Cerebrospinal Fluid

Abnormalities seen in the cerebrospinal fluid (CSF) are generally supportive of a diagnosis, but not pathognomonic. In general, all myopathies and NMJ disorders are associated with normal CSF, while the CSF is often abnormal in subacute peripheral polyneuropathies, radiculopathies, and anterior horn cell disorders. Elevated CSF protein is among the most common abnormality seen, followed by pleocytosis. The latter is usually dominated by lymphocytes except in infectious disorders where there is often early polymorphonuclear pleocytosis. CSF glucose is sometimes lowered in infectious, carcinomatous, or lymphomatous polyradiculopathies (leptomeningeal disease). In these disorders, CSF cultures and cytology are required for diagnosis.

Electrodiagnostic Tests

Nerve conduction studies (NCSs), repetitive nerve stimulation, and needle EMG are invaluable aids in the diagnosis of patients presenting with acute or subacute quadriparesis. Details are discussed in Chap. 7 on clinical electromyography and in individual chapters dealing with the above disorders.

Despite their common utility in the evaluation of patients with suspected subacute neuromuscular disorders, there are many limitations to the use of EDX studies in these subacute settings. In general, NCSs and repetitive nerve stimulation are more useful than needle EMG in the acute phase of these disorders. Although normal NCSs suggest disorders of muscle, neuromuscular junction, spinal roots, or anterior horn cell, many patients with acute axonal polyneuropathies may have normal NCSs during the first week or two of illness. In contrast, compound muscle action potential (CMAP) amplitudes may be low in botulism, drug-induced neuromuscular blockade, severe myasthenia gravis, or severe necrotizing myopathies. Sensory nerve action potentials (SNAPs) are usually abnormal in patients with subacute neuropathies, but this may be delayed also. Although it is intuitive to conclude that NCSs are sensitive in confirming demyelination such as in Guillain-Barré syndrome, these studies often reveal abnormalities that are not specific of primary demyelinating polyneuropathy during the early phases of the disease.

Foot Drop

Foot drop is defined as severe weakness of ankle dorsiflexion with intact plantar flexion. It should not be confused with a *flail foot* in which there is no or minimal ankle or foot movement in all directions, including severe weakness of ankle dorsiflexion, plantar flexion, and intrinsic foot muscles (Fig. 1.2). In contrast to a flail foot, voluntary movement at or distal to the ankle occurs in foot drop due to intact plantar flexion and intrinsic foot muscles. Many patients with severe peripheral polyneuropathy, such as CMT disease, are often

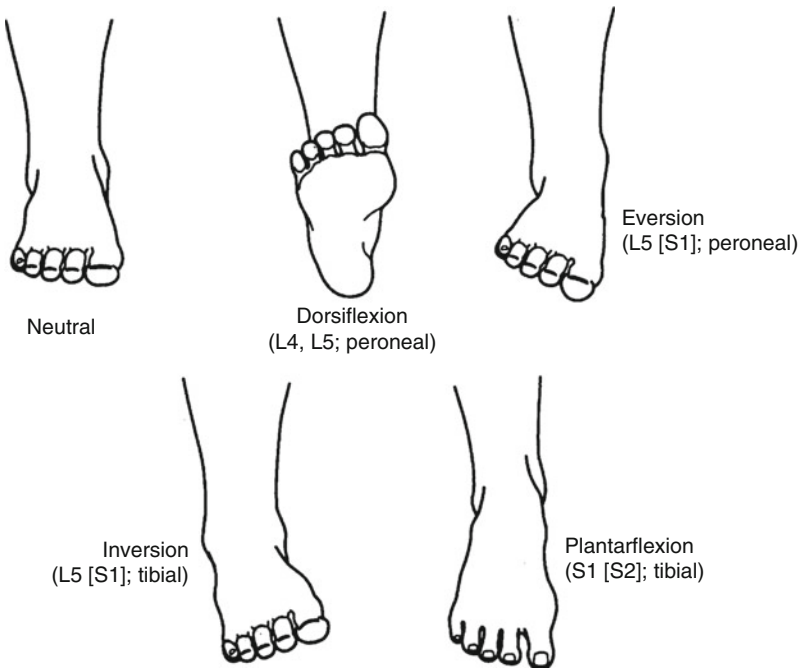

Fig. 1.2 Directions of foot movements. Note that the *L5* root is, in part, responsible for foot dorsiflexion, eversion, and inversion, while the common peroneal nerve is responsible for dorsiflexion only

Table 1.7 Causes of unilateral foot drop (listed in ascending order along the neuraxis)

Deep peroneal neuropathy
Common peroneal neuropathy
Anterior compartmental syndrome of the leg
Sciatic neuropathy
Lumbosacral plexopathy (lumbosacral trunk)
L5 radiculopathy
L4 radiculopathy (rarely)
Conus medullaris lesion (rarely)
Multifocal motor neuropathy[a]
Vasculitic neuropathya[a]
Hereditary neuropathy with liability to pressure palsy (HNPP)[a]
Amyotrophic lateral sclerosis
Poliomyelitis and postpoliomyelitis syndrome
Cortical or subcortical parasagittal cerebral lesion

[a]Usually resulting into peroneal neuropathies

Table 1.8 Causes of bilateral foot drop (listed in ascending order along the neuraxis)

Myopathies
Distal myopathies[a]
Scapuloperoneal muscular dystrophy
Facioscapulohumeral muscular dystrophy
Myotonic dystrophy
Neuropathies
Multifocal motor neuropathy with conduction block
Hereditary neuropathy with liability to pressure palsy (HNPP)
Chronic inflammatory demyelinating polyneuropathy (CIDP)
Bilateral peroneal neuropathies
Bilateral sciatic neuropathies[b]
Bilateral lumbosacral plexopathies[b]
Vasculitic neuropathy
Radiculopathies
Bilateral L5 radiculopathies (cauda equina lesion)
Conus medullaris lesion
Anterior horn cell disorders
Amyotrophic lateral sclerosis
Poliomyelitis and the postpoliomyelitis syndrome
Cerebral lesions
Bilateral cortical or subcortical parasagittal lesions

[a]Including the distal forms of limb girdle muscular dystrophy
[b]Extremely rare causes

mislabeled as having bilateral foot drop, while careful examination reveals foot and ankle weakness in all directions, compatible with bilateral flail foot.

Foot drop is a direct effect of tibialis anterior muscle weakness. It is often associated with weakness of toe extension due to weakness of the extensor hallucis and extensor digitorum longus and brevis. Unilateral foot drop is caused by disorders distinct from those leading to bilateral foot drop, with some overlap (Tables 1.7 and 1.8). In general, most cases of bilateral foot drop are caused by lumbar spine disorders such as bilateral L5 radiculopathies or more generalized disorders such as a motor neuron disease, polyneuropathy, or myopathy. In contrast, unilateral foot drop is often due to a focal disorder such as a mononeuropathy or radiculopathy.

Peroneal neuropathy or L5 radiculopathy are by far the most common causes of foot drop. They often result in unilateral foot drop which may occasionally be bilateral. The weakness in peroneal neuropathy is restricted to ankle dorsiflexion, toe dorsiflexion, and ankle eversion. Ankle eversion

Table 1.9 Differential diagnosis of common neuromuscular causes of unilateral foot drop

	Peroneal neuropathy	L5 radiculopathy	Lumbar plexopathy (lumbosacral trunk)	Sciatic neuropathy (mainly peroneal)
Common causes	Compression (weight loss, perioperative, or iatrogenic), blunt and open trauma	Disc herniation, lumbar spinal stenosis	Prolonged labor (short women and/or large infants), pelvic fracture	Hip surgery, injection injury, coma
Ankle inversion	Normal	Weak	Weak	Normal or mildly weak
Toe flexion	Normal	Weak	Weak	Normal or mildly weak
Plantar flexion	Normal	Normal	Normal	Normal or mildly weak
Ankle jerk	Normal	Normal (unless with S1)	Normal (unless with S1)	Normal or depressed
Sensory loss	Distal 2/3 of lateral leg and dorsum of foot	Poorly demarcated, predominantly big toe	Well demarcated to L5 dermat ome	Entire lateral leg and dorsum of foot and, often, the sole
Pain	Rare, deep	Common, radicular	Common, may be radicular	May be severe

is usually stronger than dorsiflexion, since the superficial peroneal nerve is often less involved than the deep peroneal nerve. In L5 radiculopathy, there is additional weakness of ankle inversion and toe flexion. Foot dorsiflexion weakness is not uncommon with L4 radiculopathy although quadriceps, iliopsoas, and thigh adductor weakness is usually more pronounced. Occasionally, a selective L4 radiculopathy may result in severe ankle dorsiflexion weakness leading to foot drop. This is probably related to the myotomal variability of the tibialis anterior muscle; in most individuals, this muscle is innervated by the L5 root predominantly but receives a major contribution from the L4 root. It is likely that in those patients with foot drop due to L4 radiculopathy, the majority of tibialis anterior segmental innervation is via the L4 root. Unilateral conus medullaris lesion involving the L5 segment may rarely cause a foot drop that is difficult to distinguish from an L5 root lesion.

Partial sciatic neuropathy usually affects the lateral division (peroneal nerve) more than the adjacent medial division (tibial nerve). This often presents as a foot drop and poses a diagnostic challenge since it imitates a distal selective peroneal nerve injury due to compression at the fibular head (Table 1.9).

Injury to the lumbosacral trunk of the lumbosacral plexus, such as occurring mostly during labor in short women delivering large infants, is relatively rare. It often present with foot drop with variable buttock pain and numbness in the lateral leg and dorsum of the foot. The neurological findings include not only weakness of ankle and toe dorsiflexion and ankle eversion but also ankle inversion and toe flexion. There is variable weakness of the glutei and hamstring muscles. A lumbosacral trunk lesion imitates clinically an L5 radiculopathy, and careful EDX studies are often essential for final diagnosis.

Anterior compartment syndrome of the leg often results in foot drop since the anterior compartment contains all muscles which function as ankle and toe evertors (tibialis anterior, extensor hallucis, and extensor digitorum longus), in addition to the deep peroneal nerve. Dysfunction of any of these structures (muscles with or without nerve) results in weakness of foot and toe dorsiflexion. There is usually leg pain out of proportion to what is anticipated from the clinical situation, particularly if it occurs after a time interval from the primary etiological event. The pain is worsened by passive flexion of toes and plantar flexion of ankle, and there is often tenseness of the anterior compartment fascia.

Bilateral foot drop is less common and is usually due to cauda equina, conus medullaris, or generalized neuromuscular disorders (Table 1.8). A significant number of the distal myopathies have a predilection for the muscles of the anterior compartment of the leg. In fact, ankle eversion weakness and foot drop are common presentations in the limb girdle muscular dystophies which present as distal myopathies (see Chap. 57). In some of them, the disorder may start with weakness in the hands, followed by bilateral foot drop. Bilateral, often asymmetrical, weakness of foot dorsiflexion, often leading to foot drop, is a common finding in patients with FSH muscular dystrophy and the scapuloperoneal syndromes (SPS). Almost all patients have associated winging of the scapulae and shoulder girdle weakness. Facial weakness is also very common. Multifocal motor neuropathy often presents with asymmetrical intrinsic hand muscle weakness, wristdrop, or foot drop. The latter is the most common manifestation in the lower extremity, usually caused by peroneal neuropathy manifesting with a demyelinative conduction block. The lack of significant atrophy and sensory loss are characteristic findings. Foot drop due to peroneal neuropathy at the fibular head may also occur in patients with hereditary neuropathy with liability to pressure palsy (HNPP). In the sporadic form of ALS, limb weakness often precedes bulbar symptoms, and the arms tend to be affected earlier than the legs. Occasionally, foot drop is an early manifestation of ALS and may pose a diagnostic challenge. In these patients, the weakness often involves all the distal L5 innervated muscles, resulting in weakness of ankle inversion (tibialis posterior) and toe flexion (flexor digitorum longus). Most patients go on to develop diffuse foot weakness, resulting in a flail foot, along with weakness in other myotomes in the same or in other limbs. Hyperreflexia, hypertonia, atrophy, and fasciculations are useful diagnostic features.

Table 1.10 Causes of unilateral atrophy and weakness of intrinsic hand muscles

All intrinsic hand muscles
Combined ulnar neuropathy and carpal tunnel syndrome
Lower brachial plexopathy (including neurogenic thoracic outlet syndrome)
C8 radiculopathy
Amyotrophic lateral sclerosis
Focal motor neuron disease (monomelic amyotrophy)
Cervical syringomyelia
High cervical or foramen magnum spinal cord compression
Peripheral polyneuropathy
Distal myopathy
All intrinsic muscles excluding the thenar muscles
Ulnar neuropathy at the elbow
Ulnar neuropathy at the wrist (Guyon's canal)
All intrinsic muscles excluding the thenar and hypothenar muscles
Ulnar neuropathy at the wrist (distal Guyon's canal or pisohamate hiatus)
Limited to the thenar muscles
Carpal tunnel syndrome
High median neuropathy (including the pronator syndrome)
Neurogenic thoracic outlet syndrome
T1 radiculopathy

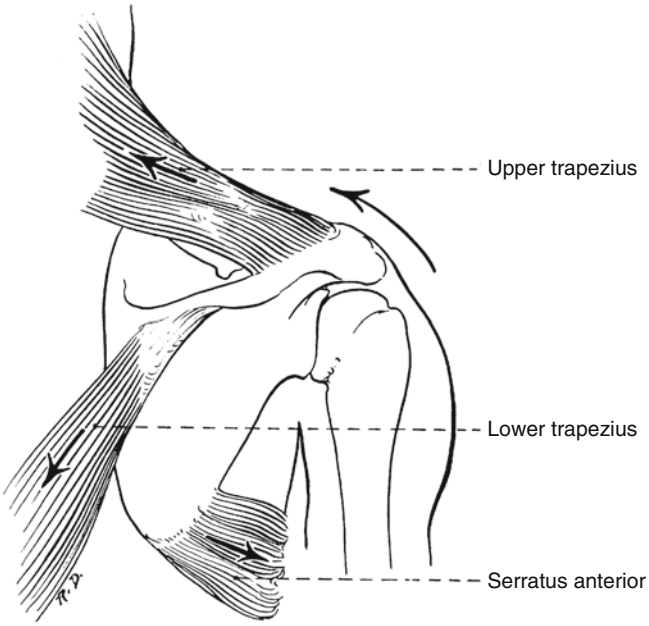

Fig. 1.3 Scapular rotators during abduction (Reprinted from Hollinshead [8], with permission)

Hand Atrophy

Patients who present with hand atrophy, often associated with weakness, may harbor a variety of neuromuscular or intrinsic cervical spinal cord disorders. It is important to distinguish whether the atrophy involves the thenar eminence, hypothenar eminence, the interossei, or all three muscle groups (Table 1.10). Interossei atrophy results in deep grooves between the metacarpal bones, best appreciated over the dorsum of the hand with the fingers extended. With ulnar nerve lesions, there is often clawing of the ring and little fingers (*benediction posture*). In this posture, weakness of the third and fourth lumbricals results in hyperextension of the metacarpophalangeal joints (due to unopposed action of long finger extensors) and flexion of the proximal and distal interphalangeal joints. With weakness of abduction of the little finger (due to weakness of the third palmar interosseous muscle), patients may catch their little finger when trying to put their hand in their pocket (*Wartenberg's* sign). With weakness of the opponens pollicis, the thumb may rotate and face the same direction as the other fingers (*simian hand*). Associated sensory manifestations, such as in the lateral hand in carpal tunnel syndrome and in the medial hand in thoracic outlet syndrome or ulnar neuropathy across the elbow, are useful signs in sorting out the cause of atrophy. Patients with hand atrophy and weakness without sensory involvement present more of a diagnostic challenge. EDX studies with detailed needle EMG are often necessary for accurate diagnosis.

Scapular Winging

During shoulder movements, the scapula maintains its position by the support of multiple muscle groups, termed the scapular fixators or stabilizers. Among them, the serratus anterior, trapezius, levator scapulae, and rhomboids muscles play the major role.

The serratus anterior is essential in synchronizing scapular movements associated with shoulder flexion or abduction and during forward pushing. During forward flexion, the serratus anterior keeps the scapula close to the thoracic wall, while during abduction, it rotates the scapula laterally and forward. The trapezius muscle works mostly during shoulder abduction by maintaining the vertebral border of the scapula vertically and rotating the scapula laterally along the vertical axis (Fig. 1.3). The rhomboids and levator scapulae muscles are antagonists to the serratus anterior. They rotate the scapula medially and backward and maintain the upper part of the scapula close to the vertebral spine during abduction.

The trapezius muscle is innervated by the spinal accessory nerve (cranial nerve XI). In addition, the lower part of the muscle receives branches from the C3 and C4 nerve roots which join the motor nerve to the trapezius distal to the takeoff of the sternocleidomastoid branch. The serratus anterior receives its motor supply exclusively from the long thoracic nerve which originates from the anterior primary rami of the C5, C6, and C7 roots. The rhomboids (major and minor) and levator scapulae are innervated by the dorsal scapular nerve which arises from the anterior primary ramus of C5. The

Table 1.11 Neuromuscular disorders associated with scapular winging

Often
Facioscapulohumeral muscular dystrophy
Scapuloperoneal syndromes
Limb-girdle muscular dystrophy
Occasional
Emery-Dreifuss syndrome
Polymyositis
Inclusion body myositis
Acid maltase deficiency
Mitochondrial myopathy
Desmin storage myopathy
Nemaline myopathy
Centronuclear myopathy
McArdle's disease

Table 1.12 Differential features of scapular winging due to trapezius or serratus anterior weakness

Muscle	Trapezius weakness	Serratus anterior weakness
Innervation	Spinal accessory nerve	Long thoracic nerve
Scapular winging at rest	Prominent	Mild
Shoulder sagging at rest	Obvious	Subtle
Levator scapulae at rest	Prominent (with chronic weakness only)	Not visible
Relation to midline at rest	Lateral translocation	Medial translocation
Winging is accentuated by	Shoulder abduction	Shoulder forward flexion or protraction (pushing) against resistance

levator scapulae receives additional and substantial motor supply from the primary rami of C3 and C4, while the rhomboids rarely are supplied from the C4 root.

Scapular winging is a descriptive term, generally referring to translocation of the scapula from its normal position. This may be apparent at rest or accentuated or improved by certain shoulder movements. Scapular winging may be unilateral or bilateral. Bilateral scapular winging is usually caused by diffuse weakness of the scapular fixators from generalized neuromuscular diseases, particularly FSH and SPS. Other neuromuscular disorders, associated occasionally with scapular winging, are listed in Table 1.11. Unilateral winging is most often caused by weakness of the trapezius or serratus anterior muscles usually due to isolated mononeuropathies of the spinal accessory or long thoracic nerves, respectively. Isolated dorsal scapular mononeuropathy, leading to weakness of the rhomboids muscle or levator scapulae, is extremely rare. Bilateral scapular winging from isolated mononeuropathies is unusual.

Patients with scapular winging often present with shoulder weakness, pain, or both. Sometimes, the patient complains of a droopy shoulder or scapular dislocation. At times, a family member notices the scapular winging, or the physician detects it during the neurological examination. Shoulder weakness is in all planes of movement but is primarily appreciated with tasks requiring shoulder abduction or forward flexion. The pain is usually deep and poorly localized to the shoulder and scapula. It is often exacerbated by activity and improved following rest. Adhesive capsulitis of the shoulder joint (frozen shoulder), a common complication of chronic winging of the scapula, often worsens the pain and shoulder weakness.

Distinguishing weakness of the trapezius from the serratus anterior may be a challenge to the clinician (Table 1.12). Although weakness of either muscle results in scapular winging with medial deviation of the inferior angle of the scapula (due to the unopposed action of the rhomboids and levator scapulae on the upper scapula), certain characteristics prevail with each. Often, two steps are required on the neurological examination to secure a diagnosis. First, observing the shoulder and scapular position *at rest* is extremely important (Fig. 1.4a, b). In trapezius weakness, the winging is striking, the shoulder is significantly sagged, and the scapula is displaced laterally from the midline. In chronic lesions, the levator scapulae is very prominent due to atrophy of the overlying upper trapezius and, possibly, compensatory hypertrophy of the levator scapulae. In contrast, with serratus anterior weakness, there is little change in the appearance of the shoulder girdle at rest, and the scapular translocation is medial. The second step in diagnosis is to watch the scapula during *specific active shoulder movements*. Shoulder abduction accentuates scapular winging with trapezius weakness, while forward flexion of the shoulder (particularly to 45° below horizontal) or protraction against resistance worsens the scapular winging with serratus anterior weakness. Occasionally, even with these steps, the clinician may not be able to determine the weak scapular fixator muscle, and needle EMG of the shoulder fixators is needed for a definitive diagnosis.

In FSH and SPS, scapular winging is often bilateral but may be asymmetrical. The weakness involves most scapular fixators but particularly the serratus anterior, rhomboids, and lower trapezius. Characteristically, the winged scapulae in FSH and SPS are laterally displaced at rest. With forward flexion, winging is accentuated with a characteristic upward protrusion of the scapulae (due to preferential weakness of the lower trapezius

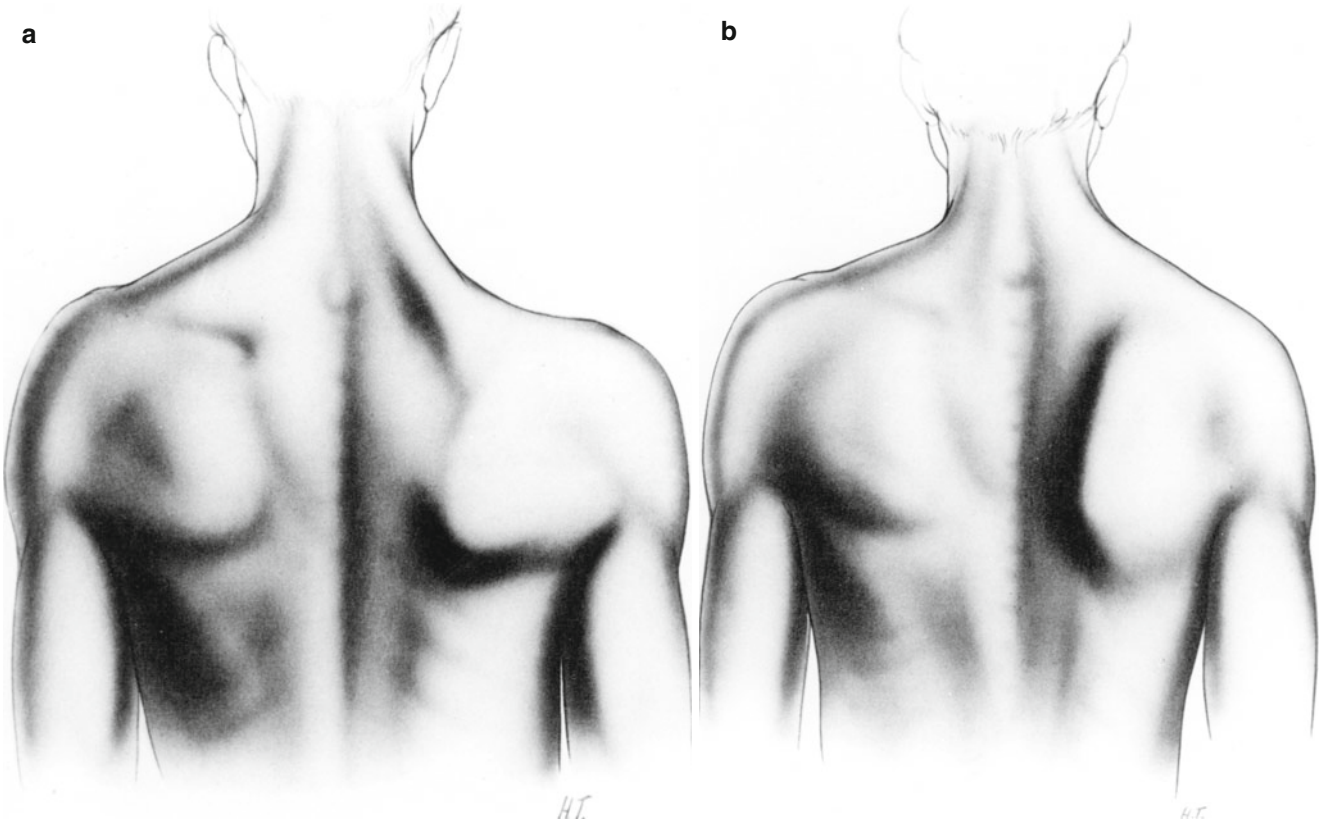

Fig. 1.4 Comparison of shoulder and scapula at rest following isolated weakness of trapezius (spinal accessory neuropathy) (**a**) and serratus anterior (long thoracic neuropathy) (**b**). Note the lateral translocation of the scapula, striking winging, droopy shoulder, and prominent levator scapulae in a and medial translocation, milder winging, and minimal depression of shoulder in (b) (Reprinted from Liveson and Spieholz [9], with permission)

muscles). Winging also worsens with shoulder abduction. Associated bilateral facial paresis; weakness of biceps, triceps, and tibialis anterior; a positive family history; and genetic studies often help in establishing the diagnosis of FSH or SPS.

Dropped Head

Severe weakness of head extension may result in the inability to hold the head up. Weakness of the cervical paraspinal muscles (neck extensors) is usually an early presentation of a generalized neuromuscular disorder, such as myasthenia gravis, polymyositis, or ALS (Table 1.13), but may also occur in isolated neck extensor or trunk extensor myopathies (paraspinous myopathies, see Chap. 66). It also may occur in patients with advanced neuromuscular diseases such as FSH or myotonic dystrophy type I or II. Dropped head may also be associated with parkinsonism and multiple system atrophy, and this may represent an association between these disorders and isolated neck extensor myopathy. It is important to distinguish dropped head syndrome due to neck extensor weakness from cervical dystonia resulting in anterocollis and from severe cervical spondylosis, particularly when associated with spondylolisthesis.

Table 1.13 Common disorders presenting with or manifesting with prominent head drop

Myopathies
Polymyositis
Dermatomyositis
Facioscapulohumeral muscular dystrophy
Myotonic dystrophies
Inclusion body myositis
Nemaline myopathy
Multicore myopathy
Mitochondrial myopathy
Acid maltase deficiency (Pompe's disease)
Hypothyroid myopathy
Hyperparathyroid myopathy
Hypokalemic myopathy
Carnitine deficiency
Paraspinous myopathies
Neuromuscular junction disorders
Myasthenia gravis
Peripheral neuropathies
Chronic inflammatory demyelinating polyneuropathy (CIDP)
Anterior horn cell disorders
Amyotrophic lateral sclerosis
Spinal muscular atrophies
Central nervous system disorders
Parkinsonism
Multiple system atrophy
Cervical dystonia (anterocollis)
Cervical spine disorders
Severe cervical spondylosis
Cervical spondylolisthesis

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Nerve and Muscle: Basic Concepts

2

Francisco H. Andrade

Introduction

Reflex and voluntary motor activity results from the integration of multiple and continuous stimuli. The hierarchical division of motor behavior reflects its particular goal. Thus, short interneuron arcs in the spinal cord mediate simple reflexes, and complex motor activities involve central processors, such as motor cortex, cerebellum, and basal ganglia. Regardless of complexity, motor activity always involves nerves and muscles as the final pathway for the production of force and movement. This chapter presents the basic aspects of neuromuscular biology: how neural signals initiate the contractile process, and how it is regulated.

Excitable Cells

Neurons and muscle cells are *excitable*, that is, an appropriate stimulus will change their electrical potential difference with the environment. Motor systems depend on this property of excitable cells to transmit information, eventually leading to force and movement.

Plasma Membrane

Cells are surrounded by a lipid-protein membrane that creates intra- and extracellular compartments, the cytoplasm and extracellular space, respectively. The plasma membrane serves as a barrier between the compartments, limiting the movement of molecules in and out of the cell; therefore, the cytoplasmic and extracellular concentrations of ions, proteins, fatty acids, and carbohydrates may be very different. In addition to being a mechanical barrier, the plasma membrane contains receptors, channels, and transporters that mediate the interactions between the cell and its environment.

The plasma membrane consists mostly of lipids and proteins in proportions that vary depending on the cell type, plus a small amount of carbohydrates, mostly in membrane glycolipids or glycoproteins [1]. The membrane lipids are mainly phospholipids containing choline (lecithins and sphingomyelins) or amino groups (phosphatidylserine, phosphatidylethanolamine), other phospholipids (phosphatidylglycerol, cardiolipin), and cholesterol. The phospholipid molecules have polar hydrophilic head groups and two nonpolar hydrophobic hydrocarbon tails. Because of this, membrane lipids are arranged to form a fluid bilayer, with the polar groups facing to the outside (cytoplasm and extracellular space) and the nonpolar groups facing inside. The proteins are found embedded in this bilayer, either exposed to only one of the surfaces (peripheral membrane proteins) or crossing the whole span of the membrane (integral membrane proteins) [2]. This is not a rigid structure: the lipids and proteins are in constant motion (parallel to the membrane's plane) in a process called *lateral diffusion*. The fluidity of the membrane is adjusted by cholesterol and limited by cytoskeletal elements that interact with membrane components, restricting their motility [3, 4]. Because cholesterol is a bulky, weakly amphipathic molecule, it stiffens the membrane, blurring the distinction between the gel and fluid states [5].

The plasma membrane controls the movement of substances between the cell and its environment. In general, passive transport across biological membranes is by diffusion: for any given substance, the rate of diffusion across a membrane is given by its lipid solubility, the concentration gradient between the compartments, and the thickness of the membrane. These factors restrict movement across a membrane to small, nonpolar molecules. The diffusion rate of charged substances is orders of magnitude less. An exception to this rule is the diffusion of water. For unknown reasons, cellular membranes show a surprisingly high permeability to water.

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Table 2.1 Typical ionic composition of mammalian skeletal muscle

	Extracellular (mM)	Intracellular (mM)	E_{ion} (mV)
Na^+	145	12	+67
K^+	4	155	−98
Cl^-	123	4	−91
Ca^{++}	1.5	$<10^{-4}$	+129

Diffusion alone is not sufficient to fulfill cellular exchange requirements. Other mechanisms exist to facilitate the transport of selected substances across the plasma membrane. Specific integral membrane proteins may act as channels or carriers (transporters) in a process called *mediated transport* (proteins *mediate* the transmembrane movement of molecules). Mediated transport is faster than diffusion and may be specific for a particular ion or compound. It may saturate (i.e., transport rate reaches a peak when all the transporters are occupied). Mediated transport may be passive, via transport proteins that do not require the expenditure of energy (facilitated transport), or active, when the movement of molecules is coupled to the release of energy, usually from ATP (active transport). In practical terms, facilitated transport follows concentrations gradients between the intra- and extracellular compartments, and active transport works ("pumps") against them. The channels and transporters that mediate these processes have distinguishing structural characteristics.

Channel proteins in mammalian plasma cells are basically membrane pores, composed of α-helical bundles packed together around a single axis, in a way that forms the permeation pathway (or channel) for ion conductance [6, 7]. Some channels are gated: they can switch from a closed to an open configuration and back in response to chemical, physical, or electrical events [6, 8, 9]. Moreover, their activity may be modified by intra- or extracellular conditions [10]. Transporters move molecules across the plasma membrane with a conformational shift that physically moves the molecules from one side of the membrane to the other [11]. By modulating the activity of different channels and transporters, cells have multiple control points for the regulation of their internal milieu.

Membrane Potential

Animal cells are polarized, that is, they have an electrical potential. Being a barrier to diffusion, the plasma membrane creates differences in the ionic concentration between the cytoplasmic and extracellular compartments, giving rise to a chemical potential difference (Table 2.1). For example, substance *X* tends to diffuse from the compartment where it is at a higher concentration to the other. Thermodynamically, this is shown by

$$\mu_x = \mu_0 + RT \ln[X] \tag{2.1}$$

where μ_x is the chemical potential for substance *X*, μ_0 is the reference electrochemical potential for *X* under standard conditions (usually 1 M and 20 °C), *R* is the gas constant (8.314 J degree^{-1} mol^{-1}), *T* is the absolute temperature, and [*X*] is the concentration of *X*. When *X* is an ion with charge *z*, a term for electrical potential must be added:

$$\mu_x = \mu_0 + RT \ln[X] + zFE \tag{2.2}$$

where *F* is Faraday's constant (96,500 C mol^{-1}) and *E* is the electrical potential (*V*). When ion *X* is at equilibrium, the electrochemical potentials inside and outside the cell must be equal:

$$\mu_{out} = \mu_{in} \tag{2.3}$$

Then, the electrical potential difference across the plasma membrane given by the distribution of ion *X* is

$$\frac{RT}{ZF} \ln \frac{[X]_{out}}{[X]_{in}} = (E_{in} - E_{out}) \tag{2.4}$$

This is the *Nernst equation* and is important for understanding that differences in the ionic composition of the intra- and extracellular compartments are partly responsible for the electrical potential of cells. The Nernst equation shows that the equilibrium potential for an ion varies linearly with temperature and logarithmically with its concentration ratio. For ions at equilibrium, the electrical potential difference given by this equation equals the resting membrane potential. In other words, the gradient created by a difference in the concentration of an ion is opposed by its electrical potential difference, resulting in no net ionic flux. Therefore, if the plasma membrane is selectively permeable to one ion (e.g., Cl^-) and it is in equilibrium across the membrane, the potential difference calculated by the Nernst equation for the $[Cl^-]_{out}$ and $[Cl^-]_{in}$ would equal the resting membrane potential.

Plasma membranes are permeable to numerous ions (mostly K^+, Na^+, Cl^-); however, the membrane's conductance (*g*) for each ionic species is different. The effect of *g* on the membrane potential is shown by the Goldman-Hodgkin-Katz equation [12, 13]:

$$E_M = \frac{RT}{F} \ln \frac{g_K [K]_o + g_{Na} [Na]_o + g_{Cl} [Cl]_i}{g_K [K]_i + g_{Na} [Na]_i + g_{Cl} [Cl]_o} \tag{2.5}$$

where the potential difference across the plasma membrane (E_M) becomes a function of the concentration ratios of the

ions present and their conductances. In more general terms, E_M is an average of the equilibrium potentials of Na^+, K^+, and Cl^-, weighted by their relative conductances:

$$E_M = \frac{(g_K E_K) + (g_{Na} E_{Na}) + (g_{Cl} E_{Cl})}{g_K + g_{Na} + g_{Cl}} \quad (2.6)$$

As the Goldman-Hodgkin-Katz equation shows, cells that have an unequal distribution of ions also have an electrical potential difference across the plasma membrane. Most animal cells are polarized in such a way that the cytoplasm is negative with respect to the extracellular space. This potential difference localizes to the plasma membrane (resting E_M), and it is largely due to the selective permeability of the membrane to the ions that are present at different concentrations in the cytoplasm and the extracellular space.

While the permeability to Na^+ is very low under resting conditions, there is a large electrochemical gradient driving a small Na^+ current (I_{Na}) into the cell. This excess of positive charges would eventually depolarize the cell, dissipating an important factor for excitability, active transport, and volume regulation. To counteract the Na^+ influx, a specialized transporter, the Na^+-K^+ ATPase (or "pump"), extrudes Na^+ from the cytosol, against its electrochemical gradient, in exchange for K^+. Reflecting its importance for cell function, about half of the ATP provided by oxidative metabolism in the brain is used to power the Na^+-K^+ pumps [14]. The Na^+-K^+ ATPase is an $\alpha 2\beta 2$ tetramer with a molecular weight of approximately 270 kD. The α-subunits contain ATP and cardiac glycoside binding sites and are responsible for transport activity. The β-subunits are glycopeptides whose function is not clear: they may serve for proper folding of the α-subunits in the plasma membrane or as an adhesion element in cell-cell interactions [15].

Because the stoichiometry of the Na^+-K^+ ATPase reaction is 3 mol Na^+, 2 mol K^+ per mol ATP hydrolyzed, this pump is electrogenic: it generates a net positive charge efflux and a greater potential across the membrane (more negative E_M). Although the outward current generated by this pump is usually small, its activity may result in large changes in excitability.

Action Potentials

In most cells, E_M has been harnessed to store and transmit information. The resting E_M changes in response to particular stimuli: chemical, electrical, and mechanical. The modality is specific to the cell type. E_M may become less (depolarization) or more negative (hyperpolarization) in response to a stimulus. These changes in the resting E_M are mediated by gated ion channels and may be divided into two general classes: slow potentials and action potentials.

Slow potentials are graded changes in E_M that occur in response to highly localized transducing mechanisms and may be the initiators of subsequent action potentials (e.g., see section "Neuromuscular Transmission"). Their amplitude and duration are determined by the intensity and duration of the stimulus being transduced. Slow potentials lose amplitude as they spread distally from their origin but may sum temporally and spatially with other slow potentials.

Neurons, skeletal muscle fibers, and other excitable cells can generate action potentials, very rapid, pulse-like membrane depolarizations that are triggered when E_M is depolarized past a threshold. Once triggered, action potentials have constant amplitude and duration, not affected by distal spread. This phenomenon is known as an *all-or-none response*. In other words, once stimulus intensity reaches the threshold, an action potential is triggered. Augmenting the stimulus does not change the shape of the action potential. Because action potentials have constant speed, amplitude, and duration, the information transmitted by them is coded by their timing.

The origin of an action potential is easier to grasp if one considers some rules that govern electrical evens. The most fundamental is Ohm's law, the relationship between voltage or potential difference (E), current (I, amperes), and resistance (R, ohms):

$$I = \frac{E}{R} \quad (2.7)$$

Because resistance is the inverse of conductance (g, siemens),

$$I = gE \quad (2.8)$$

In other words, current equals the potential difference between two points times the conductance of the medium. In a cell, the potential difference is the electrical potential for a particular ion as calculated by the Nernst equation (Eq. 2.4), and the conductance is proportional to the permeability of the membrane to the ion. When E_{ion} is not equal to E_M, there is a gradient for the movement of ion (and its charge) across the membrane. The magnitude of the resulting current (I) is determined by the membrane conductance for the ion (g).

The plasma membrane is a lipid bilayer that behaves as a capacitor, a good insulator that separates two conductors, the cytoplasm and the extracellular fluid. Potential difference (E) requires separation of charge, and capacitance (C, farads) measures how much charge (Q, coulombs) has to move from one side of the capacitor to the other for a given potential:

$$C = \frac{Q}{E} \quad (2.9)$$

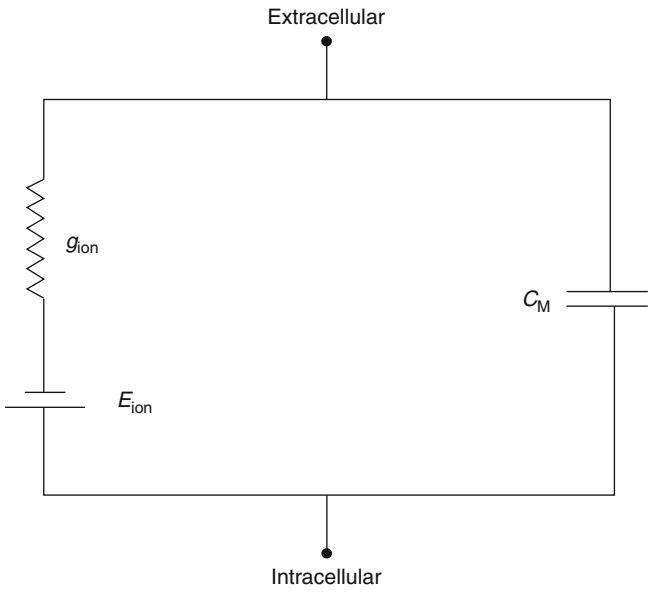

Fig. 2.1 A simplified electrical circuit equivalent of the plasma membrane showing the membrane capacitance (C_M), the potential difference (a battery) produced by ionic gradients (electrochemical potential, E_{ion}), and ionic conductance (g_{ion}, reciprocal of resistance)

Ion channels make the membrane a leaky capacitor, but their density is low and capacity is relatively high, approximately 1 μF/cm^2 of membrane area. For a spherical cell of 60 μm diameter and $E_M = -70$ mV, the amount of charges separated by the membrane's capacitance would be 46×10^6 ions, a very small fraction (less than 1/200,000) of the total number of ions in the cytoplasm. Therefore, the bulk of the cytoplasm and extracellular fluid is electroneutral, and changes in E_M do not require the movement of large numbers of ions. This fact is important for the production of action potentials.

The plasma membrane of excitable cells is basically an electric circuit: the membrane is a capacitor (C_M), and the permeability and electrochemical gradient for an ion are its conductance (g_{ion}) and a battery (E_{ion}, its electrochemical potential given by the Nernst equation) (Fig. 2.1). To include the three major ion species (Na^+, K^+, Cl^-), specific conductances (g_{Na}, g_K, g_{Cl}) and batteries (E_{Na}, E_K, E_{Cl}) are included in the circuit. Usually Na^+ and K^+ are not at equilibrium at the resting E_M, resulting in small inward (Na^+) and outward (K^+) currents that are offset by the Na^+-K^+ ATPase, included in our circuit as a current generator that gives a net flow of positive charges (I_+) from the cytosol to the extracellular fluid ($I_{Na} > I_K$) (Fig. 2.2). The Goldman-Hodgkin-Katz equation (Eq. 2.5) predicts that the potential difference measured across the plasma membrane (E_M) will change if the conductance, the ionic concentration ratio, or the function of the Na^+-K^+ ATPase is altered. Because E_M depends on the ionic concentration ratio, and the electrogenic effect of the Na^+-K^+ ATPase is relatively small, membrane potential follows changes in ionic conductance. In the resting state, the permeability to K^+ is two orders of magnitude greater than the permeability to Na^+, and E_M is closer to E_K (−70 to −90 mV) (Table 2.1). At the peak of an action potential, the permeability to Na^+ is 10–20 times greater than the permeability to K^+, bringing the membrane potential closer to E_{Na} (50 mV or higher) (Figs. 2.2 and 2.3a).

The sudden changes in ionic permeability characteristic of action potentials are due to voltage-gated channels. These ion-specific channels share certain traits: an ion-permeant pore, a voltage sensor, and a gate to open or close the pore [16–18]. Voltage-gated ion channels have motifs with six membrane-spanning α-helices (four for Na^+ and Ca^{2+} voltage-gated channels, one for K^+ channels); one helix in each motif includes seven repeats of arginine or lysine residues followed by two hydrophobic amino acids. The movement of these positively charged amino acids in response to changes in E_M is the gate that opens the channel pore [6, 8, 19].

Local depolarizations or slow potentials open voltage-gated Na^+ channels, increasing g_{Na}. E_M depolarizes, causing more Na^+ channels to open and increasing the inward Na^+ current in a positive feedback cycle that eventually drives E_M towards E_{Na} (Figs. 2.2 and 2.3b) [20]. The opening of a single voltage-gated Na^+ channel is a probability function; the channel population in a given cell opens within a depolarization range. When g_{Na} increases beyond a certain point (the action potential threshold), the depolarization enters the positive feedback cycle, and more voltage-gated Na^+ channels open. In consequence, E_{Na} exerts a greater influence on membrane potential. However, the increase in g_{Na} is time-limited, and it returns to its resting level within 1–2 ms (Fig. 2.3b). This behavior is explained as follows: when membrane depolarization reaches the threshold for a voltage-gated Na^+ channel, an activation gate opens and Na^+ can enter the cell following its electrochemical gradient (Fig. 2.4a). Shortly after the activation gate opens, a time-dependent inactivation gate closes, ending Na^+ influx (Fig. 2.4b) [21, 22]. Once voltage-gated Na^+ channels are inactivated, the cell membrane must repolarize to reverse the inactivation (Fig. 2.4c).

Depolarization also results in a slow increase in g_K, which reverses exponentially as the membrane repolarizes to its resting potential (Fig. 2.3b). The voltage-gated K^+ channels that change g_K activate about ten times slower than their Na^+ counterparts and are known as *delayed rectifiers*. They also close slowly as the membrane is repolarized. Because the voltage-gated K^+ channels close with some delay after repolarization, the membrane may hyperpolarize following an action potential (afterpotential hyperpolarization) (Fig. 2.3b). The initial description of ionic events during an action potential was made in the giant axon of the squid, which contains voltage-gated Na^+ and K^+ channels almost exclusively [23]. It is a testament to the evolutionary importance of the process that the basic mechanism of the action potential is extensively conserved with relatively minor modifications: excitable cells in other species contain these two channel types, in addition to voltage-gated channels that conduct other ions. The heart is a good example: its cells

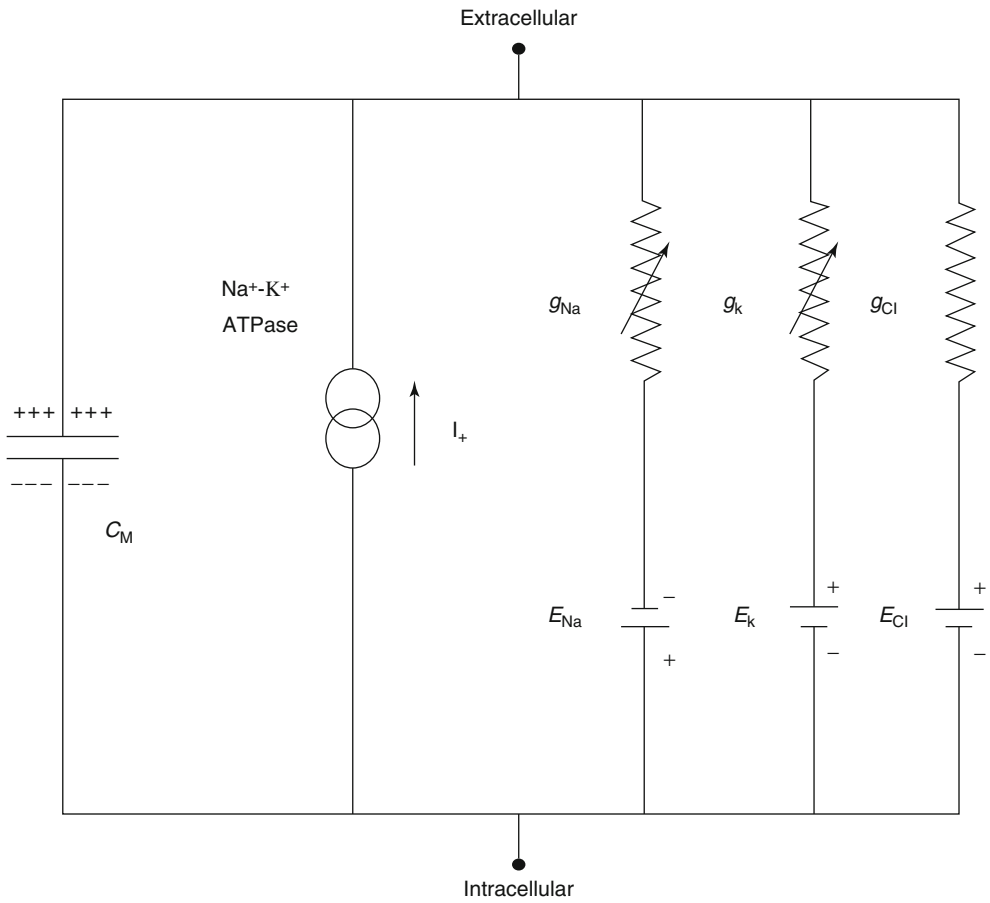

Fig. 2.2 Basic electrical circuit equivalent of the plasma membrane including membrane capacitance (C_M), ionic conductances (g), electrochemical potentials (E), and the current generator Na^+-K^+ ATPase. *Arrows* through g_{Na} and g_K indicate that these conductances can vary, for example, during an action potential

include voltage-gated Ca^{2+} channels that open during depolarization, increasing g_{Ca} which is responsible for the positive potential plateau observed during the action potentials in these cells [24].

Because action potentials are all-or-none responses, once their threshold is reached, the cell is refractory to further stimulation; during the spike of the action potential, voltage-gated Na^+ channels are either open or in their inactivated state (Fig. 2.4b, c). This portion of the action potential is the absolute refractory period: further stimuli will not alter its shape or trigger another action potential. As E_M repolarizes and g_{Na} returns to its resting level, the cell is able to initiate another action potential only if a stronger stimulus is applied. In this phase, the inactivation of voltage-gated Na^+ channels is not completely reversed, and a stronger stimulus is needed to activate enough Na^+ channels and depolarize the membrane. Moreover, g_K remains elevated, resulting in afterpotential hyperpolarization of E_M and increased opposition to depolarization.

Conduction

A notable characteristic of neurons is their enormously elongated cylindric processes known as *axons* and whose main function is the conduction of action potentials. In unmyelinated axons, action potentials are propagated by a wave of depolarization called the *local response*. This means that an action potential occurring in a finite membrane region depolarizes neighboring areas and causes the E_M to reach threshold and generate an action potential. Unless there is a change along the length of the axon in the threshold level or in the membrane resistances and capacitance, the action potential is transmitted at a constant velocity by electrotonic conduction.

The speed of electrotonic conduction is determined by the passive electrical properties of the cell. The axon or muscle fiber behaves as a poorly insulated cable: the amplitude of the E_M change induced by a focal stimulus falls exponentially with distance from its origin. In addition to the transverse resistance and capacitance due to the membrane, the axonal cytoplasm (like any cable) represents an internal resistance to current flow. The distance at which a potential difference declines to 37 % of its original intensity is the *length constant* and is equal to the square root of the ratio of membrane and cytoplasmic resistances. The length constant is typically between 1 and 3 mm, clearly shorter than the length of many axons and muscle fibers. Moreover, the speed of electrotonic conduction is determined by the resistance (inversely proportional to the cross-sectional

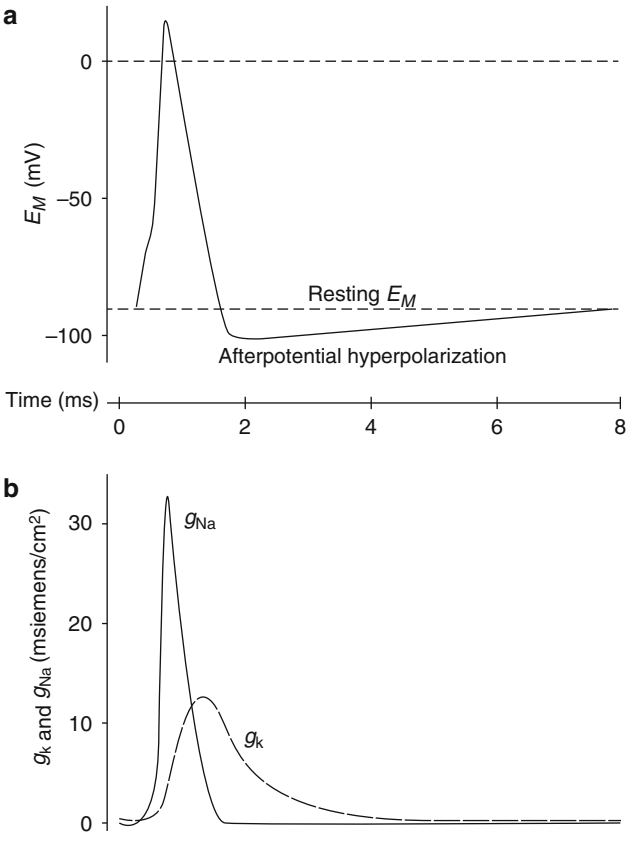

Fig. 2.3 (**a**) Change in membrane potential (E_M) and time course of an action potential. The resting E_M is shown by the dashed line on the bottom. (**b**) Voltage- and time-dependent changes in Na^+ and K^+ conductances during an action potential

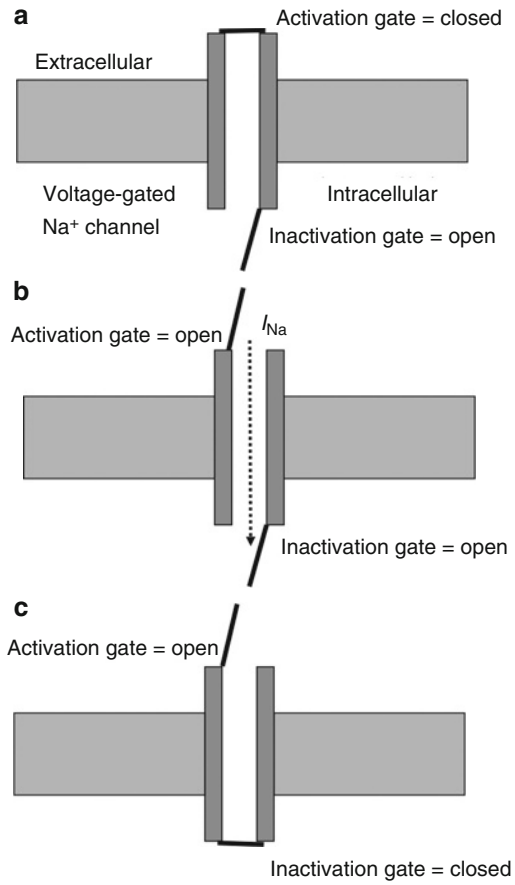

Fig. 2.4 (**a**) Position of "activation" and "inactivation" gates of a voltage-gated Na^+ channel at the resting membrane potential. (**b**) In response to a stimulus, the activation gate opens and allows Na^+ to enter the cell (I_{Na}), depolarizing the membrane; the time-dependent inactivation gate remains open. (**c**) Following a short delay, the inactivation gate closes and stops Na^+ influx; the activation gate remains open until the membrane potential repolarizes below its threshold

area of the axon or muscle cell): larger cells have faster conduction velocities.

Axons and muscle fibers regenerate action potentials by local currents, avoiding the loss of amplitude intrinsic to pure electrotonic conduction. Because conduction velocity is proportional to the cell's radius, some organisms, such as the squid and lobster, have developed giant axons (up to 1 mm in diameter) to rapidly conduct action potentials important for escape maneuvers. That is certainly not a strategy available to all organisms.

An alternative mechanism to optimize the conduction of action potentials in thin axons involves surrounding the axons with a thick layer of insulation, myelin. The axons of motor and large sensory neurons are surrounded by Schwann cells, a specialized type of glia that spirals around the axon in concentric layers that eventually condense to form myelin lamellae (Fig. 2.5). The composition of myelin is similar to that of cellular membranes, with ~70 % lipid (mostly cholesterol and phospholipids) and 30 % protein. Schwann cells are aligned regularly around axons, each covering an axon segment of approximately 0.4–1.0 mm. The small length of axon exposed to the extracellular space between each myelinated segment is called a *node of Ranvier*. The spiral of myelin around the axon increases membrane resistance and decreases its conductance. Therefore, during an action potential, the transmembrane current flow at the nodes of Ranvier is much greater than at the myelinated internodal regions: the nodal regions can generate action potentials, and the depolarization wave spreads through the internodal regions by electrotonic conduction to the next node, where another action potential is triggered. This combination of localized action potentials with electrotonic conduction allows axons to remain relatively small and minimizes the metabolic cost of the action potentials. First, the conduction velocity of unmyelinated axons is proportional to the square root of their diameter: an unmyelinated fiber would have to be 4 mm thick to conduct an action potential with the same velocity as the fastest myelinated axon (~120 m/s). Second, myelinated axons generate action potentials in the nodal regions only; therefore, the amount of transmembrane charge movement

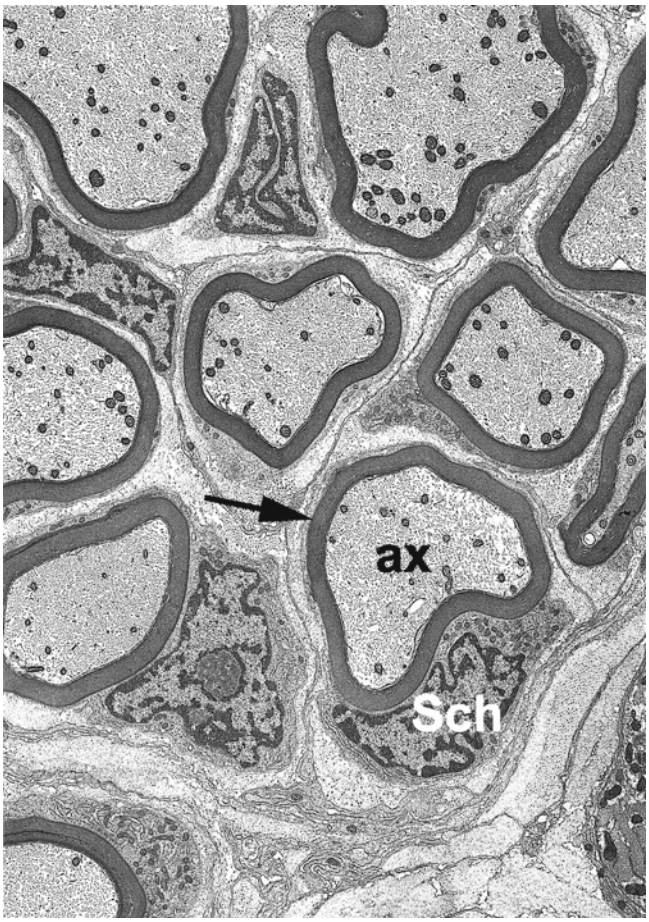

Fig. 2.5 This electron photomicrograph shows a cross section of peripheral nerve. Axons (*ax*) are surrounded by myelin sheaths (*arrow*). Myelin in peripheral nervous system is formed from the plasma membrane of Schwann cells (*Sch*), in contrast to the central nervous system where myelination is by oligodendrocytes

per action potential is less than in an unmyelinated axon, resulting in less energy consumed by ion-motive transporters to restore ionic gradients. Finally, the large internodal regions function as reservoirs for the diffusion of ions in and out of the nodes. This increases the effective nodal volume and minimizes the changes in ionic concentration ratios due to the action potential currents, which would render the axon unexcitable in a relatively short time.

Neuromuscular Junction

Skeletal muscle fibers contract under direct neural control. The activation signals coded by the action potentials are transmitted from the motor neuron's axon to the muscle fiber at a specialized site of close apposition, the neuromuscular junction. This is a type of chemical synapse that uses acetylcholine (ACh) as the transmitter that binds to specific receptor in the postjunctional (postsynaptic) membrane, inducing local depolarizations that spread outside of the neuromuscular junction and trigger all-or-none action potentials.

Organization

The neuromuscular junction is the site where the motor neuron makes contact with the membrane (sarcolemma) of a skeletal muscle fiber. The axon terminal and the sarcolemma present specialized features necessary for the transmission of the action potential from the motor neuron to the muscle fiber. Specific cytoskeletal proteins participate in the formation, consolidation, and maintenance of ACh receptors at the neuromuscular junction [25–27]. The development of the neuromuscular junction is regulated by interactions between the nerve terminal and the muscle fiber [26]. Two of its hallmarks are specialized Ca^{2+}-triggered ACh exocytotic machinery in the presynaptic terminal and the clustering of ACh receptors on the postsynaptic sarcolemma, resulting from the selective activation of ACh receptor genes at this site.

As the motor neuron reaches a group of muscle fibers, its axon loses its myelin sheath and forms very fine Schwann cell-covered branches that end in multiple varicosities. These synaptic boutons, or terminals, are filled with synaptic vesicles, 50-nm-diameter structures that contain ACh. Each synaptic vesicle has roughly the same ACh content (~5,000 mol), called a quantum. In addition, the synaptic terminals contain mitochondria and active zones, dense patches on the presynaptic membrane where vesicles fuse to release ACh into the small space between the pre- and postsynaptic membranes (synaptic cleft). These components show definite polarization within the synaptic terminal, with the synaptic vesicles in the portion facing the muscle fiber, clustering around the active zones, the site for their eventual release, and most of the mitochondria beneath the Schwann cell (Fig. 2.6).

Each terminal innervates a single muscle fiber, over a cup-shaped depression where the sarcolemma forms multiple junctional folds or invaginations. This area is called the *end plate*, and it is usually in the middle third of the muscle fiber. With few exceptions, muscle fibers have only one end-plate region, innervated by a single axon. The narrow synaptic cleft (~60 nm) is occupied by the basement membrane or lamina, an amorphous collection of collagen, glycoproteins, and enzymes, including acetylcholinesterase, which breaks down released ACh to choline and acetate. Both the presynaptic terminal and the muscle fiber secrete the basement membrane proteins. Each active zone in the synaptic terminal is opposite to a postsynaptic junctional fold (Fig. 2.6). The ACh receptors are clustered at the top of the folds, with a density of 10,000–15,000 per μm^2, 1,000-fold greater density than in the rest of the sarcolemma, and higher than for any other known channel [27–29]. Conversely, the regions extending deep into the folds are rich in voltage-gated Na^+

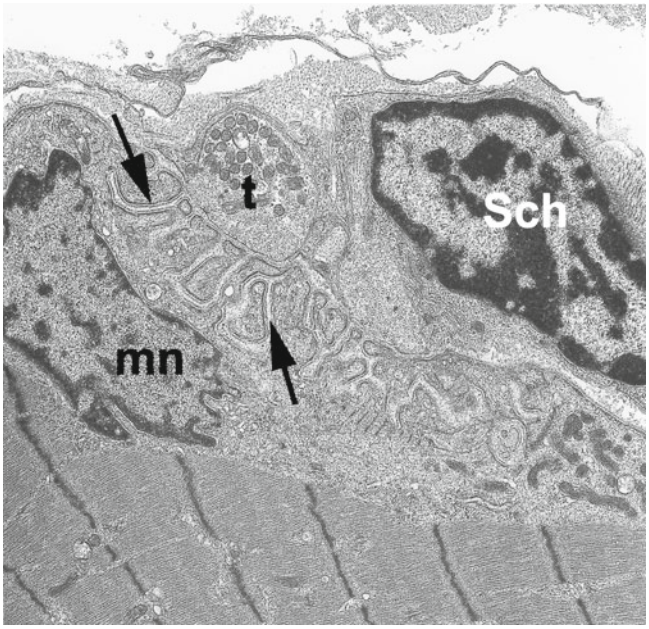

Fig. 2.6 This electron photomicrograph illustrates key elements of a neuromuscular junction. A motor axon nerve terminal (*t*), containing high concentration of mitochondria and synaptic vesicles, is overlain by Schwann cells (*Sch*). A narrow synaptic cleft separates the nerve terminal from the sarcolemma. The sarcolemma is highly involuted with postsynaptic folds (*arrows*) that concentrate acetylcholine receptors and ion channels. Nuclei (*mn*) and mitochondria are often concentrated in the muscle fiber cytoplasm immediately adjacent to the neuromuscular junction

channels, a distribution that improves transmission efficiency by decreasing action potential threshold [30, 31]. This differential distribution of integral proteins may be explained by cytoskeletal elements: rapsyn, utrophin, and α-dystrobrevin-1 co-localize with ACh receptors at the crests of the folds, whereas ankyrin, dystrophin, and α-dystrobrevin-2 are present at the bottom [30, 32].

The nicotinic ACh receptor mediating neuromuscular transmission is a funnel-like intrinsic sarcolemmal pentamer (~275,000 kD) composed of four different subunits (α2βδε) of molecular weights ranging from 40 to 65 kD [6, 33]. Each subunit has four putative sarcolemma-spanning helical domains and participates in the formation of the ion pore. The α-subunits have the binding site for ACh and α-bungarotoxin, a snake venom that is a potent specific inhibitor of the ACh receptor. The ε-subunit replaces the γ-subunit, which is present during development.

Neuromuscular Transmission

The neuromuscular junction allows the efficient transmission of the motor impulse to the muscle fiber. Although direct electrical coupling would be faster, the size of the motor axon is too small to conduct the amount of current necessary to depolarize the much bigger muscle fiber. ACh gives a necessary amplification step. The delay in the transmission of information that is characteristic of neuromuscular junctions and other chemical synapses has not proven to be an evolutionary disadvantage for vertebrate motor systems.

Neuromuscular transmission may be divided into three discrete processes: (1) synaptic terminal depolarization and ACh release, (2) ACh binding and ion channel opening, and (3) end-plate depolarization and action potential generation. The action potential travels down the motor axon, reaching the synaptic terminals. There, voltage-gated Ca^{2+} channels (mostly P-type channels in human neuromuscular junctions) open in response to the depolarization, allow Ca^{2+} to enter the presynaptic terminal, and increase cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) [34]. The increase in ($[Ca^{2+}]_i$) activates the Ca^{2+}-binding protein synaptotagmin, considered the principal sensor controlling ACh exocytosis [34, 35].

The mechanism for ACh release shares many features with other cellular secretory processes; it has evolved as a specialized form of vesicle trafficking capable of rapid Ca^{2+}-initiated exocytotic cycles. The current model for this process is the SNARE hypothesis: SNARE refers to the synaptic proteins involved [34]. According to this model, Ca^{2+} binding to synaptotagmin allows *synaptobrevin*, the synaptic vesicle v-SNARE (vesicle SNAP receptor), to interact with *syntaxin*, the neuronal t-SNAREs (target membrane SNAP receptors), and SNAP-25 to form a stable 7S complex. Synaptobrevin, SNAP-25, and syntaxin are cleaved by the proteolytic action of botulinum toxins, which block neuromuscular transmission [34, 35]. The 7S complex positions or docks synaptic vesicles at the fusion sites in the active zone and serves as a receptor for the cytosolic α/β/γ-SNAPs (soluble NSF attachment proteins). In turn, SNAP binding recruits the multimeric ATPase, NSF (N-ethylmaleimide-sensitive fusion protein). ATP hydrolysis by NSF disrupts the 7S complex and primes the vesicle for fusion and ACh release. Fusion of the vesicles with the presynaptic membrane proceeds via an unknown mechanism that probably requires synaptotagmin-mediated conformational changes in syntaxin that lead to the release of ACh into the synaptic cleft.

Upon release, ACh diffuses across the synaptic cleft and binds to ACh receptors in the postsynaptic junctional folds. For a single ACh receptor to open, two ACh molecules must bind to its α-subunits. The ACh receptor remains open for approximately 1 ms after ACh binding; then it closes, and ACh dissociates. The ACh concentration in the synaptic cleft falls rapidly by simple diffusion and the action of acetylcholinesterase; therefore, the ACh receptors are not likely to be activated a second time by rebinding of transmitter. Acetylcholinesterase is quite abundant in the mammalian neuromuscular junctions: ~2,500 mol/μm^2 of postsynaptic membrane, enough to quickly hydrolyze the ACh released into the synaptic cleft. Free choline is then taken up into the synaptic terminal by a high-affinity Na^+-choline cotransport system [28].

The release of multiple synaptic vesicles (100–300 per action potential) activates the ACh receptors at the crest of the postjunctional folds. The channel of the ACh receptor behaves as a cation channel with little selectivity: mono- and divalent cations that fit through a 0.65×0.65 nm pore are permeant [36]. Na^+ ions flow inward, and K^+ ions flow outward, following their electrochemical gradients and causing a local depolarization in the end-plate region, termed the *end-plate potential* (EPP). In contrast to an action potential, the ratio of the Na^+ and K^+ conductances does not change with time during an EPP, and the increase in ionic conductances is not initiated by a depolarization. Therefore, the EPP is a local, graded slow potential and not an all-or-none response. It does not regenerate, and its amplitude decreases as it moves away from its point of origin. EPP amplitude is 50–70 mV, unusual for chemical synapses (typically 1–2 mV) and large enough to spread electrotonically into the synaptic folds, where it triggers the opening of voltage-gated Na^+ channels and the development of an action potential that travels the length of the muscle fiber.

There is a short interval (0.3–1.0 ms) between the depolarization of the synaptic terminal and the appearance of an EPP. This delay is a general property of chemical synapses and seems to be due mostly to the exocytotic release of ACh: ACh diffusion across the synaptic cleft and binding to its receptors are not important determinants of the transmission delay [37, 38].

Skeletal Muscle

The function of skeletal muscles is to respond to neural control and efficiently transduce chemical energy (ATP) to force and movement. The structural features typical of skeletal muscle are the result of adaptation to the requirements of contractile activity and provide the checkpoints for its control. Thus, three major areas of specialization are identified: (1) the sarcolemma, including the end plate; (2) the sarcoplasmic reticulum, which regulates Ca^{2+} levels in the cytosol; and (3) the sarcomere, the basic contractile unit.

Skeletal Muscle Structure

Skeletal muscle fibers are elongated cells with multiple nuclei, usually located peripherally around the edge of the fiber. The endomysium, a thin layer of connective tissue, is attached to the sarcolemma. Another layer of connective tissue, the perimysium, surrounds bundles of muscle fibers (*fascicles*), and the whole muscle is encased within the epimysium, an outer layer of thicker connective tissue. These connective tissue layers are continuous with the muscle insertions into tendons and bones.

Skeletal muscle fibers are 10–100 μm in diameter and may be as long as the muscle in which they are located (centimeters). The most abundant cellular components are the filaments that form the sarcomeres, grouped together in myofibrils, tightly packed 1-μm-thick bundles that run the length of the fiber (Fig. 2.7.) The myofibrils are surrounded by the sarcoplasmic reticulum (SR), mitochondria, glycogen and fat droplets, and sarcolemmal invaginations called *transverse tubules* or *t-tubules*. Cardiac and skeletal muscles have a striated appearance on microscopic examination, a result of the repeated contractile units, the sarcomeres, arranged serially in the myofibrils.

Sarcolemma

The cell membrane that surrounds each muscle fiber, the sarcolemma, has multiple functional domains characterized by the clustering of specialized proteins. The individual muscle fibers are linked to the surrounding connective tissue by a trans-sarcolemmal protein network that connects the fiber's interior to the extracellular matrix. The *costameres*, riblike links containing vinculin, α- and β-spectrin, ankyrin, and talin, connect the cytoskeleton and the sarcolemma at the level of the Z line of peripheral sarcomeres. Another protein complex links the subsarcolemmal cytoskeleton, mainly F-actin filaments, to the extracellular matrix: dystrophin binds F-actin, the integral membrane protein β-dystroglycan, and cytosolic syntrophins. β-Dystroglycan also binds to the sarcoglycans (α, β, δ, γ, and possibly ε) and the extracellular protein α-dystroglycan. Finally, the heterotrimeric laminin-2 (α2β1γ1 or merosin) is the extracellular ligand of α-dystroglycan [39].

The sarcolemma has three main areas of specialization: neuromuscular junctions (Fig. 2.6), myotendinous junction, and the t-tubules (inset in Fig. 2.7.) The sarcolemma shows deep invaginations at the myotendinous junction, and sarcomeric actin filaments form close associations with the sarcolemma via α-actinin, vinculin, and talin. Desmin and dystrophin may also participate in the strengthening of the sarcolemma at the myotendinous junctions. These elements assure the continuity between the force-generating muscle fibers and the force-transmitting connective tissue that forms the tendons.

The t-tubular system is a network of narrow sarcolemmal invaginations along the length of the muscle fiber. Based purely on visible surface area, the capacitance of the sarcolemma is about 6 μFarad/cm^2, much higher than for other excitable cells. When the extra membrane area of the t-tubules is factored in the calculation, sarcolemmal capacitance is 1 μFarad/cm^2, which is typical of excitable cells. In mammalian skeletal muscle, there are two t-tubules per sarcomere, located in the planes defined by the tips of the myosin filaments (A-I band junction.) The function of the t-tubules is to propagate the depolarization wave deep into the muscle fiber and to trigger Ca^{2+} release from the SR. This latter process is called *excitation-contraction coupling* (E-C coupling) and is accomplished by the presence of

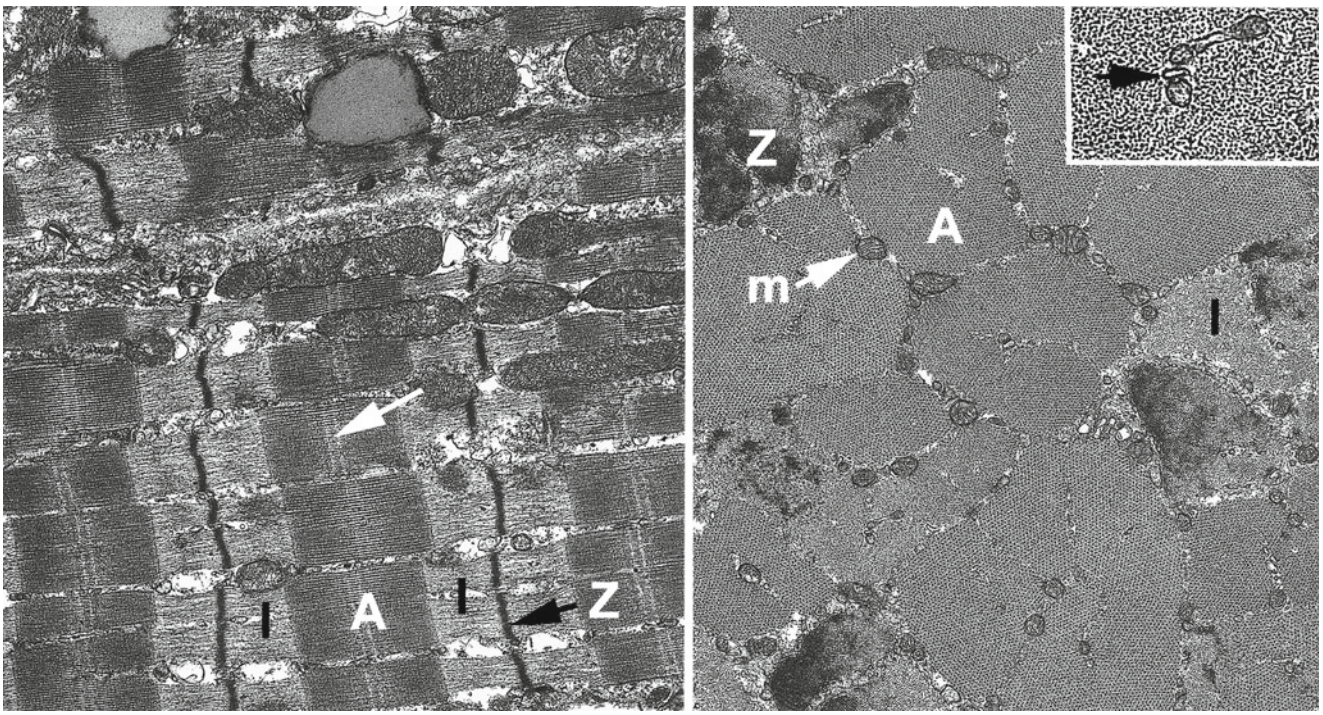

Fig. 2.7 These electron photomicrographs illustrate the basic organization of the muscle fiber contractile unit, the sarcomere, with longitudinal section at the left and cross section at the right. Z bands (*Z*) demarcate each end of individual sarcomeres. The thin filaments in the light-colored I bands (*I*) interdigitate at the Z bands and overlap with the thick filaments in the A band (*A*). The A band is usually bisected by the M line (*arrow*). The separate portions of the sarcomere also can be recognized in the muscle cross section to the right. Units of contractile proteins, known as myofibrils, are surrounded by sarcoplasmic reticulum and mitochondria (*m*). The *inset* at the *upper right* shows a triad. Note the close proximity between the t-tubule (*arrow*, in the *middle*) and the two elements of the sarcoplasmic reticulum

voltage-gated Ca^{2+} channels, the dihydropyridine receptors (DHPr). The DHPr has five subunits (α1α2, βγ, and δ). The α1-subunit (212 kD) is the central component of the complex. It has four transmembrane domains, each with six α-helices, and can function as a voltage-gated ion channel. The fourth α-helix in each domain contains positively charged amino acids every third or fourth position. This could be the structural correlate of a charge movement that is observed after sarcolemmal depolarization [40]. The other DHPr subunits modulate gating, inactivation, and current amplitude.

Sarcoplasmic Reticulum

The SR is a highly developed network of interconnected membranous vesicles, analogous to the endoplasmic reticulum. Each sarcomere is surrounded by a portion of this network. The SR forms sacs, called *terminal cisternae*, on either side of each t-tubule. These closely associated structures are called *triads* (see inset Fig. 2.7), or T-SR junctions, and play a central role in E-C coupling. The gap between the t-tubule and the terminal cisternae is 10–20 nm. It is occupied by the *junctional feet*, periodically arranged structures that seem to physically connect the two membranes and are distributed in orderly tetragonal arrays. Between two triads, the nonjunctional SR continues as narrow tubes parallel to the long axis of the sarcomere, the longitudinal SR, which then fuse to form a single structure perforated from side to side by small round opening, or fenestrae (fenestrated SR).

The junctional feet have been identified as the cytosolic portion of the Ca^{2+} release channels present in the terminal cisternae; they may also include aldolase, triadin, glyceraldehyde phosphate dehydrogenase, and immunophilin-binding proteins. The SR Ca^{2+} release channels can be activated pharmacologically with the plant alkaloid ryanodine, hence the term *ryanodine receptors* (RyR). There are three RyR genes in mammals, producing three isoforms; two of them, RyR1 and RyR3, are present in skeletal muscle [8, 10, 41]. RyR are homotetramers (>550 kD subunits) with a central canal leading to four radial cytoplasmic openings. Each tetramer has a large cytoplasmic domain (foot) that inserts into the cisternal membrane and occludes the central canal [10, 41]. There are multiple regulatory sites, mostly around the putative ion channel on the C-terminal third of the protein, including sites for phosphorylation, Ca^{2+}- and ATP-dependent activation, Mg^{2+}-dependent inhibition, calmodulin, and immunophilin binding [10, 41].

The most abundant integral SR protein is a Ca^{2+}-ATPase, a single polypeptide chain of 140 kD, corresponding to the

α-subunit of other P-type transport ATPases, such as membrane Ca^{2+}, Na^{+}-K^{+}, and H^{+}-K^{+} ATPases. The SR Ca^{2+}-ATPase belongs to the family of intracellular Ca^{2+} pumps present in sarcoplasmic and endoplasmic reticula known as *SERCA* (sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPases). Three isoforms have been identified in skeletal muscle (adult fast, neonatal fast, slow/cardiac), derived from the alternative splicing of two genes (SERCA 1 and 2) [42]. The proposed structure of SR Ca^{2+}-ATPase contains ten α-helical transmembrane and two cytoplasmic domains. One of the cytoplasmic domains contains phosphorylation and ATP binding sites [43]. The purpose of the SR Ca^{2+}-ATPase is to move Ca^{2+} ions from the cytoplasm into the lumen of the SR, ending muscle contraction. Because resting $[Ca^{2+}]_i$ in skeletal muscle fibers is on the order of 100 nM and the SR $[Ca^{2+}]$ is in the millimolar range, the SR Ca^{2+}-ATPase works against a 10^4-fold concentration gradient [42, 43]. More than 70 % of the total SR membrane protein is Ca^{2+}-ATPase, a density of 30,000 mol/μm^2 distributed uniformly along the SR [44, 45]. This high transport capacity is necessary to restore $[Ca^{2+}]_i$ to its resting level and terminate a contraction rapidly (<50 ms).

The lumen of the junctional SR contains calsequestrin, an acidic low-affinity and high-capacity Ca^{2+}-binding protein (40 mol Ca^{2+}/mol calsequestrin) that combines with the Ca^{2+}-ATPase to increase Ca^{2+} storage [41]. Less abundant SR Ca^{2+}-binding proteins (calreticulin, sarcalumenin, and histidine-rich Ca^{2+}-binding protein) may also participate in Ca^{2+} storage between SR release and uptake cycles [46].

Sarcomeres

Microscopically, thin dense transverse lines appear every 2–3 μm along the length of myofibrils. These are the Z lines, a planar network that delimits the sarcomeres (Fig. 2.7). A dark, electrodense region in the middle of each sarcomere, the A band, contains the 1.6-μm-long *thick filament*s. The A band is between two lighter (less electrodense) regions: the lighter regions of two adjacent half-sarcomeres form the I band. The I band contains two sets of 1-μm-long *thin filaments*, connected in series at the Z line. A lighter central region of variable width in the A band is the H zone, between the ends of the two sets of thin filaments. The H zone is typically bisected by a darker line, the M line, produced by links between the thick filaments in the middle of the sarcomere (Fig. 2.7). The thick filaments contain myosin and associated proteins, including C protein and H protein; M protein and myomesin localize at the level of the M line. In addition, the M line contains the skeletal muscle isoform of creatine kinase, the enzyme that catalyzes the transfer of phosphate from creatine phosphate to ADP, producing ATP [47].

The myosins in skeletal muscle thick filaments are conventional class II myosins, hexameric proteins consisting of two heavy chains (MHCs, 200 kD each) and two pairs of nonidentical light chains (MLCs, 17–23 kD), referred to as *essential* (or *alkali*) and *regulatory* light chains. The MHCs have two globular amino-terminal head domains that contain the motor function (ATPase) and a long α-helical coiled-coil carboxy tail with filament-forming properties. At least six MHC isoforms are present in human muscles: the genes coding for 5 of them (embryonic, perinatal, 2A, 2X/D, and extraocular) form a cluster in chromosome 17; the gene for slow/β is clustered next to α (cardiac-specific) in chromosome 14 [48, 49]. A few other MHC isoforms have very restricted expression and unknown functional significance [49, 50]. The MHC isoforms are highly conserved (78–98 % amino acid identity), particularly in the tail region. Two surface loops in the globular head, near the ATP- and actin-binding sites, show the most divergence and likely determine differences in motor activity.

Five major skeletal muscle MLCs (4 genes) are members of the superfamily of EF-hand Ca^{2+}-binding proteins [48]. Two isoforms of regulatory MLCs have been definitely identified: these proteins have phosphorylation sites that may modulate force production.

The main components of the thin filaments are actin, tropomyosin, the troponin complex, and tropomodulin. Skeletal muscles contain only one actin isoform (α-skeletal), a globular protein (G-form) that polymerizes to form a double helix filament that is fairly inextensible (F-actin). The amino terminal of each actin monomer has a myosin-binding site that participates in the activation of myosin ATPase.

The tropomyosins are dimeric proteins with α-helical coiled-coil subunits, α and β (34 and 36 kD, respectively). Three skeletal muscle tropomyosin genes have been identified in humans, coding for one β- and two α-isoforms (fast and slow) [48]. The tropomyosin subunits assemble in head-to-tail fashion to form filaments that associate with the F-actin double helix. Each tropomyosin binds to seven actin monomers on each of the actin filaments, end-to-end in the grooves of F-actin.

The troponin complex consists of three polypeptide chains: troponin C (TnC), an 18 kD protein with regulatory Ca^{2+}-binding sites; troponin I (TnI), a 21 kD protein that inhibits the actin-dependent activation of myosin ATPase; and troponin T (TnT), a 31 kD protein that attaches the whole complex to tropomyosin. The carboxy and amino terminals of TnC form two globular domains linked by a central helix. Each globular domain contains two divalent metal ion-binding sites formed by the helix-loop-helix EF-hand motif. The binding sites in the amino terminal are low-affinity Ca^{2+}-specific sites that regulate contraction. The binding sites in the carboxy terminal bind both Ca^{2+} and Mg^{2+} with high affinity and are probably occupied at all times. There are two TnC isoforms in skeletal muscle (fast and slow) derived from different genes [48].

In contrast, multiple TnI isoforms are produced by the alternative splicing of three TnI genes (fast, slow, and cardiac): four fast, two slow, and four cardiac isoforms [48]. TnC interacts with TnI and TnT; the strength of interaction between TnC and TnI depends on whether Ca^{2+} is bound: when it is, TnC interacts more strongly with TnI. This is the regulatory mechanism of the troponin complex. Tropomodulin (43 kD) is a protein that caps the free ends of the actin filaments and is required to maintain constant thin filament length [51].

The Z line is composed mainly of α-actinin and CapZ (β-actinin.) α-Actinin is an actin-binding homodimer that associates with the end of the thin filaments at the Z line. Its two elongated subunits (100 kD each) have antiparallel orientation, actin-binding amino terminals, and a basic structure similar to spectrin and dystrophin. CapZ, or capping protein, is a heterodimer (α-subunit, 32 kD; β-subunit, 33 kD) that binds to the Z line ends of the thin filaments.

Three giant proteins, titin, nebulin and obscurin, are thought to play important roles in the assembly and stabilization of skeletal muscle sarcomeres. Titin (connectin) is a large modular protein, the largest described to date (>3,000 kD), extending up to 1 μm from the Z line to the M line, where it binds mainly to M protein and myomesin. Titin has an elastic segment at the I band level, but it is inextensible in the A band. It serves a growing number of functions: thick filament positioning, fiber elasticity, mechanosensing [48, 52, 53]. Nebulin (500–800 kD) is a large protein associated with thin filaments. It extends the full length of the thin filament, and its carboxy terminal interacts with α-actinin in the Z line. It associates on either end with actin filament capping proteins: CapZ at the edge of the Z line and tropomodulin on the I band end. Despite its localization, nebulin does not seem to participate in the determination of thin filament length. Instead, it seems to act as a stabilizer of formed thin filaments [52]. Obscurin is the most recently identified member of this trio. Its largest variant, obscurin-A (700–900 kD), is the product of a single gene; a couple of smaller isoforms arise from different transcription initiation sites on the same gene. The location of obscurin remains a bit of a puzzle: the most recent evidence show it is found at the Z line and M line on the periphery of myofibrils [52].

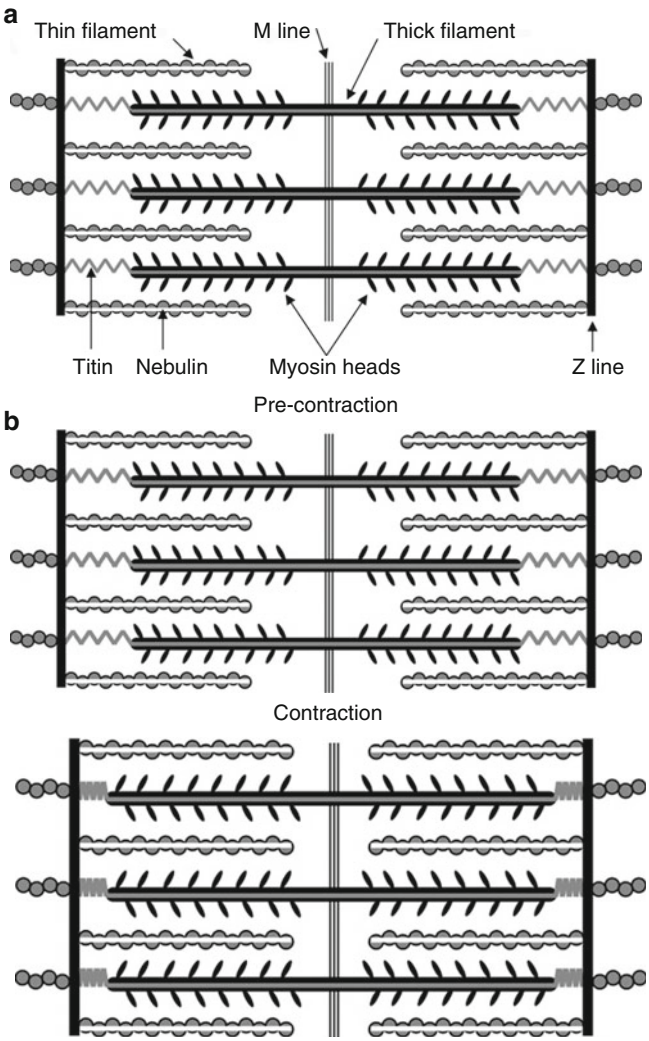

Fig. 2.8 (**a**) Schematic representation of a sarcomere. Thin filaments attach to the Z lines and provide support for the sliding of the thick filaments. Titin is a springlike protein that maintains the thick filaments in register within the sarcomere. (**b**) Sliding-filament hypothesis of contraction. The first drawing shows a sarcomere in the "resting" position. The *bottom* drawing shows sarcomere shortening resulting from the myosin power stroke (note the change in the position of the myosin heads in the thick filaments). The length of the thick and thin filaments remains unchanged

Sliding-Filament Theory

The sarcomere is the functional unit of skeletal muscle. The thick filaments contain myosin, the molecular motor that produces movement and force, and the inextensible thin filaments anchored on the Z line provide the rigid scaffold that transmits force and the regulatory proteins that initiate and terminate contraction. The globular heads of myosin attach to actin to form crossbridges, which attach and detach cyclically, sliding the thin and thick filaments by each other, thereby producing movement and force. This sliding-filament mechanism of muscle contraction is based on detailed knowledge of the structure and biochemical properties of the participating molecular elements. However, the description of bridge-like structures between the thin and thick filaments by high-resolution electron microscopy gave rise to the functional concept of the crossbridges.

During a contraction, the thick and thin filaments slide by one another, shortening sarcomere width, but the length of each filament remains constant (Fig. 2.8b). The change in sarcomere width is due to the cyclic formation and breakage of crossbridges between the thick and thin filaments. The crossbridges

pull the thin filaments towards the center of the sarcomere in a sequence of events that couple ATP hydrolysis to mechanical activity. Although each sarcomere can shorten 1 μm at the most, the serial arrangement of sarcomeres in myofibrils increases the magnitude and speed of the movement.

Myosin fulfills three basic functions: (1) it aggregates forming the thick filaments, (2) its ATPase activity transduces the energy of ATP to movement, and (3) it binds to F-actin to produce movement and force. The intrinsic ATPase activity of myosin is determined by the MHC isoform of the molecule. The ATPase rate is slower in MHC 1 (0.22 s^{-1}), followed by MHC 2X and 2A (~0.8 s^{-1}) and MHC 2B (1.15 s^{-1}) [54]. Myosin ATPase is a measure of the rate of crossbridge cycling and correlates with the speed of muscle shortening: muscles with fast myosin isoforms shorten faster than muscles with slower myosins [55, 56].

The role of F-actin in the contractile process is twofold. First, it accelerates the kinetics of the myosin-ATP interaction, making myosin a more effective ATPase. Second, it provides the cytoskeletal backbone against which the power strokes of the crossbridges exert force.

The interaction of the myosin heads with actin (crossbridges) forms actomyosin, a reaction that constitutes the basis for sarcomere shortening and is reversed by ATP. Actomyosin has a higher ATPase activity than pure myosin and represents an intermediate step in the activation of myosin as a mechanical transducer. Initially, ATP is bound to the globular head of myosin; ATP hydrolysis leads to weak actin binding and the formation of actin•myosin•ADP•Pi, seen structurally as a crossbridge. Upon ATP hydrolysis, the head of myosin rotates away from the rod domain to the position prior to the power stroke, a configuration denoted as myosin*. The release of Pi from the actomyosin complex leads to the formation of a force-producing state, actin•myosin*•ADP. Force is produced when the myosin head returns to its initial position (power stroke), ADP is released, and actin and myosin bond strongly. Finally, ATP must bind to detach myosin from actin, form myosin•ATP, and start the cycle again. This simple reaction scheme assumes that the hydrolysis of one ATP molecule results in one power stroke, an issue that has not been settled definitively. In addition, the orientation of the myosin head changes in one direction only; therefore, the swinging crossbridges generate movement towards the center of the thick filament (Fig. 2.8b). The length of each crossbridge step during ATP hydrolysis is estimated at 10–20 nm, based on the size of the myosin head, but remains unproven.

Regulation of Contraction

Generally, the translation of electrical activity into other cellular actions is accomplished by changes in $[Ca^{2+}]_i$ via voltage-gated Ca^{2+} channels. Resting $[Ca^{2+}]_i$ is maintained at low levels (<100 nM) by the combined action of cellular Ca^{2+}-ATPases and Na^{+}-Ca^{2+} exchange transport systems on the membrane, and Ca^{2+}-ATPases on intracellular compartments, including the SR in skeletal muscle fibers.

The architecture of muscle fibers hints to how Ca^{2+} regulates the contractile process: the SR, an enormous Ca^{2+} reservoir, is placed between the sarcolemma and the myofibrils (Fig. 2.7, right). Action potentials are conducted down the sarcolemmal t-tubules, activating DHPrs. Unlike cardiac and most smooth muscle, Ca^{2+} influx through DHPr is not necessary to initiate E-C coupling in skeletal muscle fibers; moreover, Ca^{2+} flux through the skeletal muscle isoforms of the DHPr channel is too slow to significantly alter $[Ca^{2+}]_i$ [57]. Sarcolemmal depolarization induces the movement of electrical charges within the DHP that cause a structural shift in the neighboring RyR (on the terminal cisternae), opening the Ca^{2+} channel and releasing Ca^{2+} from the SR to the cytosol. This process is called "electromechanical coupling" [57]. In mammals, DHPr tetrads face alternating RyR along triad junctions; therefore, electromechanical coupling may not directly cause the opening of all available SR RyR. A current E-C coupling model proposes that the kinetics of SR Ca^{2+} release in response to electromechanical coupling are sufficiently fast to mediate Ca^{2+}-induced Ca^{2+} release from RyR not coupled to DHPr.

SR Ca^{2+} release in response to sarcolemmal depolarization increases cytosolic $[Ca^{2+}]$ rapidly. Free Ca^{2+} ions bind to troponin-C on the thin filaments, producing a change in the shape of the troponin complex, shifting tropomyosin into the grooves of the thin filaments, and exposing myosin-binding sites on the actin monomers. In this "steric blocking" hypothesis, the movement of a single tropomyosin molecule unblocks seven actin monomers, allowing actomyosin formation and ATPase activity [58]. The crossbridges cycle between attachment and detachment states as long as cytosolic $[Ca^{2+}]$ remains elevated and there is sufficient ATP to sustain the reaction.

Once sarcolemmal depolarization ends, SR Ca^{2+} release stops, and the process of Ca^{2+} uptake predominates. The fast and efficient restoration of cytosolic $[Ca^{2+}]$ is mostly due to high-capacity SR Ca^{2+}-ATPase activity. As cytosolic $[Ca^{2+}]$ falls towards its resting level, Ca^{2+}-binding sites in troponin-C become unoccupied, restoring tropomyosin to its blocking position and preventing the interaction between actin and myosin.

Motor Systems

Muscle Fiber Diversity

Three factors determine the functional characteristics of a particular muscle fiber: (1) the composition of the contractile filaments, (2) the capacity and speed of the Ca^{2+}-dependent regulatory system, and (3) the efficiency of the metabolic

Table 2.2 Skeletal muscle fiber types

	Slow type 1	Fast fatigue resistant type 2A	Fast fatigable type 2B
Diameter	+	++	+++
Capillary supply	+++	+++	+
Mitochondrial content	+++	+++	+
SR volume	+	+++	+++
Myofibrillar ATPase	+	+++	++++
Myofibrillar Ca^{2+} sensitivity	+++	+	+
SR Ca^{2+} uptake	Slow	Fast	Fast
Myoglobin content	+++	+++	+
NADH dehydrogenase	+++	+++	+
Succinate dehydrogenase	+++	+++	+
Glycerophosphate dehydrogenase	+	+++	+++
Lactate dehydrogenase	+	+++	+++
Twitch kinetics	Slow	Fast	Fast
Speed of shortening	Slow	Fast	Fast
Fatigue resistant	Yes	Yes	No

pathways that supply the energy currency needed for the production of force and movement. As previously described, there are different isoforms for all the proteins involved in contraction and whose kinetics determine the timing of events and energy requirements. Particular isoform combinations in sarcomeres, their regulatory systems, and their metabolic pathways define skeletal muscle fiber types. Based on their mechanical properties, which, in turn, depend on the speed of the actomyosin reaction and the Ca^{2+}-dependent activation and relaxation regulatory systems, muscle fibers may be "fast" or "slow" [49]. Another physiological characteristic, the resistance to fatigue, is more or less directly related to fiber metabolism and classifies fibers as fatigable or fatigue resistant. Using these principles, a basic classification scheme of muscle fiber types is presented in Table 2.2. For example, fatigue resistance correlates with higher mitochondrial content, smaller fiber diameter to minimized diffusion distances, and a more abundant capillary supply to provide substrates and eliminate end products (Fig. 2.9). A caveat, while this classification assigns particular morphological, biochemical, and functional features to the different fiber types, these should be seen as a continuum.

Motor Units

The integral unit for motor activity, the motor unit, is composed of a motor neuron and the muscle fibers it innervates [59]. The original description of the motor unit assumed that (1) all the muscle fibers in the motor unit respond equally to the motor neuron and (2) each muscle fiber is innervated by to a single motor neuron and there is no polyneural innervation.

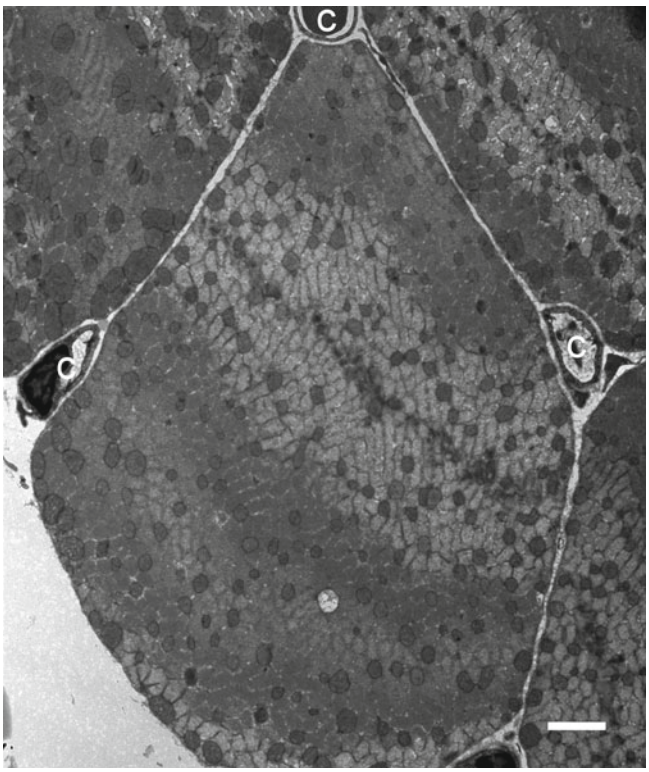

Fig. 2.9 This electron photomicrograph illustrates components of oxidative energy metabolism in skeletal muscle. The muscle illustrated is extraocular muscle, a highly oxidative, fatigue-resistant muscle. The muscle has a high mitochondrial content and an extensive capillary network. Capillaries are marked with "c". Scale bar = 2 μm.

Both assumptions are essentially correct, but not universally true. First, neuromuscular transmission reliably activates muscle fibers but may fail under certain conditions such as fatigue. Second, polyneural innervation is rare in adult muscles, but it is widespread during development. Persistent polyneural innervation may also occur after muscle damage or reinnervation of denervated muscle. Nevertheless, the motor neuron and the muscle fibers that constitute a motor unit can be considered as a functionally reliable and anatomically exclusive entity in normal adult skeletal muscles.

The characteristics of the different motor unit types reflect the functional properties and requirements of the muscle fibers and motor axons that integrate them. The number of muscle fibers innervated by a single motor axon is the innervation ratio: a low ratio indicates a greater ability for finely grading muscle force, and it is typically found in small, fine-movement muscles such as the extraocular and hand muscles. Functionally, motor units can be slow, fast fatigue resistant, and fast fatigable. The activation of motor units follows the "size principle": the smallest α-motor neurons tend to be activated first [60]. As more force is required, progressively larger motor neurons are recruited. This ascending size order of recruitment indicates that neuronal and axonal size correlates with the functional properties of the motor

units: the smallest axons form motor units that are slow and fatigue resistant, while the largest axons form fast and fatigable motor units. Thus, slow motor units are activated more frequently and for longer periods of time than the fast fatigable units [61].

Organization of Muscles

Movement and force are the consequences of skeletal muscle activation. The range and variety of movements and the forces exerted by muscles depend on the architecture of the skeleton and muscles attached to it. Most skeletal muscles fall into one of two basic anatomical organizations: "pennate" and "staggered array." In pennate (feather-like) muscles, fibers extend from origin to insertion in parallel arrays, at an angle (angle of pennation) to the axis of the force vector of the whole muscle. Muscle length is usually longer than the length of the individual fibers, and the force along the axis of the muscle is proportional to the cosine of the angle of pennation (1 for 0°, 0 for 90° pennation). Pennation increases the fiber cross-sectional area per unit volume, allowing muscles to generate relatively high forces, but limiting the range for force generation [62].

In other muscles, fascicles of relatively short muscle fibers are staggered along the length of the muscle, in parallel with the force vector. The individual muscle fibers originate and end on intramuscular connective tissue. The increased number of sarcomeres in series gives staggered array muscles a broader physiological range for force generation, although the total force output is less than in pennate muscles [63].

A small subset of muscles with circular geometry, such as trapezius, temporalis, deltoid, and diaphragm, have fibers that act on loads in different directions; the actions of different parts of a single muscle can be antagonistic or can vary over more than one degree of freedom [64].

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Part II

Approach to Neuromuscular Diseases: Neuromuscular Investigations

Serum Muscle Enzymes in Neuromuscular Disease

3

Rahila Ansari and Bashar Katirji

Introduction

Enzymes are protein catalysts found in all tissues and involved in most biochemical reactions. Even prior to the discovery of their precise catalytic functions, many enzymes were measured for diagnostic purposes [1, 2]. Based on their properties, some enzymes are also used as therapeutic agents.

Enzymes, which are intracellular, are released systemically through normal physiologic function or when there is increased membrane permeability due to cell injury or necrosis. The concentration of enzymes may also increase in the serum due to a block in metabolism, obstruction to the routes of elimination or excretion, or from increased rates of intracellular production. In general, levels tend to correlate with the extent and severity of disease. Enzymes are typically measured in serum rather than plasma and, in rare situations, in whole blood. Since enzymes are intracellular proteins, hemolysis may result in false elevations.

Certain enzymes are present in many organs, while others are more tissue specific. Isoenzymes are enzymes that catalyze the same biochemical reaction but differ in their sequence of amino acids. A given enzyme may have many isoforms, with each isoform being restricted to a specific tissue. Hence, assays for isoenzymes are often more tissue specific than assays for the parent enzyme. Enzyme-linked immunosorbent assay (ELISA), using monoclonal antibodies that specifically bind to an enzyme isoform, is a rapid method for clinically measuring isoenzymes.

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Creatine Kinase (CK)

Basic Principles

Creatine kinase (CK), also known as creatine phosphokinase and creatine phosphoryltransferase, reversibly catalyzes the conversion of creatine phosphate and ADP into creatine and ATP.

$$\text{Creatine phosphate} + \text{ADP} \xleftrightarrow{\text{Creatine kinase}} \text{Creatine} + \text{ATP}$$

Creatine phosphate is important for energy storage in muscle [3]. It is essential in providing a rapidly available store of ATP for excitation/contraction coupling of actin and myosin in muscle. The highest concentration of CK is in skeletal and cardiac muscle; however, it is also present in the brain, and minimal amounts exist in the intestine and lungs [3, 4].

CK is the single most useful routine blood test for the evaluation of weakness in neuromuscular disease, as it correlates with the functional status of muscle. In myopathies, serum CK is elevated when there is active muscle fiber necrosis, as in inflammatory myopathies, Duchenne muscular dystrophy, or rhabdomyolysis. However, it is also increased, to a lesser degree, in neurogenic processes such as in amyotrophic lateral sclerosis. CK elevation in neuromuscular disease is closely related to the available muscle mass that can leak the enzyme. Any interpretation should take into consideration normal values in relation to gender, sex, and race as well as the available muscle mass and underlying physiologic status of the patient and toxic/metabolic abnormalities.

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Table 3.1 Serum CK and its isoenzymes

Isoenzyme	BB	MB	MM
Synonym (abbreviation)	CK1	CK2	CK3
Composition of skeletal muscle	–	1–3 %	97–99 %
Composition of cardiac muscle	–	15–20 %	75–80 %
Composition of brain	≈100 %	–	–
Contribution to total serum CK	–	–	≈100 %

Apart from its common use in the diagnosis and management of neuromuscular disease, particularly myopathies, elevated serum CK is a highly valuable marker in acute myocardial infarction. Low serum CK values are associated with hyperthyroidism, connective tissue disorders, corticosteroid therapy, and alcoholism [5, 6]. Low levels are also noted during pregnancy, in subjects with sedentary lifestyle, with prolonged bed rest, and in the elderly [4, 7].

Clinical Biochemistry

CK occurs as a dimer composed of any combination of the two globular monomers: muscle (M) and brain (B) [7–9]. Each monomer has a molecular weight of 43 kDa and is encoded by a distinct gene. Human cytoplasm contains three typical dimer isoenzymes: BB, MB, and MM. They are also referred to as CK1, CK2, and CK3, respectively. Additionally, two other atypical, large molecular weight isoforms may also be found in serum: macro-CK types 1 and 2. Macro-CK type 1 is an octomeric protein that results from the polymerization of isoform BB (typically) with immunoglobulin G (IgG) [10]. This polymerization is thought to be secondary to antigen-antibody binding [11]. Macro-CK type 2 is an oligomeric protein composed of a third CK monomer found in mitochondria [11]. Macro-CK type 1 is clinically relevant as it is associated with autoimmune processes, specifically myositis [11] and autoimmune cardiovascular disease [12]. In contrast, macro-CK type 2 is increased primarily in malignancies [11–13]. The clinical benefit of measuring macro-CK is for disease prognostication. Measuring the mitochondrial CK monomer is also of clinical significance, as it is elevated in mitochondrial myopathies and found in the pathological inclusions seen on muscle biopsies [14].

In the clinical setting, the most commonly measured isoforms are: MM, MB, and BB. The CK in skeletal muscle is almost exclusively MM (97–99 %), with the remaining (1–3 %) composed of the MB fraction (Table 3.1). Myocardial CK is mostly MM (75–80 %) but with a more substantial amount of MB (15–20 %). Brain CK is comprised exclusively of the BB fraction. In normal serum, total CK is provided mainly by skeletal muscles and is almost exclusively the MM fraction. This is likely due to the small mass of myocardium and brain, as compared to skeletal muscle, and the relatively short half-life of MB and BB. An exception is that during the first 6 weeks of fetal life, only BB is synthesized. However, by the 12th week, MM predominates in skeletal and cardiac muscles [3].

As previously mentioned, serum CK is primarily composed of the MM and MB isoenzymes. BB is mostly localized to neurons and astrocytes in brain tissue. Following acute brain damage, we expect to see a rise in the BB isoenzyme, which can be measured in the cerebrospinal fluid (CSF). However, isolated cerebral injuries will not result in elevated total serum CK, unless there is associated myocardial or skeletal muscle damage [15]. Processes that may lead to increased BB levels in the CSF are parenchymal or meningeal disease, intracranial hemorrhage, traumatic brain injury, brain tumors, stroke, seizure, hypoxic/ischemic insult, infections, and electroconvulsive therapy. In general, the higher the BB level in CSF, the greater the extent of brain damage, and the worse the prognosis [16, 17]. In contrast, MB or MM isoenzymes, when detected in the CSF, are almost always due to blood contamination. An intact blood brain barrier isolates the MB and MM isoforms to the systemic circulation, while keeping the BB isoform within the central nervous system.

For our purposes, the clinical value of CK isoenzymes is primarily related to the MM, and then the MB fractions. The MM isoform is bound to the M-line, which is a myofibrillar structure that connects thick myosin fibers to one another, within a sarcomere. The M-line is a site with high energy requirements; hence, it follows that MM serves the important purpose of enzymatically regenerating ATP as required during muscle contraction [12].

Normal Serum Creatine Kinase Values

Serum CK concentration is highly variable between individuals and dependent on gender, race, age, muscle mass, and physical activity [18–25]. Among these variables, serum CK value is most strongly related to gender and race [18–20, 24]. Lean muscle mass is also an independent factor correlating with serum CK levels [23]. However, the influences of gender and race are independent of muscle bulk, height, weight, or physical exertion. In general, men have higher serum CK than women, and people of African decent have higher values than other racial groups [20]. Serum CK does not statistically differ between Asians, Caucasian, and Latinos [20, 26]. Based on race and gender, the general population could be divided into three general groups: (1) high CK group, composed of African men; (2) intermediate CK group, made up of African women and non-African men; and (3) low CK group composed of non-African women [18]. Typically, CK values in the high group are double those of the intermediate group, and the values in the low group are half those of the intermediate group. For most of the laboratories in the United States, the reference CK values are biased toward the intermediate group.

Table 3.2 Physiologic causes for sustained asymptomatic CK elevation

Gender – men
Race – African decent
Age – neonates and children
Increased amount of lean muscle mass
Regular, prolonged, or weight-bearing exercises

Normal serum CK levels also vary with age. CK is markedly elevated (three to ten times normal) in the neonatal period, specifically in the setting of a vaginal delivery [27, 28]. This increase is thought to be secondary to birth trauma. The elevated CK from birth normalizes in approximately 4 days [27]. Prepubescent children have slightly higher CK values than adults. In women, CK levels falls to nearly half the normal level during pregnancy and increase significantly during the postmenopausal period [29]. It is hypothesized that during pregnancy, the release of estrogens and proinflammatory cytokines serves to stabilize the muscle membrane and hence decrease the serum CK [30]. In adulthood, serum CK increases slightly with age [24] but then declines in the geriatric population. However, serum CK is lower in sedentary people, which may in part explain the low values found in elderly patients. The physiologic factors contributing to hyperCKemia are listed in Table 3.2.

HyperCKemia After Physical Exercise

Strenuous exercise may result in elevated serum muscle enzymes, most specifically CK. Direct mechanical damage to the contractile elements, particularly the sarcolemma and Z-disks, is the most widely accepted cause of elevated CK in athletes [31, 32]. When exercise exceeds the metabolic range of normal muscle, myocyte membrane permeability increases and enzymes leak into the surrounding interstitial fluid [12]. If the exercise intensity increases and sarcomeres reach their breakpoint, then additional CK is released into the surrounding milieu [31, 33]. The CK is then taken up by the lymphatic system and returned to circulation [34]. Rhabdomyolysis and myoglobinuria may occur after extraordinary physical stress and can lead to acute renal failure and death.

Although most of the serum CK released after exercise is of the MM fraction, the MB fraction may also be found in the serum after strenuous and prolonged physical activity. Levels of MB similar to acute myocardial infarction, reaching 8–18 % of the total serum CK, are not uncommon after intense periods of exercise, such as marathon running [31, 35–38]. The source of skeletal MB is postulated to be from undifferentiated, regenerating muscle fibers which, like many fetal myoblasts, express higher concentration of MB than mature muscle cells [9, 31, 36].

Multiple factors determine the extent of post-exercise hyperCKemia. Most notably, CK levels are highest after prolonged exercise, such as marathons or triathlons [35–39], and weight-bearing exercises with eccentric muscle contractions, such as bench stepping or running downhill [12, 40]. Another important factor is the training level of the subject [12, 31]. Serum CK elevation after exercise is variable between individuals and even within the same individual. Among these factors, the duration of physical activity is the most significant. For example, post-exercise serum CK values in marathon runners and triathletes reach levels as high as 50-fold above normal [35–38]. In contrast, a short-duration running, such as sprinting 400 m, results in a much lower rise in CK. Non-weight-bearing exercises such as swimming or cycling have little or no effect on serum CK. With training, CK levels tend to decrease in athletes. This is thought to be due to an adaptive response either in enzyme clearance from blood [41] or through adaptive muscle changes leading to decreased enzyme leakage [42]. Due to a greater amount of lean muscle mass, baseline CK levels remain higher in athletes (approximately 1.5 times normal) [43] as compared to nonathletes [44, 45]. However, the rise in post-exercise CK is associated with the level of training. Hence, experiments looking at athletes and their sedentary, yet healthy, age-matched controls show that with the same degree of physical exertion, the CK level will rise less in athletes [46, 47].

Timing of CK collection following exercise is important. Serum CK usually begins to rise a few hours after the completion of exertion and peaks at 1–4 days [4, 31, 39, 48–50]. With eccentric or intense exercises, the peak CK levels are at 4 days, and with continued training, the values normalize after 4–10 days [42]. Duration more so than fitness level corresponds to when the peak CK is reached [51]. CK normalization time is associated with the length of the rest period following exercise [52]. However, it is important to note that there is no correlation between impairment of muscle function and CK [53]. Therefore, CK levels cannot be used to monitor or quantify post-exertional muscle recovery. The likelihood of skeletal muscle injury increases with exercising in the cold or using androgenic steroids [54, 55].

Frequent or intense training, particularly with weight-bearing exercises, may result in persistent elevation of CK, mimicking neuromuscular disease [56]. Nonetheless, athletes with very high post-exercise CK, or resting CK may have an underlying myopathy, such as McArdle's disease, Becker's muscular dystrophy, caveolin-3 deficiency, or an alpha-dystroglycanopathy [57–60]. Hence, these individuals should be evaluated for a chronic hyperCKemia at rest and with exertion, to look for a subclinical myopathy.

Distinguishing Acute Myocardial Infarction from Muscle Disease

In the hospital setting, the most common reason to check a CK level is for the evaluation of acute myocardial infarction

(MI). Although the nuances of diagnosing an MI are beyond the scope of this chapter, it is important to discuss how to distinguish hyperCKemia from a cardiac versus a skeletal muscle etiology.

As previously stated, the heart is rich in CK, specifically with the MB isoform accounting for about 15–20 % of total myocardial CK (see Table 3.1). Following the onset of an MI, the total serum CK begins to rise at 4–8 h, peaks within 12–24 h, and declines to normal values within 2–3 days (Fig. 3.1). Elevated serum MB isoenzyme is highly sensitive (98–99 %) and specific (95–97 %) for the diagnosis of an MI [62–64]. Since a small amount of the MB isoenzyme is present in skeletal muscles (1–3 %), the percentage elevation of MB (i.e., MB/total CK × 100) is more important than the absolute MB level in the diagnosis of an MI. In the first 2–3 days after an MI, the MB portion usually exceeds 5 % of the total CK activity, is often 10–15 %, but never reaches a value greater than 40 %. Thus, using the ratio of the MB isoform to total serum CK is essential in preventing false-positive results. This, in turn, minimizes further unnecessary, and at times invasive, cardiac evaluations.

Of note, ratios of MB to total CK greater than 5 % have been documented in rhabdomyolysis, crush injury, malignant hyperthermia, Duchenne muscular dystrophy, dermatomyositis, polymyositis, healthy marathon runners, and professional athletes [35–38, 65–68]. The origin of MB elevation in these patients is usually skeletal, and without a cardiac component [69]. In addition to the history and physical examination, criteria to distinguish that the rise in MB is of skeletal origin rather than cardiac include the following:

1. A peak MB ratio less than 5 % is not consistent with an acute MI.
2. Marked elevation of the total serum CK to more than 20 times above normal is not compatible with an acute MI.
3. An atypical time course of MB elevation, such as prolonged elevation, should raise suspicion for a noncardiac source.

In addition to the MB isoform, additional cardiac enzymes are useful in distinguishing between a cardiac and skeletal etiology. Troponins I and T, which regulate the calcium-mediated contractile process of striated muscle, are present in cardiac and skeletal muscles. However, they have different amino acid sequences and are encoded by different genes [62, 64, 70, 71]. Cardiac isoforms of troponins, particularly troponin I, are highly specific and not present skeletal muscle. As the serum concentration of troponin I in normal subjects is near zero, its sensitivity is higher than MB, enabling the detection of minor degrees of myocardial necrosis. Following an acute MI, the initial rise of cardiac troponin I in serum is similar to MB, but its return to baseline is much more gradual, over 7–10 days (Fig. 3.1). Thus, in addition to being highly sensitive and specific, troponin I is useful for the subacute diagnosis of an MI. Hence, in conjunction with MB and CK ratios, it is a valuable tool to distinguish between neuromuscular diseases and cardiac diseases.

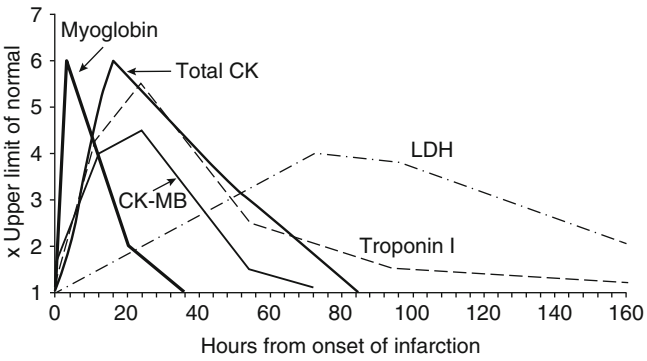

Fig. 3.1 Time course of serum marker elevations following an AMI (Reprinted with permission from Antman [61])

Creatine Kinase in Neuromuscular Diseases

Serum CK is the single most useful, reliable, and studied biochemical blood test in neuromuscular disorders. HyperCKemia is most commonly associated with primary muscle diseases but may also be seen in neurogenic disorders.

Creatine Kinase Elevation in Myopathies

As CK is a sarcolemmal enzyme, destruction of the sarcomere or damage leading to increased membrane permeability will allow for enzyme leakage. Sustained serum CK elevation is most often due to myopathies [66, 68, 72–74]. The degree of hyperCKemia is usually dependent on the following factors:

1. *Severity of disease*: Diseases with marked muscle destruction are responsible for the highest serum CK concentrations (Table 3.3). Duchenne muscular dystrophy and rhabdomyolysis are documented to have CK concentrations well over 100 times greater than normal.
2. *Course of disease*: Rapidly progressive myopathies such as Duchenne muscular dystrophy or polymyositis are associated with higher CK levels than slowly progressive disorders such as facioscapulohumeral muscular dystrophy or inclusion body myositis.
3. *Absolute muscle mass*: Since CK serum concentration is dependent on muscle mass, advanced muscle diseases are often associated with a declining CK. For example, CK values in Duchenne muscular dystrophy are highest early during the disease course when children are asymptomatic, or during their ambulatory phase. Serum CK gradually declines toward normal values during advanced phases of the disease as muscle is replaced with fibrous tissue.
4. *Myofiber necrosis*: Sarcomere necrosis and membrane leakage are the main causes of serum CK elevation. Thus, myopathies not associated with muscle destruction or

Table 3.3 Myopathies commonly associated with marked elevation of serum CK (sometimes more than 50–100-fold above normal)

Dystrophinopathies (Duchenne and Becker muscular dystrophies)
Rhabdomyolysis and myoglobinuria
Malignant hyperthermia[a]
Neuroleptic malignant syndrome
Polymyositis
Miyoshi distal myopathy

[a]During attack

Table 3.4 Myopathies commonly associated with normal serum CK

Steroid myopathy
Hyperthyroid myopathy
Mitochondrial myopathies
Channelopathies[a]

[a]Excluding malignant hyperthermia

those which maintain an intact sarcolemma, such as mitochondrial myopathies or steroid myopathy, often have a normal CK (Table 3.4). Thus, a normal serum CK level does not necessarily exclude a myopathy.

The skeletal MM isoform is the predominant isoenzyme in myopathies. However, as in the case of severe post-exercise hyperCKemia, other isoenzymes can also be markedly increased with muscle diseases. A high ratio of MB, imitating an acute myocardial infarct, has been reported with Duchenne muscular dystrophy, dermatomyositis, polymyositis, rhabdomyolysis and malignant hyperthermia, as well as following traumatic crush injury [31, 35–38, 65, 69]. As previously stated, this is explained by the CK activity of regenerating muscle fibers, which express higher MB more than mature myocytes [9, 31, 36]. Although cardiac disease is associated with many primary myopathies, an elevated MB isoform does not automatically point to a cardiac etiology. Hence, checking a troponin I, in addition to further neuromuscular testing may be beneficial for such patient presentations.

Creatine Kinase Elevation in Neurogenic Disorders

Occasionally, CK is mildly elevated in neurogenic disorders, such as amyotrophic lateral sclerosis, spinal muscular atrophies, acute poliomyelitis, post poliomyelitis syndrome, and Guillain-Barré syndrome [75–79]. As a muscle fiber loses its innervation due to primary nerve or anterior horn cell damage, it atrophies and is unable to function. Hence, as the surrounding muscle fibers experience increased force requirements, they may also suffer mild damage leading to CK leakage. Since neurogenic diseases do not result in significant myocyte destruction, the CK levels are typically less than five times above normal [80].

Creatine Kinase Elevation in Secondary Muscle Disorders

Many systemic diseases may result in secondary muscle damage, which in turn can lead to increased CK levels. It is always important to evaluate for systemic causes before making a neuromuscular disease diagnosis. Table 3.5 lists systemic and traumatic causes for hyperCKemia. Hypothyroidism is the most common cause of secondary myopathy and is often associated with elevated CK [81, 82]. Viral infections, electrolyte imbalances, celiac disease, seizures, dystonia, malignancy, acute psychosis, violent behavior, and trauma are other causes of CK elevation [83–92]. The degree of muscle involvement and CK elevation is variable for the above etiologies. Aside from supportive management, treatment of the underlying condition is important. However, unexplainable residual elevations in CK may be related to a subclinical neuromuscular disorder and should be investigated.

Table 3.5 Systemic diseases and trauma leading to secondary CK elevation

Hypothyroidism
Viral infections
Influenza
Coxsackie
Echovirus
Adenovirus
Herpes
Connective tissue diseases
Electrolyte imbalance
May be secondary to acute kidney disease or heart disease
Celiac disease
Malignancy
Iron-sulfur cluster diseases
Muscle trauma/ischemia
Generalized epileptic seizures
Malignant hyperthermia
Neuroleptic malignant syndrome
Serotonin syndrome
Severe dystonia
High fever with rigors
Muscle bacterial infections
Compartment syndrome
Crush injury
Needle electromyography
Repeated intramuscular injections
Surgery
Acute psychosis
Violent behavior

Additionally, mild transient CK elevations are common after iatrogenic muscle trauma, including intramuscular injections and needle electromyography (EMG), or surgery. Needle EMG, especially with concentric needles, may result in a mild rise of serum CK which returns to baseline after about 2–3 days [93]. Thus, serum CK measurements should be avoided up to 3 days after mild muscle trauma to prevent false-positive results. In contrast to the mild asymptomatic transient serum CK increase, a significant rise is usually symptomatic and associated with crush injury, compartment syndrome, or rhabdomyolysis.

Elevated Creatine Kinase Due to Drug Toxicity or Nutritional Deficiency

Reversible serum CK elevation is usually due to medication side effect or toxicity, nutritional deficiency, or the treatable systemic diseases listed above. Medication-induced hyperCKemia may be clinically asymptomatic or associated with myalgia, subjective weakness or fatigue, or objective weakness. One of the most common classes of offenders, especially in the setting of prescribing frequency and likelihood of myopathy, is statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors). These cholesterol-lowering agents may cause symptomatic or asymptomatic hyperCKemia. Although the exact mechanism of injury is unknown, it is known that statin blocks the synthesis of cholesterol and of isoprenoids. Cholesterol is important for the structural integrity of muscle membranes. Isoprenoids are required for mitochondrial function and cytoskeletal stability. Either or both of these mechanisms may result in myotoxicity [94].

In addition to statins, there are many other classes of medications that induce hyperCKemia including: fibrates, antiretrovirals, angiotensin II receptor antagonists, immunosuppressants, chloroquines, antipsychotics, antidepressants, and antiemetics. Table 3.6 summarizes a more complete list of the known drugs and vitamins associated with myopathy.

Typically, sustained pathological elevation of CK occurs and persists only as long as the offending agent remains in the system. Depending on the patient, the same etiological factor may cause mild to marked elevations of CK. Severe myonecrosis is particularly common when multiple offending factors (such as two drugs) are present. Early detection, management, and withdrawal of the offending factor(s) often results in normalization of serum CK. However, there are instances in which the hyperCKemia persists, despite discontinuation of the medication. In these cases, it is important to search for an underlying neuromuscular disease that may have been unveiled by the addition of a stressor, such as a statin medication [95].

Patients with reversible serum CK elevation may be asymptomatic but often complain of myalgia, muscle tenderness, subjective weakness, or fatigue with exertion. Objective weakness due to overt myopathy is not uncommon, but often reversible. Failure in early recognition may result in frank rhabdomyolysis, malignant hyperthermia, or neuroleptic malignant syndrome; conditions which carry high morbidity and mortality.

Table 3.6 CK elevations secondary to reversible conditions

Drugs or toxins
Cholesterol lowering agents
Statins – HMG-CoA reductase inhibitors
Fibrates
Antiretrovirals
Zidovudine
Angiotensin II receptor antagonists
Angiotensin converting enzyme inhibitors
Steroids
CNS stimulants
Amphetamines
Cocaine
Phencyclidine (PCP)
Lysergic acid diethylamide (LSD)
5-methoxy-disopropyltryptamine
Opioids
Alcohol
Antidepressants
Monoamine oxidase inhibitors
Tricyclic antidepressants
Selective serotonin reuptake inhibitors
Serotonin norepinephrine reuptake inhibitors
Mirtazapine
Lithium carbonate
Antipsychotics
Typical
Atypical
Anesthetics
Inhaled – halothane
Muscular blockade – succinylcholine
General
Local
Beta-blockers with intrinsic sympathomimetic activity
Pindolol, carteolol
Antiepileptics
Phenobarbital, phenytoin
Antimalarials
Hydroxychloroquine, chloroquine, quinidine
Antiemetics
Metoclopramide, emetine
Herbals
St John's wort, Syrian rue, ginseng, nutmeg, yohimbe
Others
Albuterol, colchicines, carbenoxolone, carbimazole, vitamin E, epsilon aminocaproic acid (EACA), digoxin, hydralazine, procainamide, furosemide, penicillamine, gabapentin, pregabalin
Nutritional deficiencies
Vitamin D
Vitamin B_2
Retinoid (vitamin A derivatives)
Selenium
Hyponatremia

Idiopathic HyperCKemia

Although serum CK elevation is often a sign of a neuromuscular disease, it may be encountered in non-pathological conditions. An elevated CK in a healthy individual is sometimes discovered incidentally, especially in institutions

Table 3.7 Suggested criteria for the diagnosis of idiopathic hyperCKemia

Inclusion criteria
Persistent, asymptomatic or minimally symptomatic, elevation of serum CK of skeletal muscle origin
Normal neurological examination
Normal EMG study
Normal muscle biopsy – histopathology, immunohistochemistry, and electron microscopy
Normal genetic testing
Exclusion criteria
Family history of neuromuscular disease
Clinical and/or laboratory evidence of other medical diseases, ex. thyroid disease
Intake of medications or vitamin deficiency, associated with elevated serum CK
History of trauma
History of strenuous or persistent exercise

where CK is included in the routine blood chemistry profiles. It is not uncommon for these patients to undergo extensive cardiac work-up before they are referred to a neurologist. Idiopathic hyperCKemia is a term coined in 1980 by Rowland et al. [96, 97]. They defined it as a persistent elevation of serum CK-MM isoform, with a normal neurological examination, EMG, and muscle biopsy.

Subjects with idiopathic hyperCKemia are of all ages but have a male predominance. Serum CK elevation is modest, usually between three and ten-fold above normal. Although none of these patients have objective weakness, some individuals report myalgia, stiffness, or cramps. Long-term follow-up of asymptomatic patients with idiopathic hyperCKemia reveals that about a third go on to develop clinical and/or pathological evidence of a neuromuscular disorder [98–103]. As discoveries of new genes in inherited neuromuscular diseases continue, more patients with idiopathic hyperCKemia will be diagnosed with a neuromuscular disease or carrier state of such a disease. Reported diagnoses have included distal myopathy, inclusion body myositis, polymyositis, myoadenylate deaminase deficiency, McArdle's disease, central core disease, and the carrier state of Duchenne muscular dystrophy.

A specific protocol should be followed before a diagnosis of idiopathic hyperCKemia can be made (Table 3.7). First, when a patient presents with an increased CK level, the family history should be investigated thoroughly. In addition, the physiologic and secondary causes of elevated CK need to be considered (see Tables 3.2, 3.5, and 3.6). If there is a history of recent myotoxic medication use, trauma, strenuous exercise, or other medical diseases, then the underlying etiology or offending agent needs to be appropriately addressed. The CK should then be repeated after 15 days. If it continues to be abnormal, then the patient should be referred to a neuromuscular subspecialist for consultation, a thorough neuromuscular examination, and an EMG study. If there is no electrodiagnostic evidence for a specific myogenic or neurogenic etiology, then a muscle biopsy can be obtained. The biopsy processing should include histology, immunohistochemistry, and electron microscopy. Also, blood and/or tissue samples may be analyzed for genetic DNA analysis for carrier states of different muscle diseases [104–106]. As long as this initial evaluation is exhaustive and the patient remains asymptomatic with a normal neurological exam, then a diagnosis of idiopathic hyperCKemia is permissible [100, 101, 107–110]. Importantly though, if the patient develops symptoms or weakness on clinical exam, then reevaluation is required. The above protocol will diagnose the majority of etiologies for hyperCKemia. However, additional tests are available and may be useful depending on the circumstance. Most notably, it may be beneficial to obtain a contracture test on all patients with diagnosed idiopathic hyperCKemia, prior to giving general anesthesia for a procedure [102, 103]. Although the likelihood of diagnosing malignant hyperthermia, which is often associated with central core myopathy, is very low, the consequences for missing this diagnosis are great.

Other Muscle Enzymes

Similar to creatine kinase, other serum enzymes of muscular origin are released when muscle is destroyed. Most of these other enzymes (aldolase, lactate dehydrogenase, pyruvate kinase, and muscle-specific enolase) are essential components required for glycolysis. Hence, they are typically found in tissues with high metabolic requirements, such as: muscle, liver, and/or kidney. Hence, unlike CK, these enzymes are less specific for muscle. With less specificity, there is an increased likelihood that serum elevations are secondary to nonmuscular diseases or medication use. Nevertheless, based on the clinical context, the following muscle enzymes can be useful in diagnosing myopathies and/or identifying specific pathophysiological etiologies.

Aldolase

In glycolysis, aldolase catalyzes the reversible conversion of fructose 1,6-bisphosphate into glyceraldehydes 3-phosphate and dihydroxyacetone phosphate. As such, it is found in tissues with a high metabolic demand. In addition to muscle, aldolase is also found in the liver, kidney, intestines, and brain. There are three major isoforms of aldolase. Type A is the most prevalent and is nearly isolated to muscle. Type B is found in the liver and kidneys, and type C (plus trace amounts of type A) are found in the brain and other nervous system tissues [111]. Within skeletal muscle, aldolase A is

typically bound to actin. Therefore, a myopathic process results in the release of aldolase into the serum. It is important to note that most clinical laboratory testing is not specific for the aldolase A isoform. Hence, aldolase levels may be increased with liver disease and/or hepatotoxic drugs.

Importantly, studies have shown that increased aldolase levels, in the setting of muscle discomfort and weakness, are associated with myopathology secondary to perimysial disorders (such as dermatomyositis, fasciitis, and perimyositis) [112, 113]. This increase in aldolase can be in isolation and seen with a normal CK, especially in patients with muscle pain or mild weakness.

Lactate Dehydrogenase

Lactate dehydrogenase (LDH) catalyzes the reversible oxidation of lactate to pyruvate, with concomitant reduction of NAD (nicotinamide adenine dinucleotide) to NADH. There are five, tetrameric, immunoglobulin-bound, LDH isoenzymes (LHD-1 through LDH-5), which are normally expressed in tissues. Each of the four subunits can either be an M polypeptide or an H polypeptide. LDH-1 is composed of 4 H units, LDH-2 has 1 M and 3 H units, LDH-3 has 2 M and 2 H units, LDH-4 has 3 M and 1 H units, and LDH-5 has 4 M units. The more M monomers an isoform has, the more likely it is for that enzyme to favor an anaerobic conversion of pyruvate to lactate. Conversely, more H monomers favor an aerobic oxidation of pyruvate [12]. Additionally there is an LDH-6, composed of 4 M units, but not immunoglobulin-bound. LDH-6 is not normally produced and is associated with a poor prognosis in patients with hepatic circulatory disease, which is beyond the scope of this chapter [114].

LDH is not tissue specific and can be increased in lung cancer, other malignant cancers, fibrotic lung disease, chronic granulocyte leukemia, non-Hodgkin's lymphoma, ischemic hepatitis, cardiac infarction, and intravascular hemolysis. However, isoenzyme determination may increase its tissue specificity. Generally, heart and red blood cells, with predominant aerobic metabolism, are highest in LDH-1 and LDH-2. In comparison, skeletal muscle and liver, with predominant anaerobic metabolism, are highest in LDH-4 and LDH-5. In the brain, LDH isoenzyme composition is evenly distributed from LDH-1 to LDH-4. For all clinical purposes, elevated LDH-1 and LDH-2 is related to hemolysis, or an acute myocardial infarction. Similarly, elevations of LDH-5 typically reflect liver or skeletal muscle disease. In acute rhabdomyolysis, LDH-5 rises significantly and remains elevated for up to 10 days [115].

A subtype analysis looking at the ratio of the M to the H polypeptides is more useful in distinguishing between progressive myopathology and nonprogressive neuromuscular diseases. The M monomer is generally more associated with muscle, while the H can be thought of as being associated with the heart. In progressive myopathies, as the muscle deteriorates and is replaced by adipose and fibrous tissue, the M polypeptide gradually disappears [116]. Hence, the M/H ratio is markedly lower when there is a severe myopathic process [117]. Similarly, in carriers with an abnormal dystrophin gene, a shift is seen from the LDH-4 and LDH-5 isoenzymes into the LDH-1 and LDH-2 isoforms [118].

Pyruvate Kinase

Through transfer of a phosphate group, pyruvate kinase (PK) catalyzes the reaction of phosphoenolpyruvate and ADP into pyruvate and ATP. This is the final step of aerobic glycolysis. In humans, there are four distinct isoforms: PKM1, PKM2, PKL, and PKR [119]. The PKL and PKR isoenzymes are expressed in liver and red blood cells, respectively. PKM1 is expressed in skeletal muscle, heart, and brain; whereas PKM2 is expressed in lung, pancreas, retina, adipose, and fetal tissue. Additionally, PKM2 is also expressed in cells with high rates of proliferation: embryonic cells and neoplasms [120]. PKM1 is a cytosolic protein. In contrast, PKM2 is a nuclear protein, which is also associated with apoptosis. The PKM gene encodes for both the PKM1 and PKM2 isoenzymes [121].

When PK activity is measured in the hospital setting, it is not specific for a distinct isoform. Using isoenzyme specific assays can increase the sensitivity and specificity of making a neuromuscular diagnosis. However, clinically significant conclusions may still be drawn from nonspecific PK measurements. In myopathies, such as Duchenne muscular dystrophy and limb-girdle muscular dystrophy, PK is often markedly elevated (up to 28 times above normal) [122, 123]. Although this is typically associated with increases in CK and aldolase, this is not an invariable finding. As the muscular dystrophy progresses and muscle is replaced with fibrosis and fatty infiltration, PK, along with other muscle enzymes, decreases. The combination of measuring CK and PK is also beneficial in identifying carriers of myopathic diseases [124]. In one study, all individuals out of 17 known carriers, had either an elevated CK or PK. Ten of the carriers had elevations in both enzymes [122].

Secondary to the nonspecificity of PK measurements, it is important to distinguish between muscle and non-muscle etiologies. In the setting of an acute MI, PK levels rise to peak within 2 days and then return to the baseline [123]. In contrast, PK levels remain elevated in muscle diseases and only decrease during the end stages of the myopathy. In liver diseases, elevations in aminotransferases and LDH are

much higher than changes seen in PK [123]. Hence, by understanding the patterns of change in muscle enzymes, it is easier to identify a neuromuscular disease.

Muscle-Specific Enolase

Enolase is a class of enzymes that catalyze the conversion of 2-phosphoglycerate to phosphoenolpyruvate during glycolysis. Although it is present in all tissues, its concentration is associated with the degree of metabolic activity within the tissue. Enolase is a dimer composed of two out of the three distinct subunits (α, β, and γ). There are five specific isoforms: αα, αβ, αγ, ββ, and γγ. Three of these isoenzymes are commonly found in adult human tissues: (1) non-neuronal enolase (NNE or enolase 1-αα isoform found in the liver, brain, kidney, spleen, and adipose tissue); (2) neuron-specific enolase (NSE or enolase 2-γγ isoform); and (3) muscle-specific enolase (MSE or enolase 3-ββ isoform) [125].

MSE is an unbound muscle enzyme, with a much lower concentration than CK in skeletal muscle. Although its clinical significance in neuromuscular disorders is theoretical, elevations in MSE have been documented in muscular dystrophies and spinal muscular atrophies [126, 127].

Carbonic Anhydrase III

Carbonic anhydrases (CA) reversibly catalyze the interconversion of carbon dioxide and water into bicarbonate and protons. The primary function of these enzymes is to maintain the acid–base balance in blood and tissues. There are five distinct families of CA (α, β, γ, δ, and ε) found throughout the animal and plant kingdom. The α-CA family is specific to humans. There are well over a dozen isoforms within the α-CA family. The enzyme of particular interest in muscle diseases is CA-III, as it is present in high concentrations in skeletal muscle and to a lower degree in cardiac and smooth muscle [128].

CA-III has much higher concentration in type I muscle fibers and is localized primarily to the actin within the I-band of muscle [129, 130]. Studies have shown that elevation in CA-III is comparable to the rise seen in CK with muscle damage [126, 128, 131–133]. CA-III may even be a more sensitivity marker for ruling out a myopathy than CK [133]. Carriers of Duchenne muscular dystrophy have been identified to have elevated CA-III levels [128]. However, CA-III is also elevated in neurogenic diseases (such as amyotrophic lateral sclerosis) [133]. Hence, it is important to evaluate for neurogenic causes of muscle damage before using CA-III to make a definitive diagnosis of a primary muscle disease.

Aminotransferases

Typically, a body's energy requirements are met by metabolizing carbohydrates or adipose tissue. However, there are instances when muscle protein needs to be catabolized into amino acids, which can be used to make different proteins, or be shunted into the glycolytic pathway. Aminotransferases (or transaminases) are the enzymes that catalyze the interconversion between amino acids and α-keto acids via transfer of amino groups. There are numerous transaminases. The most clinically significant and commonly measured aminotransferases are: alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) [3, 4].

ALT is predominantly a liver enzyme but is also present in the kidneys. The most common clinical use for ALT is to evaluate for hepatocellular diseases. It is normal or slightly elevated in acute myocardial infarction and rarely elevated in necrotizing myopathies. AST is less tissue specific due to its predominance in mitochondria. Its greatest concentration is in the heart, liver, skeletal muscle, kidney, brain, pancreas, spleen, and lung. Hence, elevated serum AST is sensitive but not specific for muscle diseases [134]. As with the aforementioned muscle enzymes, elevations of transaminases should be interpreted within the context of the clinical setting and as an adjunct to other enzymes. However, in the appropriate context, these enzymes can provide a valuable tool in diagnosing muscle diseases.

One of the benefits of AST and ALT is that they are frequently measured. Multiple studies have shown that persistent elevations can point to muscle pathology [135–137]. Unfortunately, due to the emphasis on evaluating for a hepatocellular etiology, the diagnosis of a muscle disease can take months to years, and often after invasive gastrointestinal testing is completed. Therefore, it is recommended that prior to obtaining invasive testing, such as a liver biopsy, other muscle enzymes, such as CK, be checked [138]. Furthermore, it is useful to analyze changes in the AST/ALT ratio. In liver disease, the ratio is less than 1. In contrast, with myopathology, the AST/ALT ratio is greater than 1. With acute muscle damage, the sudden rise in AST can often yield a ratio greater than 3 [139]. However, this ratio approaches 1 within a few days, due to a steady and more rapid decline of AST as compared to ALT. Additionally, to help establish a pattern of enzyme elevation, it is also worthwhile to check a GGT level. GGT is not elevated in muscle diseases, and is highly specific for hepatocellular disease. In one study specifically evaluating the GGT level in 28 patients with Duchenne muscular dystrophy, no patient was ever found to have an abnormal level [140]. Hence, this is a useful marker in differentiating between liver and muscle pathology, especially when analyzed in conjunction with other muscle enzymes.

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Autoantibody Testing in Peripheral Neuropathy

4

Alan Pestronk

Neuromuscular disorders result from a wide variety of pathological processes. In clinical practice immune-mediated neuromuscular disorders are an important focus of diagnostic efforts as treatment often leads to improvements in function and quality of life in patients. Categorization of immune-mediated neuromuscular disorders provides information about prognosis and possible responses to different therapeutic agents.

Immune-mediated polyneuropathies have historically been categorized by defining clinical patterns of involvement and tissue or subcellular targets of disease. Clinical patterns of polyneuropathy that are diagnostically useful include involvement of different functional classes of cells or axons, the anatomical patterns of symptoms and signs, and the time course of disease [1–3]. Tissue targets of the pathologic processes in immune-mediated polyneuropathies include myelin, axons, cell bodies, vessels, and connective tissue. Electrodiagnostic testing is useful for defining the anatomic patterns and tissue targets of immune disorders [4, 5].

Serum autoantibodies are an increasingly important biomarker for many immune neurologic and neuromuscular disorders. Autoantibodies to specific antigens are commonly used in the formulation of neuromuscular diagnoses. Autoantibodies can also provide useful clues to the pathogenesis of some neuromuscular disorders [6]. General consideration of the autoantibody types, classes, locations, and kinds of target antigens provide useful diagnostic classifications of immune neuromuscular disorders, identify likely accompanying systemic abnormalities, and suggest likely responses to different treatments. Table 4.1 is organized according to a general classification of neuromuscular disorder-associated autoantibodies.

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Autoantibody Classification

IgG in Serum Directed Against Cell Membrane Antigens: IgG Autoantibody Type 1 (IgG-AAb1)

IgG-AAb1 are polyclonal and located in the serum and occasionally the CSF. IgG-AAb1 antigenic targets are cell surface molecules, including receptors or ion channels. Specific neuromuscular disease antigenic targets in cell surface membranes include acetylcholine receptors in muscle [7–9] and nerve [10], calcium channels in presynaptic membranes [11], and molecules in complex with voltage-gated potassium channels [12]. Many IgG-AAb1 are likely to be pathogenic, acting by cross-linking antigenic targets and increasing their degradation rate, binding complement and damaging membranes, or, less often, altering channel or receptor function. Associated neuromuscular syndromes are usually chronic. They often improve with immunomodulating therapy, rapidly with intravenous immunoglobulin or plasma exchange, and over a longer term with corticosteroids or T-cell immunosuppressants. After treatment, persistent reductions in antibody levels often correlate with clinical improvement. The presence of IgG-AAb1 usually increases the likelihood of finding an associated neoplasm. The type of neoplasm depends on the specific antigenic target and its associated neuromuscular syndrome. Several different IgG-AAb1 antibodies may occur simultaneously in individual patients.

Serum IgG Versus Ganglionic (α3) Acetylcholine Receptors (AChR)

α3-AChRs are nicotinic AChR located on neurons in autonomic ganglia [10]. Anti-α3-AChR antibodies are detected and quantitated with radioimmunoprecipitation methodology that relies on serum IgG autoantibody binding to a complex of α3-AChR (solubilized from a human neuroblastoma) with iodine 125-labeled epibatidine (from the Ecuadorian frog, Epipedobates tricolor). Radioimmunoprecipitation

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Table 4.1 Classification of types of neuromuscular autoantibodies

Antibody					Antigen		Disease		
	Class	Location	Type	Pathogenic properties	Features	Antigen examples	Neuromuscular disease examples	Associations, systemic	Common treatments
IgG-AAb1	IgG	Serum	Polyclonal	Often	Cell surface membrane protein	Receptors ion channels	Myasthenia gravis Autonomic PN LEMS Isaac's	Neoplasms Thymoma Adeno Ca Small cell lung	Corticosteroids T-cell suppressants IVIg Plasma exchange
IgG-AAb2	IgG	Serum	Polyclonal	Possible	Carbohydrate	Glycolipids GM1; GQ1b	AMAN Miller Fisher	Infection Prodromal	? Disease often monophasic
IgG-AAb3	IgG	Serum	Polyclonal	Few	Intracellular protein	tRNA synthetases SRP ANCA	Immune myopathies Vasculitis, small vessel	Organ system disease, neoplasm, or none	Corticosteroids T-cell suppressants Rituximab
IgG-AAb4	IgG	Serum + CSF	Polyclonal	No	Intracellular protein	Hu nuclear antigens CRMP5	Sensory or autonomic neuronopathy	Neoplasms Small cell lung Gynecologic	Screen for and treat associated neoplasm
IgG_4-AAb	IgG_4	Serum ± CSF	Polyclonal	Possible	Cell surface or extracellular protein	MuSK Lgi1	MG-MuSK Encephalopathy + neuropathy		Corticosteroids Rituximab
IgM-AAb	IgM	Serum	Monoclonal, or polyclonal	Possible	Carbohydrate	Glycolipids or glycoproteins GM1, MAG, TS-HDS	Motor MAG	Neoplasms M-protein	Rituximab Cyclophosphamide Intravenous Ig (conduction block)
M-protein	IgM, IgG, or IgA	Serum	Monoclonal	Some	Not identified	Not identified	Polyneuropathy	POEMS Waldenström's Cryoglobulins	

Table Legend: *PN* polyneuropathy, *LEMS* Lambert–Eaton myasthenic syndrome, *AMAN* acute motor axonal neuropathy, *Adeno Ca* adenocarcinoma, *Ig* immunoglobulin, *GM1* GM1 ganglioside, *MAG* myelin-associated glycoprotein, *TS-HDS* trisulfated heparin disaccharide, *SRP* signal recognition particle, *ANCA* antineutrophil cytoplasmic antibody, *CRMP5* collapsin response mediator protein 5, *POEMS* polyneuropathy, organomegaly, endocrine (edema), M-protein, skin, *M-protein* monoclonal protein

methodology is useful for identifying and quantitating antibody binding to conformation-sensitive epitopes on antigens, such as membrane proteins, that cannot be entirely purified.

Anti-α3-AChR antibodies occur in about 50 % of patients with acute-onset pure dysautonomia syndromes [13, 14]. Both parasympathetic and sympathetic nervous systems are typically involved. Occasional patients have selective cholinergic or adrenergic involvement. Initial clinical features are most commonly associated with abnormal orthostatic blood pressure or pulse changes, or gastrointestinal motility disorders. Other features include sudomotor disorders (especially postganglionic anhidrosis), dry eyes and mouth, disorders in pupillary responses to light, and urinary bladder dysfunction. The disease course is often monophasic with partial recovery. There are anecdotal reports of improvement of antibody-related dysautonomia syndromes after treatment with various modes of immunomodulation, including intravenous immunoglobulin, plasma exchange, corticosteroids, rituximab, and mycophenolate. High levels of anti-α3-AChR typically occur with a wide spectrum of autonomic signs and have specificity (83 %) for autonomic disorders. Lower levels occur in a variety of limited autonomic syndromes, but are not specific for autonomic disorders. The most common neoplasms associated with anti-α3-AChR antibodies (30 % overall) are adenocarcinoma and lymphoma. The presence of paraneoplastic dysautonomic syndromes has been associated with a poor prognosis [15]. Evidence that anti-α3-AChR antibodies may be pathogenic includes their ability to inhibit α3-AChR function and synaptic transmission in autonomic ganglia in vitro [16].

IgG Versus P/Q Voltage-Gated Calcium Channels (VGCC)

P/Q voltage-gated calcium channels ($Ca_v2.1$) are found on neuronal membranes, especially presynaptic terminals [17]. Antibody binding to P/Q voltage-gated calcium channels is quantitated with radioimmunoprecipitation methodology that relies on serum IgG autoantibody binding to a complex of $Ca_v2.1$ (solubilized from human cerebral cortical membranes) with iodine 125-labeled ω-conotoxin peptides (MVIIC or GVIA from piscivorous snails) [18].

Serum IgG binding to P/Q voltage-gated calcium channels is found with Lambert–Eaton syndrome and its associated moderately severe, syndromic autonomic neuropathy [11, 18]. Dry mouth, erectile dysfunction in men, and constipation are the most common features of the autonomic neuropathy. Blood pressure, micturition and sweating disorders, and dry eyes also occur. Weakness and fatigability are manifestations of dysfunction of motor axon presynaptic terminals at neuromuscular junctions. IgG anti-P/Q VGCC antibodies are commonly associated with small cell lung neoplasms. Some patients with small cell lung neoplasms and anti-P/Q VGCC antibodies (1–4 %) are asymptomatic or have a subacute cerebellar syndrome. Other possibly associated neoplasms are prostate, thymus, and lymphoid. Patients with additional serum IgG binding to SOX1 (initially defined by immunohistochemical binding of IgG to Bergmann glia in cerebellum) may be at the greatest risk for small cell cancer [19]. Neuromuscular syndromes associated with anti-P/Q VGCC antibodies may show good responses to immunomodulating therapies. Evidence that anti-P/Q VGCC antibodies are pathogenic includes presynaptic nerve terminal dysfunction induced by passive transfer of human autoantibodies to mice.

IgG Versus Voltage-Gated Potassium Channel (VGKC) Protein Complexes

Serum IgG autoantibodies, which were originally thought to bind to VGKC, were identified in several complicated central and peripheral nervous system syndromes. Most of these antibodies are now thought to bind to molecules that are complexed with VGKC and not the potassium channel molecule itself [12, 20–22]. Antigenic targets include contactin-associated protein-2 (Caspr2), leucine-rich, glioma-inactivated 1 protein (Lgi1) and contactin-2. Antibodies to the VGKC complex were initially identified and quantitated with radioimmunoprecipitation methodology that relies on serum IgG autoantibody binding to VGKC-associated proteins (solubilized from brain) complexed to iodine 125-labeled α-dendrotoxin (from mamba snakes (Dendroaspis)). Antibodies specifically to Caspr2 or Lgi1 molecules are detected qualitatively using immunocytochemistry to detect IgG binding to human embryonic kidney 293 (HEK293) cells transfected to express those antigens. Comparison of antibody binding to HEK293 cells with and without antigen expression provides specificity to the assays. *Caspr2 protein* is associated with potassium channels at juxtaparanodes of myelinated peripheral nerve axons and is involved in neuron–glia interactions. Serum IgG vs. Caspr2 is polyclonal, predominantly IgG_1, and binds to CNS neuropil, but not neurons.

Autonomic, motor, and painful sensory, peripheral neuropathic disorders are associated with serum IgG binding to Caspr2 and possibly Lgi1 (see IgG_4 antibodies below). IgG anti-Caspr2 autoantibodies are associated with peripheral nerve hyperexcitability in the form of neuromyotonia. Neuromyotonia may occur in isolation, or with other components of Morvan syndrome such as dysautonomia and encephalopathy with marked insomnia [20]. Ninety percent of patients are male. Other frequent associated systemic features can be weight loss, thymoma, and myasthenia gravis. Immunomodulating treatment of Caspr2 antibody-related syndromes can produce improvement. However, there is a high mortality in the setting of Caspr2 antibody syndromes with associated neoplasms.

IgG in Serum Directed Against Carbohydrate Moieties on Glycolipids: IgG Autoantibody Type 2 (IgG-AAb2)

IgG-AAb2 are polyclonal and located in the serum, but not usually the CSF. IgG-AAb2 bind to cell surface glycolipids, often gangliosides. Gangliosides occur in neuron membranes, anchored in the external leaflet of the lipid bilayer by a ceramide moiety. Their sialylated oligosaccharide moieties are exposed extracellularly. In the peripheral nervous system gangliosides are present in both axons and myelin. There are no significant quantitative biochemical differences of the major gangliosides in human ventral and dorsal roots [23]. Gangliosides GM1, GD1a, and GD1b are enriched at, or near, the nodes of Ranvier, a critical region for generation and propagation of action potentials, and contribute to stability of paranodal junctions and ion channel clusters. Many IgG-AAb2 were originally characterized by showing selective serum IgG binding to specific glycolipids among those separated on thin layer chromatography plates. Clinical testing to detect IgG-AAb2 now generally uses enzyme-linked immunosorbent assays (ELISA) that can quantitate antibody binding to purified glycolipids that are attached to wells in ELISA plates. Nonspecific IgG binding is ruled out by comparing binding to the test antigen and another similar glycolipid.

Clinical neuromuscular syndromes associated with IgG-AAb2 are usually acute-onset immune polyneuropathies (AIP) with a monophasic course [23]. Serum antibodies may also be only transiently present during the first few weeks of disease. This temporal pattern contrasts with IgM anti-glycolipid antibodies (see below) which are most often associated with chronic, persistent neuropathies. Antecedent infections in patients with IgG-AAb2 are commonly reported [24]. Some AIP prodrome-associated bacteria contain glycolipid epitopes similar to those on nervous tissue and may induce a cross-reactive immune reaction with peripheral nerve antigens that underlies the disease syndrome. AIP can be subdivided into clinical categories that include motor–sensory demyelinating (classically described Guillain–Barré; AIDP), motor axonal, sensory axonal, and Miller Fisher-like syndromes. For some of these subgroups, and in some regions of the world, IgG-AAb2 are common, while in others, like AIDP in most of the United States, IgG-AAb2 are infrequently detected [24, 25]. There is no increased frequency of neoplasms with IgG-AAb2. Evidence of clinical utility of immunomodulating therapy for these acute immune neuropathy syndromes, such as more rapid improvement or shorter disease course, is sparse. Some IgG-AAb2 may be pathogenic, binding to and causing dysfunction or damage to axons and sodium channel clusters at the nodes of Ranvier, juxtaparanodes, or presynaptic nerve terminals [26–28].

IgG Versus GM1 Ganglioside

Serum IgG binding to GM1 ganglioside is most strongly related to acute motor axonal neuropathies (AMAN) which have weakness, but little sensory loss, that evolve over a period of weeks [29, 30]. The incidence of AMAN is highest in China, Japan, and Bangladesh. Compared to AIDP, AMAN patients have more rapid progression and less frequent facial weakness, respiratory failure, sensory loss, and autonomic instability. AMAN patients can have retained or brisk tendon reflexes. Acute motor and sensory axonal neuropathy (AMSAN) may be a more severe form of AMAN [31]. Conduction block can occur early in the course of AMAN, but definite demyelinating features such as prominent or persistent conduction velocity slowing are unusual [32, 33]. While GM1 ganglioside is the most frequently described target of IgG autoantibodies in AMAN, IgG binding to GD1a, GalNAc-GD1a [34–36], and GM1b gangliosides also occurs. Up to 90 % of AMAN patients have IgG binding to at least one of these gangliosides. Several IgG autoantibody specificities can occur in the same serum. IgG anti-GM1b antibodies are associated with rapidly progressive distal weakness, few cranial or sensory deficits, and slow recovery [37]. IgG anti-GD1a antibodies are associated with prolonged artificial ventilation and poor recovery [38]. Reports of selective IgG binding to GD1a ganglioside are subject to some doubt as it is difficult to purify GD1a from GalNAc-GD1a. Patients can have IgG or IgM binding to complexes containing two or more glycolipids, but not to single gangliosides alone [39–43]. The presence of anti-glycolipid antibodies in AMAN syndromes can be related to infection by *Campylobacter jejuni* which contains glycolipids having structural similarity to the carbohydrate moieties on gangliosides [44]. GM1 ganglioside is present on both motor and sensory neural structures [45, 46]. The anatomical distribution of GM1 ganglioside cannot explain the association of anti-GM1 antibodies with predominantly motor syndromes. Anti-GM1 antibodies may have pathogenic effects. Immunization of rabbits with GM1 ganglioside can cause a subclinical neuropathy with conduction block and axonal degeneration [47]. Anti-GM1 antibody containing serums can produce conduction block, loss of sodium channel clusters from membranes, and spinal motor neuron damage [48–52].

IgG Versus GQ1b or GT1a Gangliosides

GQ1b is highly expressed in the paranodal myelin of the human oculomotor, trochlear, and abducens nerves and is present at neuromuscular junctions [53, 54]. Serum IgG vs. GQ1b ganglioside is associated with features of Miller Fisher syndromes including ophthalmoplegia and ataxia [55, 56]. An epidemiological association between *C. jejuni* and *Haemophilus influenzae* infections has been established in Miller Fisher syndromes [57, 58]. Serum IgG vs. GQ1b also

occurs with more severe syndromes such as Bickerstaff brainstem encephalitis with disordered consciousness along with ataxia and ophthalmoplegia and acute immune neuropathies with ophthalmoplegia and generalized weakness [59]. An acute onset of oropharyngeal, neck and shoulder weakness, and areflexia is associated with IgG vs. GT1a ganglioside in serums that also bind to GQ1b [60, 61]. Milder isolated ataxia, ophthalmoplegia, or oropharyngeal syndromes have also been described with IgG binding to GQ1b [62]. IgG vs. GQ1b may play a role in disease pathogenesis [26–28].

IgG Versus GD1b Ganglioside

GD1b ganglioside is present in primary sensory neurons, muscle spindles, and paranodal myelin of motor and sensory axons [63, 64]. Serum IgG binding to GD1b ganglioside is associated with an acute-onset, large fiber sensory axonopathy syndrome that may involve ganglion cells in more severe cases. Clinical features can include sensory ataxia, impaired vibratory and joint position sensations, and lost deep tendon reflexes with normal strength. Nerve conduction studies show absent or reduced sensory nerve action potentials with spared motor potentials. Antecedent infections are common. The disease course is typically monophasic with recovery within 2 months. Antibodies that bind selectively to GD1b ganglioside can cause a sensory neuropathy [65–67]. Antibodies to GD1b may be cytotoxic to sensory ganglion cells. Rabbits immunized with GD1b ganglioside develop a syndrome of ataxia and areflexia with structural damage to sensory neurons and large sensory axons in peripheral nerves.

IgG Versus Other Glycolipid or Carbohydrate Antigens

Polyclonal IgG or IgM antibody binding to galactocerebroside occurs in some patients with classical motor–sensory demyelinating Guillain–Barré syndrome (1–12 %) [68, 69]. Patients with anti-galactocerebroside reactivity can have serologic evidence of previous infection with *Mycoplasma pneumonia* [68]. Immunization with galactocerebroside can lead to a demyelinating neuropathy [70]. Anti-galactocerebroside antibodies can produce demyelination in vitro [71]. Polyclonal IgG or IgM antibodies to heparan sulfate occur in some patients with acute immune, demyelinating motor–sensory neuropathies [72].

IgG in Serum Directed Against Intracellular Proteins: IgG Autoantibody Type 3 (IgG-AAb3)

IgG-AAb3 are polyclonal IgG and located in the serum, but not usually the CSF. They bind to intracellular proteins. Although IgG-AAb3 often have strong disease specificity, it is often difficult to show pathogenic effects. Associated clinical neuromuscular syndromes include immune myopathies (myositis-specific antibodies) [73] and neuropathies with a subacute or progressive onset and a chronic course (antineutrophil cytoplasmic antibodies (ANCA)). Many IgG-AAb3-associated neuromuscular syndromes are treatable with immunomodulating agents.

ANCA

Detection of ANCA plays an important role in the diagnosis and classification of systemic immune vasculitides [74, 75]. Two types of ANCA assays are used. Indirect immunofluorescence (IIF) assays that detect patterns of serum IgG binding to cultured cells are more sensitive. Quantitative ELISA measurement of antibody binding to purified antigens is more specific for ANCA-related vasculitis [76].

ANCA are most often IgG. Immunofluorescence studies show antibody binding to azurophilic granules of peripheral blood neutrophils in two distinct patterns with different clinical associations. Diffuse cytoplasmic binding (c-ANCA) usually (90 %) targets proteinase 3 (Pr-3). c-ANCA are typically associated with Wegener's granulomatosis, especially with renal involvement [77]. Antiproteinase 3 ANCA are associated with HLA-DP and the genes encoding α(1)-antitrypsin (SERPINA1) and proteinase 3 [78]. Perinuclear binding (p-ANCA) commonly (70 %) targets myeloperoxidase (MPO). p-ANCA are frequent in several systemic inflammatory vasculopathy syndromes which frequently target small- to moderate-sized vessels. Clinical syndromes, which often include neuropathies, include microscopic polyangiitis (MPA) and Churg–Strauss syndromes [77]. There may be more frequent fibrinoid necrosis in vessel walls and less tissue eosinophilia in Churg–Strauss neuropathies with p-ANCA [79]. Anti-myeloperoxidase ANCA are genetically associated with HLA-DQ [78]. ANCA are unusual in some other inflammatory vasculopathies, including polyarteritis nodosa (PAN) and nonsystemic vasculitic neuropathies [80]. p-ANCA can be induced by drugs (propylthiouracil, minocycline, hydralazine) in the absence of a vasculitis. Rheumatoid arthritis or systemic lupus may have ANCA, but the target antigen is often neither Pr-3 nor MPO. Neuropathies in ANCA-related syndromes usually have both motor and sensory features. They are often a component of multisystem disorders that include general systemic (arthralgia, arthritis, myalgia, fever, and weight loss), cutaneous, mucous membrane, and ENT involvement. There is no strong association of ANCA-positive neuropathies with life-threatening organ involvement (chest, renal, cardiovascular, or abdominal) [81]. Nerve or muscle biopsy confirmation of the inflammatory vasculopathy, with epineurial perivascular mononuclear cellularity, is useful before treatment of the neuropathy. Immunomodulating treatment, including high-dose corticosteroids, cyclophosphamide (pulse, intravenous), methotrexate, and rituximab, is typically followed by improvement or resolution of both the neuropathy and

systemic features. ANCA can provide prognostic information. Continued or recurrent ANCA positivity after treatment increases the likelihood of a relapse [82]. Although IgM and IgA ANCA have been described, for routine diagnostic purposes only IgG antibodies are measured. ANCA can stimulate degranulation of neutrophils, but their pathogenicity in producing tissue and vascular damage is debated. T cells, rather than humoral pathology, may be the main effector mechanism [74].

IgG in Serum and the CSF Directed Against Intracellular Proteins: IgG Autoantibody Type 4 (IgG-AAb4)

IgG-AAb4 are polyclonal IgG and located in both serum and the CSF. IgG-AAb4 bind to intracellular protein antigens. Associated clinical syndromes usually have a subacute onset over weeks to months with little subsequent progression. Associated neoplasms are common. Many of these antibodies are more strongly associated with a neoplasm than a specific neurologic syndrome. Response of the associated neurologic or neuromuscular disorders to immunomodulating treatment is typically poor. There is generally little evidence showing pathogenic effects of IgG-AAb4.

Hu

Hu antigens are a family of nuclear proteins, three of which, Hel-N1, HuC, and HuD, have specificity for normal neurons [83]. A fourth protein, HuR, is ubiquitous. Hu proteins can also occur in cells of some neoplasms like small cell lung carcinoma, but, other than HuR, are not generally present in normal systemic tissues. Several different qualitative methods are used clinically to detect IgG antibodies that bind to Hu proteins. Immunohistochemistry to visualize patterns of IgG binding to neuronal nuclei (in animal or human CNS tissue) is used alone, or along with confirmatory methods [83]. When immunohistochemistry is used alone, tested serum is often first pre-adsorbed with a preparation containing systemic nuclear antigens to remove other types of antinuclear antibodies. These immunohistochemical results are also known as antineuronal nuclear antibodies (ANNA-I). IgG binding to Hu antigens in CNS tissue or preparations of recombinant Hu protein (often HuD) are also detected using Western blot methods. The most specific evaluation for Hu antibodies probably includes testing with both immunohistochemistry and Western blot [84]. Anti-Hu autoantibodies from patients generally bind to all four Hu protein family members.

High-titer IgG antibody binding to Hu proteins is associated with several central and peripheral neurologic paraneoplastic syndromes which may occur individually, or in combination [85, 86]. Associated clinical syndromes have a subacute onset between ages 20 and 80. Clinical syndromes with anti-Hu antibodies include encephalitis (limbic or brainstem), cerebellar ataxia, subacute sensory neuronopathy, and autonomic neuropathy. The subacute sensory neuronopathy presents with numbness and pain, often involving the upper extremities, progressing over 1–8 weeks. Sensory loss is asymmetric, involves large and small fiber modalities, and may occur on the face, trunk, and proximal as well as distal regions of the upper and lower extremities. Patients are often disabled by the severe sensory ataxia and pseudoathetosis resulting from the sensory loss. Pain is experienced by some patients. Strength is usually normal but mild distal weakness is described. Tendon reflexes are diffusely absent. Anti-Hu antibodies are unusual in patients with distal, symmetric sensory neuropathies. About 25 % of patients with anti-Hu antibodies have features of dysautonomia, with gastrointestinal dysmotility as the most common. Orthostatic hypotension or urinary dysfunction can also occur. A history of smoking is obtained in most patients. Nerve conduction studies show diminished or absent sensory responses with normal motor studies. Subacute sensory neuronopathy with anti-Hu antibodies is associated with central nervous system signs, ranging from mild nystagmus to severe encephalopathy, in 75 %. The CSF commonly shows a mild pleocytosis and elevated protein. Anti-Hu antibodies are very strongly (>95 %) associated with neoplasms, especially small cell lung cancer (SCLC). Extrathoracic neoplasms occur in 15 %. Anti-Hu testing is typically performed on serum, although the antibodies are usually also present in the CSF. The highest titers of anti-Hu antibodies are associated with autonomic gastrointestinal dysmotility syndromes or subacute sensory neuronopathy [83]. Median survival is 1 year. Three-year survival is 20 %. Low levels of IgG binding to Hu can occur with neoplasms without associated neurologic signs. Death can be related to either the paraneoplastic syndrome or tumor progression. Worse prognosis is associated with age greater than 60 years, involvement of multiple regions of the nervous system, and lack of treatment. There is no correlation of Hu antibody titer with disease progression or outcome [87]. The finding of anti-Hu antibodies mandates screening for cancer. When a neoplasm is not found at initial evaluation, periodic follow-up evaluations, every 1 or 2 years, are required. Treatment consists of therapy for the associated neoplasm. There is almost no improvement in the SSN itself. Physical therapy may allow patients to partially compensate for the sensory loss over time. There is little experimental support for a role of Hu antibodies in neural tissue damage.

CRMP5

Collapsin response mediator protein 5 (CRMP5; CV2; DPYSL5) is involved in neuronal and glial development, migration, and neurite extension [88]. In adults, CRMP5 is normally expressed in non-myelinating Schwann cells and a

subpopulation of oligodendrocytes and is upregulated during axonal regeneration. Two methods are used clinically to detect IgG antibodies that react with CRMP5. Immunoreactivity of anti-CRMP5 IgG to the cerebellum includes binding to synaptic regions in the granular and molecular layers with sparing of molecular and Purkinje layer neuron cell bodies [89]. Western blot confirmation uses recombinant CRMP5 protein or brain proteins as antigens [90, 91].

Peripheral neuropathy is the most frequent neurologic manifestation with IgG binding to CRMP5 [91, 92], occurring in a majority of patients. The polyneuropathy has a progressive onset over months. The signs are sensory and distal predominant, more severe in the legs. Distal leg or toe weakness occurs in some patients. Electrodiagnostic testing shows axon loss. Demyelinating features occur in some patients. Nerve pathology shows axon loss and regeneration. Some patients have thin myelin sheaths or macrophage-mediated demyelination. Accompanying clinical features most commonly include cerebellar ataxia, uveo-retinal features, limbic encephalitis, and Lambert–Eaton myasthenic syndrome (LEMS). CRMP5 antibodies are associated with neoplasms, especially small cell lung but occasionally thymoma. The neurologic syndrome typically precedes diagnosis of the neoplasm. Treatment consists of therapy for the associated neoplasm. There are reports of improvement of the neuropathy after treatment. Long-term mortality caused by the neoplasm or paraneoplastic syndromes is about 30 %.

IgG_4 Autoantibodies (IgG_4-AAb) Directed Against Surface Membrane or Extracellular Proteins

IgG_4 antibodies account for less than 5 % of total IgG in normals [93, 94]. They do not effectively activate the classical complement pathway. IgG_4 can undergo a distinctive process of "half-antibody exchange" in vivo, resulting in recombined antibodies with two different binding specificities. IgG_4-AAb are polyclonal and located in the serum and in some cases also the CSF. IgG_4-AAb often bind to surface membrane or extracellular proteins. Disease-related antigens include desmogleins in types of pemphigus, collagen VII in epidermolysis bullosa acquisita, M-type phospholipase A2 receptor in membranous glomerulonephritis, and MuSK in a subtype of acquired myasthenia gravis. IgG_4-related disease is a multiorgan disorder with tumefactive lesions, extensive fibrosis, and lymphoplasmacytic infiltrates that are rich in IgG_4-positive plasma cells and T cells and, commonly, elevated serum IgG_4 levels. Most IgG_4-related disorders have low frequencies of associated neoplasms, but an association with lymphoma is reported. Corticosteroid treatment can produce benefit. Short-term treatment with rituximab may be effective in corticosteroid-resistant IgG_4-related disorders [95–97]. Some IgG_4 autoantibodies may be pathogenic [98, 99].

Lgi1

Lgi1 is a secreted neuronal protein that interacts with presynaptic ADAM23 and postsynaptic ADAM22, regulates some VGKC, and enhances AMPA receptor-mediated synaptic transmission. Lgi1 antibodies are polyclonal, can be detected in serum and the CSF, and bind to CNS neurons. Predominant features in Lgi1 autoantibody-associated clinical syndromes are limbic encephalitis with delusions and mood changes, generalized or focal seizures, and memory loss [12, 21]. MRI shows increased T2 signal in medial temporal lobes. Pain with sensory neuropathies may occur [20]. Hyponatremia occurs in 60 %. Although associated neoplasms have been reported, they are present in relatively few patients (10 %) and there is no consistent tissue type. The disease course may be monophasic after immunomodulating treatments. At least partial improvement occurs, over a period of months, in 75 % of patients.

Serum IgM Autoantibodies (IgM-AAb) Directed Against Carbohydrate Moieties

IgM-AAb are typically located in serum, can be monoclonal or polyclonal, and bind to extracellular carbohydrate moieties on glycoproteins or glycolipids [100–102]. Testing for IgM-AAb generally utilizes ELISA methodology for quantitative or semiquantitative measurement of binding to purified antigens. Clinical neuromuscular disorders with IgM-AAb are commonly polyneuropathies with a chronic, slowly progressive course. Some syndromes predominantly involve motor axons, causing weakness. Others produce disability due to sensory involvement or gait disorders. Patients with IgM antibodies directed against carbohydrates have an increased frequency of serum IgM monoclonal proteins (M-proteins), usually benign but occasionally due to lymphomas, Waldenström's macroglobulinemia, or other bone marrow dyscrasias. Treatment of IgM antibody-associated neuropathies can be difficult. There are few controlled trials. Corticosteroids and T-cell immunomodulating agents rarely produce benefit. Patient subgroups with motor conduction block on electrodiagnostic testing are more likely to improve with IVIg treatment although there is no change in IgM-AAb titers [103]. Intravenous cyclophosphamide, rituximab, or fludarabine may be useful in neuropathies that produce disability [104, 105]. The benefit of these drugs in IgM-AAb-associated disorders is more likely with reduction in antibody titers of 50–60 % or more. Reduction in IgM antibody titers may be more rapid in patients with Waldenström's macroglobulinemia than in those with monoclonal gammopathies of unknown significance (MGUS) or no detected M-proteins. Improvement in IgM-AAb syndromes is less likely with short-term treatments which produce less reduction in antibody titers [106]. Some IgM-AAb may be pathogenic.

Motor Neuropathies (IgM Versus GM1 Ganglioside or NS6S Disaccharide)

Serum IgM binding to GM1 ganglioside or NS6S is associated with motor neuropathy syndromes. The sensitivity and specificity of ELISA testing for IgM binding to GM1 ganglioside or NS6S heparin disaccharide depend to an important extent on methodology of antibody testing [100, 107, 108]. Covalent linkage of these antigens to ELISA plates increases the sensitivity and specificity of antibody testing. Embedding GM1 ganglioside in lipid complexes that may mimic its membrane environment can allow detection of IgM binding to GM1 that is not found in pure GM1 [39–41]. In some serums IgM binding GM1 or NS6S is the result of polyspecific IgM that binds to multiple antigens and has no strong clinical correlations. Disease specificity of IgM binding to GM1 ganglioside or NS6S for motor neuropathies is greatly increased by subtracting polyspecific IgM antibody levels which are measured by determining serum binding to other antigens such as GD1a ganglioside or histone H3 [109].

Immune motor neuropathies associated with IgM autoantibodies are characterized by asymmetric, slowly progressive weakness that typically begins distally in the arms [110–112]. With disease progression proximal muscles can be involved [108]. Onset ranges from 20 to 70 years of age with male predominance. Cramps, fasciculations, or myokymia occur in over 50 % of patients, but sensory symptoms are rare. Laboratory testing is useful in distinguishing immune motor neuropathies from untreatable motor neuron diseases. Motor conduction block, a focal reduction (>50 %) in CMAP amplitudes in distal nerves at locations other than sites of compression [113], can be found in about 60 % of patients with immune motor neuropathies. The identification of motor conduction block in motor neuropathies supports a diagnosis of multifocal motor neuropathy (MMN) [110]. Some patients with a typical motor neuropathy phenotype have no conduction block. IgM binding to GM1 ganglioside or NS6S disaccharide are independent serum markers of immune motor neuropathies [108], occurring with similar frequencies of 40–50 % in immune motor neuropathies. At least one antibody is present in 60–70 %. GM1 antibodies are more specific for immune motor neuropathies than NS6S antibodies [114]. About 90 % of patients with high-titer serum IgM binding to GM1 have motor neuropathies. IgM binding to NS6S is uncommon in amyotrophic lateral sclerosis but can occur in patients with sensory neuropathies who have IgM binding to MAG or TS-HDS. The combination of electrodiagnostic and antibody testing has about 90 % sensitivity for immune motor neuropathies. Responses of immune motor neuropathies to immunomodulating treatment are typical of IgM-AAb syndromes. Intravenous immunoglobulin is useful in patients with multifocal motor neuropathy with conduction block [110, 115, 116]. Benefits can decline over time [117, 118] and are less likely in motor neuropathies without conduction block. IVIg treatment does not generally produce a change in anti-GM1 antibody titers [103]. Treatment with cyclophosphamide or rituximab may produce functional benefit and a reduction in IgM-AAb titers [104]. Corticosteroids and T-cell immunosuppressive treatments are rarely associated with improvement. Corticosteroids can produce exacerbations in weakness [119–121].

IgM Versus Myelin-Associated Glycoprotein (MAG)

MAG is a cell surface glycoprotein that is present in Schwann cells and uncompacted myelin in the peripheral nervous system [122]. IgM binding to semi-purified MAG protein is often initially measured by ELISA assay. Validation of serum binding to MAG using Western blot methods is important for disease specificity [123]. Serums with IgM binding to MAG by ELISA that are low titer, or negative by Western blot, are not specific for the characteristic-associated demyelinating polyneuropathy syndrome [109, 124–126].

High-titer serum IgM binding to MAG is often found in patients with an IgM monoclonal protein and a demyelinating polyneuropathy [105, 127, 128]. The polyneuropathy is typically slowly progressive, symmetric, and predominantly distal. The legs are involved more severely than the arms. Sensory loss, involving all modalities, occurs earlier than any weakness. A gait disorder, manifest on examination as difficulty with tandem gait, is often an early manifestation and develops with a severity and dysfunction out of proportion to the degree of sensory loss. Weakness, most severe in the distal legs or toes, eventually develops in 80 % of patients with anti-MAG antibody-associated polyneuropathies. Tendon reflexes are usually absent at the ankles and hypoactive or absent elsewhere. Tremor, predominantly in the hands, can be a severe late manifestation [129]. The neuropathy is slowly progressive. Moderate disability due to the gait disorder or tremor develops over a period of years [130, 131]. Electrodiagnostic testing shows a polyneuropathy with demyelinating features and some axon loss. The earliest and most consistent demyelinating change is prolonged distal motor latencies [132–134]. Slowing of nerve conduction velocities occurs in 50 % of patients, becoming more common with disease progression. Focal conduction block is unusual in anti-MAG antibody-related demyelinating polyneuropathies, in contrast to CIDP and multifocal motor neuropathy. Characteristic pathologic abnormalities in peripheral nerve myelin in anti-MAG polyneuropathies include wide spacing of myelin lamellae, especially near the nodes of Ranvier, and swelling of terminal myelin loops and tomaculae [135]. Axon loss develops with disease progression and may be associated with IgM penetration into nerve fascicles [136]. Nerve biopsy is not used to diagnose anti-MAG polyneuropathies. Anti-MAG polyneuropathies are difficult to treat [105]. There is no response to prednisone, azathioprine, or IVIg. Rituximab or cyclophosphamide may produce benefit [137–139]. Most

patients who improve after treatment have titers of anti-MAG antibodies reduced by at least 50 %. Improvement usually begins 3–6 months after starting rituximab or cyclophosphamide treatment and can continue for 1–2 years. Relapses after rituximab treatment are more common in patients with initial high titers of IgM binding to MAG, less reduction in antibody titers, and shorter-term treatments with rituximab [140, 141]. Fludarabine, a drug with significant possible toxicity, may also be useful [142, 143].

IgM anti-MAG antibodies may cause the demyelination and axonal loss [135, 136]. The target antigens in nerve may be MAG, or glycolipids that contain similar carbohydrate epitopes [144]. Anti-MAG antibodies bind to compact peripheral nervous system myelin and associated Schwann cell cytoplasm. Deposits of IgM and complement can be found on myelin sheaths in biopsies from patients. Direct injection into cat sciatic nerve of serum from patients with anti-MAG antibodies has produced widening of myelin lamellae and demyelination in experimental animals [145–147]. Passive transfer of human anti-MAG IgM into chicks produces pathology that is similar to the human disorder [148].

IgM Versus GD1b Ganglioside

ELISA testing showing IgM binding selectively to GD1b ganglioside, without binding to GM1, indicates antibody recognition of gangliosides containing disialosyl groups [149]. Selective IgM anti-GD1b antibodies cross-react with Pr2 antigens on red blood cells and may cause cold agglutination [150]. Serum IgM binding to GD1b ganglioside with concurrent binding to GM1 occurs in some patients with entirely different syndromes, immune motor neuropathies.

Selective serum IgM binding to GD1b occurs in chronic sensory ataxic neuropathy syndromes with panmodal, distal sensory loss, sensory gait ataxia, normal or relatively preserved strength, and, in some patients, cranial nerve features, including ophthalmoplegia and dysphonia (50 %) [151, 152]. Electrodiagnostic testing consistently shows axonal loss. Demyelinating features, such as prolonged distal latencies or slowed conduction velocities, may also be present. Serum IgM M-proteins are common. There are reports of partial improvement after IVIg [153] or rituximab [154] therapy. Corticosteroid treatment is not effective. Similar ataxic sensory neuropathy syndromes without cranial nerve features have been reported with IgM binding to GM2 and GalNAc-GD1a gangliosides without binding to GM1 ganglioside [155, 156]. Nerve conduction testing can show demyelination with conduction block and slowed velocities.

Antibodies against GD1b ganglioside bind to dorsal root ganglion neurons, paranodal myelin, myelinated axons, and motor nerve terminals [157]. An affinity-purified anti-disialosyl antibody impaired nerve excitability and reduced quantal release of neurotransmitter from nerve terminals [158]. Rabbits immunized with GD1b ganglioside develop ataxia and areflexia with structural damage to sensory neurons. Passive transfer of IgG anti-GD1b antibodies can cause degeneration of rabbit sensory neurons and induce nodal disruption predominantly in sensory nerves [27, 159].

IgM Versus TS-HDS

Trisulfated heparin disaccharide (TS-HDS) is the most abundant disaccharide component of heparin oligosaccharides. The distribution of TS-HDS in the nervous system is not well defined. Detection of serum IgM-AAb binding to TS-HDS depends strongly on specific methods of covalent binding of TS-HDS antigen to ELISA plates [109]. Serums with IgM binding to MAG frequently also have IgM vs. TS-HDS, often in higher titers than to MAG.

Selective serum IgM binding to TS-HDS is the most common neuropathy-related autoantibody. Patients with IgM vs. TS-HDS commonly have slowly progressive, distal, predominantly sensory, painful axonal polyneuropathies. Sensory loss more commonly involves small fiber modalities. Sensory symptoms and pain often occur in regions that are not length dependent. Distal weakness occurs in some patients (20 %) and is more common in the presence of IgM M-proteins. IgM binding to TS-HDS is often monoclonal, frequently κ class. Detection of serum IgM binding to TS-HDS raises the likelihood of finding an IgM M-protein in patients with neuropathies by tenfold. Biopsies of muscle and nerve show endomysial and endoneurial capillary pathology with thickened basal lamina and C5b-9 complement deposition. Serum IgM binding to TS-HDS suggests a possible immune etiology underlying some otherwise idiopathic sensory polyneuropathies. No treatment studies have been reported. Serum IgM from some patients with TS-HDS antibodies binds to endomysial capillaries in normal muscle, suggesting that the antibodies could play a role in producing capillary pathology. Possible causes of a neuropathy associated with capillary pathology include ischemia due to reduced blood flow or leakage of pathologic factors through capillary walls that have reduced integrity of their blood–nerve barrier.

IgM Versus Sulfatide

Sulfatide is a major anionic glycolipid in CNS myelin [160]. Many neural proteins have binding domains for sulfogalactolipids, like sulfatide. Sulfatide, like MAG, is associated with myelin-related inhibition of axonal outgrowth [161]. Sulfatide is an antigenic target of antibodies generated by immunizing mice with CNS myelin. IgM antibody binding to purified sulfatide is quantitated by ELISA [128].

High titers of IgM anti-sulfatide antibodies have specificity for predominantly sensory axonal neuropathy syndromes [101, 133, 162–165]. Distal, symmetric, panmodal, slowly progressive sensory loss in the legs and arms is typical. Pain and paresthesias are more common symptoms with polyclonal anti-sulfatide antibodies. Distal weakness is more

frequent with monoclonal anti-sulfatide antibodies. Some patients with IgM anti-sulfatide antibodies have an ataxic gait disorder or tremor similar to that seen in anti-MAG neuropathies. IgM M-proteins probably have an increased frequency. Electrodiagnostic testing shows an axonal sensorimotor polyneuropathy with occasional demyelinating features. Reports of treatment responses are sparse. Moderate or low titers of anti-sulfatide antibodies have been reported in patients with infections, including human immunodeficiency virus [166, 167] and trypanosomiasis [168]. Patients with the GALOP syndrome (gait disorder, autoantibody, late-age onset, and polyneuropathy) have IgM binding to sulfatide in a lipid membrane (cholesterol, galactocerebroside) environment. The clinical GALOP syndrome combines gait ataxia and a sensorimotor polyneuropathy with late-age onset (mean 70 years of age) [125]. Electrophysiologic studies are heterogeneous, but some patients have features suggesting demyelination, similar to those found in patients with anti-MAG neuropathies. Immunomodulating treatment with IVIg or cyclophosphamide may result in functional improvement in patients with GALOP syndromes. Nerve biopsies in patients with IgM binding to sulfatide show that IgM and components of complement bind to myelin and could play a role in myelin wide spacing [169]. Serum IgM anti-sulfatide antibodies can bind to dorsal root ganglia [170]. Monoclonal IgM anti-sulfatide antibodies bind to peripheral nerve myelin, while polyclonal antibodies can bind to peripheral nerve axons [171]. Experimental demyelinating neuropathies develop after immunization with sulfatide [172] or passive transfer of patient serum from a patient with an IgM monoclonal anti-sulfatide antibody [173].

Other IgM Target Antigens

Sulfated Glucuronyl Paragloboside (SGPG)

SGPG and other sulfoglucuronosyl glycosphingolipids are present in axons and myelin in human peripheral nerve [174]. IgM binding to the glycolipid SGPG occurs in some patients with IgM anti-MAG antibodies. Anti-MAG antibodies that cross-react with SGPG more often bind to axons, while anti-MAG antibodies without SGPG cross-reactivity usually bind to areas of noncompact myelin [175]. Anti-SGPG antibodies are not strongly associated with a specific clinical syndrome and may occur in demyelinating neuropathies, motor syndromes, and other disorders [123, 127, 176, 177]. There is no clear clinical indication to test for anti-SGPG antibodies. Immunization with SGPG can cause an ataxia syndrome with inflammation in dorsal root ganglia [178].

Tubulin

IgM monoclonal antibodies that bind selectively to a specific epitope on β-tubulin, amino acids 301–314, occur in a few patients with chronic demyelinating neuropathies with similarities to CIDP [179–181]. Weakness is often slowly progressive and may be asymmetric. There has been a poor response to prednisone in the few patients described with this CIDP variant. IgM or IgG antibodies that bind to β-tubulin are also seen in some patients with classic Guillain–Barré syndrome.

Neurofilaments

An IgM M-protein with high-titer binding to the high molecular weight subunit (200 kDa) of neurofilaments has been reported in a patient with a chronic sensory axonal neuropathy [182]. Lower-titer serum IgM binding to neurofilaments has no specific clinical associations and has been described in many different disorders [183].

GM2 and GalNAc-GD1a Gangliosides

Monoclonal IgM antibodies with binding to both GM2 and GalNAc-GD1a gangliosides are associated with a chronic progressive demyelinating neuropathy [155, 156]. Clinical features include panmodal distal sensory loss, minimal weakness, and an ataxic gait. IgM binding to GalNAc-GD1a may also occur with chronic demyelinating motor neuropathies [184] and variant acute immune neuropathy syndromes with weakness, facial paresis, prodromal cytomegalovirus infections, and a good prognosis [34].

M-Proteins or Other Antibodies Without Binding to a Specific Antigen

Monoclonal gammopathies are characterized by the proliferation of a clone of plasma cells that produces a homogeneous monoclonal antibody [185, 186]. No antigenic target is generally identified for IgA and IgG monoclonal proteins (M-proteins). Some IgM M-proteins have no identified antigenic target. Neuropathy syndromes associated with IgG or IgA are different from those with IgM [187]. Some distinctive neuropathy syndromes are associated with serum M-proteins without defined antigenic targets. These include POEMS syndrome [188, 189], Waldenström's macroglobulinemia [133, 190], amyloidosis [191, 192] and similar disorders [193], cryoglobulinemia [194], and scleromyxedema [195]. There may be an increased frequency of IgG or IgA M-proteins without identified antigenic targets associated with some neuropathy syndromes, including CIDP [196].

POEMS (Crow–Fukase) Syndromes

POEMS is a multisystem clinical syndrome that is associated with serum IgG or IgA M-proteins [188, 189]. POEMS is an acronym for polyneuropathy, organomegaly, endocrinopathy (and edema), M-protein, and skin changes. Not all features are required to make the diagnosis. Dominant

features are most often neuropathy, endocrine disorders, and fluid volume overload. The mean onset of POEMS syndrome is in the fifth decade. The polyneuropathy begins with distal panmodal sensory signs and symptoms, including paresthesias and pain. With time, often over several years, weakness can become a major cause of disability. Examination reveals diffuse, symmetric weakness that is more severe distally. Areflexia is common. Systemic manifestations vary. Organomegaly can involve the liver, lymph nodes, or spleen. Edema or anasarca is a common accompaniment of POEMS. Endocrinopathies are diverse, including diabetes or thyroid, adrenal, or gonadal failure (with gynecomastia or testicular atrophy). Skin disorders can include pigmentation, hypertrichosis, angiomas, and sclerodermatous changes. Some patients have only a subset of these disorders (incomplete POEMS syndromes). On nerve conduction studies in POEMS syndrome, demyelination accompanied by axonal loss is the rule [197, 198]. Slowed motor and sensory conduction velocities, along the length of nerves, are the most prominent demyelinating feature. Motor distal latencies are less prolonged compared to other demyelinating neuropathies, and conduction block is rare. Axon loss is reflected by low-amplitude compound muscle and sensory nerve action potentials. Nerve biopsies show uncompacted myelin lamellae and axon loss. A defining feature of POEMS syndrome is the presence of an IgG or IgA M-protein. M-proteins usually have a λ light chain (95 %) with restricted immunoglobulin light chain variable gene usage (IGLV1). Immunofixation is the most sensitive test in searching for a serum M-protein in POEMS as the amount of the M-protein is characteristically small. A Castleman's disease variant of POEMS has no clonal plasma cell proliferative disorder. Non-antibody biomarkers of POEMS diagnosis and disease activity include high serum levels of VEGF [199] and interleukin-12 [200]. In POEMS syndrome, X-ray screening for bone lesions is necessary as irradiation of a focal plasmacytoma can produce disease improvement. Treatment of diffuse disease involves risk stratification according to the clinical severity and can require chemotherapy or stem cell transplantation.

Waldenström's Macroglobulinemia

Waldenström's macroglobulinemia is an IgM-associated lymphoplasmacytic lymphoma. IgM monoclonal proteins, most commonly with κ light chains, are a hallmark of Waldenström's macroglobulinemia. In Waldenström's macroglobulinemia there is anemia (hemoglobin level less than 12.6 g/dl), higher levels of serum IgM monoclonal proteins, and lower frequency of demyelinating neuropathy and serum IgM binding to MAG compared to IgM monoclonal gammopathy of unknown significance (MGUS) [133, 190]. Rituximab may produce a more rapid fall in levels of total IgM and IgM-AAb in Waldenström's macroglobulinemia compared to MGUS patients. In Waldenström's macroglobulinemia patients, the presence of serum IgM binding to MAG is associated with more frequent distal weakness in the legs and demyelinating features (especially prolonged distal latencies) and more severe sensory axon loss, and the presence of serum IgM binding to sulfatide is associated with more severe axonal loss [133]. Other types of neuropathy in Waldenström's macroglobulinemia, or with IgM M-proteins, include mononeuritis multiplex or asymmetric, sensory–motor neuropathies associated with immunoglobulins, such as light chains or amyloid, deposited in nerve [126, 193, 201]. Hyperviscosity syndromes, associated with the high total levels of serum IgM and cryoglobulins, may be responsible for other manifestations such as bleeding, focal central nervous system signs, and organomegaly [202]. High levels of serum IgM (greater than 1,830 mg/dl) help to identify Waldenström's macroglobulinemia and its association with malignancy. In the presence of an IgM M-protein, high, or rising, levels of total IgM, or suppressed levels of IgG or IgA, indicate the necessity for increased vigilance in screening for Waldenström's macroglobulinemia, myeloma, or other hematopoietic neoplasms.

Cryoglobulinemia

Cryoglobulins are serum immunoglobulins that abnormally precipitate with cooling [203] and may redissolve with rewarming. Cryoglobulins composed of one type of immunoglobulin (type 1) are associated with lymphoproliferative disorders such as Waldenström's macroglobulinemia and are frequently asymptomatic [204]. Mixed cryoglobulins (types 2 and 3) are immune complexes composed of polyclonal IgG and mono- or polyclonal IgM, respectively. The IgM component of mixed cryoglobulins typically has rheumatoid factor activity and forms immune complexes by binding to the IgG Fc fragment. Mixed cryoglobulins are most often related to hepatitis C (up to 90 %) and other infections. Connective tissue diseases, especially Sjögren's syndrome (up to 15 %) and lupus, also predispose to mixed cryoglobulinemia. Some patients have "essential" syndromes with no other associated disease [205, 206]. The associated clinical syndrome of cryoglobulinemia is a triad of purpura, asthenia and arthralgias, and peripheral neuropathy. Serum features include low C4 complement levels and rheumatoid factor. Essential mixed cryoglobulinemia may be more severe than secondary syndromes with more frequent renal and peripheral nerve involvement. Polyneuropathy syndromes in mixed cryoglobulinemia include a predominantly sensory, often small fiber, axonal disorder and, with more active cryoglobulinemia, a more severe sensory–motor syndrome [194]. Nerve conduction studies show patchy axon loss. Nerve pathology in the sensory–motor neuropathies includes epineurial inflammatory vasculopathy involving small- and intermediate-sized vessels [207]. Axon loss can be multifocal. Treatments for mixed

cryoglobulinemias include corticosteroids and rituximab [208] and management of associated infections (interferon-α plus ribavirin in hepatitis C) or malignancy.

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5 Autoantibody Testing of Autoimmune Neuromuscular Junction, Hyperexcitability, and Muscle Disorders

Elham Bayat and Henry J. Kaminski

Introduction

Serological evaluation for neuromuscular disorders expands commensurate with understanding of their autoimmune etiology. In myasthenia gravis (MG) and Lambert-Eaton syndrome (LES) and stiff person syndrome (SPS), there is a clear link between an autoantibody and disease pathogenesis, while the association of autoantibodies and inflammatory myopathies is less clear. Despite the uncertainty of the pathogenic role of autoantibodies in certain disorders, their detection may be useful in diagnosis and prognosis. This chapter reviews use of serological evaluation in diagnosis of neuromuscular junction disorders, hyperexcitability syndromes, and inflammatory muscle diseases.

Autoantibodies Associated with Neuromuscular Junction Disorders

There are two autoimmune disorders that compromise neuromuscular transmission, MG and LES [1, 2]. The pathology of MG is localized to the postsynaptic membrane of the neuromuscular junction where nicotinic acetylcholine receptors (AChRs) are reduced in number and function. In the majority of patients, antibodies directed against the AChR are responsible for the disorder, and detection of these antibodies strongly supports the diagnosis. Antibodies to the muscle-specific receptor tyrosine kinase (MuSK) are present in 20–40 % of AChR antibody-negative patients with generalized MG [3, 4]. MuSK antibodies are usually not observed in pure ocular myasthenia although rare patients have been reported with ocular myasthenia with MuSK antibody [5, 6]. Classification as seronegative MG now applies to patients without AChR or MuSK antibodies using conventional assays at presentation and at follow-up of 12 months. Antistriational muscle antibodies are also detected in patients with MG, usually in late-onset MG and in association with thymoma, but these are not diagnostic of an autoimmune neuromuscular transmission disorder. In LES, antibody-mediated voltage-gated calcium channel dysfunction causes reduced calcium influx to the nerve terminal leading to impaired release of acetylcholine. Serological testing for antibodies to calcium channels is highly sensitive and specific for LES. The sections below describe autoantibodies found in patients with LES and MG and focus on their diagnostic utility.

Acetylcholine Receptor Antibodies

AChR antibodies are detected in about 90 % of patients with generalized MG and in about 50 % of patients with MG involving only the ocular muscles [7]. Three commercially used tests for detection of AChR antibodies are the binding, modulating, and blocking assays. Each differs in methodology as well as sensitivity and specificity for diagnosis of MG.

Binding antibodies are identified by a standard radioimmunoassay. The binding assay should be used for initial screening of patients for suspected MG and is the primary assay used in reporting seropositivity in research studies. However, patients with mild disease and those who are early in their disease course are often seronegative (Fig. 5.1) [8, 9]. As a population, there is a moderate correlation between antibody concentration and disease severity. Titers fall with successful treatment and therefore may be used as a measure of therapeutic response; however, ultimately clinical response is the only true measure of efficacy. However, it must be

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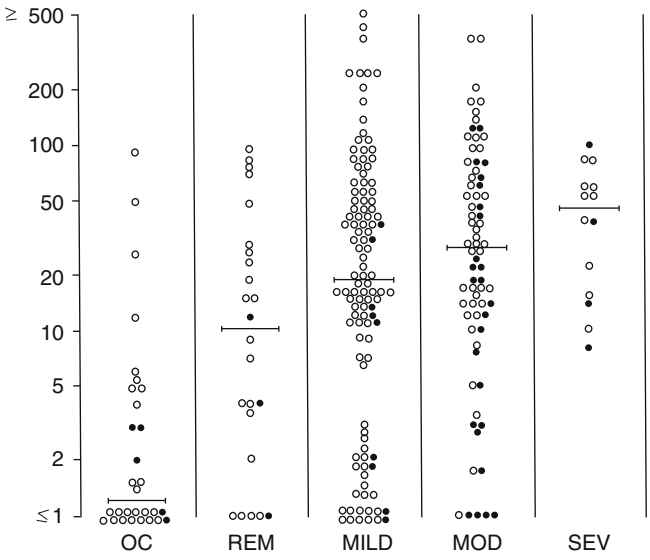

Fig. 5.1 Distribution of AChR binding levels (nM) in 250 patients with myasthenia gravis as a function of the severity of the disease. *OC* ocular myasthenia, *REM* remission, *MOD* moderate, *SEV* severe disease (Reprinted from Limburg et al. [8])

appreciated that an individual antibody level in an individual patient is not predictive of the severity of the disease; a patient with a low level may have severe weakness. AChR antibodies are polyclonal and all are not pathogenic, which offers an explanation for why an individual patient may have high titers but be in remission. Also, about 15 % of patients initially found to be seronegative become positive a year later [10]. Therefore, there is value in retesting to confirm a diagnosis if AChR antibodies are initially negative.

About 10 % of otherwise typical patients with MG do not have detectable AChR antibodies. Antibodies against constituents of the motor endplate that are not detected by the conventional assays probably cause some cases of "seronegative" MG, but antibodies directed at other endplate components, including MuSK, are also likely pathogenic [11, 12].

Binding AChR antibodies are highly specific for MG, but they are rarely detected in patients with other conditions (Table 5.1). False-positive binding antibodies are observed in amyotrophic lateral sclerosis (3–5 %), polymyositis (<1 %), and other neurological conditions at low levels [13]. LES is often misdiagnosed as MG, and it is particularly important to appreciate that about 7 % of patients with LES may have antibodies directed against the AChR [8, 9]. Careful electrodiagnostic and serologic testing for calcium channel antibodies should differentiate the two conditions. AChR antibodies are rarely identified in non-neurologic disorders including systemic lupus, thymoma without MG, primary biliary cirrhosis, and in first degree relatives of patients with MG [14–16].

Serological confirmation of the diagnosis of MG is often more difficult in patients with only ocular manifestations. At most, 70 % of patients with ocular myasthenia have AChR binding antibodies. There are several potential factors that influence the susceptibility of the ocular muscles to MG and the low seropositivity of these patients [17, 18]. One appears to relate to the source of antigen for the binding assay. Because the AChR is derived from partially denervated muscle, or cultured muscle cells, there is a high concentration of the fetal isoform of the AChR. One report indicates that if adult AChR produced by genetically engineered cells is used for the radioimmunoassay, then seropositivity rates are higher, in particular, the seropositivity rate for ocular myasthenia is increased about twofold [19]. However, this test is not widely commercially available.

AChR-modulating antibodies are detected using cultured, human cells, which express primarily the fetal AChR. These antibodies when applied to the cell cultures increase degradation of AChR by cross-linking receptors. The reduction of receptors is detected by a decrease in binding of radioactive bungarotoxin. The modulating assay has a similar sensitivity but is technically more difficult than the binding assay. This assay should be performed in patients who test negative for binding antibodies (Table 5.1). The sensitivity of this assay is similar to the binding assay, but performing the combination of binding and modulating assays raises the sensitivity of detection by approximately 5 %. False-positive results are problematic, and technical errors should be considered especially in the setting of a normal binding and blocking results [8, 9, 16].

AChR-blocking antibodies prevent the binding of bungarotoxin. The assay involves preincubating the antigen source with sera and then incubating with ^{125}I-labeled bungarotoxin. A decreased level of binding indicates the presence of blocking antibodies. Less than 1 % of patients have blocking antibodies without detectable binding antibodies, and therefore, blocking antibodies should not be ordered as a screening test in the authors' opinion [8, 9, 16]. The assay is positive in roughly 50 % of patients with generalized myasthenia. They are rarely positive in other conditions and, therefore, may be of some utility in differentiating patients with a possible false-positive binding assay.

MuSK antibodies occur in up to 50 % of patients with MG who are negative for AChR antibodies [4]. MuSK is a neuromuscular junction protein that plays an important role in the clustering of AChR on the postsynaptic surface. The antibodies are predominantly of the IgG4 subclass which suggests they do not activate complement as a pathogenic mechanism in contrast to AChR antibody-associated MG. The patients tend toward having a predominance of bulbar manifestations, and the response to cholinesterase inhibitors is variable. Patients with MuSK antibodies appear to respond less well to immunosuppressive treatments, while plasma exchange appears preferentially effective. The presence of MuSK antibodies is not associated with thymoma [20]. MuSK antibody detection aids in diagnosis and may assist in therapeutic

Table 5.1 Acetylcholine receptor antibody tests

	Sensitivity (%)			
Antibody test	OcMG	Mild	Mod-Sev	False positive
AChR binding	71 %	88	93	LES, graft-versus-host disease, immune-mediated liver disorders, healthy relatives of MG patients, thymoma, and rarely lung cancer and motor neuron disease
AChR blocking	30	52	66	LES, curare-like muscle relaxants
AChR modulating	72	89	91	Sample damage (bacterial contamination, heating, hemolysis) if modulating antibody +, but others negative suspect false elevation

Adapted from Howard et al. [9]
AChR acetylcholine receptor, *OcMG* ocular myasthenia, *Mod-Sev* moderate to severe *LES* Lambert-Eaton syndrome

choices. The clinical picture of MuSK antibody-associated neuromuscular disorders and in patients with atypical myopathic presentations their evaluation should be considered.

Striational Antibodies

Striational antibodies were the first autoantibodies discovered in patients with MG. Nearly half of patients with MG presenting after the age of 50 years have striational antibodies; however, normal individuals above the age of 60 have high rates of striational antibody detection limiting their diagnostic value [21]. These antibodies are heterogeneous and reactive against thymic myoid cells as well as the contractile elements of skeletal muscle including titin, ryanodine receptor, actin, myosin, potassium channels, and other muscle proteins [22]. Titin and ryanodine receptor antibodies have been found in association with the presence of thymoma [23, 24]. Striational antibodies are present in about a quarter of patients with MG and up to 90 % of patients with MG and concurrent thymoma [25, 26]. Patients with striational antibodies and no radiographic evidence of thymoma, if they do not undergo a therapeutic thymectomy, should have serial imaging performed. A progressive rise in antistriational antibody titers may be the first indication of thymic tumor recurrence, but their clinical usefulness in monitoring recurrence compared to chest imaging is not known. Rarely, striational antibodies may be present in the absence of AChR antibodies [27].

Titin antibodies are detected in 90 % of MG patients with thymoma and are almost never detected in early-onset MG with thymic hyperplasia [23]. Titin antibodies are associated with more severe MG in late-onset patients, but there is no convincing evidence that titin antibodies are pathogenic [28]. In older patients the specificity of titin antibodies for thymoma is much lower, and they are found in about half of late-onset patients with thymic atrophy.

Ryanodine receptor (RyR) antibodies are detected in about half of MG patients with thymoma, rarely in late-onset MG patients without thymoma, and never in early-onset MG patients without thymoma [29, 30]. They are often found in patients with an invasive or malignant thymoma [31]. Thymoma patients with RyR antibodies, especially those with high concentrations, have more severe clinical manifestations of MG than RyR antibody-negative thymoma patients. RyR antibodies could prove to be helpful in identifying thymoma patients at risk for developing MG with poor prognosis. However, at present, tests for RyR and titin antibodies are not available commercially in the United States.

Ten to fifteen percent of patients with LES have antistriational antibodies, regardless of whether a lung cancer is present. Also, individuals with lung cancer, autoimmune liver disease, undergoing penicillamine treatment, and thymoma without MG may have striational antibodies [27]. Striational antibodies are detected in about 90 % of thymoma patients but also in 20–30 % of non-thymoma patients leading to the problems of false positives, either suggesting a thymoma in a myasthenic or myasthenia in a nonmyasthenic.

The diagnostic utility of striational antibodies for thymoma detection is dependent on patient age [21]. Under age 20 years, striational antibody studies are not useful since the probability of a thymoma is so low in this age group that results of antibody testing do not significantly alter the clinical suspicion for the tumor. In patients older than 60 with a relatively high frequency of thymoma and increased rates of false-positive values, the positive predictive value of the test is poor, and so the test does not offer additional diagnostic value. In patients between 20 and 60 years, a positive test increases the likelihood of a thymoma being present. Unfortunately, striational antibody testing is not sensitive or specific enough to guide whether chest imaging should be performed, and therefore, all patients with MG should undergo imaging in search of a thymoma.

Calcium Channel Antibodies

The development of diagnostic assays for calcium channel autoantibodies was largely dependent on identification of toxins from cone snails that bind specifically to calcium channel subtypes [32]. The ω-conotoxin MVIIC binds P/Q-type channels expressed at motor nerve terminals, while ω-conotoxin GVIA binds N-type channels of central and autonomic synapses. Calcium antibodies in LES patients are

measured by a radioimmunoassay using immunoprecipitation of ^{125}I-conotoxin-labeled solubilized, calcium channel extracts [33]. Calcium channel antibodies to either channel isoform are detected in 95–99 % of LES patients. Small cell lung cancers express calcium channels of various types and presumably induce an immune response with production of autoantibodies that cross-react with normal neuronal calcium channels. P/Q-type calcium channel antibody testing is a highly reliable method of confirming the diagnosis of LES. Calcium channel antibodies are detected in almost 100 % of LES patients with cancer and in 90 % of nonparaneoplastic LES patients. Although antibody concentrations do not correlate well with clinical severity across groups of patients [34], in a single individual, calcium channel antibody titers do decrease with clinical improvement [35].

Calcium channel antibodies are detected in some patients with paraneoplastic cerebellar degeneration and other paraneoplastic syndromes without LES, in small cell lung cancer and ovarian carcinoma patients without LES, and in some MG patients. Fewer than 2 % of normal control patients possess calcium channel antibodies. False-positive tests are rare and occur in clinical situations that are easily differentiated from LES on clinical or electrodiagnostic grounds. Immunosuppressive treatment of LES patients often leads to a suppression of calcium channel antibody levels and negative results of serologic testing. This observation needs to be considered in patients with possible LES who have been treated with corticosteroids or other immunosuppressives for presumed MG or polymyositis.

Neuronal AChR Antibodies

Neuronal AChR antibodies have also been detected in subacute autonomic neuropathy and neuromyotonia with autonomic dysfunction [36]. The AChR in autonomic ganglia mediates fast synaptic transmission. Antibodies against ganglionic AChR are measured by a radioimmunoassay with immunoprecipitation of ^{125}I-epibatidin-labeled AChR from peripheral neuroblastoma membranes [37]. Autonomic dysfunction is a feature of LES that may be related to the presence of antibodies to neuronal nicotinic AChR in autonomic ganglia. Antibodies specific for the neuronal ganglionic AChR have also been found in Isaacs syndrome [38].

Other Autoantibodies in Neuromuscular Transmission Disorders

Autoantibodies are observed at higher frequencies among patients with MG. Thyroid peroxidase, thyroglobulin, gastric parietal cell, and glutamic acid decarboxylase (GAD65) autoantibodies are found at a frequency two to three times above that of neurological controls [39]. The same is true for patients with LES [40]. Detection of these antibodies in a patient with a strong clinical suspicion of an autoimmune neuromuscular transmission disorder, but without detectable antibodies against the AChR or calcium channels, provides indirect evidence for the diagnosis of MG or LES.

Autoantibodies Associated with Hyperexcitability Disorders

Three neuromuscular disorders associated with increased muscle activity appear to be caused by autoantibodies, rippling muscle disease, neuromyotonia, and stiff person syndrome. Rippling muscle syndrome has inherited and immune etiologies, including association with MG and thymoma [41, 42]. Patients experience slow, undulating muscle movements sometimes with muscle ache and stiffness. Some consider cramp-fasciculation syndrome and acquired rippling muscle syndrome as autoimmune disorders that are part of a pathophysiological continuum with neuromyotonia [38].

Neuromyotonia (Isaacs syndrome, continuous muscle fiber activity) is an autoimmune disorder with hyperexcitability of peripheral motor nerves causing muscle stiffness and cramps on attempted muscle contraction, slow relaxation after voluntary movement, and often visible myokymia. Needle electromyography in patients with visible myokymia shows characteristic bursts of high-frequency motor unit action potential discharges. Neuromyotonia may occur as a paraneoplastic disorder related to lung cancer or thymoma [30] and may occur in association with MG without thymoma. In a variant of neuromyotonia called as Morvan's syndrome, besides muscle manifestations, patients have CNS dysfunction, including confusion, memory loss, insomnia, hallucinations, or seizures. In all these disorders the cause appears to be antibodies against voltage-gated potassium channels. The differential affinity of antibodies to subunits of the potassium channel may explain the different tissue involvement (Isaac, Moravan and VGKC-Ab limbic encephalitis) [43].

Potassium Channel Antibodies

VGKC are widespread in the peripheral, autonomic, and central nervous systems and play a key role in controlling neuronal excitability [44]. Autoimmune neuromyotonia appears to be caused by antibody-mediated dysfunction of voltage-gated potassium channels of peripheral nerves [45, 46]. Antibodies to VGKC have been described in half of patients with acquired neuromyotonia and are found in rare patients with myasthenia gravis but without neuromyotonia [30]. The VGKC antibodies in neuromyotonia are probably directed against potassium channels concentrated in the paranodal and

terminal regions of myelinated axons and may decrease channel density, either through increased degradation or by decreased expression of VGKC [47]. Their effect prevents potassium efflux and chronically lowers resting membrane potential, resulting in decreased repolarization and neuronal hyperexcitability. Passive transfer of neuromyotonia can be achieved by injection of purified VGKC antibodies from neuromyotonia patients into mice.

VGKC antibodies may be identified by a radioimmunoassay using immunoprecipitation of ^{125}I-dendrotoxin-labeled extracts of human frontal cortex. However, the sensitivity of the assay is low with antibodies detected in not more than half of patients. Immunohistochemistry using *Xenopus* oocytes, which express various different types of human potassium channels, detects antibodies in nearly all neuromyotonia patients [46], but the assay is not commercially available.

Stiff Person Syndrome

Stiff person syndrome is a rare disorder of the central nervous system with muscle manifestations characterized by continuous muscle contraction with spasm, progressive axial muscle spasm and rigidity [48], abnormal postures, and progressive disability. EMG studies demonstrate continuous motor activity in the paraspinal muscles in patients with SPS which is typically decreased by intravenous diazepam, sleep, and local or general anesthesia. Autoantibodies to the GABA-synthesizing enzyme glutamic acid decarboxylase (GAD), present in about 60–85 % of patients, have indicated an autoimmune pathogenesis. Among patients with SPS, there is evidence of marked intrathecal GAD antibody synthesis [49–51].

GABA-Synthesizing Enzyme Glutamic Acid Decarboxylase (GAD)

GAD is an enzyme selectively concentrated in neurons secreting GABA and in pancreatic beta cells. In one study by Solimena et al. 20 of 33 (60 %) patients with stiff person syndrome had anti-GAD, making it the principal autoantigen in this syndrome [52, 53]. Although these antibodies associate with type I diabetes, their detection in the CSF is specific for neurologic disease. Although elevated GAD antibody titers is a specific marker for SPS, they are observed occasionally in patients with other neurologic manifestations without SPS, such as myoclonus, epilepsy, cerebellar ataxia, eye movement disorders, and neuromyotonia [49].

Amphiphysin Antibodies

Amphiphysin antibodies (amphiphysin Ab) are associated with paraneoplastic variant of SPS [54, 55]. Small cell lung and breast cancers are the most common [55]. Amphiphysin antibody-associated SPS is strongly associated with several clinical observations: cervical region stiffness, female sex, older age groups, electrophysiological abnormalities, and benzodiazepine responsiveness. The condition may respond to steroids and can dramatically improve with cancer treatment [49, 54]. The pathogenic role is suggested by passive transfer studies demonstrating that administration of purified IgG from an amphiphysin antibody-positive patient results in muscle stiffness and spasms [56, 57]. However, amphiphysin antibodies are not specific to SPS, as they are identified in several neurologic disorders, usually paraneoplastic cerebellar degeneration, sensory neuropathy, and limbic encephalitis, often coexisting with other onconeural antibodies [57, 58].

Autoantibodies Associated with Disorders of Muscle

Three distinct inflammatory myopathies (IM) are recognized: dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM). Although autoantibody testing is useful in diagnosis and prognosis of certain IM, the pathogenic role of these antibodies is uncertain. The autoantibodies may be an epiphenomenon of the immune destruction of muscle [59]. Autoantibodies to nuclear and cytoplasmic antigens are found in up to 80 % of patients with IM. Half of autoantibodies are of recognized specificity, i.e., myositis-specific antibodies, while others occur in association with systemic immune disorders. The myositis-specific autoantibodies (MSA) are unique to patients with myositis and are helpful in predicting manifestation of myositis, response to therapy, and prognosis. Most of MSA are associated with decreased risk of malignancy (except anti-155/140) [60]. To date, 60–80 % of patients with autoimmune myopathy are found to have at least one myositis-specific antibody (MSA) [60, 61], each of which is associated with a distinct clinical phenotype (Table 5.2).

Myositis-Specific Antibodies

Antisynthetase Autoantibodies

Aminoacyl-transfer RNA (tRNA) synthetases catalyze the binding of amino acids to their corresponding tRNA. Autoantibodies to six synthetases (histidyl, threonyl, alanyl, asparaginyl, isoleucyl, and glycyl-tRNA synthetase) are identified in patients with PM and less frequently in DM [64]. Each patient has only one of these autoantibodies. Despite individuals having antibodies to different types of the synthetases, patients share common clinical features, so-called antisynthetase syndrome, including PM, polyarthropathy, pulmonary fibrosis, scaling and cracking of the lateral

Table 5.2 Myositis-associated antibodies

Antibodies	Frequency (%)	Nature of target antigens	Clinical features	Corticosteroid responsiveness	Prognosis
Myositis-specific autoantibodies					
			Antisynthetase syndrome		
Anti-Jo-1	20–30	Histidyl-tRNA synthetase (50KD)	3/4 of patients have interstitial lung disease	Moderate	Fair
Anti-PL-7	<5	Threonyl-tRNA-synthetase (80 kD)		Moderate	Fair
Anti-PL-12	<5	Alanyl-tRNA-synthetase (110 kD)	Correlate more with pulmonary fibrosis	Moderate	Fair
Anti-OJ	<5	Isoleucyl-tRNA-synthetase		Moderate	Fair
Anti-EJ	<5	Glycyl-tRNA-synthetase (75 kD)		Moderate	Fair
Anti-KS		Asparaginyl-tRNA-synthetase	Correlate more withpulmonary fibrosis	Moderate	Fair
Anti-SRP	<5	Signal recognition particle (SRP)	Severe, refractory PM myocarditis	Poor	Poor
Anti-Mi-2	<8	Helicase family protein	Acute DM	Good	Good
Anti-KJ	<1	Translation factor? (30–34 kD)	PM with pulmonary fibrosis		
Anti-Fer	<1	Elongation factor 1 alpha (48 kD)	Nodular myositis		
Myositis-overlap syndrome-associated autoantibodies					
Anti-Ku	20–30	70 kD/80 kD DNA-PK regulatory subunit	PM-scleroderma (Japanese)	Good	Good
Anti-PM-Scl	<10	Nucleolar protein complex	PM-scleroderma (Caucasians)	Good	Good
Anti-U2RNP	<5	U2 small nuclear RNP	PM-sclerodrerma	Good	Good
Anti-DN-PKcs	<5	460 kD DNA-PK catalytic subunit	PM, PM-SSc	Good	Good
Other muscle-related antibodies					
Anti-U1 RNP	10	U1 small nuclear RNP (pre-mRNA splicing factor)	MCTD, PM overlap, SLE	Good	Variable
Anti-SSA/Ro	<20	Y1-Y5 scRNP (60 kD/52 kD and Y1-Y5 RNA)	PM/DM with Sjögren's syndrome	Good	Variable
Anti-56kD	87	56-kD unidentified nuclear RNP	Seen in all Ims; predict muscle involvement in SLE		
Anti-calpastatin	24	Inhibitor of calpain (72 kD)	Predominantly found in rheumatoid arthritis		

Data from Miller [62] and Targoff [63]
tRNA transfer RNA, *SRP* signal recognition particle, *PM* polymyositis, *DM* dermatomyositis, *PK* protein kinase, *RNP* ribonucleoprotein, *SSc* systemic sclerosis, *MCTD* mixed connective tissue disease, *SLE* systemic lupus erythematosus, *mRNA* messenger RNA, *IM* inflammatory myopathy

fingers (mechanic's hand), and (less frequently) Raynaud's phenomenon. Their presence predicts moderate response to immunotherapy and persistent disease [65].

Among the autoantibodies to tRNA synthetases, anti-histidyl-tRNA or anti-Jo1 is the most common, found in 25–30 % of patients with myositis [61, 66]. Anti-Jo-1 continues to be a particular focus because of its relative frequency as the most common "myositis-specific" autoantibody (MSA) and its strong association with the clinical manifestations of the antisynthetase syndrome [67]. About three quarters of PM and DM patients with anti-Jo-1 antibodies have interstitial lung disease. The anti-Jo-1 patients have a relatively good prognosis compared with other ILD patients [67]. These patients usually are considered to have lower cancer risk. The antibodies are associated with the HLA-DR3 or HLA-DRw6 haplotype. The other anti-tRNA synthetases are much less common. The prevalence of each of these antibodies in patients with DM or PM is approximately 1–5 % [61, 66]. Anti-alanyl-tRNA and anti-asparaginyl synthetase antibodies correlate more closely with pulmonary fibrosis with myositis compared to the four other tRNA synthetases [66]. Presence of anti-Jo-1 antibodies essentially excludes the diagnosis of inclusion body myositis, although these patients may have low titers of nonspecific autoantibodies and other associated immune disorders [66, 68–70].

Anti-signal Recognition Particle Antibodies

Antibodies against SRP occur in 3–5 % of PM patients [71, 72]. The SRPs are cytoplasmic proteins that facilitate translocation of newly translated proteins and direct them to the endoplasmic reticulum. Patients with these antibodies usually have an acute onset of a severe myositis with cardiac involvement and respond poorly to corticosteroids. Because of the poor response to treatment and early myocarditis, the prognosis is poor. Necrotizing myopathy is not uncommon and supported with findings in muscle biopsy consistent with necrotic fibers [72, 73].

Anti-Mi-2

Antibodies against Mi-2 react with a 220-kD nuclear antigen which is of unknown function. Unlike antisynthetases, anti-Mi-2 is mainly found in DM patients with a prevalence of 20 % [61, 74, 75]. Anti-Mi-2-positive patients present with prominent dermatologic findings and an acute myositis. In contrast to the anti-SRP-positive patients, they respond well to steroids and have a relatively good prognosis. Despite a similar clinical presentation, DM seropositive Mi-2 patients have a lower risk of malignancy compared with DM anti-Mi-2 seronegative [61, 75].

Anti-p155/140 and Anti-MJ (Anti-NXP-2)

Anti-p155/140 is present in up to 20 % of DM patients [76–78]. DM patients who are anti-p155/140 seropositive have a significantly higher risk of cancer (71 %) compared with DM seronegative patients (11 %) [61, 77, 78].

Anti-MJ has been found primarily in patients with juvenile DM and is associated with calcinosis (54 %) and joint contracture [61, 72]. The function of the antigenic targets of these antibodies is not known.

Myositis-Overlap Antibodies

PM and DM which occur in association with other well-defined connective tissue diseases are defined as overlap syndromes (OS). Several antibodies serve as serologic markers for the OS, and some investigators suggest that the myositis occurring with OS responds better to treatment [79]; however, this opinion is not universally shared [80]. The major OS and associated muscle-related antibodies are described below.

Polymyositis-Scleroderma Overlap Syndrome

Myositis occurs in up to 17 % of patients with scleroderma and may develop in patients with progressive systemic sclerosis or CREST syndrome (calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia). Up to a quarter of such patients have antibodies to PM-Scl, a nuclear antigen that may be important in ribosomal assembly [80]. Anti-PM-Scl antibodies are identified in about 8 % of DM and PM patients and in 3 % of patients with systemic sclerosis without muscle disease. Therefore, identification of these antibodies is not necessarily diagnostic of muscle disease. Anti-PM-Scl antibodies are found in 75–100 % of patients with HLA-DR3. Patients with scleroderma who are seropositive for anti-Pm-Scl usually have a young age of onset (average 33 years), a high rate of lung involvement, and a trend toward a higher rate of kidney involvement (25 %) [61]. The response to steroid therapy and the long-term outcome appears better in patients with this syndrome with a more favorable response of immunosuppression [81]. Recognition of the anti-PM-Scl antibody-associated overlap syndrome may be of practical importance, because patients may not require aggressive therapy.

Mixed Connective Tissue Disease (MCTD)

MCTD has features of several connective tissue diseases, i.e., systemic lupus erythematosus (SLE), scleroderma, and rheumatoid arthritis, but does not fulfill clinical criteria to diagnose a specific disorder. DM occurs more frequently than PM in the context of MCTD. The anti-U1RNP antibody, directed at a ribonucleoprotein [77], is most commonly associated with MCTD, and 16–79 % of patients with this antibody will have myositis [81]. However, the antibody is not specific for myositis or MCTD and is found in patients with SLE. The clinical features resemble those of patients with

anti-tRNA synthetase syndrome. Prognosis depends largely on the degree of major organ involvement.

Lupus Myositis and Other Overlap Syndromes

PM occurs in 4–16 % of patients with SLE and differs little in presentation from patients without lupus. No meaningful differences exist in extent of creatine kinase elevation at presentation or during the course of the disease, duration of symptoms, degree of weakness, or response to therapy [82]. Anti-56-kD nuclear RNP antibody is a relatively specific marker for primary myositis, occurring rarely in patients with SLE without myositis and thus may help predict muscle involvement in patients with SLE. The antibody is found among patients with all types of myositis and some patients with pure connective tissue disorders [83]. Patients with Sjögren's syndrome and rheumatoid arthritis less commonly develop a myositis. Muscle disorders in these patients more often are related to corticosteroid treatment or disuse [65].

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Forearm Exercise Testing

6

Eugene Dulaney and Bashar Katirji

Introduction

In 1951, Brian McArdle described a patient with muscle cramps on exertion and failure to generate lactate when exercising under ischemic conditions [1]. He postulated that the patient's muscle disease resulted from "a gross failure of the breakdown of glycogen to lactic acid," which was later shown to be due to muscle phosphorylase deficiency [2, 3]. Subsequently, the ischemic forearm exercise test, first used by McArdle, has become the most widely employed assay of muscle anaerobic metabolism.

Exercise testing in muscle disorders quantitates exercise capacity, reproduces exercise-induced symptoms, and helps define the pathophysiology of exercise limitations. Exercise is a useful tool for evaluating the integrity of the metabolic pathways which power muscular work. Hence, exercise testing is of particular use in detecting disorders of muscle energy metabolism. Forearm exercise test is relatively simple to perform and interpret and has proved to be a robust tool in diagnosing defects in muscle energy metabolism

Exercise testing may be carried under conditions of ischemia or unrestricted blood flow. Reports of complications of the ischemia during forearm exercise testing in patients with glycogenoses have led some researchers to modify the test so that muscle ischemia is not intentionally produced [4–6]. Results of these modified forearm exercise tests have been similar to those of the ischemic forearm exercise testing.

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Basic Principles

Forearm exercise testing is performed as a screening test for patients with suspected metabolic myopathies, due to defects in glycogenolysis and glycolysis (Fig. 6.1). It is also a useful test for myoadenylate deaminase deficiency. Ischemia blocks oxidative phosphorylation and ensures dependence on anaerobic energy pathways during exercise. An overview of these pathways is provided below.

During periods of maximal exercise and energy demand (high rate of adenosine triphosphate [ATP] hydrolysis), three anaerobic pathways are available to re-phosphorylate adenosine diphosphate (ADP). These include transfer of phosphate from phosphocreatine to ADP and the transphosphorylation of ADP catalyzed by myokinase to form ATP and adenosine monophosphate (AMP). However, the main source of ATP in anaerobic exercise is metabolism of muscle glycogen stores via glycolysis. During glycolysis, nicotinamide adenine dinucleotide (NAD) serves as a hydrogen acceptor, converting to NADH. The consequent elevation of the NADH-to-NAD ratio shifts the lactate dehydrogenase equilibrium from pyruvate toward lactate, resulting in a disproportionate increase in lactate. Alanine, produced via transamination of pyruvate, also increases during anaerobic glycolysis [7]. The accumulation of ADP shifts the equilibrium of the myokinase reaction toward production of AMP, and the combination of increased ADP and AMP promotes AMP deamination via myoadenylate deaminase, with production of ammonia, inosine monophosphate (IMP), hypoxanthine, and xanthine (Fig. 6.2) [8, 9]. Thus, lactate, ammonia, purine compounds, and alanine are by-products of ischemic exercise.

A regulatory relationship exists between these anaerobic pathways. Inorganic phosphate (Pi) accumulating as a net product of the creatine kinase reaction activates glycogenolysis at the level of glycogen phosphorylase [10]. AMP, IMP, and Pi produced by the myokinase/myoadenylate deaminase reactions also activate glycogenolysis [11]. Similarly, the $[H^+]$ derived from glycolysis promotes phosphocreatine hydrolysis and AMP deamination [12]. A disturbance in any

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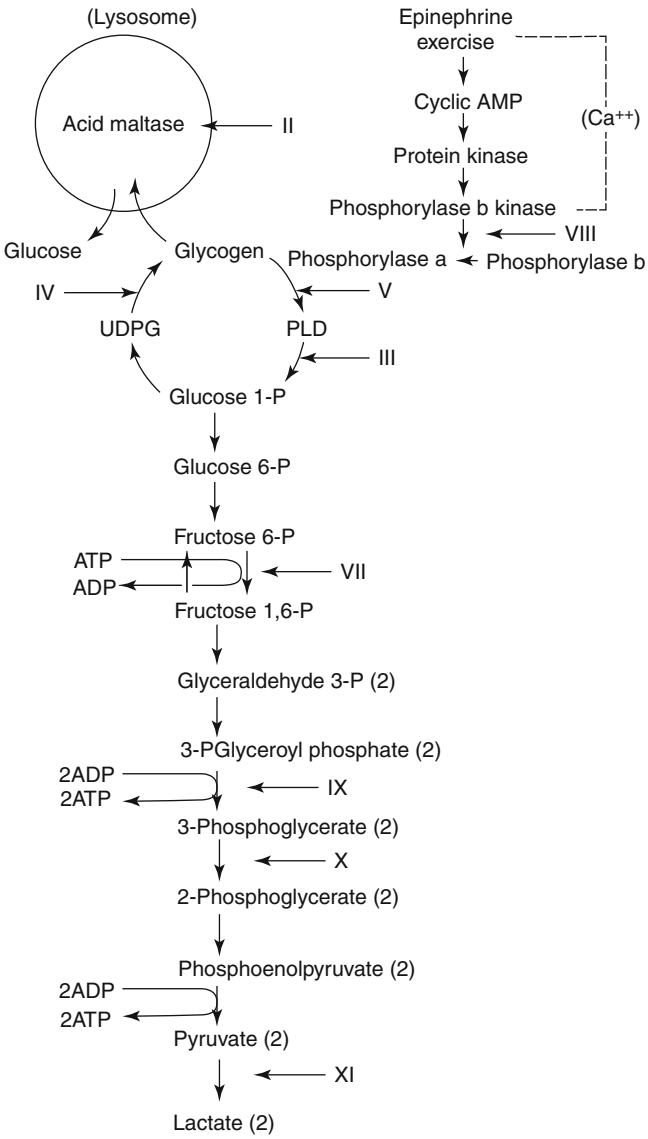


Fig. 6.1 Glycogen metabolism and glycolysis showing the common defects in glycogenosis. *Roman numerals* indicate enzymes with deficiencies that are associated with glycogenosis (see text). *Bold numerals* indicate disorders presenting with cramps, exercise intolerance, and myoglobinuria. *Italic numerals* indicate disorders presenting with fixed muscle weakness (Adapted from DiMauro and Haller [77])

of these energy pathways can affect the remaining mechanisms for ATP production.

Lactate, pyruvate, ammonia, alanine, hypoxanthine, and related purine metabolites readily diffuse from working muscle. Their levels in venous blood can be used to monitor the metabolic pathways from which they arise. However, only lactate, ammonia, and sometimes pyruvate levels are followed in clinical practice. The venous concentration of a muscle metabolite after exercise depends on the activity of rate-limiting muscle enzymes and intensity of force generated per unit of muscle tissue. Thus, exercise of similar relative intensity is necessary for valid comparison of metabolite levels. In addition, the rate of metabolite efflux from working

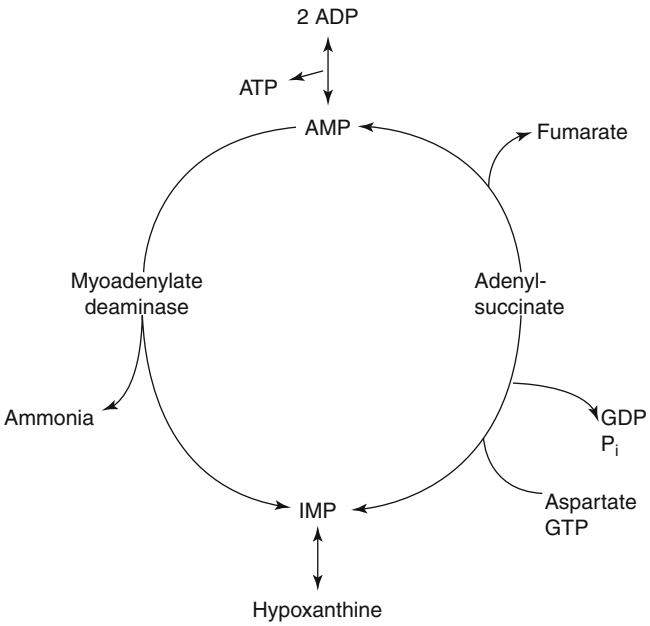


Fig. 6.2 The adenylate kinase, adenylate deaminase, and purine nucleotide cycle

muscle may modify levels of metabolites in blood. For example, a defect of lactate transport would be expected to delay the clearance of lactate from contracting muscle (see below). Finally, muscle blood flow, particularly following exercise, may affect the clearance rates of muscle metabolites. An exaggerated blood flow response to ischemic and aerobic exercise has been identified in myophosphorylase deficiency [6, 13].

Forearm Exercise Procedure

Protocols for performance of the forearm exercise testing are not standardized and differ somewhat between institutions. The procedure described below has been used successfully at University Hospitals Case Medical Center in Cleveland, Ohio, for over two decades.

The staff required for the forearm exercise testing includes a nurse or medical assistant for catheter insertion and blood sampling and a physician to oversee the test. Provisions must be made to rapidly transport the blood samples to a clinical laboratory. Materials needed for performing the forearm exercise testing include a sphygmomanometer, dynamometer, timer, ice bucket, phlebotomy supplies (intravenous catheter, syringes, alcohol swabs, gauze, etc.), and two sets of six blood drawing tubes (gray top [fluoride and oxalate] for lactate and green top [heparin] for ammonia) prelabeled as B (baseline) – 0, 1, 3, 6, and 10 min postexercise. Additional tubes for pyruvate collection may be also prepared, particularly if lactate dehydrogenase deficiency is suspected. Performing the forearm exercise test in the fasting or nonfasting state does not appear to alter the results [14].

Table 6.1 Forearm exercise procedure

1. Draw baseline (resting) samples of ammonia and lactate and place them on ice (make sure that the baseline samples are drawn after hand is rested for five minutes)
2. Ask the patient to hold the dynamometer and apply force to measure the maximal voluntary contraction (MVC). Calculate 80 % of the MVC
3. If done under ischemic conditions, place the sphygmomanometer cuff over the upper arm and inflate it above systolic blood pressure
4. Ask the patient to hold the dynamometer and perform repetitive forearm exercise by squeezing it once per second with a force aiming at 80 % of MVC. This standardized method of exercise is superior to nonstandardized exercise such as opening and closing the fist vigorously for 2 min [16]. If a muscle cramp or contracture occurs, exercise should be terminated and the cuff deflated immediately
5. After 1 min, the exercise is halted and the blood pressure cuff is quickly deflated (if done under ischemic conditions). Collection of blood samples without first deflating the cuff can result in false-positive results [17]
6. Collect venous blood samples immediately after the cuff is deflated (samples labeled 0) and at 1, 3, 6, and 10 min postexercise. Perform small blood draws between these intervals to keep the flow of the blood and preserve the patency of the vein
7. Place the blood samples on ice, and take them to the laboratory to be tested as soon as possible. Plasma lactate concentration may remain stable for several hours when samples are collected in grey top tubes containing sodium fluoride and potassium oxalate [18]. However, plasma ammonia concentration increases by 4 μmol/L per hour at 0 °C and by 25 μmol/L per hour at body temperature [19]. Thus, rapid chilling and processing of the ammonia samples is necessary to avoid spuriously elevated values

Prior to performing the forearm exercise test, the test should be explained in detail to the patient, and informed consent should be obtained. Patients should be aware that discomfort or cramping may occur and that there are rare reported cases of more serious complications after performing this test (see below). The importance of cooperation to achieve adequate exercise should be emphasized. Then, following determination of the patient's systolic and diastolic blood pressure in the dominant arm, a tourniquet is applied and an intravenous catheter inserted into the ipsilateral antecubital vein. Catheter placement in a hand vein or contralateral antecubital vein should not be done since this will result in reduced postexercise lactate values [14]. To prevent a premature rise of baseline lactate and ammonia, the patient should avoid making a forceful fist to help visualize the veins. Also, caution should be taken to prevent clotting of the catheter. This can be achieved by introducing a small amount of saline or heparin, which should be discarded before blood sample collection. Before starting the procedure, ensure that the catheter is in the vein by withdrawing a small amount of blood into a syringe [15]. The method in performing the forearm exercise test is described in Table 6.1.

Indications for the Forearm Exercise Test

The forearm exercise test is a screening test for patients with suspected metabolic myopathies, particularly the glycogenoses, before more expensive or invasive testing is performed. A final diagnosis of these disorders is usually established by appropriate biochemical or genetic testing (see Chap. 63). These disorders may present with a variety of clinical syndromes including exercise-induced muscle cramps, myoglobinuria, exercise intolerance, and weakness. Table 6.2 outlines a list of the clinical symptomatology in which the forearm exercise test is helpful or of low yield. It should be noted that the forearm exercise test is typically normal in patients with chronic fatigue syndrome [20].

Table 6.2 Indications for forearm exercise test

Clinical manifestations in which forearm exercise test is helpful
Exercise-induced myoglobinuria
Exercise-induced muscle pain or cramps
Exercise intolerance
Exertional fatigue
Myopathy with fixed weakness or myotonia
Clinical manifestations in which forearm exercise test is probably not helpful
Muscle cramps at night or unrelated to exercise
Diffuse muscle pain, continuous or at rest
Generalized fatigue

Although the test is usually performed in adults, a modified version has been performed successfully in children [4].

Forearm Exercise Test Findings

Normal Patterns

With effort near 80 % of MVC, the typical response to the forearm exercise test in normal subjects is as follows:

- Venous lactate level increases four- to sixfold over baseline, with the peak occurring at 1–2 min following exercise (i.e., a rise in venous lactate from 1 to 4–6 mmol/L).
- Venous ammonia level rises five- to tenfold, with peak levels usually seen at 2–5 min following exercise.
- Venous ammonia and lactate levels are linearly related. Thus, subjects in whom lactate levels are low due to poor effort show proportionally low ammonia levels [15, 21].

Abnormal Patterns

Abnormal responses to forearm exercise test occur in predicted patterns, as follows:

- No rise in lactate with increase in ammonia suggests a glycolytic or glycogenolytic disorder.

- A normal rise in the lactate level with no rise in the ammonia level suggests myoadenylate deaminase deficiency.
- No rise in lactate level with marked increase in pyruvate level suggests a deficiency of lactate dehydrogenase.
- If lactate and ammonia levels are proportionally low, this is usually due to poor patient effort. However, the rare occurrence of myoadenylate deaminase deficiency along with a glycogenosis ("double trouble") may also produce this finding [22].
- An elevated baseline level of serum lactate may occur if the forearm muscles are contracted while the baseline sample is taken.
- Mitochondrial disorders myopathies may be associated with elevated baseline lactate [14], as may numerous other toxic and metabolic disorders [5, 23].
- An elevated baseline serum ammonia level may be due to medications such as valproic acid, smoking, and undue exertion prior to the test [24]. In the setting of a baseline elevation of ammonia or lactate, the validity of the forearm exercise test is questionable, and caution should be used in interpreting the results.

Findings in Metabolic Myopathies

The clinical manifestations, inheritance, definitive diagnosis, and treatment of these disorders are detailed in Chap. 63. The common findings on forearm exercise test in patients with metabolic myopathies are summarized in Table 6.3 and discussed below.

Myophosphorylase Deficiency

Myophosphorylase deficiency (glycogenosis type V; McArdle's disease) is the prototypical glycogenosis and the most common one. Myophosphorylase catalyzes the first step in glycogen breakdown by removing 1,4 glucosyl residues phosphorylitically, with liberation of glucose-1-phosphate (Fig. 6.1). Absence of myophosphorylase prevents use of muscle glycogen stores for glycolysis and thereby blocks any rise in lactate during forearm exercise test (Fig. 6.3a). In contrast, ammonia levels are typically higher than those recorded in normal subjects, probably due to increased deamination of AMP [25]. Although, the forearm exercise test is capable of identifying the vast majority of patients with myophosphorylase deficiency, it can yield low-normal elevation of lactate in rare patients with milder phenotypes of this disorder [26, 27]. Biochemical assay of myophosphorylase levels in muscle tissue or genetic testing for mutations in the myophosphorylase gene is required for definitive diagnosis.

Table 6.3 Forearm exercise test findings in metabolic myopathies

Disorder	Forearm exercise test findings[a]
Glycogenosis[a]	
Myophosphorylase deficiency (glycogenosis V, McArdle's disease) (see Fig. 6.3a)	No rise in lactate in complete absence of the enzyme Possible normal rise in partial deficiency Possible exaggerated rise in ammonia
Phosphofructokinase deficiency (glycogenosis VII, Tarui's disease)	No or little rise in lactate
Phosphorylase kinase deficiency (glycogenosis VIII)	Normal rise in lactate
Phosphoglycerate kinase deficiency (glycogenosis IX)	No or little rise in lactate
Phosphoglycerate mutase deficiency (glycogenosis X)	Attenuated rise in lactate
Lactate dehydrogenase (glycogenosis XI)	No rise in lactate and marked increase in pyruvate
Acid maltase deficiency (glycogenosis II)	Normal rise in lactate
Debrancher deficiency (glycogenosis III, Cori-Forbes disease)	No or little rise in lactate
Brancher deficiency (glycogenosis IV, Andersen's disease)	Normal rise of lactate
Phosphoglucomutase deficiency (glycogenosis XIV)	Normal rise in lactate
Glycogen synthase deficiency (glycogenosis 0)	No rise in lactate
Beta-enolase deficiency	No rise in lactate
Other metabolic myopathies	
Lactate transporter defect	Normal rise in lactate with prolonged delay in return to baseline
Myoadenylate deaminase deficiency (see Fig. 6.3b)	No rise in ammonia (and hypoxanthine) with normal lactate rise
Carnitine palmitoyltransferase II deficiency (see Fig. 6.3c)	Normal lactate rise with possible exaggerated increase in ammonia

[a]All glycogenoses result in normal rise of ammonia

Phosphofructokinase Deficiency

Phosphofructokinase deficiency (glycogenosis type VII; Tarui's disease) results in failure of a key regulatory step in glycolysis, the conversion of fructose-6-phosphate to fructose-1, 6-diphosphate. Lack of functioning phosphofructokinase impedes glycolysis and typically prevents an elevation in lactate, a finding identical to that of myophosphorylase deficiency [28, 29]. However, an otherwise classic case of phosphofructokinase deficiency with reproducible elevation of serum lactate 2.5 times above baseline during forearm exercise test has been reported [30]. An adult-onset variant of phosphofructokinase deficiency exists, demonstrating

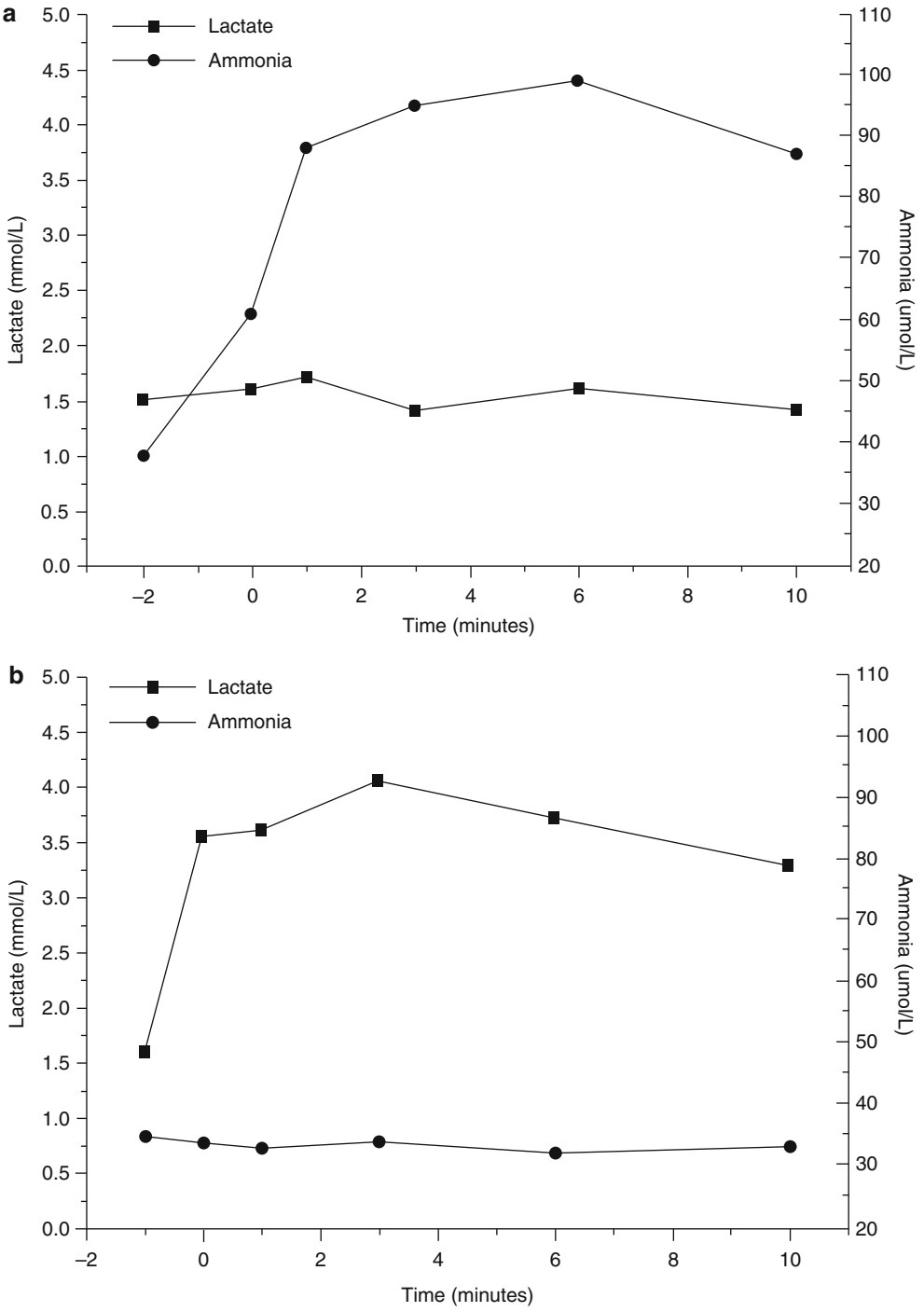
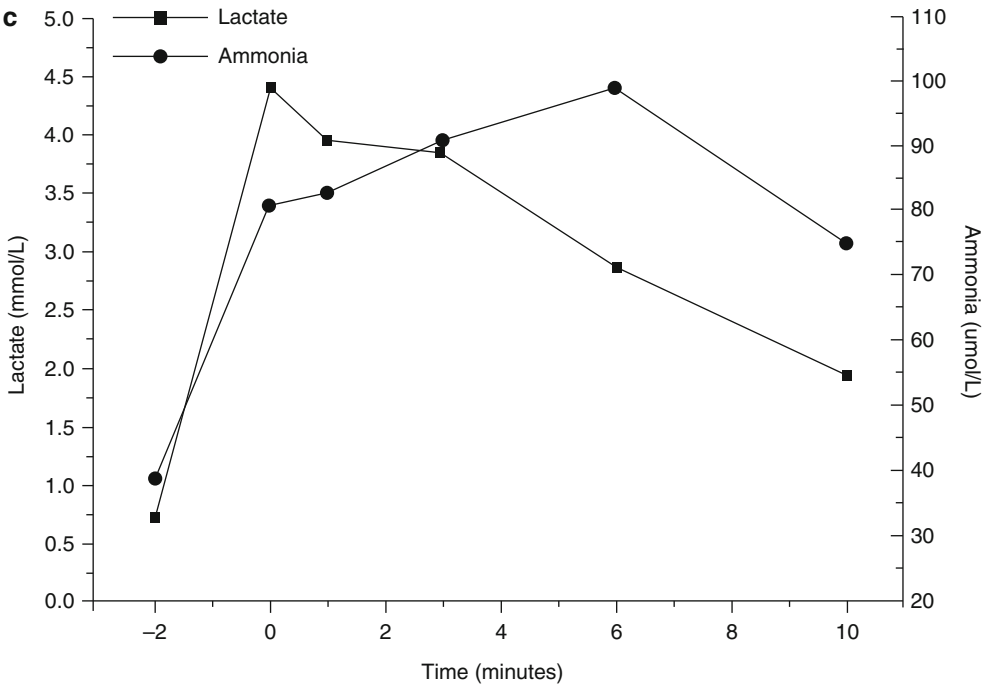


Fig. 6.3 (**a**) The forearm exercise test in a 10-year-old boy with exercise intolerance and cramps. Note the flat lactate curve (no rise) with normal elevation of ammonia. Subsequent investigations confirmed McArdle's disease. (**b**) The forearm exercise test in a 35-year-old woman with myalgia, fatigue, and elevated creatine kinase. Note the flat ammonia and normal lactate curve. Immunostaining and biochemical analysis confirmed myoadenylate deaminase deficiency. (**c**) The forearm exercise test in a 12-year-old girl with repeated episodes of myoglobinuria after strenuous exercise. Note the normal rise in lactate and ammonia after exercise. Subsequent investigations revealed CPT II deficiency

Fig. 6.3 (continued)



progressive proximal muscle weakness. The lactate response to forearm exercise test is typically flat in these patients, though one case showed a 2.6-fold rise in lactate [31–33].

Phosphorylase Kinase Deficiency

Phosphorylase kinase deficiency (glycogenosis type VIII) impairs glycogen breakdown by preventing phosphorylation, and thereby activation, of myophosphorylase. Since the biochemical defect affects the function of myophosphorylase, one might expect little or no rise in lactate during exercise. The forearm exercise test data, however, are typically normal, indicating preserved anaerobic glycogenolysis [34, 35]. This paradox may be explained by recent findings indicating that metabolites such as AMP, IMP, and inorganic phosphate are the major activators of myophosphorylase during anaerobic exercise [36, 37]. In contrast, during aerobic exercise, phosphorylase kinase plays the major role in activating myophosphorylase.

Phosphoglycerate Kinase Deficiency

Phosphoglycerate kinase deficiency (glycogenosis type IX) results in little or no rise in lactate level following exercise [38–42]. Phosphoglycerate kinase catalyzes the transfer of the acylphosphate group of 1,3-diphosphoglycerate to ADP with formation of 3-phosphoglycerate and ATP.

Phosphoglycerate Mutase Deficiency

Phosphoglycerate mutase deficiency (glycogenosis type X) prevents the interconversion of 2-phosphoglycerate and 3-phosphoglycerate. The forearm exercise test usually yields a mild but definite rise in lactate level of 1.3–3 times baseline [43–47]. Although this response is less than the four- to six-fold rise in lactate seen in normal subjects, it is distinct from the essentially flat response seen in patients with myophosphorylase, phosphofructokinase, or phosphoglycerate kinase deficiencies. A single case of phosphoglycerate mutase deficiency with a rise in serum lactate of five times baseline has been reported [48]. A symptomatic heterozygous carrier of a phosphoglycerate mutase gene mutation also had normal forearm exercise test results [49].

Phosphoglucomutase Deficiency

Phosphoglucomutase deficiency (glycogenosis type XIV) prevents conversion of glucose-1-phosphate to glucose-6-phosphate. In a single case report, forearm exercise test showed a normal fivefold increase in lactate coupled with an eightfold rise in ammonia [50].

Glycogen Synthase Deficiency

Glycogen synthase deficiency (glycogenosis type 0) prevents the addition of glucose monomers to the growing glycogen chain. There is profound depletion of glycogen within muscle fibers. Forearm exercise test showed no elevation of lactate in a single patient; ammonia levels were not reported [51].

Beta-Enolase Deficiency

Beta-enolase deficiency prevents the conversion of 2-phosphoglycerate to phosphoenolpyruvate in skeletal muscle. In a single case report, forearm exercise test showed no increase in lactate; ammonia levels were not reported [52].

Lactate Dehydrogenase Deficiency

Lactate dehydrogenase (LDH) deficiency (glycogenosis type XI) blocks the final step in the glycolytic pathway, the conversion of pyruvate to lactate with NADH as a cofactor. Since pyruvate cannot be further metabolized during ischemia, the forearm exercise test fails to show the usual rise in venous lactate level and also shows a marked increase in pyruvate. This is a unique feature of LDH deficiency [53–56].

Acid Maltase Deficiency

Acid maltase deficiency (acid alpha-glucosidase deficiency, glycogenosis type II) causes two major syndromes: a severe, often lethal disease of infancy (Pompe's disease) and a slowly progressive proximal myopathy presenting in juveniles and adults [57]. Respiratory muscle weakness is the initial feature in 30 % of cases. Acid maltase is a lysosomal enzyme with glucosidase activity, capable of digesting glycogen completely to glucose. The forearm exercise test in the adult form of acid maltase deficiency shows a normal rise in venous lactate, indicating that phosphorolytic breakdown of glycogen and glycolysis is able to proceed normally [58].

Debrancher Deficiency

Debrancher deficiency (glycogenosis type III; Cori-Forbes disease) produces little or no rise in lactate level during the forearm exercise test [59, 60]. The debrancher enzyme releases glucose from glycogen.

Brancher Deficiency

Brancher deficiency (glycogenosis type IV; Andersen's disease) effect on forearm exercise test is limited. The brancher enzyme catalyzes the last step in glycogen synthesis by adding short glucosyl chains to linear peripheral chains of nascent glycogen. Its deficiency causes accumulation of abnormal glycogen known as polyglucosan, which can cause myopathy as well as central and peripheral nervous system dysfunction. In three patients with brancher deficiency presenting as myopathy, the forearm exercise test showed a normal rise in lactate level [61–63].

Lactate Transporter Defect

Lactate transporter defect also affects the forearm exercise test. Lactate transporter, a protein found in skeletal muscle and erythrocytes, facilitates movement of lactate across cell membranes. In a single patient with a lactate transporter defect, forearm exercise test produced a normal rise in serum lactate. However, the lactate level failed to decline over the subsequent 6 min postexercise [64]. Of note, other patients have been diagnosed with deficient lactate transport based on an erythrocyte lactate transporter assay. Forearm exercise testing in these patients has not shown prolonged elevation of venous lactate [65].

Myoadenylate Deaminase Deficiency

Myoadenylate deaminase deficiency (MADD) is a disorder of purine metabolism. Myoadenylate deaminase, an enzyme found only in skeletal muscle, catalyzes the deamination of AMP, yielding IMP and an ammonia molecule (Fig. 6.2). The forearm exercise test in MADD patients produces a normal increase of venous lactate but no rise in ammonia, hypoxanthine, or other ATP degradation products (Fig. 6.3b) [66, 67]. When enzymatic testing for myoadenylate deaminase and *AMPD1* genetic mutation analyses are used as gold standards, the sensitivity of the forearm exercise test for MADD is 100 %, but the specificity is 37 % [14]. Submaximal exercise performance due to weakness, pain, or poor effort commonly causes a failure of serum ammonia to rise. False-positive forearm exercise testing results have also been reported in patients heterozygous for the common C34T *AMPD1* mutation [14]. An increase in serum lactate but not ammonia has been reported in a patient with "exertional myalgia syndrome" who had normal MADD activity in a muscle biopsy specimen [68]. Measurement of hypoxanthine and other ATP degradation products (IMP and inosine) reportedly increases the specificity of forearm exercise test for MADD, but is not usually performed in the clinical setting [67, 69, 70]

Carnitine Palmitoyltransferase

Carnitine palmitoyltransferase (CPT) deficiency is a disorder of lipid metabolism. Two genetically distinct enzymes make up the CPT system: CPT I and CPT II. CPT II, located on the inner mitochondrial membrane, mediates transport of long-chain fatty acids into the mitochondrial matrix where beta-oxidation occurs. In patients with CPT II deficiency, the forearm exercise test produces a normal rise in lactate but an exaggerated elevation of ammonia (Fig. 6.3c) [71, 72].

Forearm Exercise Test Complications

There are case reports of rhabdomyolysis and compartment syndrome developing after ischemia in patients with myophosphorylase deficiency. Meinck et al. reported a 57-year-old man with late-onset myophosphorylase deficiency who developed a 20-min-long contracture of the right forearm during forearm exercise test [73]. He subsequently developed myoglobinuria and marked elevation of serum creatine kinase. A whole-body nuclear medicine scan showed uptake of 99Tc methylene diphosphonate restricted to the musculature of the right forearm, and a diagnosis was made of focal rhabdomyolysis. The patient recovered following oral hydration. Lindner et al. described a 22-year-old woman with myophosphorylase deficiency who developed a 10-min-long contracture of the left forearm during forearm exercise test [74]. Six hours after the test, the patient was suffering severe

pain in the forearm and had hypoesthesia in the distribution of the ulnar nerve. A decompressive fasciotomy was performed for acute compartment syndrome of the forearm, after which pain and cutaneous sensation improved dramatically. The authors speculate that acute failure of energy production during forearm exercise test led to both muscle contracture and intracellular edema of muscle fibers, producing an increase in tissue pressure to a level that caused tamponade on blood flow.

Niepel et al. reported a 32-year-old man with brancher deficiency who had forearm compartment syndrome following forearm exercise test [75]. The patient completed 40 s of exercise without contracture, but had prolonged forearm pain and developed sensory loss in the distribution of the median nerve. Despite superficial and deep forearm fasciotomy, he was left with residual median sensory neuropathy.

There are no reports of forearm exercise test complications in subjects with normal carbohydrate metabolism, including those with myoadenylate deaminase deficiency or mitochondrial disorders.

Given the potential for complications, the forearm exercise test must be performed by an experienced physician in a setting where evaluation and treatment for rhabdomyolysis and compartment syndrome are available. Compartment syndrome is an orthopedic emergency in which the degree of recovery is determined by the rapidity of surgical decompression (see Chap. 37). The forearm exercise test should be immediately discontinued if a contracture develops. Any patient with prolonged pain or contracture should be closely observed. Development of sensory symptoms is an indication for surgical consultation.

Modified Forearm Exercise Tests

Concerns about discomfort, rhabdomyolysis, and compartment syndrome produced by the forearm exercise test have prompted modifications of the test. Hogrel et al. utilized isometric exercise for 30 s at 70 % of maximal voluntary contraction, without a sphygmomanometer cuff [5]. Although the authors describe their test as "nonischemic," this level of isometric contraction is probably sufficient to block blood flow [76]. Therefore, the main difference between this test and the standard forearm exercise test is the reduced duration of exercise. Of 7 patients with a glycogenosis (most with myophosphorylase deficiency), 4 could maintain the force target for only 15–25 s. However, no patient experienced prolonged pain or contracture, and all had a flat lactate curve with elevation of ammonia. A control group of 26 healthy volunteers showed a fourfold increase in lactate, but only a threefold increase in ammonia. Nevertheless, these results identified patient with a glycogenosis with 100 % sensitivity. Kazemi-Esfarjani et al. compared 10 patients with a glycogenosis and 9 healthy volunteers using a standard ischemic forearm exercise test and 3 modified, nonischemic, exercise tests [6]. Their ischemic test included repetitive squeezing of a dynamometer at 100 % of maximum voluntary contraction for one minute during blocked blood circulation. All patients, most of whom had myophosphorylase deficiency, experienced pain or cramps during the ischemic exercise test, but tolerated the modified forearm exercise test with minimal symptoms. A protocol identical to their ischemic forearm exercise test but without a cuff blocking circulation was as sensitive and specific as their ischemic test in distinguishing patients with glycogenoses from volunteers.

In summary, patients with myophosphorylase deficiency appear to experience less discomfort during various modifications than during the standard forearm exercise test. It remains to be seen whether serious complications such as rhabdomyolysis and compartment syndrome occur with a modified test. Since only one study has directly compared ischemic to nonischemic exercise tests, physicians contemplating the use of a modified exercise testing should consider performing a comparison using their own forearm exercise test protocol.

Performing forearm exercise test in children represents a significant challenge. Bruno et al. reported a modified forearm exercise test designed to be tolerable and safe for children [4]. Under their protocol, a sphygmomanometer cuff was inflated to, but not above, mean arterial pressure, and nonstandardized forearm exercise was performed for 1 min. Out of 25 patients 10 years of age or older, 23 were able to exercise adequately, and two were identified with a glycogenosis. No patients experienced painful cramps or contractures. Four out of 5 patients below the age of 10 failed to show a rise in either lactate or ammonia, suggesting inadequate effort. The authors concluded that their modified forearm exercise test was well tolerated and reliable in children ten or older.

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Clinical Electromyography (Nerve Conduction Studies and Needle Electromyography)

7

Barbara E. Shapiro, Bashar Katirji, and David C. Preston

Introduction

Nerve conduction studies (NCSs) and needle electromyography (EMG), often referred to collectively as electrodiagnostic (EDX) or EMG studies, play a pivotal role in the evaluation of patients with neuromuscular disorders. They are well suited to aid in the diagnosis of disorders of the peripheral nervous system, including those involving sensory nerves and the dorsal root ganglia, as well as those involving the motor unit, which includes the anterior horn cells, motor nerves, neuromuscular junctions, and muscles (Fig. 7.1). These studies may also provide useful diagnostic information in disorders of the central nervous system (e.g., tremor, upper motor neuron weakness).

EDX testing serves as an extension of the clinical neurologic examination. A directed history and a brief neurologic examination prior to the EDX studies guide the electromyographer in selecting the appropriate tests to reach the correct diagnosis. *Each EDX study must be individualized, based on the manifestations and differential diagnosis, and modified as the study progresses and further information is gained*. A meaningful EDX examination relies upon (1) choosing the correct studies, (2) obtaining accurate data, and (3) properly interpreting the data collected. If the interpretation is incorrect, then technically accurate data may be of little value. Each study is then properly interpreted within the clinical context. The same EDX data may have very different meanings in different clinical situations. For example, long-duration motor unit action potentials (MUAPs) with reduced recruitment in the proximal arm may indicate a chronic

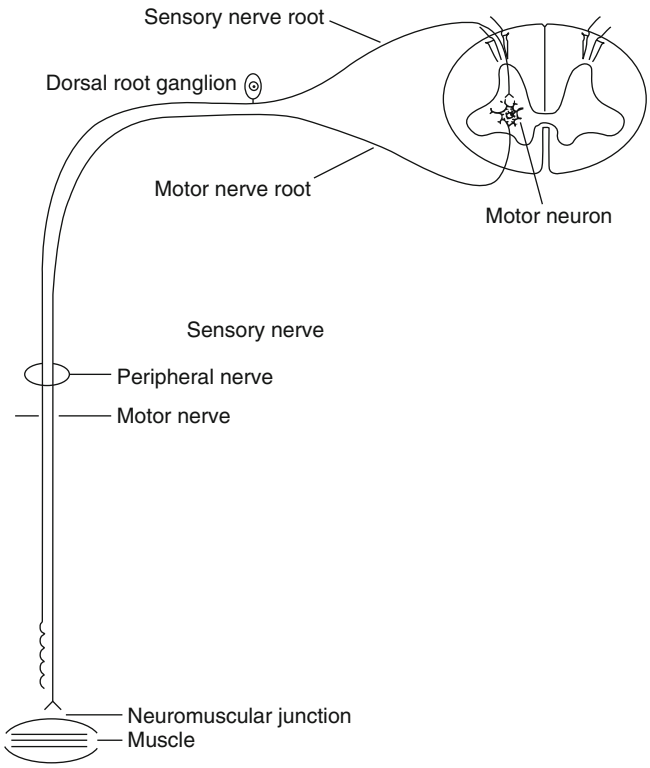

Fig. 7.1 Elements of the peripheral nervous system. Note that the primary motor neuron resides within in the spinal cord, whereas the primary sensory neuron, the dorsal root ganglion, lies outside of the spinal cord. The dorsal root ganglion is a bipolar cell. Its proximal process forms the sensory nerve root; the distal process becomes the peripheral sensory nerve (Reproduced with permission from Preston and Shapiro [1])

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Table 7.1 Goals of nerve conduction studies and EMG

Localization of the lesion
Nerve
Mononeuropathy
Mononeuritis multiplex
Polyneuropathy
Plexopathy
Radiculopathy, polyradiculopathy
Neuronopathy
Neuromuscular junction
Presynaptic
Postsynaptic
Muscle
Underlying nerve pathophysiology
Fiber type involved
Motor
Sensory
Motor and sensory
Pathology
Primary demyelination
Acquired
Inherited
Primary axonal loss
Assessment of severity
Correlation with clinical symptoms
Assessment of temporal course
Hyperacute
Acute
Subacute
Chronic

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radiculopathy, plexopathy, spinal muscular atrophy, or the effects of old poliomyelitis. Likewise, data that are not technically accurate may obscure an accurate diagnosis.

Basic Principles and Indications for Performing the Electrodiagnostic Examination

The primary goals of EDX studies are to localize the lesion, characterize the underlying nerve pathophysiology, quantitate the severity, and assess the temporal course of the disorder (Table 7.1). For example, in neurogenic lesions, the underlying primary pathophysiology, that of axonal loss or demyelination, can usually be determined. Once the pathophysiology is determined, one can then localize the lesion (based on the distribution of abnormalities) and assess its severity and time course. Although EDX findings may be distinctive as to suggest a precise etiology, in most cases the exact cause cannot be determined based on these studies alone.

In order to arrive at a final EDX, one must first recognize the pattern of abnormalities on NCSs (motor, sensory, and late responses), repetitive nerve stimulation (slow and rapid rate), and needle EMG (insertional and spontaneous activity and MUAP morphology, recruitment, and activation). The pattern of EDX findings usually marks the underlying disorder as neuropathic, myopathic, secondary to a neuromuscular junction (NMJ) disorder, or consistent with a disorder of the central nervous system. The final diagnosis can only be determined when the overall pattern of EDX findings is analyzed and interpreted in the context of the clinical history and examination.

The EDX Evaluation Localizes the Lesion or Disorder

EDX studies often help localize the disorder precisely, a task which is not always possible clinically. For example, in a patient with hand weakness and numbness of the fourth and fifth fingers, the EDX examination helps in the differential diagnosis which includes a lesion of the ulnar nerve, the lower trunk of the brachial plexus, or the C8–T1 spinal nerve roots. More important, the study may demonstrate an ulnar neuropathy across the elbow, a condition only caused by few disorders (e.g., cubital tunnel syndrome, compression at the ulnar groove). Similarly, a patient with proximal weakness may have a motor neuron disorder (e.g., spinal muscular atrophy), a neuromuscular junction disorder (e.g., Lambert-Eaton myasthenic syndrome – LEMS), or a muscle disorder (e.g., polymyositis). EDX studies can readily discriminate between these disorders, thereby providing important information to guide the subsequent evaluation and treatment.

The EDX Evaluation Often Characterizes the Underlying Pathophysiology

EDX studies can often determine the primary pathological process. For example, in a patient with peripheral polyneuropathy, findings on NCSs often narrow the differential diagnosis by defining the involved fiber types (motor, sensory, or both) and the underlying pathophysiology (axon loss or segmental demyelination). While sensorimotor polyneuropathies are common and subsume a fairly large differential diagnosis, predominantly motor or sensory polyneuropathies are rare and have a limited number of causes. The determination of whether the pathology is primary demyelination or axonal loss has important implications for both diagnosis and prognosis. While most peripheral polyneuropathies are associated with primary axonal degeneration, the causes of demyelinating polyneuropathies are few, limiting the differential diagnosis. Finally, if the EDX findings are characteristic of an acquired demyelinating polyneuropathy, this group of disorders is often potentially treatable and may have a good prognosis.

The EDX Evaluation Is Useful in Quantitating the Severity of Illness and Assessing Its Prognosis

The EDX examination is useful in assessing the degree of axonal loss versus demyelination in peripheral nerve disorders. This has implications for severity and prognosis. After a demyelinating injury, a nerve can often remyelinate in a short time, usually within weeks. However, if significant axonal loss occurs, the prognosis is considerably more guarded. Axonal regrowth is limited by the rate of slow axonal transport, which is approximately a millimeter a day. For example, a patient with a 50 % axonal loss lesion of the peroneal nerve has a much graver prognosis and a longer rehabilitation time than a patient with a demyelinating lesion causing a 50 % conduction block at the same location.

The EDX Evaluation Is Useful in Assessing the Temporal Course, Stage, and Rate of Progression of the Disorder

This is especially pertinent in disorders of peripheral nerve, where there is an orderly, temporal progression of abnormalities that occurs on NCSs and needle EMG. This allows differentiation between hyperacute (<1 week), acute (< few weeks), subacute (weeks to a few months), and chronic (> few months) lesions. The electromyographer must therefore be aware of the patient's clinical time course in order to accurately interpret any electrophysiologic abnormalities, or lack thereof.

The EDX Studies Must Be Planned According to the Clinical Context

Every EDX evaluation should begin with a brief history and directed physical examination. The duration, type, and distribution of symptoms, along with the neurologic findings, help determine the differential diagnosis. This information is essential in planning the EDX studies. The electromyographer must decide which nerves and muscles to study and whether specialized tests such as repetitive nerve stimulation are indicated. The study is often amended as the testing proceeds. For example, in a patient with intermittent double vision, dysphagia, and proximal weakness, the differential diagnosis may include disorders of the neuromuscular junction, muscle, anterior horn cell, or motor nerve. EDX studies in this patient should include repetitive nerve stimulation and needle EMG of at least two limbs. In contrast, the differential diagnosis of a patient with occasional neck pain and numbness of their fourth and fifth fingers includes an ulnar neuropathy, lower trunk brachial plexus lesion, or cervical radiculopathy. EDX studies may include ulnar sensory and motor NCSs, preferably in both upper extremities, along with needle EMG of muscles in multiple upper limb myotomes including the C8/T1 myotome.

The EDX Evaluation Should Maintain a Proper Balance Between Collecting the Data Necessary to Answer the Clinical Question and Minimizing Patient Discomfort

After explaining the test to the patient in simple terms to reduce anxiety, NCSs are performed followed by the needle EMG. Sufficient nerve conduction studies and needle EMG can usually be performed within one to one and a half hours in order to arrive at an accurate electrophysiologic diagnosis. If specialized tests, such as repetitive nerve stimulation, quantitative motor unit analysis, or single-fiber EMG, must be performed, a longer study may be necessary. In children, agitated or demented patients, or when there is any question whether a patient will tolerate the entire examination, the electromyographer should begin the study with the area of most interest. For instance, in a patient with numbness and tingling of the second and third fingers, the median motor and sensory studies should be done first. Likewise, needle EMG of the median innervated muscles as well as C6–C7, non-median innervated muscles (e.g., the triceps) are of greatest interest in such a patient. By planning ahead and considering which NCSs should be performed first and which muscles should be sampled on needle EMG, an accurate diagnosis may be reached in most patients, even when only a few NCSs are performed or muscles are examined.

EDX studies rely on meticulous attention to technical details, while keeping in mind the larger picture of why the study is being performed. As more data is obtained, the study must be analyzed and the test altered as needed. Analysis of results in real time gives the electromyographer the opportunity to modify one's strategy as the test proceeds.

The EDX Studies May Identify Minor Abnormalities That May Suggest Subclinical Disease or May Be Irrelevant

EDX tests are very sensitive; occasionally, one may detect mild abnormalities that are subclinical or insignificant. Subclinical disease that is below the threshold for clinical identification may be easily detected during the EDX evaluation. Examples include asymptomatic median mononeuropathy at the wrist, myotonic discharges in asymptomatic carriers of a myotonic dystrophy gene mutation, and NCS slowing in asymptomatic relatives of patients with Charcot-Marie-Tooth disease.

Clinically insignificant findings occur partly because of the wide range of normal values, which vary with the nerve and muscle being tested, and the numerous physiological and nonphysiological factors that affect NCSs and needle EMG (see below). Making a diagnosis based on minor EDX abnormalities that do not correlate with the clinical manifestations may be hazardous. Examples include isolated denervation of the extensor digitorum brevis; fasciculation potentials and long-duration, high-amplitude MUAPs in the intrinsic foot muscles; and complex repetitive discharges in the iliacus muscle that may be of no clinical importance [2].

An unexpected abnormal finding on NCSs or needle EMG, which does not fit the clinical examination, should always raise the possibility of a technical problem. Accurate EDX studies depend on properly functioning equipment (i.e., EMG machine, electrodes, and stimulator) and an experienced EDX technologist and electromyographer. One clue to determining that an abnormality is due to technical problems is the lack of clinical-electrophysiologic correlation.

There are times when the clinical diagnosis or EDX findings are not clear and a definite diagnosis cannot be reached. Occasionally, nerve conduction studies or needle EMG is abnormal, yet a precise diagnosis cannot be determined. For example, in a patient with a tardy ulnar palsy due to remote trauma to the elbow, EDX studies may demonstrate an axon-loss ulnar mononeuropathy without localizing features (i.e., conduction block or focal slowing across the elbow). While the referring physician usually wants to know if the lesion is at the elbow, and is sometimes confident that it is, often the only correct impression the electromyographer can give is one of a nonlocalizable ulnar mononeuropathy which is at or proximal to the most proximal abnormal ulnar innervated muscle as determined by needle EMG.

One can usually be certain of a diagnosis only when the clinical findings, NCSs, and needle EMG abnormalities all correlate well. If all three fit together, the diagnosis is secure. However, if the NCSs and needle EMG do not fit together and, more importantly, if they do not correlate with the clinical findings, one should strongly question the significance of the EDX abnormalities. The electromyographer must understand the limitations of EMG, keep technical factors well controlled, and establish a good differential diagnosis before beginning the study. Otherwise, the study may do a disservice to the patient and to the referring physician by potentially leading one astray with minor, irrelevant, or technical abnormalities. However, by keeping these general principles of EMG in mind, EDX studies are usually of great help to the referring clinician and the patient with a neuromuscular disorder.

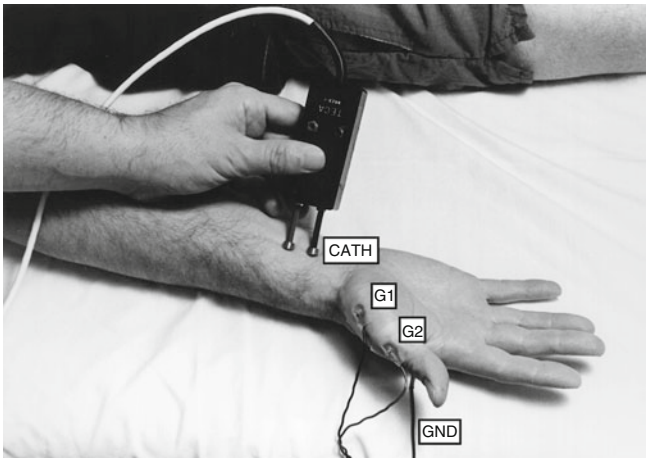


Fig. 7.2 Motor conduction study setup. Median motor study, recording the abductor pollicis brevis muscle, stimulating the median nerve at the wrist. In motor studies, the "belly-tendon" method is used for recording. The active recording electrode (*G1*) is placed on the center of the muscle, with the reference electrode (*G2*) placed distally over the tendon (*CATH* cathode, *GND* ground) (Reproduced with permission from Preston and Shapiro [1])

Methodology

Nerve Conduction Studies (NCS)

Motor Nerve Conduction Studies

Motor NCSs are technically less demanding than sensory and mixed nerve studies. Motor responses are typically in the range of several millivolts (mV), while sensory and mixed nerve responses are in the range of microvolts (μV). Thus, motor responses are less affected by external noise and other technical factors (see section "Factors Affecting Nerve Conduction Studies and Needle Electromyography").

Motor NCSs are usually obtained by percutaneous (surface) stimulation of a mixed peripheral nerve while recording from a muscle innervated by the same nerve. Recording electrodes are placed over the muscle of interest, using the belly-tendon montage (i.e., the active recording electrode (G1) is placed on the center of the muscle belly, which usually correlates with the motor end plate, and the reference electrode (G2) placed distally, over the tendon to the muscle) (Fig. 7.2). The stimulator is then placed over the nerve to the muscle, with the cathode closest to the recording electrode. To perform motor conduction studies, the gain is usually set at 2–5 mV/div. The duration of the electrical pulse is usually set to 200 μs. The current is slowly increased, usually by 5–10 milliampere (mA) increments. This generates nerve action potentials in increasing numbers of underlying fibers, which in turn result in more activated muscle fiber action potentials. When the current is increased to the point that the motor response no longer increases in size, one presumes

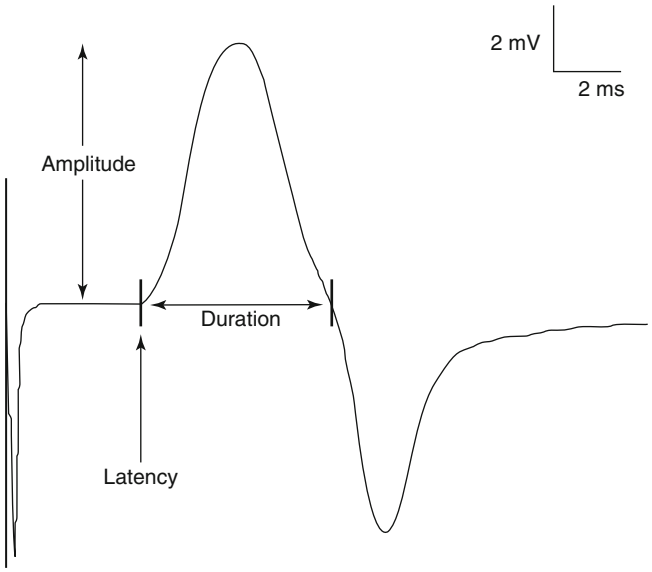


Fig. 7.3 Compound muscle action potential (CMAP). The CMAP represents the summation of all the underlying muscle fiber action potentials. With recording electrodes properly placed, the CMAP is a biphasic potential with an initial negative deflection. Latency is the time from the stimulus to the initial negative deflection from baseline. Amplitude is most commonly measured from baseline to negative peak, but can also be measured peak to peak. Duration is measured from the initial deflection from baseline to the first baseline crossing (i.e., negative-peak duration). In addition, negative CMAP area (i.e., the area *above* the baseline) is calculated by most modern computerized EMG machines. Latency reflects only the fastest conducting motor fibers. All fibers contribute to amplitude and area. Duration is primarily a measure of synchrony (Reproduced with permission from Preston and Shapiro [1])

that all nerve fibers are stimulated. The current is then increased by another 20 % to ensure *supramaximal stimulation*. Most nerves require a current flow in the range of 20–50 mA to achieve supramaximal stimulation. Deeply seated nerves, diseased nerves, and nerves in obese patients may require higher stimulus intensity or duration.

The recorded potential with supramaximal stimulation is known as the *compound muscle action potential* (*CMAP*), sometimes referred to as the motor response or the M (for motor) wave. It results from the sum of all the synchronously activated muscle fiber action potentials generated through all the axons destined to the recorded muscle. The CMAP is an indirect measurement of the number of axons that conduct between the stimulating and recording points.

If the recording electrodes are properly placed with G1 over the motor end plate, the CMAP is a biphasic potential with an initial negativity (i.e., an upward deflection from the baseline). For each stimulation site, the latency, amplitude, duration, and area of the CMAP are measured (Fig. 7.3). A motor conduction velocity can be calculated after two sites, one distal and one proximal, are stimulated.

Amplitude

CMAP amplitude may be measured from baseline to first negative peak or, less commonly, from the first negative peak to the next positive peak. CMAP amplitude (and area) reflects the number and size of muscle fibers that ultimately fire. Low CMAP amplitude following distal nerve stimulation most often results from loss of motor axons or neurons. Less often, it is due to a conduction block (i.e., demyelination located between the distal stimulation site and recorded muscle), a neuromuscular junction (NMJ) disorder, or a myopathy.

Area

CMAP area is also conventionally measured between the baseline and negative peak (negative-phase area). Less often, the total area (negative- and positive-phase areas) may be calculated. Although area cannot be manually determined, this calculation is readily performed by most modern computerized EMG equipment. CMAP area also reflects the number of muscle fibers in the CMAP. Differences in CMAP area between distal and proximal stimulation sites assume special significance in the determination of conduction block from a demyelinating lesion (see section "Electrophysiologic Findings in Neuromuscular Disorders").

Duration

CMAP duration is usually measured from the initial deflection from baseline to the first baseline crossing (i.e., negative-peak duration), but less commonly calculated from the initial to the terminal deflection back to baseline (total duration). The latter may be less accurate because the CMAP returns to baseline very slowly and its terminal point may be imprecisely marked. CMAP duration is primarily a measure of synchrony (i.e., the extent to which each of the individual muscle fibers fire at the same time). Duration characteristically increases in conditions which result in selective slowing of some motor fibers (e.g., in a demyelinating lesion).

Latency

The latency is the time from the stimulus to the initial CMAP deflection from baseline. Latency includes three separate times: (1) nerve conduction time from the stimulus site to the NMJ, (2) the time delay across the NMJ, and (3) the depolarization time across the muscle fibers. Latency measurements are usually in milliseconds (ms). Distal latencies are often the only reported latency because measurements of latencies from proximal stimulation sites are often incorporated in conduction velocity calculations (see section Conduction Velocity).

Conduction Velocity

Motor conduction velocity is a measure of the speed of the fastest conducting motor axons, which is calculated by dividing the distance traveled by the nerve conduction time.

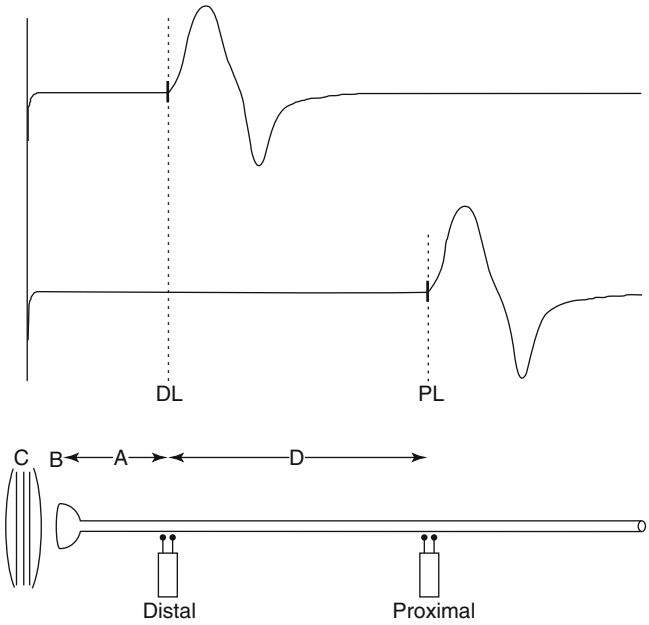


Fig. 7.4 Motor conduction velocity calculation. *Top figure*: Median motor study, recording abductor pollicis brevis, stimulating wrist and elbow (*DL* distal motor latency, *PL* proximal motor latency). The only difference between distal and proximal stimulations is the latency, with the proximal latency being longer than the distal. *Bottom figure*: DL represents three separate times: the nerve conduction time from the distal stimulation site to the NMJ (*A*), the NMJ transmission time (*B*), and the muscle depolarization time (*C*). Accordingly, DL cannot be used alone to calculate a motor conduction velocity. Two stimulations are necessary. The PL includes the distal nerve conduction time (A), the NMJ time (B), and the muscle depolarization time (C), as well as the nerve conduction time between the proximal and distal stimulation sites (*D*). If the distal latency (A + B + C) is subtracted from the proximal latency (A + B + C + D), only the nerve conduction time between the distal and proximal stimulation sites (D) remains. The distance between those two sites can be measured, and a conduction velocity can be calculated (distance/time). Conduction velocity reflects only the fastest fibers (Reproduced with permission from Preston and Shapiro [1])

However, motor conduction velocity cannot be calculated by performing a single stimulation. Motor latencies include nerve conduction time, NMJ transmission, and muscle depolarization time. Thus, to calculate a motor conduction velocity, without including NMJ transmission and muscle depolarization times, two stimulation sites must be used: one distal and one proximal. When the distal latency is subtracted from the proximal latency, then only the nerve conduction time between the proximal and distal stimulation sites remains (Fig. 7.4). The distance between these two sites can then be approximated by measuring the surface distance with a tape measure in millimeters. Thus, conduction velocity (CV) is usually measured in meters per second (m/s) and is calculated as follows:

$$\mathrm{CV}\left(\mathrm{m/s}\right)=\frac{\mathrm{Distance}\left(\mathrm{mm}\right)}{\mathrm{Proximal\ latency}-\mathrm{distal\ latency}\left(\mathrm{ms}\right)}$$

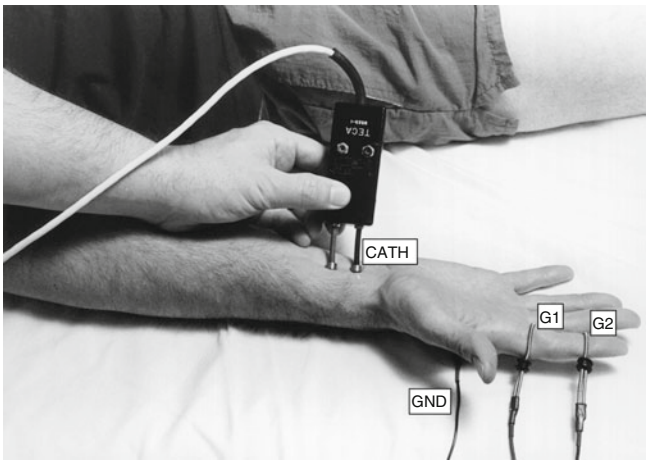


Fig. 7.5 Sensory conduction study setup. Median sensory study, antidromic technique. Ring electrodes are placed over the index finger, 3–4 cm apart. The active recording electrode (*G1*) is placed more proximally, closest to the stimulator. Although the entire median nerve is stimulated at the wrist, only the cutaneous sensory fibers are recorded over the finger (*CATH* cathode, *GND* ground) (Reproduced with permission from Preston and Shapiro [1])

It is important to note that the latencies and conduction velocity reflect only the fastest conducting fibers. Action potentials of these nerve fibers reach the muscle first and determine the onset of the CMAP. The slower conducting motor fibers participate in the CMAP area and amplitude, but are not reflected in the measurements of either the latencies or conduction velocity.

Sensory Nerve Conduction Studies

In contrast to motor NCSs where the CMAP reflects conduction along motor nerve, NMJ and muscle fibers, sensory NCSs are true nerve action potentials and only measure sensory nerve fibers. Because *sensory nerve action potentials* (*SNAPs*) are much smaller than the CMAP (usually in the range of 1–50 μV), technical factors and external noise assume greater importance. At times, signal averaging is utilized, particularly when the SNAP is small or partially contaminated by baseline noise. To perform sensory NCSs, the gain is usually set at 10–20 μV/div. Ring electrodes around the fingers and 5 mm disk electrodes are common recording electrodes (Fig. 7.5). A pair of recording electrodes (G1 and G2) is placed in line over the nerve, at an interelectrode distance of 3–4 cm, with the active electrode (G1) placed closest to the stimulator. Sensory fibers usually have a lower threshold to stimulation than motor fibers with most nerves requiring a current in the range of 5–30 mA to achieve supramaximal stimulation. For sensory studies, an electrical pulse of either 100 or 200 μs in duration is used. Similar to motor studies, the current is slowly increased, usually by smaller (3–5 mA) increments, until the recorded SNAP is supramaximal.

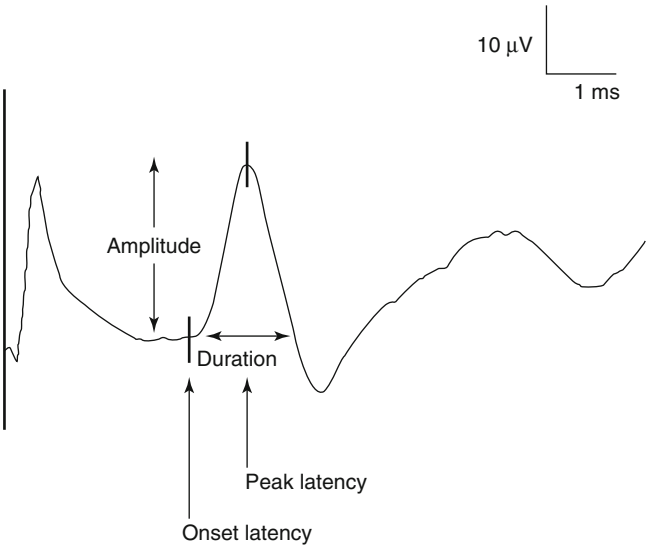


Fig. 7.6 Sensory nerve action potential (SNAP). The SNAP represents the summation of all the underlying sensory fiber action potentials. The SNAP is usually biphasic or triphasic in configuration. Onset latency is measured from the stimulus to the initial negative deflection for biphasic SNAPs (as above) or to the initial positive peak for triphasic SNAPs. Onset latency represents nerve conduction time from the stimulus site to the recording electrodes for the largest cutaneous sensory fibers. Peak latency is measured at the midpoint of the first negative peak. Amplitude is most commonly measured from baseline to negative peak, but can also be measured from peak to peak. Duration is measured from the initial deflection from baseline to the first baseline crossing (i.e., negative-peak duration). Only one stimulation site is required to calculate a sensory conduction velocity, as sensory onset latency represents only nerve conduction time (Reproduced with permission from Preston and Shapiro [1])

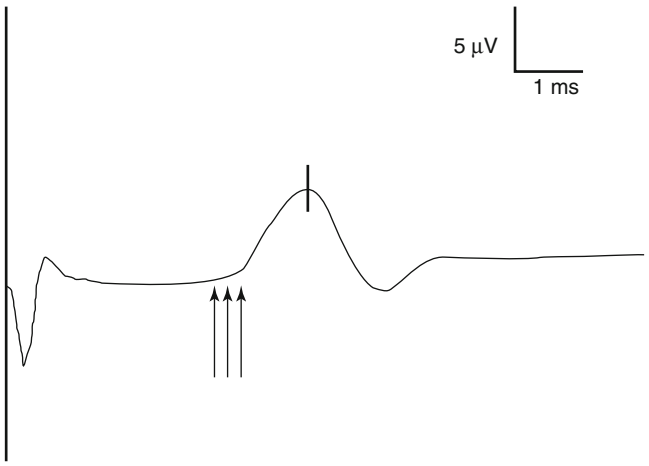


Fig. 7.7 SNAP onset and peak latencies. Onset and peak latency measurements each have their own advantages and disadvantages. Onset latency represents the fastest conducting fibers and can be used to calculate a conduction velocity. However, for many potentials, especially small ones, it is difficult to precisely place the latency marker on the initial deflection from baseline (*arrows*: possible onset latencies). Marking the peak latency is straightforward, with nearly no inter-examiner variation. However, the population of fibers represented by peak latency is unknown; it cannot be used to calculate a conduction velocity (Reproduced with permission from Preston and Shapiro [1])

The SNAP is a compound potential that represents the summation of all the individual sensory fiber action potentials. SNAPs are usually biphasic or triphasic potentials. For each stimulation site, the onset latency, peak latency, duration, and amplitude are measured (Fig. 7.6). In contrast to motor studies, a sensory conduction velocity may be calculated with just one stimulation site, because there is no transmission along NMJ or muscle fibers. In general, the SNAPs are more sensitive than the CMAPs to focal and generalized neuropathies and may occasionally provide evidence of subclinical neuropathy.

Amplitude

SNAP amplitude is often measured from baseline to negative peak, but can also be measured from the first negative peak to the next positive peak. The SNAP amplitude reflects the number of sensory axons that depolarize and contribute to the potential. Low SNAP amplitude usually indicates loss of axons due to a disorder of the dorsal root ganglion or peripheral nerve, but may be due to technical factors, including limb edema, skin induration, or incorrect placement of the stimulating or recording electrodes.

Duration

Similar to CMAP duration, SNAP duration is usually measured from the onset of the potential to the first baseline crossing (i.e., negative-peak duration), but may also be measured from the initial to the terminal deflection back to baseline (total duration). The former is preferred as the terminal deflection returns to baseline very slowly and is difficult to mark precisely. Because the SNAP duration is typically much shorter than the CMAP duration (typically 1.5 ms for a SNAP duration vs. 5–6 ms for a CMAP duration), duration is useful in identifying a response as a sensory as opposed to a motor potential.

Onset Latency

The onset latency is the time from the stimulus to the initial negative deflection from baseline for biphasic SNAPs or to the initial positive peak for triphasic SNAPs. Sensory onset latency represents nerve conduction time of the largest cutaneous sensory fibers from the stimulus site to the recording electrodes. The onset latency is not uncommonly imprecise, particularly in small SNAPs or when associated with baseline noise or stimulus artifact (Fig. 7.7). However, it should be always used whenever one calculates conduction velocity of the fastest fibers.

Peak Latency

The peak latency is measured at the midpoint of the first negative peak. Although the population of sensory fibers represented by the peak latency is not known (in contrast to the

onset latency that represents the fastest conducting fibers), measurement of the peak latency is precise with minimal interindividual variation in its determination. Another potential advantage of using peak latency as opposed to onset latency in sensory and mixed nerve studies is that peak latency is not affected by changes in either sweep speed or sensitivity. Because of their accuracy, peak latencies are often used, except when calculating sensory conduction velocities.

Conduction Velocity

Unlike motor CV that requires two stimulation sites to calculate, sensory CV may be calculated with one stimulation site by dividing the distance traveled by the onset latency. Essentially, the distal conduction velocity and onset latency are the same measurements, differing only by a multiplication factor (i.e., the distance). Proximal CV requires a second and more proximal stimulation; it may be calculated by simply dividing the distance traveled by the proximal onset latency or in a manner similar to the motor CV (see above). However, proximal stimulations result in smaller-amplitude SNAPs, and are often more difficult to perform than distal sensory studies even in normal individuals, due to the normal processes of phase cancellation and temporal dispersion (see below). Similar to motor CV, sensory CV represents the speed of the fastest, myelinated cutaneous sensory fibers.

Mixed Nerve Conduction Studies

Mixed NCSs are similar to sensory studies. Both are compound nerve action potentials, with similar stimulation and recording techniques. However, for mixed NCSs, the potential reflects both motor and sensory fiber action potentials generated along the nerve. An advantage of mixed NCSs over routine sensory and motor NCSs is that these studies incorporate the IA afferent fibers which innervate the muscle spindles. These are the largest and fastest fibers of mixed nerves and are not recorded during routine motor or sensory NCSs. Hence, mixed nerve CVs are usually faster than either routine motor or sensory CVs. Furthermore, as the IA fibers have the largest diameter and, accordingly, the greatest amount of myelin, they are often the fibers earliest affected by demyelinating lesions, such as occurs in entrapment neuropathies.

Although any mixed nerve may be studied, the median, ulnar, and plantar nerves are most often selected during the electrodiagnosis of median mononeuropathy at the wrist, ulnar mononeuropathy at the elbow, and tibial mononeuropathy across the tarsal tunnel, respectively. To perform a mixed nerve conduction study, the settings are similar to those used in sensory conduction studies. The gain is usually set at 10–20 μV/div, as the responses are quite small (i.e., usually in the range of 5–100 μV). A pair of recording electrodes (G1 and G2) is placed in line over the mixed nerve, at an interelectrode distance of 3–4 cm, with the active electrode (G1) closest to the stimulator (Fig. 7.8). The recorded potential, the *Mixed Nerve Action Potential*, is a compound potential which represents the summation of all the individual sensory and motor fiber action potentials. It is usually a biphasic or triphasic potential. Onset latency, peak latency, duration, amplitude, and conduction velocity are measured in a fashion similar to the methods used for sensory conduction studies.

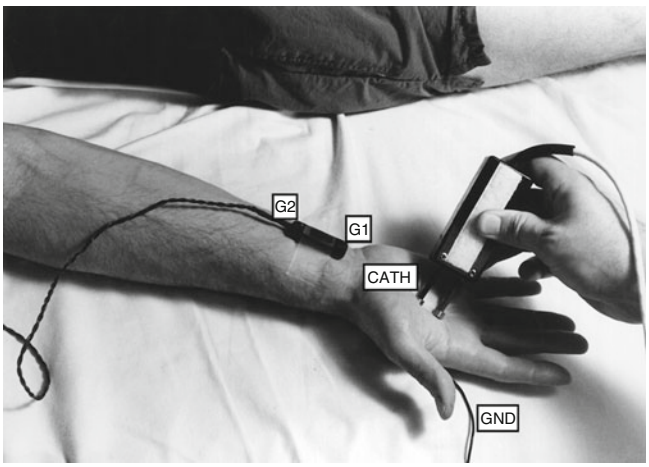


Fig. 7.8 Mixed nerve study setup. Median mixed study, stimulating median nerve in the palm, recording median nerve at the wrist. The active recording electrode (*G1*) faces the cathode (*CATH*) of the stimulator. Mixed studies stimulate and record all motor and sensory fibers, including the muscle afferents, the IA fibers, which are not recorded in either routine sensory or motor conduction studies (*GND* ground) (Reproduced with permission from Preston and Shapiro [1])

Special Considerations in Nerve Conduction Studies

Antidromic Versus Orthodromic Sensory Studies

When a nerve is depolarized, conduction occurs in both directions away from the stimulation site. Consequently, because SNAPs are true nerve action potentials, sensory NCSs may be performed either orthodromically or antidromically. By definition, antidromic sensory NCSs are performed by stimulating toward the sensory receptors and orthodromic studies are performed by stimulating away from the sensory receptors. For instance, when studying median sensory fibers to the index finger, the median nerve may be stimulated at the wrist and the SNAP recorded with ring electrodes over the index finger (antidromic study). Conversely, the same ring electrodes may be used for stimulation of the digital nerves of the index finger and the SNAP recorded over the median nerve at the wrist (orthodromic study).

Sensory latencies and conduction velocities are identical with either method (Fig. 7.9). However, the SNAP amplitude is generally higher in antidromic potentials, because it is directly proportional to the proximity of the recording

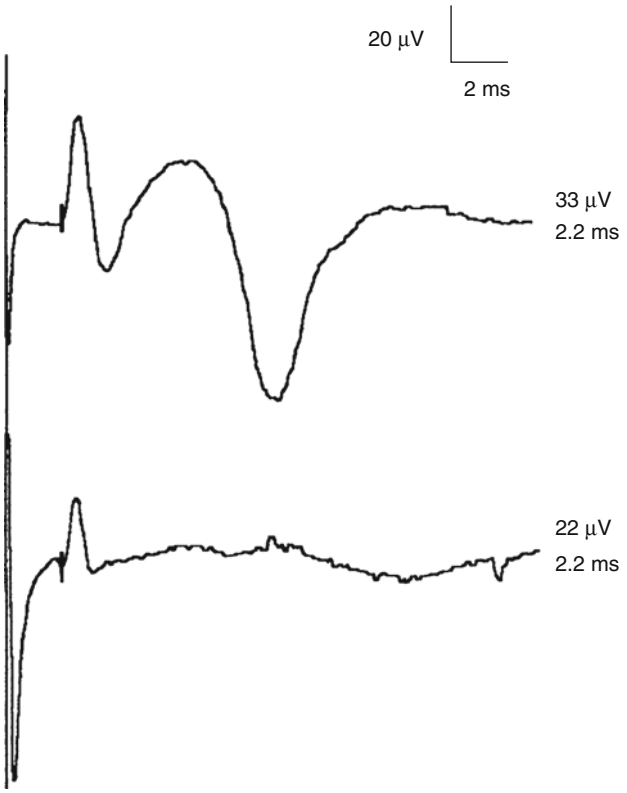


Fig. 7.9 Antidromic and orthodromic sensory studies. Median SNAPs. *Top trace*: antidromic study, stimulating wrist, recording index finger. *Bottom trace*: orthodromic study, stimulating index finger, recording wrist. Latencies and conduction velocities are identical for both. The antidromic method has the advantage of a higher-amplitude SNAP, but is followed by a large volume-conducted motor potential. If the SNAP is absent in an antidromic study, care must be taken not to confuse the volume-conducted motor potential as the sensory potential. Note the difference in duration between the SNAP and CMAP, which helps discriminate between the SNAP and the volume-conducted motor potential that follows (Reproduced with permission from Preston and Shapiro [1])

electrode to the nerve. For most antidromically conducted potentials, the recording electrodes are closer to the nerve than are orthodromic SNAPs. For example, with the antidromically conducted median SNAP, the recording ring electrodes are placed on the finger, very close to the underlying digital nerves from which the potential is recorded. When the montage is reversed for orthodromic recording, the long thick finger flexor tendons and other supporting connective tissues separate the nerve from the recording electrodes placed over the wrist. This results in relative attenuation of the SNAP amplitude. The major advantage of the antidromic technique is the higher SNAP amplitude obtained with antidromic recordings. Furthermore, because the antidromic potential is generally larger than the orthodromic potential, it is less subject to electrical noise or other artifacts. The antidromic technique is especially helpful when recording small SNAPs associated with pathologic conditions.

A disadvantage of the antidromic method is the possible contamination of the waveform by a volume-conducted motor potential which often follows the SNAP (see Fig. 7.9). This results from stimulation of the entire mixed nerve, including the motor fibers. There is usually little trouble differentiating between the two, because the volume-conducted motor potential typically occurs after the SNAP and has a longer duration. However, problems may occur if the two potentials have a similar latency or, more importantly, if the sensory potential is absent or much reduced in amplitude. When the SNAP is absent, one may mistake the first component of the volume-conducted motor potential for the SNAP. Measuring the duration of the potential is useful to distinguish a sensory from a motor potential (SNAP duration is typically 1.5 ms while vs. CMAP duration is usually 5–6 ms).

Preganglionic Lesions

Peripheral sensory fibers are derived from the dorsal root ganglia (DRG) located extradurally outside of the spinal cord within the intervertebral foramina. The primary sensory neurons are unique bipolar cells with central processes forming the sensory (dorsal) nerve rootlets and peripheral projections becoming the peripheral sensory axons. Axon-loss lesions of the dorsal nerve root only affect the central processes, leaving the dorsal root ganglion and the peripheral sensory axons intact. In these situations, the central processes degenerate, effectively disconnecting the ganglion and its peripheral processes from the spinal cord. Except on rare occasions [3], the SNAPs remain normal in lesions proximal to the DRGs, including intraspinal canal lesions affecting the spinal roots and spinal cord (Fig. 7.10). Patients with such preganglionic lesions commonly have sensory manifestations. In fact, the combination of dermatomal sensory loss with normal SNAPs in the distribution of sensory abnormalities should always suggest the possibility of a lesion proximal to the dorsal root ganglia. In postganglionic lesions, such as extraspinal radiculopathies, plexopathies, or peripheral mononeuropathies, SNAPs are usually low in amplitude or absent.

In contrast to the DRGs, the anterior horn cells are located in the ventral gray matter of the spinal cord. Axons projecting from these motor neurons form the motor roots and the motor fibers in the peripheral nerves. Axon-loss lesions of the motor (ventral) roots effectively disconnect the peripheral motor fibers from their primary neurons, resulting in degeneration of motor fibers throughout the peripheral nerve. Consequently, an axon-loss intraspinal nerve root lesion results in abnormalities on needle EMG and, if severe, on motor NCSs.

Physiologic Temporal Dispersion and Phase Cancellation

When proximal and distal motor stimulations are performed, the resultant CMAPs are slightly different in configuration:

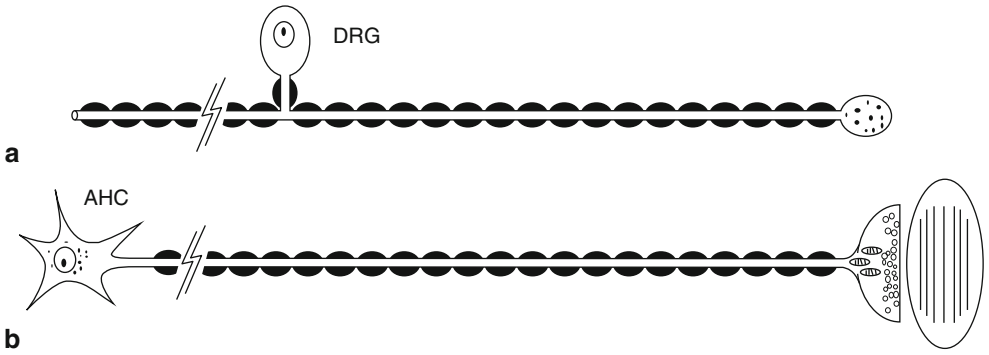


Fig. 7.10 Nerve root lesions and nerve conduction studies. Anatomic differences between sensory and motor nerve fibers result in different patterns of nerve conduction abnormalities in nerve root lesions. The sensory nerve (**a**) is derived from the dorsal root ganglia (*DRG*). The DRG are bipolar cells whose central processes form the sensory roots and distal processes continue as the peripheral sensory nerve fibers. The motor nerve (**b**) is derived from the anterior horn cell (*AHC*), which resides in the ventral gray matter of the spinal cord. Lesions of the nerve roots separate the peripheral motor nerve from its neuron, the AHC, but leave the DRG and its distal processes intact. Thus, nerve root lesions may result in degeneration of the motor fibers distally and, accordingly, abnormalities on motor nerve conduction studies and/or needle EMG. However, the distal sensory nerve remains intact in lesions of the nerve roots, as the lesion is proximal to the DRG. Thus, sensory conduction studies remain normal (Reproduced with permission from Preston and Shapiro [1])

the proximal CMAP amplitude and area may fall and duration increases slightly. These changes are normal findings which result from a combination of temporal dispersion and phase cancellation.

In motor NCSs, the recorded CMAP represents the summation of all individual MUAPs directed to the muscle through the stimulated nerve. The motor axons are not uniform and differ in size, thickness of myelin, and, thus, conduction velocities. The range of conduction velocities between the fastest and slowest individual human motor axons is 12–13 m/s. Because of this variability, the CMAP drops in amplitude and area and increase in duration with proximal stimulation (temporal dispersion), as the slower fibers progressively lag behind the faster fibers (Fig. 7.11). This situation is analogous to a marathon race in which one runner runs a 5 min mile and the other a 6 min mile. At the beginning of the race, both runners are very close to each other (less dispersion), but by the end of the race, they are far apart (greater dispersion). Thus, as the stimulus site moves proximally, slowly conducting fibers are increasingly dispersed in time with respect to the fast-conducting fibers.

If temporal dispersion alone was at work, the amplitude would decrease as the potential duration increases, but the area would be preserved. This would be the case if each motor unit action potential was monophasic in configuration. However, surface-recorded motor unit action potentials are biphasic, with an initial negative phase followed by a positive phase. Their negative duration is 5–6 ms, which is similar to the CMAP negative duration. With such similar durations, most MUAPs are in phase with each other. This results in a slight positive/negative phase overlap and cancellation of the MUAP waveforms, thus reducing both the CMAP amplitude and area while prolonging its duration (see Fig. 7.11).

Temporal dispersion and phase cancellation are more prominent in sensory NCSs, because the disparity of sensory fiber CVs is almost double that of the motor axons (25 m/s) and the recorded single sensory fiber action potentials are often triphasic in configuration. This results in more pronounced temporal dispersion and phase cancellation; the SNAP may drop by 50 % or more and the duration increase by 100 % or more in normal individuals following proximal stimulation (Fig. 7.12) [4]. Temporal dispersion of potentials results from individual sensory fiber action potentials occurring at different times, because faster fibers depolarize before slower ones. A single large myelinated sensory fiber action potential has a negative duration of about 0.5 ms, approximately half the normal duration of the distal SNAP (typical duration = 1.3 ms). This implies that after the first 0.5 ms, the trailing positive phase of the fastest potential overlaps with the leading negative phases of the slower fibers. When overlap occurs between the positive phase of one sensory fiber action potential and the negative phase of another, phase cancellation occurs, resulting in a smaller summated potential. This results in a drop of SNAP area and amplitude.

Needle Electromyography (EMG)

The needle EMG examination is an essential component of the EDX evaluation. It provides an efficient and rapid mean of testing the electrical activity of motor units in a widespread number of muscles. Like NCSs, each needle EMG study must be individualized, based on the clinical findings, EDX data, and the differential diagnosis. The test is often modified as the test proceeds and more data is obtained.

The needle EMG is often uncomfortable for the patient due to needle insertion into skin and muscle. When performed

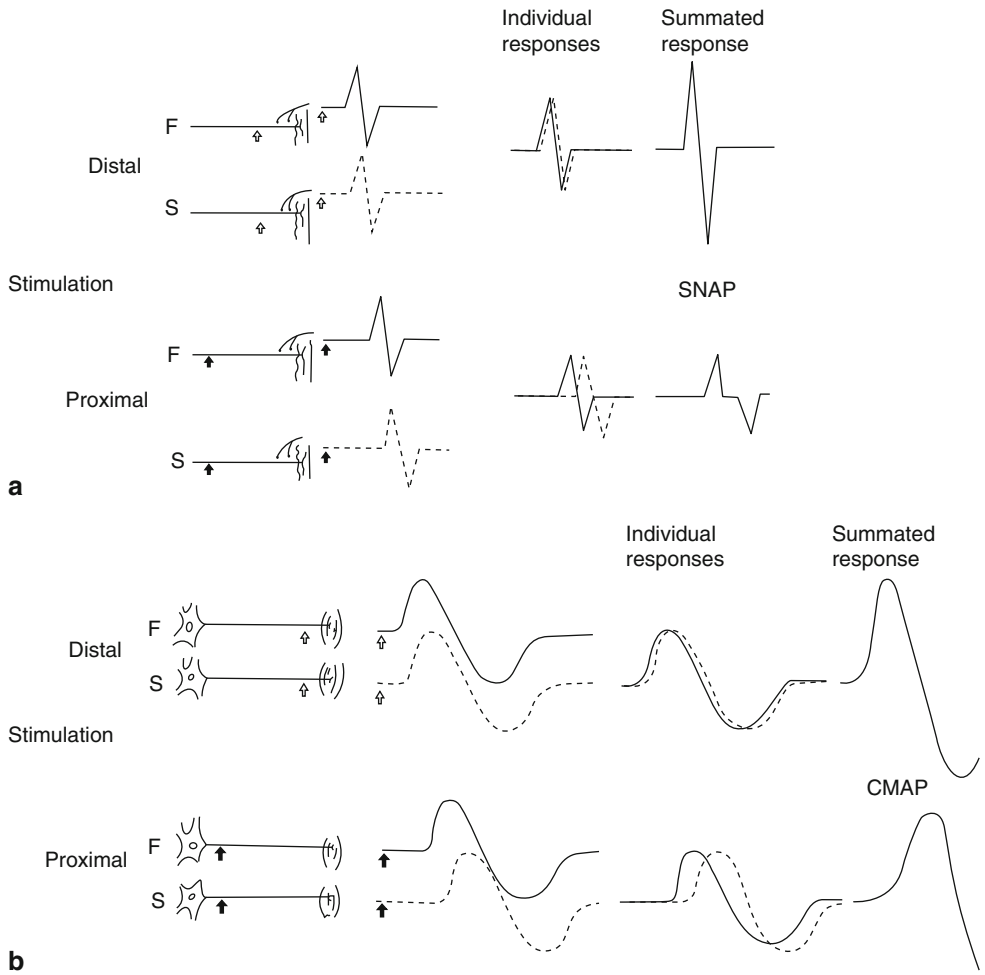


Fig. 7.11 Temporal dispersion and phase cancellation in nerve conduction studies. (**a**) Sensory nerve action potentials (*SNAPs*) and compound muscle action potentials (*CMAPs*) are both compound potentials, representing the summation of individual sensory and muscle fiber action potentials, respectively. In each case there are fibers which conduct faster (*F*) and those which conduct more slowly (*S*). With distal stimulation, fast and slow fiber potentials arrive at the recording site at approximately the same time. However, with proximal stimulation, the slower fibers lag behind the faster fibers. For sensory fibers (*top traces*), the amount of temporal dispersion at proximal stimulation sites results in the negative phase of the slower fibers overlapping with the positive trailing phase of fastest fibers. These superimposed positive and negative phases then cancel each out, resulting in a decrease in area and amplitude, beyond the decrease in amplitude and increase in duration from the effects of temporal dispersion alone. (**b**) The effects of temporal dispersion and phase cancellation are less prominent for motor fibers (*bottom traces*). The duration of individual motor fiber potentials is much longer than that of single sensory fibers. Thus, for the same amount of temporal dispersion, there is much less overlap between negative and positive phases of motor fiber action potentials (From Kimura et al. [4]. With permission of Little, Brown and Company)

skillfully and following explanation and reassurance, most patients tolerate the exam well. On rare occasions, the patient may be extremely apprehensive or needle phobic and the needle EMG cannot be completed. Children, who may tolerate the NCSs, frequently have difficulty with the needle EMG. Although most muscles may be sampled with needle EMG, an extensive needle EMG examination is rarely indicated. For each study, a minimal number of muscles need to be sampled to reach a diagnosis or exclude other clinical suspicions.

Before proceeding with the needle EMG study, it is often useful to consider the possibility that the patient may only tolerate EMG of only one or two muscles. Thus, the choice of muscle to be sampled must be based on the differential diagnosis (determined by the clinical findings and NCS data), the accessibility of the muscle, the ability to activate it, and the degree of pain associated with needle insertion. For example, while both the tibialis anterior (TA) and medial gastrocnemius (MG) are distal leg muscles, sampling the TA is less painful, and the muscle is much easier to activate than the MG. Similarly, during needle EMG of a patient with suspected polyneuropathy or cervical radiculopathy, the first dorsal interosseous (FDI) is often chosen over the abductor pollicis brevis (APB), because the APB is much more painful to sample than the FDI, while both muscles are distal and innervated by the C8 and T1 roots.

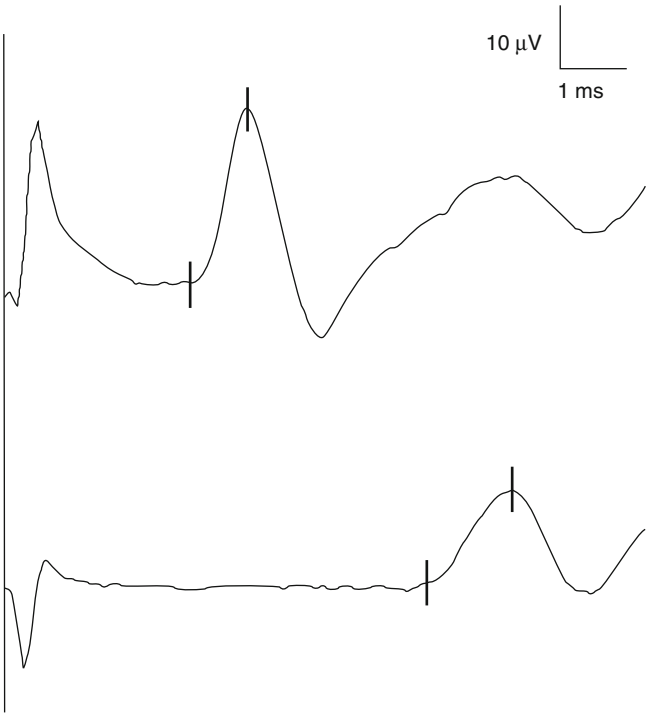


Fig. 7.12 Proximal sensory studies. Normal Median Sensory Study, recording index finger, stimulating wrist (*top*), and elbow (*bottom*). Note: In healthy subjects, proximal stimulation results in SNAPs which are longer in duration and lower in amplitude and area. This occurs as a result of normal temporal dispersion and phase cancellation. If the SNAP is small at the distal stimulation site, it may be difficult or impossible to obtain a potential with proximal stimulation (Reproduced with permission from Preston and Shapiro [1])

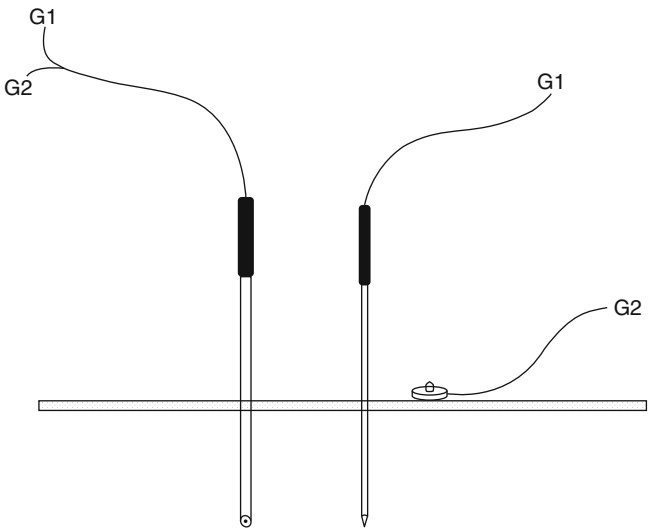


Fig. 7.13 EMG needles. (*Left*) Concentric needle. The concentric needle contains both the active (*G1*) and reference (*G2*) electrodes. The active electrode runs as a small wire through the needle center and is exposed at the tip while the shaft of the needle serves as the reference electrode. (*Right*) Monopolar needle. In the monopolar montage, the needle is Teflon-coated with the exposed tip serving as the as the active electrode (G1); an additional surface disk electrode is needed as the reference electrode (G2) (Reproduced with permission from Preston and Shapiro [1])

Table 7.2 Difference between monopolar and concentric needle electrodes

Concentric	Monopolar
Does not require an independent reference electrode	Requires an independent reference electrode
More painful	Less painful
More expensive	Less expensive
Low baseline noise	High baseline noise
Lower MUAP amplitude	Higher MUAP amplitude
Sharper MUAP rise time	MUAP rise time not as sharp
Shorter MUAP duration	Longer MUAP duration

MUAP motor unit action potential

In children or apprehensive patients, or in a patient who may not tolerate or complete the entire exam, the most important muscles should be sampled first. For instance, if a patient has proximal weakness, in whom the differential diagnosis rests primarily between a myopathy and a proximal neurogenic process (e.g., plexopathy, radiculopathy, and motor neuron disease), a weak proximal muscle should be tested first. If one begins the exam by sampling distal muscles, which are clinically normal, the chance to reach a diagnosis may have been lost if the patient cannot tolerate further examination.

Interpreting the findings on the needle EMG is a challenging part of the EDX examination. Many of the muscle abnormalities are subtle, and the range of normal values is wide and varies with age and the muscle studied. Knowledge of anatomy and physiology and EMG techniques is necessary. Although the basics of the needle EMG study, such as needle placement and recognition of certain types of abnormal spontaneous activity, can usually be learned in a short period of time, recognition of many of the uncommon and subtle needle EMG findings may take years to master.

Recording Technique

In addition to the EMG machine, an EMG needle electrode, needle cable, ground electrode, and gloves are necessary to perform the needle EMG study. The ground electrode is applied to the limb being studied in order to ensure electrical safety and suppress noise. Disposable gloves should be worn to prevent the transmission of blood-borne infections between the patient and the electromyographer. The EMG needle is connected to a cable and then plugged into the EMG machine.

Either a concentric or monopolar EMG needle may be used for recording EMG activity (Fig. 7.13 and Table 7.2). Because the voltage of an electrical potential is measured as the difference between the active and reference recording electrodes, a reference electrode is required. In the concentric

needle, the active electrode is a very small wire in the center of the needle which is exposed at the needle tip, with the needle shaft serving as the reference electrode. In contrast, the monopolar needle is a Teflon-coated electrode exposed at its tip and serves as the active recording electrode. An additional surface disk electrode is required as the reference electrode. The concentric needle has the advantage of not requiring an additional reference electrode, while the monopolar needle has the advantage of being slightly less painful because of a smaller caliber, sharper point, and Teflon coating.

The major disadvantage of the monopolar needle is the need for an additional reference electrode which has to be moved to be near the active electrode with each muscle sampled. Another disadvantage of the monopolar needle is the much greater electrical noise due to electrode impedance mismatch between the intramuscular active electrode and the surface reference disk.

Concentric and monopolar needles are equally satisfactory in recording muscle potentials, with little appreciable differences. MUAP amplitude is slightly smaller and the major spike rise time shorter with a concentric needle, compared to the MUAP obtained with a monopolar needle (see Table 7.2).

Typical Needle Electromyography Examination

Before beginning the needle EMG examination, it is important to explain the procedure to the patient to allay any fears. Good patient rapport both before and during the study is essential. In general, the more cooperative the patient, the more quickly the test proceeds, leading to less discomfort and more reliable data. The following points are useful to clarify to the patient, or if the patient is a child, both the child and family should have the following explained, in a language they can understand:

1. A small needle is used to record electrical potentials from inside the muscle, first while relaxed and then during muscle contraction.
2. Only a short segment of the total length of the needle is inserted (depending on subcutaneous fat).
3. There is no electrical stimulation applied through the needle electrode.
4. The electrical signal from the muscle will be displayed on the screen and heard on the loud speaker. We encourage the patient to watch, listen, and ask any questions.
5. Several muscles are sampled, and their number depends on the clinical symptoms, the questions asked by the referring physician, and the findings as the study proceeds.
6. The patient can take a break at any time.

For each muscle sampled, the electromyographer has to identify the needle insertion point by recognizing the proper anatomical landmarks and the activation maneuver for the muscle. For deeply seated muscles, the electromyographer may ask the patient to contract and relax the selected muscle several times while palpating to locate the muscle contraction. Once the muscle location is identified, the needle is quickly inserted through the skin into the relaxed muscle. Inserting a needle into a contracted muscle is more painful and should always be avoided. To confirm the correct location of the needle, particularly when in doubt or with deeply seated muscles, the patient should be asked to gently contract the muscle. With proper needle location, very sharp and crisp MUAPs (i.e., MUAPs with a short rise time) are displayed. If sharp MUAPs are not seen with minimal muscle contraction, the needle tip location should be adjusted (pulled back slightly or moved slightly deeper) before assessing the findings on the needle EMG. If this fails to produce sharp MUAPs, the needle must be removed, the muscle re-palpated, and the needle reinserted.

Because spontaneous potentials may be low in amplitude, the sensitivity is set at 50 μV/div to evaluate insertional and spontaneous activity. Once insertional and spontaneous activities have been characterized, the needle is left in place, and the analysis turns to the evaluation of MUAPs (see below). Because MUAPs are typically much larger than spontaneous activity waveforms, the sensitivity must be changed to 200 μV/div, while the sweep speed remains at 10 ms/div. To analyze MUAPs, the patient is asked to slightly contract the sampled muscle, preferably in an even manner. MUAPs are very difficult to interpret in patients with uneven muscle contraction, especially those with a tremor. With minimal activation of the muscle, the needle is moved slightly until the MUAPs become "sharp" (i.e., louder and crisper). As the tip of the needle moves closer to the MUAP, there is less intervening tissue to attenuate and filter the potential. Thus, the closer the tip of the needle to the MUAP, the higher the amplitude and the shorter the major spike rise time. It is at this point that the MUAP can be properly evaluated. MUAPs are assessed for duration, amplitude, and number of phases. In addition, the number of MUAPs and their relationship to the firing frequency (recruitment and activation pattern) are also determined (see section "Firing Pattern [Activation, Recruitment, and Interference Pattern]"). As the patient slowly increases force, both the firing frequency and the number of MUAPs normally increase. After the MUAPs are assessed at one location, the needle is moved slightly within the muscle to a different site, and the process is repeated. Ideally, 10–20 different MUAPs should be analyzed.

Once the insertional and spontaneous activity are characterized and the MUAP size, recruitment, and activation patterns are determined for each muscle sampled, one can generally determine if a lesion is present. If a lesion is present, one can use the data to determine its severity and chronicity and, most importantly, whether the primary problem is

Table 7.3 Spontaneous activity

Potential	Source generator/morphology	Sound on loud speaker	Stability	Firing rate	Firing pattern
End-plate noise	Miniature end-plate potential (monophasic negative)	Seashell		20–40 Hz	Irregular (hissing)
End-plate spike	Muscle fiber initiated by terminal axonal twig (brief spike, diphasic, initial negative)	Sputtering fat in a frying pan	–	5–50 Hz	Irregular (sputtering)
Fibrillation potential	Muscle fiber (brief spike, diphasic or triphasic, initial positive)	Rain on a tin roof or ticktock of a clock	Stable	0.5–10 Hz (occ. up to 30 Hz)	Regular
Positive sharp wave	Muscle fiber (diphasic, initial positive, slow negative)	Dull pops, rain on a tin roof, or ticktock of a clock	Stable	0.5–10 Hz (occ. up to 30 Hz)	Regular
Myotonia	Muscle fiber (brief spike, initial positive, or positive wave)	Revving engine	Waxing/waning amplitude	20–150 Hz	Waxing/waning
Complex repetitive discharge	Multiple muscle fibers time-linked together	Machine	Usually stable, may change in discrete jumps	5–100 Hz	Perfectly regular (unless overdriven)
Fasciculation potential	Motor unit (motor neuron/axon)	Corn popping	–	Low (0.1–10 Hz)	Irregular
Myokymia	Motor unit (motor neuron/axon)	Marching soldiers		1–5 Hz (interburst) 5–60 Hz (intraburst)	Bursting
Cramp potential	Motor unit (motor neuron/axon)			High (20–150 Hz)	Interference pattern or several individual motor units
Neuromyotonia	Motor unit (motor neuron/axon)	Pinging	Decrementing amplitude	Very high (150–250 Hz)	Waning

Adapted with revisions from Preston and Shapiro [1], with permission

neuropathic or myopathic. The distribution and pattern of abnormalities in different muscles, along with the nerve conduction studies and the clinical data, should allow one to make the final electrophysiologic diagnosis.

Insertional and Spontaneous Activity

Table 7.3 summarizes the main features of the common spontaneous potentials seen during the needle EMG discussed below.

Insertional Activity

The needle EMG examination begins with the assessment of insertional activity. As noted above, the sensitivity is set at 50 μV/div. Once the needle electrode is correctly placed in the muscle, brief and rapid needle movements result in insertional bursts of potentials, known as *normal insertional activity*, which lasts less than 300–500 ms. At least 4–6 brief needle movements are made in each of the four quadrants of the sampled muscle. This can be accomplished without removing the needle from the muscle by first inserting the needle into one quadrant, moving from shallow to deeper along a line, and then pulling back the needle to sample the next quadrant.

Prolonged (increased) insertional activity occurs in neurogenic, myopathic, and myotonic disorders. It may also represent normal variants, which often are familial, have widespread distributions, and consist of short bursts of positive waves (see next section) or irregularly firing potentials (sometimes referred to as "snaps," "crackles," and "pops") [5]. The latter are more prevalent in large muscular subjects and in the calf muscles. Reduced (decreased) insertional activity occurs mainly when there is severe muscle atrophy with replacement of muscle by adipose and connective tissue. It may also be encountered during the paralytic attack of periodic paralysis.

Normal Spontaneous Activity

Normal muscle fibers show no spontaneous activity at rest except in the motor end-plate region, which is usually found near the center of the muscle belly. When the needle is placed in that region, patients frequently perceive a deep burning sensation. Two types of normal spontaneous activity occur in this region, together or independently: end-plate noise and end-plate spikes.

End-Plate Noise

These are low-amplitude, monophasic negative potentials which fire irregularly at 20–40 Hz and have a characteristic "seashell" sound on the loud speaker (Fig. 7.14). They represent miniature end-plate potentials (MEPPs) and result from the normal spontaneous exocytosis of individual quanta of

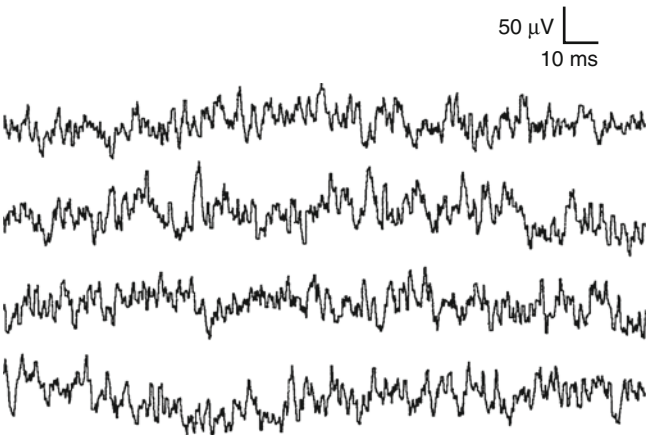


Fig. 7.14 End-plate noise. Small, high-frequency, predominantly monophasic negative potentials which are recognized by their characteristic shape and "seashell" noise on EMG (Reproduced with permission from Preston and Shapiro [1])

acetylcholine traveling across the neuromuscular junction, leading to a non-propagated, subthreshold end-plate potential. They are recognized by their characteristic shape and sound and frequent association with end-plate spikes (see below).

End-Plate Spikes

These are rapid, irregular, and biphasic potentials with an initial negative deflection, reflecting that the needle is at the site where the action potential is generated (Fig. 7.15). They are muscle fiber action potentials which fire irregularly up to a frequency of 50 Hz and are usually seen along with end-plate noise (Fig. 7.16). They are thought to occur as a result of needle mechanical activation of terminal nerve twigs with subsequent activation of a nerve twig action potential leading to a muscle fiber action potential. They have a cracking or buzzing sound on the loud speaker, imitating "sputtering fat in a frying pan." It is of utmost importance to properly identify these potentials, so as not to mistake them for fibrillation potentials. *The key features that differentiate end-plate spikes from fibrillation potentials, which are also brief spikes, are their initial negative deflection and their highly irregular firing rate.*

Abnormal Spontaneous Activity

Muscle is normally electrically silent outside of the end-plate zone. Any persistent spontaneous activity, usually defined as lasting longer than 2–3 s, is abnormal. Spontaneous activity may be ongoing when the needle is placed in the muscle or may be triggered by needle movement, voluntary muscle contraction, muscle percussion, or electrical stimulation.

Fibrillation Potentials

Fibrillation potentials are *spontaneous action potentials of denervated single muscle fibers* (Fig. 7.17). Denervating potentials from single muscle fibers signify active denervation

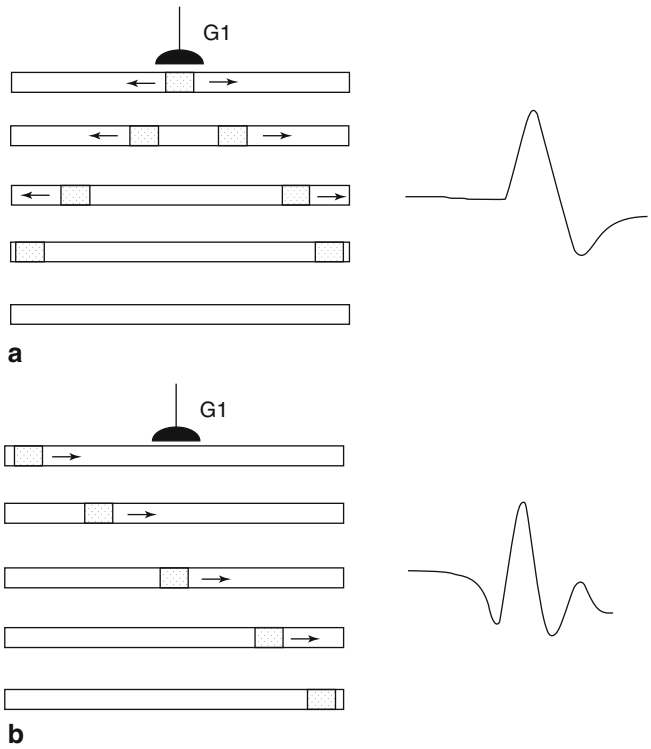


Fig. 7.15 Waveform morphology and site of depolarization. (**a**) (*Top trace*) A traveling depolarizing wave will create a biphasic potential if the waveform begins under the recording needle electrode (initial negative peak) and then moves away from the electrode (positive peak). This is known as an end-plate spike. (**b**) (*Bottom trace*) If the waveform begins at a distance from the needle, there is an initial positive deflection as it moves toward the needle, followed by a negative phase as it moves beneath the needle, and then a final positive deflection as it travels away. This is known as a fibrillation potential. End-plate spikes are differentiated from fibrillations by their absence of an initial positive deflection, as the depolarization begins at the end plate (Reproduced with permission from Preston and Shapiro [1])

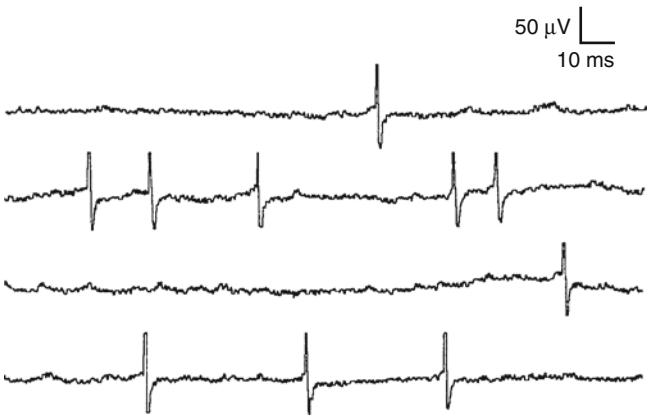


Fig. 7.16 End-plate spikes. End-plate spikes result from needle-induced irritation of the terminal nerve twigs near the end plate. Note the initial negative deflection, brief duration, biphasic morphology, and the irregular, sputtering firing pattern which differentiates them from fibrillation potentials (Reproduced with permission from Preston and Shapiro [1])

Fig. 7.17 Fibrillation potential. Spontaneous depolarization of a single muscle fiber. Note the initial positive deflection, brief duration, and triphasic morphology (Reproduced with permission from Preston and Shapiro [1])

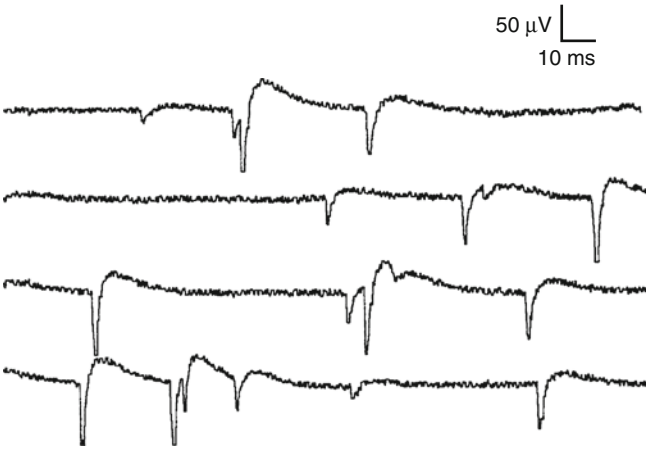


Fig. 7.18 Positive waves (*rastered traces*). Positive waves have the same significance as fibrillation potentials: they are the spontaneous depolarization of a muscle fiber. Note the initial positive deflection and the slow negative phase (Reproduced with permission from Preston and Shapiro [1])

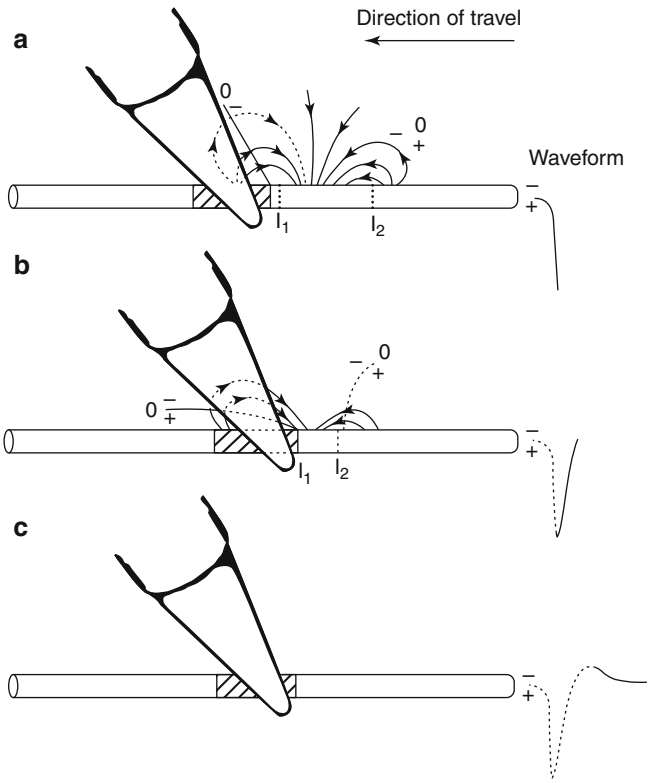


Fig. 7.19 Generation of a positive wave. The cross-hatched area is deformed by the needle electrode which becomes electrically inexcitable. (**a**, **b**) As the traveling depolarization wave approaches, an initial positive wave is generated. (**c**) With failure of conduction beyond the needle, the steep negative phase is aborted and the waveform returns to baseline (Reprinted with permission from Dimitru [8])

and may take one of two forms, either fibrillation potentials (brief spikes) or positive waves.

Fibrillation potentials are brief spikes that have an initial positive deflection and a triphasic morphology, because depolarization starts at a distance from the recording needle's tip (see Fig. 7.15). Their duration is about 1–5 ms, and their amplitude is typically 10–200 µV. In very chronic conditions (>6–12 months), the amplitude may be very low (<10 µV). Their firing pattern is *regular*, with a rate usually 0.5–15 Hz, but occasionally up to 30 Hz. On a loud speaker, fibrillation potentials may sound like "rain on the roof" or "the tick/tock of a clock." Although fibrillation potentials are regular, their firing rate may decrease (or sometimes increase) in a predictable fashion over several seconds before stopping.

Positive Waves

Positive waves have the same significance as brief spike fibrillation potentials (Fig. 7.18). They have a brief initial positive phase followed by a long negative phase. They sound like a dull pop, due to their slow negative phase and long duration. Their amplitude is variable (usually 10–100 µV, occasionally up to 3 mV). Like fibrillation potentials, their firing pattern is regular, with a rate usually 0.5–15 Hz, occasionally up to 30 Hz. This distinguishes them from MUAPs at a distance, which occasionally have positive wave morphology. Positive waves are often accompanied by brief spike fibrillation potentials, but they may be seen alone, sometimes early in denervation.

The explanation for the difference in morphology between a positive wave and a fibrillation potential is not completely agreed upon [6, 7]. One hypothesis is that fibrillation potentials are derived from the extracellular recording of a single muscle fiber depolarization, while positive waves are generated by the intracellular recording of a single muscle fiber depolarization. The more likely explanation for the positive wave is that the needle deforms an irritable muscle fiber, inducing a denervating potential at a distance down the fiber which propagates to the area of the needle but not beyond it (Fig. 7.19). This might explain why positive waves are occasionally seen earlier than fibrillation potentials: the presence of the needle is required to help generate these potentials. Occasionally, fibrillation potentials change to positive waves with EMG needle movement.

Fibrillation potentials are typically associated with neurogenic disorders (i.e., neuropathies, radiculopathies, motor neuron disease). In acute axon-loss lesions, fibrillation potentials appear in affected muscles at about the second week,

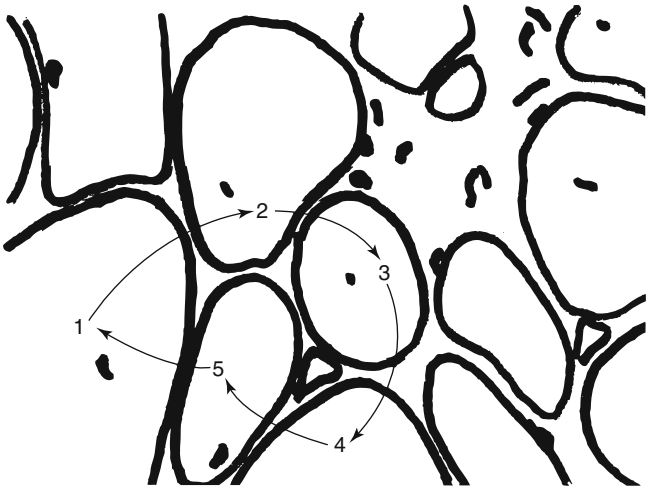


Fig. 7.20 Pathophysiology of a complex repetitive discharge. Ephaptic transmission from one denervated muscle fiber to an adjacent one. If the original pacemaker is reactivated, a circus movement is formed without an intervening synapse (Reproduced with permission from Preston and Shapiro [1])

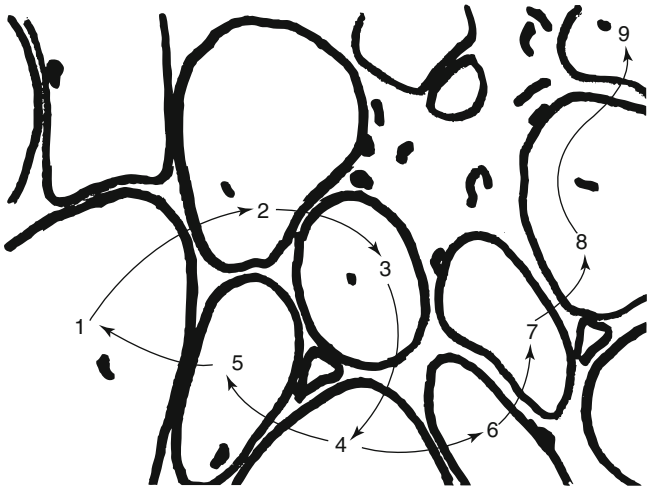


Fig. 7.21 Complex repetitive discharge. CRDs may change abruptly in frequency or number of potentials when extra loops drop in and out (Reproduced with permission from Preston and Shapiro [1])

Fig. 7.22 Typical complex repetitive discharge. Note the multiple spikes (each spike within the complex representing a different single muscle fiber) and the perfectly repetitive nature (Reproduced with permission from Preston and Shapiro [1])

first in proximally situated muscles and then more distally. They do not become widespread in all denervated muscles until about 4–6 weeks after an axonal nerve injury. They will ultimately decrease due to either reinnervation of muscle fibers or fatty degeneration of chronically denervated muscle fibers.

Fibrillation potentials may also be seen in muscle disorders (e.g., inflammatory myopathies and muscular dystrophies) and very rarely in severe diseases of the NMJ (e.g., myasthenia gravis and botulism). There are two possible explanations for the occurrence of fibrillation potentials in myopathies. The first is segmental necrosis of muscle fibers, leading to effective denervation of distal segments, because they become physically separated from the neuromuscular junction. The second explanation is damage to the terminal intramuscular motor axons, presumably by the inflammatory process, which results in denervation of some muscle fibers. In NMJ disorders, fibrillation potentials are rare and are likely due to persistent transmission block at NMJs, resulting in "effective" denervation of some muscle fibers.

The density of fibrillation potentials is a rough estimate of the extent of denervated muscle fibers. Hence, fibrillation potentials are graded from 0 to 4: 0 no fibrillations; +1 persistent single trains of potentials (>2–3 s) in at least two areas; +2 moderate number of potentials in three or more areas; +3 many potentials in all areas; and +4 full interference pattern of potentials.

Complex Repetitive Discharges

Complex repetitive discharges (CRDs) occur from the depolarization of a *single muscle fiber followed by ephaptic spread to adjacent denervated fibers* (Fig. 7.20). If a circus movement is created whereby the original pacemaker muscle fiber is reactivated, a recurrent discharge develops (Fig. 7.20). Occasionally, individual phases or additional ephaptic loops drop in and out, creating an abrupt change in frequency, configuration, and sound (Fig. 7.21). These discharges, referred to previously as bizarre repetitive discharges or bizarre high-frequency discharges, usually occur spontaneously or after needle movement. Less commonly, they are triggered by a stimulated or a voluntary MUAP. CRDs are regular, high-frequency (typically 20–150 Hz), and polyphasic (typically with 3–10 spikes) repetitive discharges with an abrupt onset and cessation (Fig. 7.22). The individual discharges within each CRD are uniform in morphology from one discharge to the next, creating a machine-like sound on loud speaker (Fig. 7.23).

CRDs are pathologic but nonspecific. They occur in chronic neuropathic and myopathic disorders. They may arise in any setting where denervated muscle fibers lie adjacent to each other. In neuropathic disorders, this occurs when there is denervation, reinnervation, and subsequent denervation (i.e., grouped atrophy). This situation may also occur in myopathic disorders associated with denervation/reinnervation (e.g., inflammatory myopathies) or with muscle fiber splitting. CRDs usually persist with neuromuscular junction blockade and have an abnormally low jitter on single-fiber

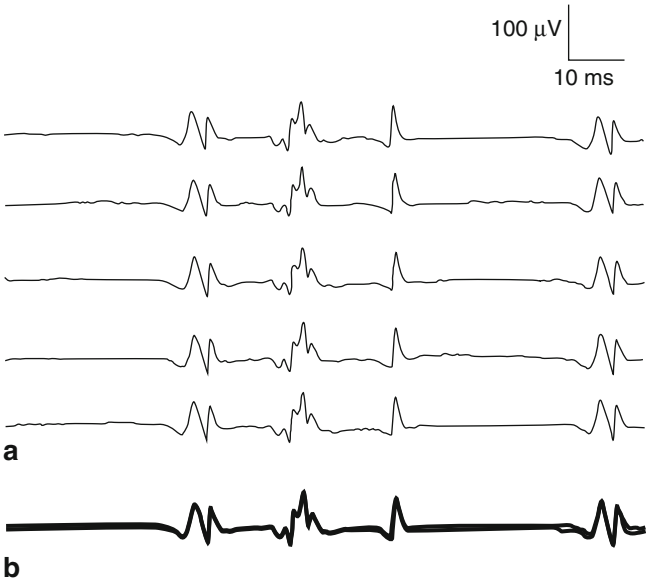


Fig. 7.23 Complex repetitive discharge. (**a**) (*Top traces*) CRD triggered on a delay line; (**b**) (*bottom trace*) Traces superimposed. Note the perfectly repetitive nature of a CRD. When superimposed, there is little or no jitter between successive potentials (Reproduced with permission from Preston and Shapiro [1])

Fig. 7.24 Myotonic discharge (needle induced). *Arrow marks* needle movement triggering the discharge. Myotonic discharges may occur spontaneously or be triggered by needle movement, voluntary contraction, or muscle percussion (Reproduced with permission from Preston and Shapiro [1])

EMG because the discharge spreads ephaptically with no intervening synapse.

Myotonic Discharges

A myotonic discharge is the spontaneous prolonged discharge of a muscle fiber, often induced by mechanical stimulation, which is characterized by waxing and waning of both amplitude and frequency. An individual myotonic potential may have either a positive wave or brief spike morphology. It is the waxing and waning of amplitude and frequency that differentiates a myotonic discharge from denervating potentials (i.e., fibrillation potentials and positive waves) (Fig. 7.24). The firing rate generally ranges between 20 and 150 Hz, which gives them a "revving engine" sound on the loud speaker.

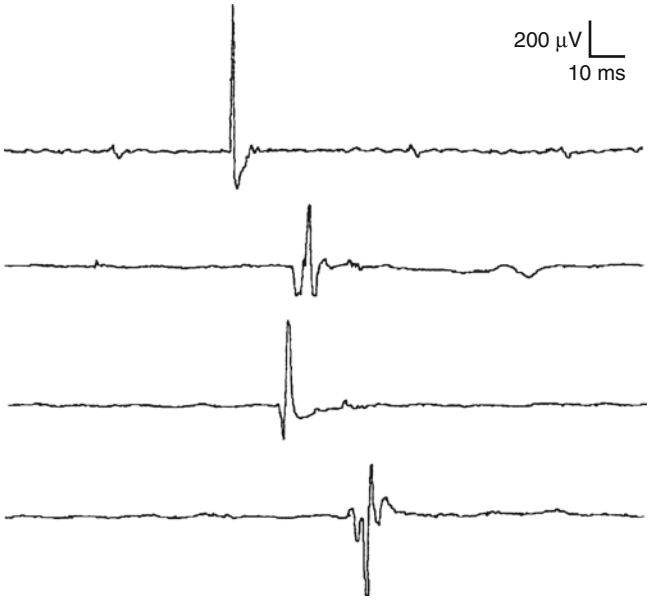


Fig. 7.25 Fasciculations (*rastered traces*). Each potential has the morphology of a motor unit. They are recognized by their morphology and irregular slow firing pattern (Reproduced with permission from Preston and Shapiro [1])

Myotonic discharges may occur with or without clinical myotonia in the myotonic dystrophies, myotonia congenita, paramyotonia congenita, and in some patients with hyperkalemic periodic paralysis. They may also occur in some myopathies (i.e., acid maltase deficiency, polymyositis, and myotubular myopathy). Rarely, they may be encountered in neurogenic disorders, usually as a single brief run where they are never the predominant waveform.

Fasciculation Potentials

A fasciculation potential is the *spontaneous discharge of an individual motor unit* (Fig. 7.25). Unlike a voluntary motor unit, fasciculation potentials generally fire randomly and irregularly, generally between 0.1 and 10 Hz. They usually have variable morphology, depending on the motor unit from which they arise, giving them a "popping corn" sound on the loud speaker. The source generator is the motor neuron or its axon prior to its terminal branches. Despite the notorious association of fasciculation potentials with diseases of the anterior horn cell, the actual site of origin of most fasciculation potentials is likely in the distal segment of the axon [9].

Fasciculation potentials are associated with disease processes affecting the lower motor neuron (e.g., motor neuron disease, amyotrophic lateral sclerosis) as well as radiculopathies, polyneuropathies, and entrapment neuropathies. In addition, they may occur in normal individuals. There is no reliable method of distinguishing "benign" from "malignant" fasciculation potentials except that benign discharges tend to fire faster and affect the same site repetitively (e.g., eye lid twitching).

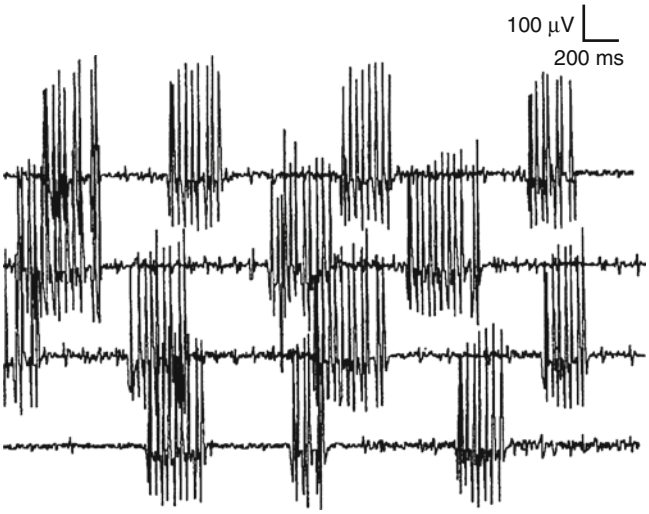


Fig. 7.26 Myokymic discharges (*rastered traces*, long sweep speed). Note that the number of potentials may change from burst to burst (Reproduced with permission from Preston and Shapiro [1])

Table 7.4 Disorders associated with myokymic discharges

Myokymic discharges commonly seen in:
Radiation injury (usually brachial plexopathy)
Guillain-Barré syndrome (facial)
Multiple sclerosis (facial)
Pontine tumors (facial)
Hypocalcemia
Timber rattlesnake envenomation
Myokymic discharges occasionally seen in:
Guillain-Barré syndrome (limbs)
Chronic inflammatory demyelinating polyneuropathy
Nerve entrapments
Radiculopathy

From Preston and Shapiro [1], with permission

Myokymic Discharges

Myokymic discharges are *rhythmic*, *spontaneous*, *grouped repetitive discharges of the same motor unit* (i.e., grouped fasciculations). The firing frequency within the burst is typically 5–60 Hz. The number of potentials within a burst varies widely and may change slightly from burst to burst (Fig. 7.26). The firing frequency between bursts is much slower (typically <2 Hz) and produces a sound like marching soldiers on the loud speaker. Changing the screen sweep to a longer sweep speed often helps to recognize the bursting pattern as that of a myokymic discharge. The origin of myokymic discharges likely involves spontaneous depolarization or ephaptic transmission along demyelinated segments of nerve.

Clinically, myokymia is recognized as continuous, involuntary, fine, wormlike, and quivering movement of muscle. Limb myokymia occurs in a variety of conditions including radiculopathy, entrapment neuropathy, and radiation-induced nerve damage (Table 7.4). In a patient with brachial plexopathy and a history of cancer and radiation, the presence of myokymia strongly supports a diagnosis of radiation plexopathy rather than recurrent neoplastic invasion. Facial myokymia occurs with brainstem lesions associated with multiple sclerosis, pontine gliomas, stroke, and following radiation. In Guillain-Barré syndrome, facial myokymia may occur in 15 % of patients, usually occurring early in the illness and remitting as the patient clinically improves. Generalized myokymia associated with Isaac's syndrome (syndrome of continuous motor unit activity) is often accompanied by neuromyotonic discharges [10] (see below).

Hypocalcemia may lead to spontaneous grouped repetitive discharges. These myokymic discharges, known as *tetany*, tend to occur initially in bursts of 2 or 3 s (doublets, triplets) and are more prevalent in distal muscles. When severe, they may result in involuntary spasms of the hands and feet (carpopedal spasms), with a characteristic hand posture (adduction of the thumb and fingers, extension of the interphalangeal joints, and flexion of the metacarpal-phalangeal joints and wrist). Similarly, myokymia of peripheral nerve origin may be provoked or enhanced by lowering serum ionized calcium with hyperventilation or the use of acid-citrate-dextrose anticoagulant (e.g., during plasma exchange). Administration of calcium can transiently decrease the generation of myokymic discharges.

Cramp Potentials

Cramps are painful, involuntary contractions of muscle which tend to occur when a muscle is in the shortened position and contracting. On EMG, a cramp discharge is either a *full interference pattern of motor unit action potentials with a normal morphology or several motor unit potentials firing repetitively and sometimes irregularly at high frequencies* (*usually 40–60 Hz*) (Fig. 7.27). The discharge often has an abrupt onset and cessation.

Cramps are common in normal individuals and often benign (e.g., nocturnal calf cramps, postexercise), but may be associated with a variety of neuropathic, endocrine, and metabolic conditions (see Chap. 71). Clinically, cramps may resemble muscle contractures that occur in several of the metabolic muscle diseases. However, the latter is characterized by complete electrical silence on needle EMG.

Neuromyotonic Discharges

Neuromyotonic discharges are high-frequency (150–250 Hz) decrementing repetitive discharges of a single motor unit that have a characteristic "pinging" sound on loud speaker (Fig. 7.28). They are rare and are seen either in chronic neuropathic diseases (e.g., patients with a history of poliomyelitis or adult spinal muscular atrophy) or in the syndrome of continuous motor unit activity (Isaac's syndrome) (see Chap. 70).

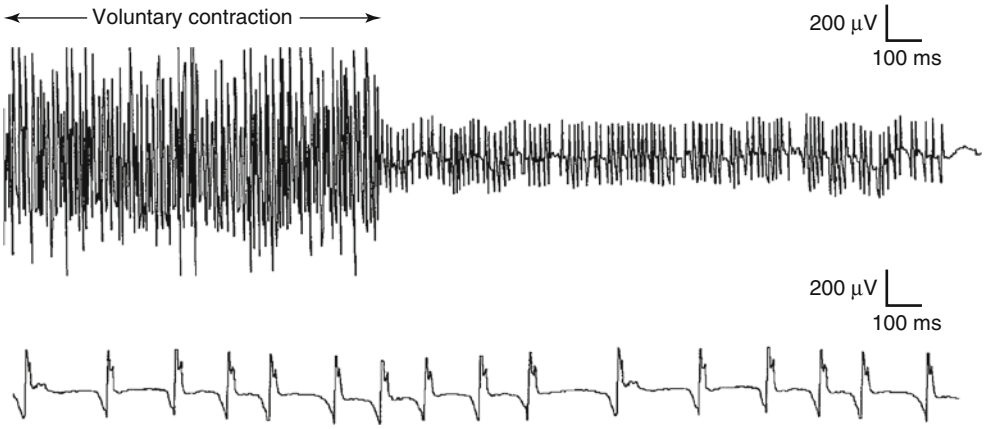


Fig. 7.27 Cramp potential. Note the involuntary repetitive discharge of a motor unit following voluntary contraction (Reproduced with permission from Preston and Shapiro [1])

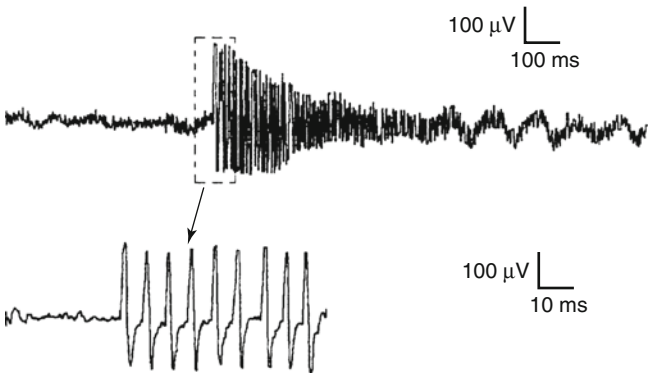


Fig. 7.28 Neuromyotonic discharges. Spontaneous discharge of a single motor unit at very high frequencies (150–250 Hz). Note the decrementing response. *Insert*: change in sweep speed identifies each potential as the same motor unit (Reproduced with permission from Preston and Shapiro [1])

There is strong evidence that neuromyotonic discharges, similar to myokymic discharges, are generated by damaged peripheral motor axons. This activity persists during sleep, as well as during spinal or general anesthesia, and is abolished by curare. Progressively distal nerve blocks diminish the intensity of the spontaneous discharges [11]. Many cases of neuromyotonia or continuous motor unit activity may have an autoimmune etiology, with the target antigen a peripheral nerve potassium channel [12].

Neuromyotonic disorders are associated with involuntary spontaneous discharges of MUAPs that manifest on EMG with neuromyotonic discharges as well as fasciculations, myokymic discharges, or complete interference patterns of MUAPs. The delay in relaxation and improvement with use are clinical features shared by both neuromyotonia and myotonia. However, what distinguishes them is that neuromyotonic discharges are spontaneous discharges generated by peripheral nerve (hence MUAPs), whereas myotonic discharges are the spontaneous discharges of muscle fibers (positive waves or brief spike morphology), hence the term *neuromyotonia*. Note that neuromyotonic discharges are not seen in Stiff man syndrome, a central disorder of spinal interneurons.

Analysis of Voluntary Motor Unit Action Potentials

Similar to the analysis of spontaneous activity, MUAPs must be assessed for morphology (duration, amplitude, phases), stability, and firing characteristics. The pattern of MUAP abnormalities seen on needle EMG often helps determine whether a disorder is primarily neuropathic or myopathic, its time course (acute versus chronic), and its severity. Assessment of MUAPs is often demanding and improves with the experience of the electromyographer over time. The task of evaluating MUAPs is made all the more difficult by the fact that there is wide variation in what is considered a normal MUAP, depending on the muscle being studied and the age of the patient.

Physiology

The motor unit, composed of an individual lower motor neuron and its associated neuromuscular junctions and muscle fibers, mediates all voluntary muscle activity. The number of muscle fibers per motor unit varies greatly, from 5 to 10 in laryngeal muscles to hundreds in the soleus. The territory of a motor unit usually ranges from 5 to 10 mm in adults, with many motor unit territories overlapping with one another, giving muscle a highly mosaic innervation. Hence, two muscle fibers from the same motor unit rarely lie adjacent to each other in healthy muscle. Motor unit territory increases greatly with age, doubling from birth to adulthood, mostly due to the increase in individual muscle fiber size.

When a motor neuron depolarizes, a nerve action potential is generated and propagates down the axon. Under normal circumstances, this results in muscle fiber action potentials of all muscle fibers of the motor unit. These potentials depolarize more or less simultaneously, except for what accounts for differences in the length of the terminal axons and NMJ transmission times. *The motor unit action potential* (*MUAP*) *is the extracellular electrode recording of a small portion of a motor unit* (Fig. 7.29).

The *size principle* governs many of the properties of motor units. The size of the motor neuron is directly related to (1) the size of the axon, (2) the thickness of the myelin sheath,(3) the conduction velocity of the axon, (4) the threshold to

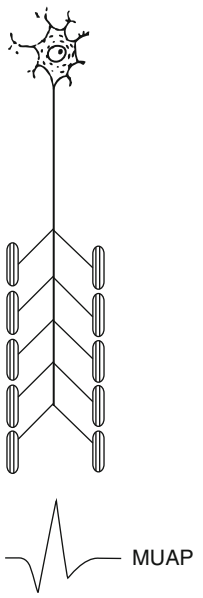


Fig. 7.29 The motor unit. The basic component of the peripheral nervous system is the motor unit, defined as an individual motor neuron, its axon, and associated neuromuscular junctions and muscles fibers. The extracellular needle EMG recording of a motor unit is the motor unit action potential (MUAP) (Reproduced with permission from Preston and Shapiro [1])

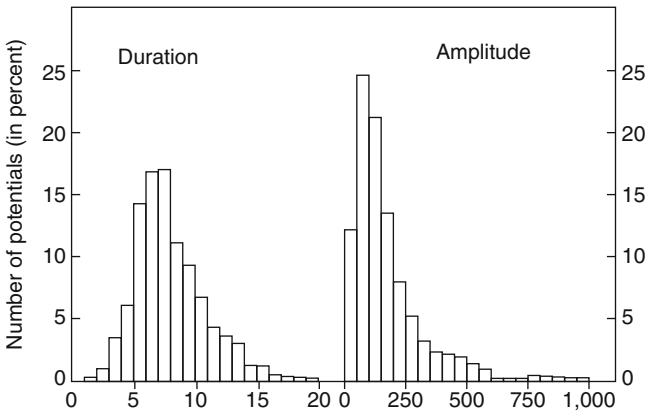


Fig. 7.30 Range of normal MUAP duration and amplitude. Histogram of MUAP duration and amplitude in the biceps brachii of a normal subject. Note: both MUAP duration and amplitude vary markedly in normal muscles with small and large units in the same muscle. MUAP duration or amplitude should not be classified as abnormal based on one or two MUAPs, but requires a mean of many units (Reprinted with permission from Bucthal et al. [13])

depolarization, and (5) the metabolic type of muscle fibers which are innervated. Larger motor neurons have larger axons, thicker myelin sheath, faster conduction velocity, and a higher threshold to depolarization. They innervate type II, fast-twitch muscle fibers. Conversely, smaller motor units have smaller axons, less myelin sheath, slower conduction velocity, and a lower threshold to depolarization. They generally innervate type I, slow-twitch muscle fibers. Thus, with voluntary contraction, the smallest motor units with the lower thresholds fire first. As contraction increases, progressively larger motor units begin to fire. The largest motor units fire only with maximum contraction. Hence, during routine needle EMG, most MUAPs analyzed are the smaller motor units which innervate type I muscle fibers.

During the needle EMG exam, each MUAP recorded represents the extracellular compound action potential of the muscle fibers of a motor unit, weighted heavily toward the fibers nearest to the needle. A MUAP, recorded at the outer surface of muscle membrane, is 1/10 to 1/100 the amplitude of the actual transmembrane potential and decreases rapidly as the distance between the needle and the membrane increases.

The classification of a MUAP as normal, neuropathic, or myopathic is based on the analysis of a MUAP's morphology (duration, polyphasia, and amplitude), stability, and firing pattern.

Motor Unit Action Potential Morphology

There is a wide range of normal MUAP morphology, with both large and small MUAPs present within each muscle (Fig. 7.30). The morphology of a MUAP can be judged on either a qualitative or quantitative basis (see Chap. 9). Over time and with experience, however, the well-trained electromyographer can usually perform qualitative MUAP assessment with the same precision as the quantitative methods. For both procedures, the needle is moved to several locations within the muscle until approximately 20 different MUAPs are examined and analyzed, comparing the findings to the expected normal values for that particular muscle and age group.

MUAP configuration varies depending on the muscle studied, the patient's age, and the location of the needle within the muscle (Table 7.5). This is especially true for MUAP duration. In general, MUAPs in proximal muscles tend to be shorter in duration than those in distal muscles. MUAPs are larger in adults than in children, primarily due to an increase in the size of muscle fibers during development. In addition, MUAPs are larger in older individuals, probably as the result of dropout of motor units from the normal effects of aging, leading to some degree of reinnervation. By comparing mean MUAP morphology in each muscle studied to normal values for that particular muscle and age group, one can judge whether the morphology is normal or abnormal.

The major spike of the MUAP is the largest positive to negative component of the MUAP, usually occurs after the first positive peak, and is the highest-frequency component of the potential (Fig. 7.31). Because tissue acts as a high-frequency filter, as the needle is moved closer to the MUAP, the major spike increases in amplitude, its rise time shortens, and its sound on the loud speaker becomes "sharp." MUAP parameters should only be measured when the needle is very close to the motor unit, with the major spike rise time being less than 500 μs (Fig. 7.32).

Table 7.5 Mean MUAP duration based on age and muscle group

	Arm muscles					Leg muscles					
Age of subjects	Deltoid	Biceps	Triceps	Thenar	ADM	Quad, BF	Gastroc	Tib Ant	Per Long	EDB	Facial
0–4	7.9–10.1	6.4–8.2	7.2–9.3	7.1–9.1	8.3–10.6	7.2–9.2	6.4–8.2	8.0–10.2	6.8–7.4	6.3–8.1	3.7–4.7
5–9	8.0–10.8	6.5–8.8	7.3–9.9	7.2–9.8	8.4–11.4	7.3–9.9	6.5–8.8	8.1–11.0	5.9–7.9	6.4–8.7	3.8–5.1
10–14	8.1–11.2	6.6–9.1	7.5–10.3	7.3–10.1	8.5–11.7	7.4–10.2	6.6–9.1	8.2–11.3	5.9–8.2	6.5–9.0	3.9–5.3
15–19	8.6–12.2	7.0–9.9	7.9–11.2	7.8–11.0	9.0–12.8	7.8–11.1	7.0–9.9	8.7–12.3	6.3–8.9	6.9–9.8	4.1–5.7
20–29	9.5–13.2	7.7–10.7	8.7–12.1	8.5–11.9	9.9–13.8	8.6–12.0	7.7–10.7	9.6–13.3	6.9–9.6	7.6–10.6	4.4–6.2
30–39	11.1–14.9	9.0–12.1	10.2–13.7	10.0–13.4	11.6–15.6	10.1–13.5	9.0–12.1	11.2–15.1	8.1–10.9	8.9–12.0	5.2–7.1
40–49	11.8–15.7	9.6–12.8	10.9–14.5	10.7–14.2	12.4–16.5	10.7–14.3	9.6–12.8	11.9–15.9	8.6–11.5	9.5–12.7	5.6–7.4
50–59	12.8–16.7	10.4–13.6	11.8–15.4	11.5–15.1	13.4–17.5	11.6–15.2	10.4–13.6	12.9–16.9	9.4–12.2	10.3–13.5	6.0–7.9
60–69	13.3–17.3	10.8–14.1	12.2–15.9	12.0–15.7	13.9–18.2	12.1–15.8	10.8–14.1	13.4–17.5	9.7–12.7	10.7–14.0	6.3–8.2
70–79	13.7–17.7	11.1–14.4	12.5–16.3	12.3–16.0	14.3–18.6	12.4–16.1	11.1–14.4	13.8–17.9	10.0–13.0	11.0–14.3	6.5–8.3

Reprinted with permission from Bucthal and Rosenfalck [14], Munsgaard International Publishers Ltd, Copenhagen, Denmark
ADM abductor digiti minimi, *BF* biceps femoris, *Quad* quadriceps, *Tib Ant* tibialis anterior

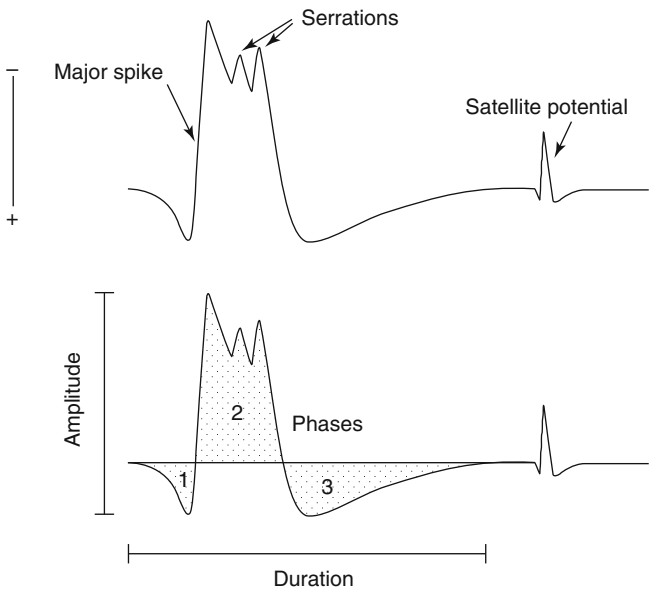


Fig. 7.31 Motor unit action potential measurements. Duration is measured as the time from the initial deflection of the MUAP from baseline to its final return to baseline. It is the parameter that best reflects the number of muscle fibers in the motor unit. Amplitude only reflects muscle fibers very close to the needle and is measured peak to peak. Phases (*shaded areas*) can be determined by counting the number of baseline crossings and adding one. MUAPs are generally triphasic. Serrations (a.k.a. turns) are changes in direction of the potential that do not cross the baseline. The major spike is the largest positive to negative deflection, usually occurring after the first positive peak. Satellite or linked potentials occur following the main potential and usually represent early reinnervated muscle fibers (Reproduced with permission from Preston and Shapiro [1])

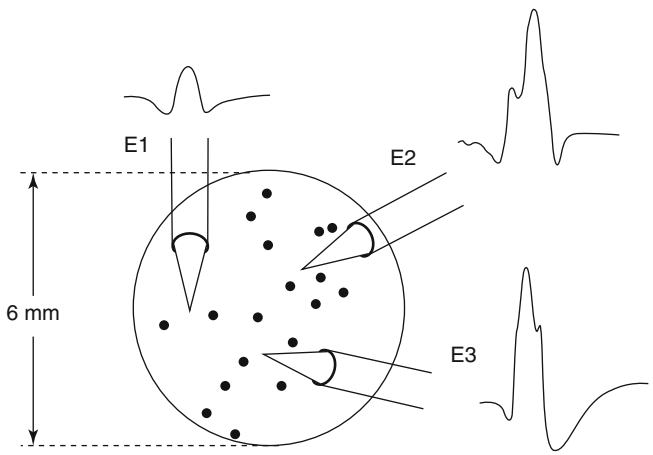


Fig. 7.32 MUAP morphology and needle EMG position. The position of the EMG needle influences the morphology of the recorded MUAP. To properly assess MUAP parameters, the major spike must be as steep as possible, indicating the proximity of the needle to the motor unit. Note that needle electrode position E3 has the shortest major spike rise time and is the preferable position in which to assess the MUAP. Also note that while MUAP amplitude changes markedly with needle position (compare position E1–E3), duration is relatively unaffected (From Dumitru and DeLisa [15]. Muscle Nerve © 1991. Reprinted by permission of John Wiley & Sons, Inc.)

Duration

MUAP duration is the parameter that best reflects the number of muscle fibers within a motor unit. MUAP duration is measured from the initial deflection away from baseline to the final return to baseline. Typical MUAP duration is between 5 and 15 ms. It depends primarily on the number of muscle fibers within the motor unit and the dispersion of muscle fiber depolarizations overtime. This dispersion depends on the longitudinal and transverse scatter of end plates and variations in distances and conduction velocities of distal nerve terminals.

MUAP duration increases with age and with low temperature. MUAP duration correlates well with pitch on the loudspeaker. Long-duration MUAPs (low frequencies) sound dull and thuddy, whereas short-duration MUAPs (higher frequencies) sound crisp and sharp. As the electromyographer gains experience, the sound of a long-duration versus short-duration MUAP becomes unmistakable.

Long-duration MUAPs often show high amplitude and decreased recruitment (see section "Firing Pattern [Activation, Recruitment, and Interference Pattern]"). They are the best indicators of reinnervation. They are usually seen in chronic neurogenic disorders, but may be encountered in chronic myopathies, such as inclusion body myositis, polymyositis, or muscular dystrophy. Long-duration MUAPs are due to increased fiber density in the motor unit, increased number of fibers in the motor unit, or decreased synchrony among its muscle fibers.

Short-duration MUAPs often have low amplitude and early (rapid) recruitment (see section "Firing Pattern [Activation, Recruitment, and Interference Pattern]"). They are caused by loss of muscle fibers from the recorded motor unit, physiologic blockade of end plates, or atrophy of muscle fibers. Short-duration MUAPs are the hallmarks of myopathic disorders, particularly when associated with muscle fiber necrosis. However, they may also be seen in NMJ disorders (e.g., myasthenia gravis and LEMS).

Polyphasia, Serrations, and Satellite Potentials

MUAP configuration may be monophasic, biphasic, triphasic, or polyphasic. Polyphasia depends primarily on the synchrony of muscle fibers firing. The number of phases can easily be calculated by counting the number of baseline crossings of the MUAP and adding one. Normally, MUAPs have two to four phases. However, in normal subjects, 5–10 % of MUAPs may be polyphasic, and this may be up to 25 % in proximal muscles, particularly the deltoid and iliacus muscles. Polyphasic MUAPs have a high-frequency clicking sound on EMG. Increased polyphasia is a nonspecific abnormality, because it may be seen in myopathic and neuropathic disorders.

Serrations (turns or potential reversals) are defined as a change in direction of the potential which does not

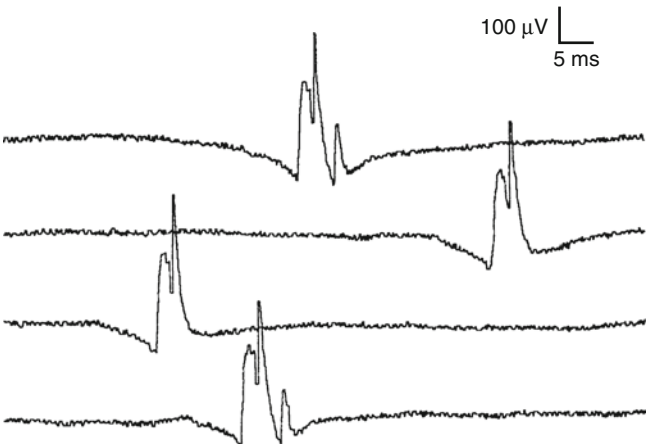


Fig. 7.33 Unstable motor unit action potentials (MUAPs). MUAPs that change in amplitude or number of phases from impulse to impulse are called unstable MUAPs. Unstable MUAPs occur in both primary NMJ disorders and disorders associated with new or immature NMJs as commonly occurs early in reinnervation. Note the blocking of last phase in the second and third MUAPs. This late phase likely represents an early reinnervated muscle fiber attached to the main MUAP (Reproduced with permission from Preston and Shapiro [1])

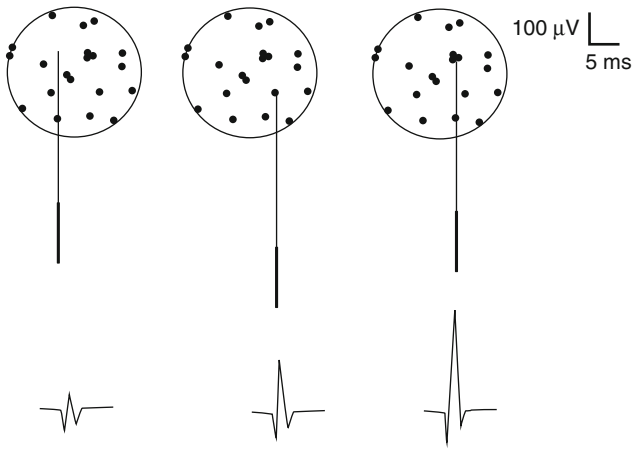


Fig. 7.34 Relationship of MUAP amplitude to needle position. Of all MUAP parameters, amplitude is most dependent on needle position. Only those muscle fibers very close to the needle contribute to amplitude, as opposed to duration where most muscle fibers contribute. Note the change in amplitude as needle is moved to different locations within the same motor unit (Reproduced with permission from Preston and Shapiro [1])

subsequently cross the baseline (see Fig. 7.31). Increased serrations have similar implications as polyphasia, indicating less synchronous firing of muscle fibers within a motor unit. Often, a MUAP turn may be changed into a phase with slight needle movement.

Satellite potentials (a.k.a. linked potentials or parasite potentials) are late spikes of the MUAP, which are distinct, but time locked with the main potential (see Fig. 7.31). Satellite potentials are often seen following early reinnervation of denervated muscle fibers by collateral sprouts from adjacent motor units. The newly formed nerve terminal may be long and is often small, thinly myelinated, and, hence, slowly conducting. Because of slow conduction time, increased distance, or both, reinnervated muscle fibers are seen as satellite potentials that trail the main MUAP. It is useful to record the main MUAP on a trigger line to appreciate a satellite potential and demonstrate that it is time locked to the main potential. Satellite potentials may be unstable (see below), resulting in firing rate variability or intermittent blocking (Fig. 7.33). Over time, the sprout matures, the myelin thickens, and consequently the conduction velocity increases. The satellite potential then fires more closely to the main potential and ultimately fuses with it to become an additional phase or serration within the main complex.

Amplitude

MUAP amplitude is the maximum peak-to-peak amplitude of the potential and varies widely among normal individuals. Most MUAPs have amplitudes greater than 100 µV and less than 2 mV. Unlike duration, only a few muscle fibers of a motor unit contribute to the amplitude. MUAP amplitude only reflects those few fibers nearest to the needle's tip.

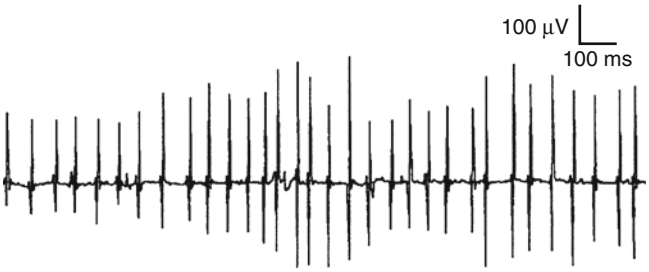


Fig. 7.35 Unstable motor unit action potentials. MUAPs that change in either amplitude or number of phases from impulse to impulse are called unstable MUAPs. Unstable MUAPs occur in both primary NMJ disorders and disorders associated with new or immature NMJs as commonly occurs early in reinnervation. Note the change in amplitude from potential to potential (Reproduced with permission from Preston and Shapiro [1])

Several factors are associated with increased amplitude, including (1) the proximity of the needle to the motor unit (Fig. 7.34), (2) increased density of muscle fibers (increased number of muscle fibers in a motor unit), (3) increased size of muscle fibers (i.e., muscle fiber hypertrophy), and (4) increased synchrony of muscle fibers' firing. On the loudspeaker, the amplitude of the MUAP correlates with volume rather than the pitch.

Stability

Under voluntary control, each firing MUAP is usually stable and has the same amplitude, duration, and morphology. This stability is due to effective transmission across the neuromuscular junction (NMJ), resulting in firing of all muscle fibers of the motor unit. If there is impaired NMJ transmission, unstable (variable) MUAPs may result (Figs. 7.33 and 7.35). Unstable MUAPs occur when individual muscle fibers

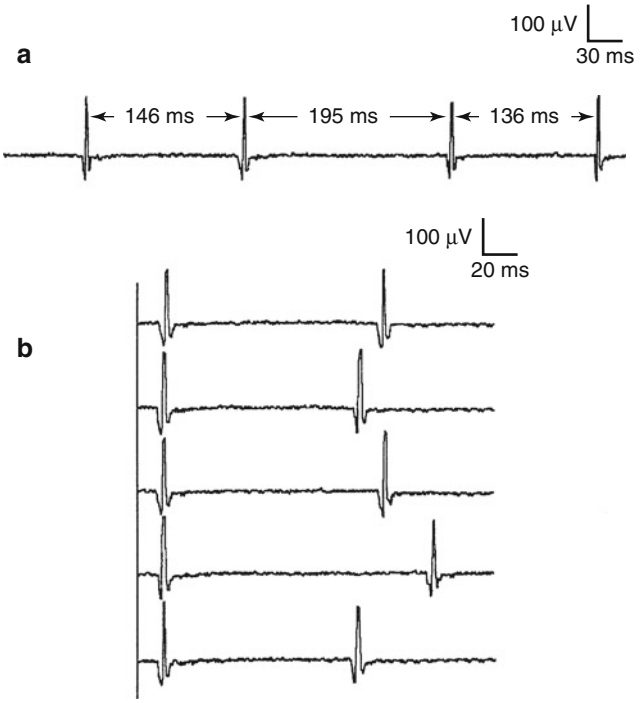


Fig. 7.36 MUAP firing pattern. Normally, MUAPs firing in a semi-rhythmic pattern, with a slight variation in the interval between potentials. (**a**) (*Top trace*) Single voluntary MUAP firing at ë 6 Hz. Note the variation in interpotential intervals; (**b**) (*Bottom trace*) Single voluntary MUAP placed on a delay line and rastered. First potential of each sweep triggers sweep. Note the variation between firing time of the next consecutive MUAP. The pattern is not quite regular (i.e., semi-rhythmic). This firing pattern is only seen with voluntary activated MUAPs (Reproduced with permission from Preston and Shapiro [1])

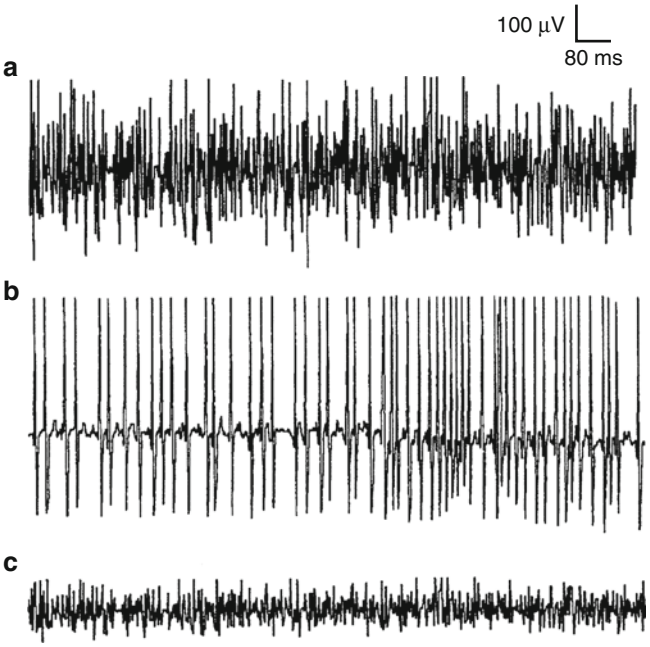


Fig. 7.37 Interference patterns. (**a**) (*Top trace*) Normal; (**b**) (*Middle trace*) Neurogenic; (**c**) (*Bottom trace*) Myopathic. In each trace, the patient is asked to maximally contract. In normals, so many MUAPs fire during maximal contraction that differentiating individual units is difficult. In neurogenic recruitment, a reduced number of MUAPs fire at a high frequency, resulting in an incomplete interference pattern. In myopathic recruitment, while the number of MUAPs is normal, the interference pattern consists of short-duration, small amplitude MUAPs (Reproduced with permission from Preston and Shapiro [1])

are either blocked or come to action potential at varying intervals. An unstable MUAP changes in configuration from impulse to impulse. Either the amplitude or number of phases or serrations changes between potentials. Unstable MUAPs always indicate unstable NMJs and occur in primary disorders of the NMJ (e.g., MG, LEMS), as well as in neuropathic and myopathic disorders associated with denervation and reinnervation. During the early process of reinnervation, newly formed (immature) NMJs often fail to conduct NMJ transmission faithfully. This results in variability in end-plate transmission or intermittent blocking of transmission across some of the muscle fibers within a motor unit.

Firing Pattern (Activation, Recruitment, Interference Pattern)

Under voluntary control, MUAPs normally fire in a *semi-rhythmic pattern*, with slight variation in the time interval between the same MUAP as it fires consecutively (Fig. 7.36). This unique firing pattern distinguishes MUAPs from fibrillation potentials or positive waves, which are fairly regular; CRDs, which are perfectly regular; myotonic discharges, which have a waxing/waning quality; myokymic discharges, which fire in a bursting pattern; and fasciculation potentials, which are very irregular.

At a given time, one may enhance muscle force by either increasing the firing rate of motor units or by adding (recruiting) additional motor units. In normal conditions, one increases force using a combination of these two processes, resulting in an orderly recruitment of motor units. Initially, a single motor unit begins firing semi-rhythmically at 4–5 Hz. As one attempts to increase force, the first motor unit increases its firing rate, and then a second motor unit begins to fire, and so forth. This process continues, with the firing rate increasing and additional motor units being recruited, as force is increased. *Normally*, *the ratio of firing frequency to the number of different MUAPs firing is approximately 5:1*. Hence, by the time the first MUAP firing frequency reaches 10 Hz, a second MUAP should begin to fire; by 15 Hz, a third unit should fire; and so forth. For most muscles, the maximal firing frequency is 30–50 Hz. Important exceptions include quick ballistic contraction, in which the firing frequency may transiently reach 100 Hz, and muscles that are predominantly slow twitch (e.g., soleus), in which the maximal firing frequency is approximately 15 Hz.

During maximal contraction, multiple MUAPs normally overlap and create an *interference pattern* in which no single MUAP can be distinguished (Fig. 7.37). The interference pattern reflects the number of MUAPs firing in relation to their firing rate and depends on two processes: activation and

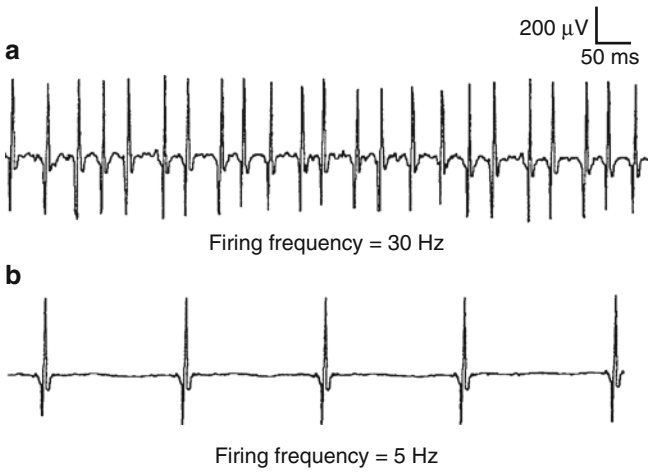


Fig. 7.38 Incomplete interference patterns. In both traces, the patient is asked to maximally contract their muscle with the needle EMG in place. (**a**) The *top trace* demonstrates an incomplete interference pattern due to reduced recruitment. (**b**) The *bottom trace* demonstrates an incomplete interference pattern due to reduced activation (Reproduced with permission from Preston and Shapiro [1])

recruitment. *Activation*, a central process, refers to the ability to increase motor units' firing rates. Hence, poor activation may be seen in central nervous system (CNS) disorders affecting motor unit control or as a manifestation of pain, poor cooperation, or functional disorders. *Recruitment* refers to the ability to add motor units as the firing rate increases. Recruitment is reduced in lower motor neuron disorders and, occasionally, in severe end-stage myopathy.

Recruitment may be assessed during maximum contraction by examining the interference pattern or during moderate levels of contraction by estimating the number of MUAPs firing for the level of activation (firing rate). For example, if only one MUAP is firing at 15–20 Hz (medium level of activation), then recruitment is decreased, regardless of the interference pattern. During maximal contraction, judging the relationship between the number of MUAPs firing and the firing rate can actually be difficult. Maximal contraction is most valuable in excluding mild degrees of decreased recruitment.

An incomplete interference pattern may be due to either poor activation or reduced recruitment. *Decreased recruitment* occurs when there has been loss of MUAPs, usually through axonal loss or conduction block. It may also occur in severe myopathy, wherein MUAPs are effectively lost, due to complete loss of muscle fibers within a MUAP. In Fig. 7.38, tracings from two patients are shown; both were asked to maximally contract the sampled muscle. In the first case (top trace), there is a single MUAP firing rapidly at 30 Hz. Thus, while the firing rate is maximal, only one MUAP is seen firing at 30 Hz. In a normal muscle, one should see 5–6 different MUAPs firing by the time the firing rate reaches 30 Hz (approximately 5:1 ratio). Thus, in this upper trace, the interference pattern is reduced due to decreased recruitment, but activation (firing rate) is normal. Contrast this with the tracing from the second patient (bottom trace), in whom there was a single MUAP firing at 5 Hz. Thus, the firing rate (activation) is clearly submaximal, although the number of MUAPs firing (recruitment) is normal for the firing rate (approximately 5:1 ratio). In this case, the interference pattern is reduced primarily due to decreased activation, but recruitment (number of MUAPs) is appropriate for the level of activation. In this case, the patient's weakness is reflected in the decreased activation of motor units, judged by submaximal sustained firing rate. This pattern of reduced activation may be seen if a patient cannot fully cooperate, perhaps secondary to pain, or if they have a CNS lesion (e.g., stroke, multiple sclerosis).

Poor activation and decreased recruitment may occur simultaneously in disorders affecting both upper and lower motor neurons, such as amyotrophic lateral sclerosis, or in patients with neuropathic disorders and pain (e.g., difficulty flexing or abducting the hip in a patient with painful L5 radiculopathy).

Early (*increased*) *recruitment* refers to the inappropriate firing of many motor units to generate a small amount of force. In diseases in which there is dropout of individual muscle fibers from a motor unit (e.g., myopathies or NMJ diseases with block), the motor unit becomes smaller and subsequently can generate less force. Because each motor unit generates less force, many motor units must fire to generate even a small amount of force. This is known as early recruitment, which refers to the inappropriate firing of many motor units to generate a small amount of force. On the EMG monitor, many MUAPs will appear to fire almost simultaneously with small amounts of force, as assessed by the electromyographer. In addition to early recruitment, mild and severe myopathies may result in normal or reduced recruitment, respectively.

Factors Affecting Nerve Conduction Studies and Needle EMG

Failure to understand the artifacts and technical factors that can influence EDX studies may lead to difficulty obtaining potentials, may prolong a study, and, most importantly, can result in the mistaken impression of pathology where none exists (Table 7.6). Physiologic variables, such as limb temperature, age, and anomalous innervations, as well as nonphysiologic factors, such as electrode impedance and electrical noise, may lead to difficulty obtaining potentials, variability of results among different studies, and misinterpretation of results.

Table 7.6 Important technical factors influencing nerve conduction studies and EMG

Physiologic factors
Temperature
Age
Height
Proximal versus distal nerve segments
Anomalous innervations
Nonphysiologic factors
Electrode impedance mismatch and 60 Hz interference
Stimulus artifact
Filters
Cathode position
Supramaximal stimulation
Co-stimulation of adjacent nerves
Electrode placement
Antidromic versus orthodromic recording
Distance between recording electrodes and nerve
Distance between active and reference recording electrodes
Limb position and distance measurements
Sweep speed and sensitivity

From Preston and Shapiro [1], with permission

Physiologic Factors

Temperature

Temperature is the most important physiologic factor, affecting nearly every parameter measured in NCSs and needle EMG, including conduction velocity, distal latency, and waveform morphology. Cooling produces a delay in activation of sodium channels in axon and muscle membranes, which lead to an increase in the size of the nerve and muscle fiber action potentials.

Cool limb temperature results in slowing of distal latencies and conduction velocities, more so in large than small myelinated fibers. As the large myelinated fibers are those typically recorded during routine NCSs, changes in temperature may have significant effects. Conduction time slows in a fairly linear manner within the normal physiologic range of limb temperature (approximately 21–34 °C). In normal peripheral nerve, motor and sensory conduction velocities slow between 1.5 and 2.5 m/s for every 1 °C drop in temperature, and distal latencies prolong by approximately 0.2 ms/°C.

Cooling also has a significant effect on CMAP and SNAP morphology. Cooling results in higher-amplitude and longer-duration CMAP and SNAP (Fig. 7.39). This effect is more pronounced in sensory fibers. *The combination of increased amplitude with slow distal latency* (*or slowing of conduction velocity*) *is characteristic of a cool limb*.

Lowering the temperature has a similar, though less marked and somewhat controversial, effect on MUAPs. MUAP duration and amplitude increase with cooler temperatures (Fig. 7.40) and, correspondingly, the number of phases may also increase.

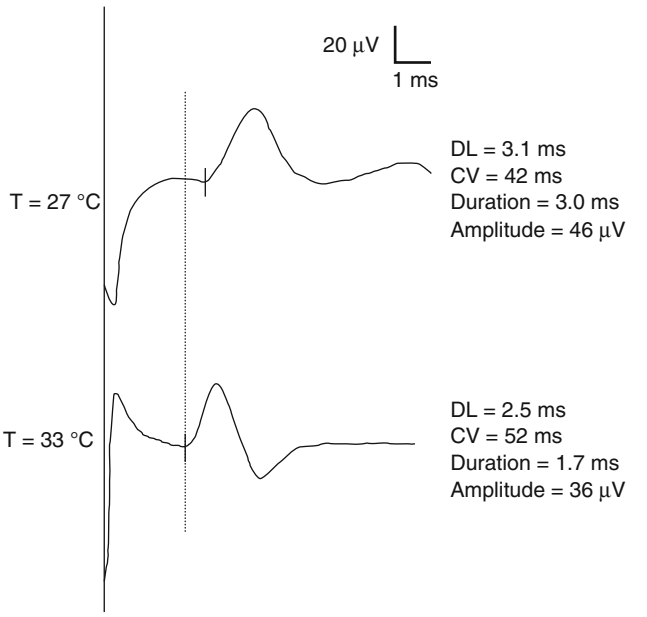


Fig. 7.39 Temperature effect on nerve conduction studies. Median antidromic sensory studies, stimulating wrist, recording second digit. Same patient at different limb temperatures. Note that with cooler limb temperature (*top*), distal latency and conduction velocity slow, while duration and amplitude increase (Reproduced with permission from Preston and Shapiro [1])

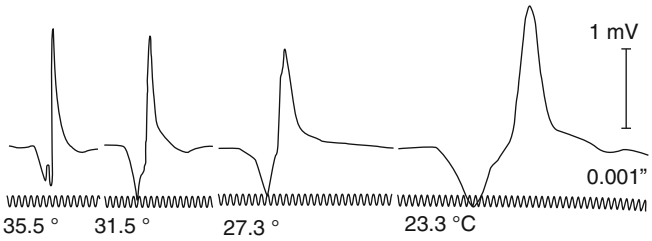


Fig. 7.40 Effect of muscle temperature on motor unit action potential (From Daube [16])

Therefore, limb temperatures should be routinely recorded and monitored in all patients and ideally maintained between 33 and 34 °C. If a limb is cool, immersing the limb in warm water and allowing it to heat up over several minutes is the best warming method. Surface heating with a heating lamp can be used, but often requires a long time to heat the limb adequately and may be hazardous (resulting in burns particularly in patients with impaired sensation). Warming packs or a hydroculator can also be used, particularly in bedridden or intensive care unit patients. Nerve conduction time correction factors can be used for cool temperatures, but are not as preferable as rewarming the limb; correction factors may not necessarily apply in a similar manner to patients with diseased peripheral nerves.

Age

Myelination is incomplete at birth. Peripheral nerves continue to myelinate over the first few years of life, with myelination completed between the ages of three and five. Nerve conduction velocities in newborn infants are approximately 50 % of normal adult values. They quickly increase after birth, reach approximately 75 % of adult normal values by 1 year of age, and are equivalent to adult values by the age of 2–3 years. Distal latencies and conduction velocities remain relatively unchanged throughout adulthood, but have a tendency to slow slightly with advancing age. This effect is slightly more pronounced for sensory than motor fibers, begins as early as the age of 20 years, and becomes more prominent after the age of 40. Overall, motor and sensory conduction velocities decrease by approximately 0.5–4 m/s/decade.

Age also has an effect on CMAP and SNAP amplitudes, both increasing in the first 2–3 years of life and declining slowly after the age of 60 years. This also affects SNAP amplitudes more prominently, so much that normal SNAP amplitude drops up to 50 % by age 70.

Nerve conduction studies reference values should account for age-related changes in SNAP and CMAP amplitudes and in conduction velocities. Commonly, tables of normal control values provide lower limits of normal of nerve conduction parameters, usually for subjects between ages 10 and 60 years. Because normal values for the elderly are not generally available, additional correction factors of 0.5–4 m/s/decade can then be used for older patients. For example, a median motor conduction velocity of 46 m/s (lower limit of normal = 49 m/s) in a 90-year-old patient would be considered normal, within the expected range for advanced age.

Assessment of lower extremity SNAPs in an elderly individual, such as the sural or superficial peroneal sensory response, can be difficult. Because the sural sensory response is often a small potential in healthy subjects above the age of 60 years, it may be challenging to elicit. Thus, very low amplitude or absent lower extremity SNAPs in the elderly must always be interpreted with caution and are not necessarily considered abnormal without other confirmatory data.

Age also affects many parameters of the MUAP on needle EMG. The most prominent change is an increase in MUAP duration. From birth through childhood, the duration increases due to the physiologic increase of muscle fiber and motor unit size. In later life, the aging process is associated with a drop-out of motor units, which results in a small degree of reinnervation, which in turn results in slight prolongation of MUAP duration. Additionally, long-duration and high-amplitude MUAPs may be seen in the intrinsic muscles of the foot, particularly in the elderly patient [2].

Height

Height influences nerve conduction velocity. Taller individuals commonly have slower conduction velocities than shorter persons. The effect of nerve length also explains, in part, the slower conduction velocities in the lower extremities, compared to the upper extremities. For example, on average, the normal sural sensory conduction velocity is 5 m/s slower than the median sensory conduction velocity, and the peroneal and tibial motor velocities are typically 6–9 m/s slower than the median and ulnar motor.

Two separate factors likely account for the effect of height or limb length on conduction velocity. First, nerves taper as they proceed distally. In general, the taller the individual, the longer the limb, and the more tapered the distal nerve. Because conduction velocity is directly proportional to nerve diameter, the more distally tapered nerves in taller individuals conduct more slowly. By the same reasoning, nerves in the leg conduct more slowly than those in the arm, because of the longer limb length and more distal tapering. Second, limbs are cooler distally than proximally, and the legs are generally cooler than the arms. Thus, conduction velocity slowing due to cooling is usually more prominent in the legs than the arms and in tall subjects. Modifications must be made for individuals of extreme height, just as they are for extremes of age. In practice, this adjustment is usually no more than 2–4 m/s below the lower limit of normal. For example, for an individual who is 6′10″ (208 cm) tall, a tibial conduction velocity of 38 m/s (normal >41 m/s) should be considered within the normal range.

Location of Nerve Segment

Nerve conduction velocities vary between the distal and proximal segments of a limb because of changes in nerve diameter and temperature. As outlined above, proximal nerve segments tend to conduct slightly faster than distal segments in a normal individual. This is likely due to: (1) distal nerve segments are tapered and therefore conduct more slowly than proximal segments and (2) distal limb segments are cooler than proximal segments and therefore conduct more slowly as well.

Anomalous Innervations

There are important anatomical anomalous innervations of peripheral nerve that must be recognized routine nerve conduction studies. If these anomalies are not recognized, they may easily be mistaken for technical abnormalities or, in some cases, actual pathology. The most common are the Martin-Gruber anastomosis and the accessory deep peroneal nerve.

Martin-Gruber Anastomosis

The Martin-Gruber anastomosis (MGA) is a crossover of median-to-ulnar fibers. This anastomosis involves only motor fibers with sensory fibers being spared. The crossover usually occurs in the mid-forearm and rarely in the proximal forearm, either directly from the main trunk of the median

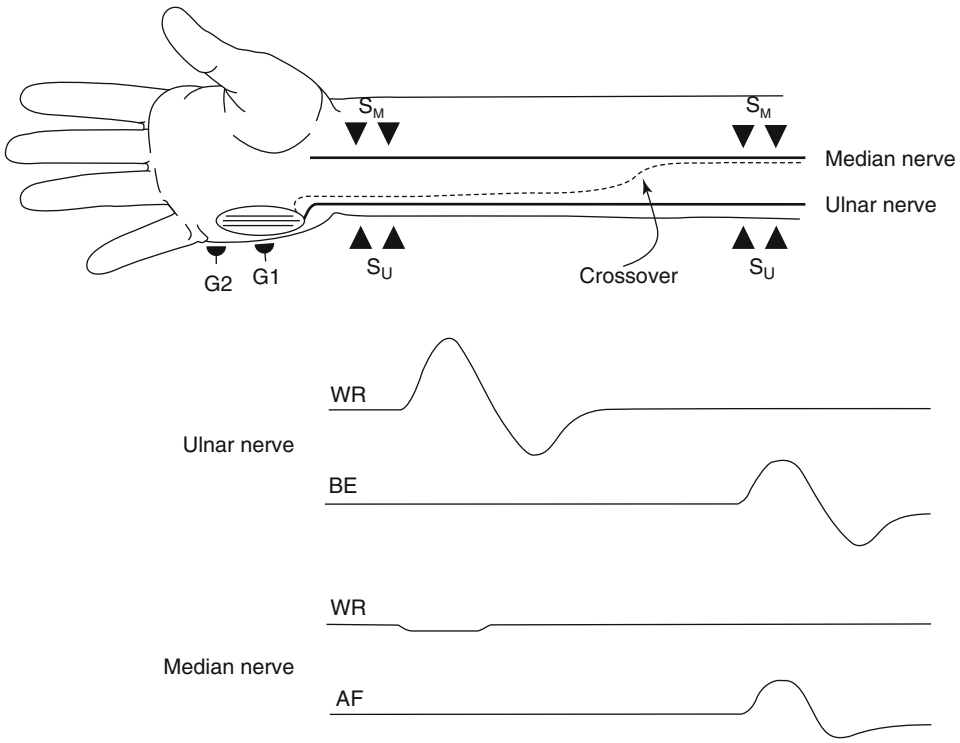


Fig. 7.41 Martin-Gruber anastomosis. Crossover of median-to-ulnar fibers supplying the hypothenar muscles may occur in MGA. During routine ulnar motor studies, recording the abductor digiti minimi and stimulating the ulnar nerve (S_U) at the wrist (*WR*) and below elbow (*BE*), the ulnar CMAP amplitude with below-elbow stimulation is lower than with wrist simulation. If not recognized, a mistaken impression of a conduction block may occur. To demonstrate a MGA in this situation, the median nerve is stimulated (S_M) at the wrist and antecubital fossa, while recording the hypothenar muscles, looking for a CMAP stimulating at the antecubital fossa that is not present stimulating at the wrist (*G1* active electrode, *G2* reference electrode) (Reproduced with permission from Preston and Shapiro [1])

nerve or from one of its branches, most commonly from the anterior interosseous nerve. The median fibers that have crossed over then run with the distal ulnar nerve to innervate either of the following ulnar muscles: (1) the hypothenar muscles (abductor digiti minimi), (2) the first dorsal interosseous muscle, (3) the thenar muscles (adductor pollicis, deep head of flexor pollicis brevis), or (4) a combination of these. This anomaly is quite common and occurs in approximately 15–30 % of patients. When present, it may be unilateral or bilateral.

During routine nerve conduction studies, the MGA may be recognized during several circumstances. First, the anomaly is often recognized during routine ulnar motor studies, recording either the abductor digiti minimi or first dorsal interosseous, stimulating at the wrist and below-elbow sites (Fig. 7.41). If a MGA is present, a characteristic pattern results with a drop in the ulnar CMAP amplitude between the wrist and the below-elbow stimulation sites. With stimulation at the wrist, the CMAP reflects all motor fibers innervating the ulnar muscles, including those that have crossed over from the median nerve. However, stimulation below the elbow activates fewer numbers of fibers, as some fibers innervating the ulnar muscles originate from the median nerve and cross over in the forearm. Other than a MGA, this pattern may also be seen with excessive stimulation of the ulnar nerve at the wrist, resulting in co-stimulation of the median nerve, submaximal stimulation of the ulnar nerve at the below-elbow site, and in true conduction block of the ulnar nerve between the wrist and below-elbow sites. Occasionally, MGA is proximal and the conduction block occurs across the elbow (between below-elbow and above-elbow stimulations), mimicking ulnar neuropathy at the elbow [17].

If a reduced ulnar CMAP is found at the proximal ulnar stimulation site (below elbow or above elbow) compared to the wrist, it is essential to first check that co-stimulation has not occurred at the wrist and that submaximal stimulation has not occurred at the proximal sites. Note that up to a 10–20 % drop in the ulnar CMAP amplitude at the below-elbow sites compared to wrist sites may occur in normal subjects, secondary to physiologic temporal dispersion. The major danger in not recognizing a MGA in this situation is to mistakenly interpret the findings as an unequivocal sign of ulnar nerve demyelination, that is, a conduction block in the forearm or across the elbow [17]. Whenever there is a >10–20 % drop in amplitude between the wrist and proximal sites on routine ulnar motor studies, median nerve stimulation should be performed at the wrist and at the antecubital fossa. If there is no MGA present recording the hypothenar muscles, no CMAP is noted or a small broad response positive deflection is recorded with both the wrist and antecubital fossa stimulation sites, reflecting a volume-conducted potential from median muscles. If a MGA is present recording the hypothenar muscles, median stimulation at the antecubital fossa will evoke a small CMAP over the abductor digiti minimi, while no CMAP or a small and broad positive volume-conducted potential will be present with median nerve stimulation at the wrist. The amplitude of the CMAP, evoked

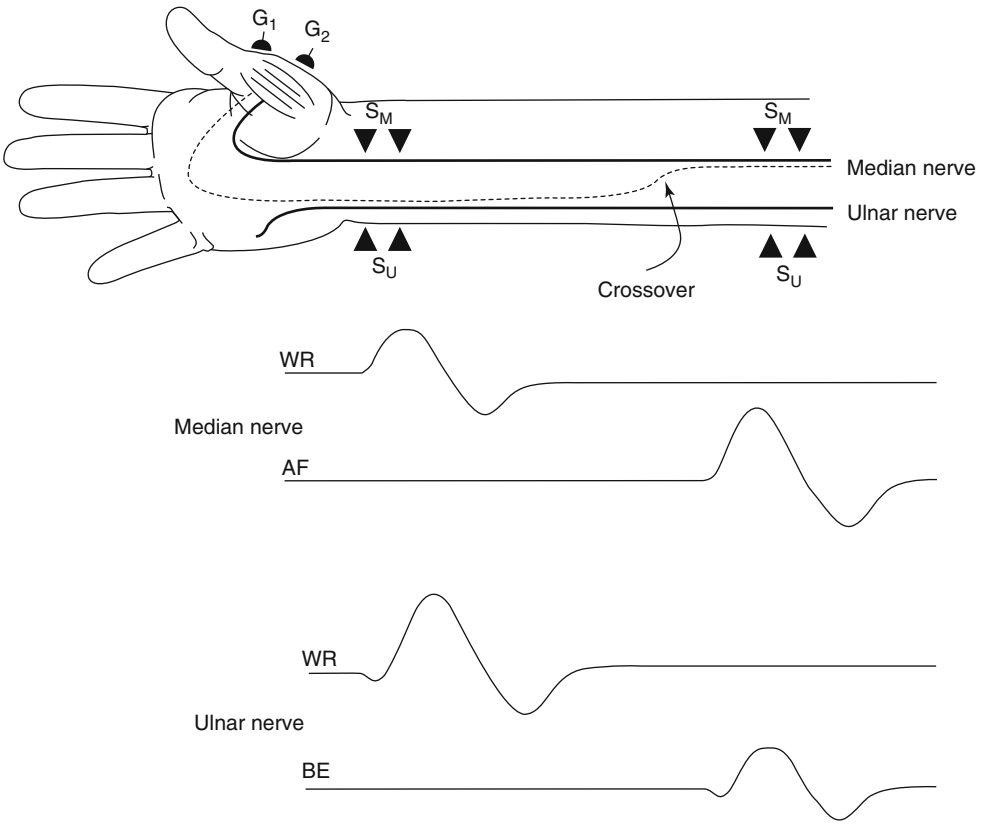


Fig. 7.42 Martin-Gruber anastomosis. Crossover of median-to-ulnar fibers supplying the thenar muscles may occur in MGA. During routine median motor studies, recording the abductor pollicis brevis and stimulating (S_M) at the wrist (*WR*) and the antecubital fossa (*AF*), the median CMAP amplitude stimulating the antecubital fossa is higher than that obtained with wrist simulation. Routine ulnar studies, recording the hypothenar muscles, are normal. To demonstrate a MGA in this situation, the ulnar nerve is stimulated (S_U) at the wrist and below elbow (*BE*), while recording the thenar muscles, looking for a drop in CMAP amplitude between the wrist and below elbow (*G1* active electrode, *G2* reference electrode) (Reproduced with permission from Preston and Shapiro [1])

by stimulating the median nerve at the antecubital fossa (recording the hypothenar muscles), will approximately equal the difference between the CMAP amplitudes evoked with ulnar nerve stimulation at the wrist and below-elbow site (or between below-elbow and above-elbow sites). If there is no MGA present recording the first interosseous muscle, small CMAPs with equal amplitudes are noted with both median nerve stimulations at the wrist and antecubital fossa, reflecting volume-conducted potential from the median thenar muscles into the first interosseous muscle recording site. If a MGA is present recording the first dorsal interosseous muscle, median stimulation at the antecubital fossa and wrist will evoke a CMAP over the first dorsal interosseous muscle, with the CMAP stimulating the antecubital fossa being larger than when stimulating the wrist. The difference in amplitudes of the CMAP, evoked by stimulating the median nerve at the antecubital fossa and wrist (recording the first dorsal interosseous muscle), will approximately equal the difference between the CMAP amplitudes evoked with ulnar nerve stimulation at the wrist and below-elbow sites (or below-elbow to above-elbow sites).

The second instance where a MGA should be suspected is during routine median motor studies, when the median-to-ulnar crossover innervates one of the ulnar innervated thenar muscles (i.e., adductor pollicis or deep head of the flexor pollicis brevis). With this type of MGA, routine ulnar motor studies, recording the abductor digiti minimi, will be normal. However, during routine median motor studies, recording the thenar muscles, a characteristic pattern develops: a higher CMAP amplitude stimulating the median nerve at the antecubital fossa than at the wrist (Fig. 7.42). Causes of this pattern include (1) submaximal stimulation of the median nerve at the wrist, (2) excessive stimulation of the median nerve at the antecubital fossa resulting in co-stimulation of the ulnar nerve, or (3) a MGA with crossing fibers innervating the thenar eminence.

To demonstrate that a MGA is present, the ulnar nerve must then be stimulated at the wrist and below-elbow sites while recording the thenar muscles. Normally, ulnar stimulation at the wrist, recording thenar muscles, evokes a thenar CMAP, usually with an initial positive deflection. This CMAP reflects the normal ulnar innervated muscles in the thenar eminence. If no MGA is present, subsequent stimulation of the ulnar nerve at the below-elbow site will evoke the same size CMAP potential. If a MGA is present, the CMAP amplitude will be substantially lower, stimulating the ulnar nerve at the below-elbow site than at the wrist. The difference in amplitude between these two potentials approximately equals the contribution of the crossing fibers.

When performing routine needle EMG, anatomical localization is based on the pattern of muscles involved and those spared. However, a patient with a MGA may have a different pattern than what is expected. For instance, a proximal lesion of the median nerve at or above the antecubital fossa may

cause abnormalities in median innervated muscles as expected. However, in a patient with a coexistent MGA, EMG abnormalities may also be seen in ulnar innervated hand muscles (especially the FDI and ADM that are commonly sampled during routine EMG). The opposite may occur with lesions of the ulnar nerve at or above the elbow. In this situation, there may be paradoxical sparing of ulnar innervated hand muscles if they receive a substantial portion of their innervation from the median-to-ulnar crossover fibers. This underscores that nerve conduction studies are needed to properly interpret any findings on needle EMG.

Accessory Deep Peroneal Nerve

The accessory deep peroneal nerve (ADPN) in the lateral calf is the most common anomalous innervation in the lower extremity. It is present in 19–28 % of the general population, based on electrophysiological studies, and in up to 67 %, based on anatomical studies, with a likely autosomal dominant mode of inheritance [18, 19]. This anomaly involves the innervation of the extensor digitorum brevis (EDB) muscle. The EDB is the usual muscle recorded during routine peroneal motor conduction studies and is normally innervated exclusively by the deep peroneal nerve. Patients with an ADPN will have an anomalous innervation to the EDB with the medial portion of the EDB supplied by the deep peroneal nerve as usual, but with the lateral portion supplied by an anomalous motor branch originating from the superficial peroneal nerve, the ADPN (Fig. 7.43).

During routine nerve conduction studies, this anomaly is recognized during peroneal motor studies. If the anastomosis is present, the peroneal CMAP amplitude, recording the EDB, is higher stimulating at the below-fibular neck and lateral popliteal sites than with stimulation at the ankle (Fig. 7.44). This pattern can be caused by either (1) submaximal stimulation of the peroneal nerve at the ankle site, (2) excessive stimulation of the peroneal nerve at the below-fibular neck and lateral popliteal sites causing co-stimulation of the tibial motor fibers, or (3) an ADPN.

To demonstrate the presence of an ADPN is quite simple and straightforward. An ADPN, if present, originates from the distal superficial peroneal nerve and travels down the lateral calf, posterior to the lateral malleolus. Following stimulation posterior to the lateral malleolus while recording the EDB, a small CMAP will be evoked if an ADPN is present. Commonly, the amplitude of CMAP, evoked by stimulating the ADPN posterior to the lateral malleolus, will approximately equal the difference between the CMAP amplitudes evoked with ankle and below-fibular neck/lateral popliteal stimulation sites of the peroneal nerve, recording the EDB.

Rarely, the EDB is totally and exclusively innervated by the ADPN [20]. This will result in an absent CMAP stimulating the peroneal nerve at the ankle with a normal CMAP stimulating proximally. The peroneal CMAP evoked behind the lateral malleolus is large and almost equals the below-fibular neck peroneal CMAP. When such a rare anomaly occurs along with a deep peroneal nerve lesion, EDB function is preserved, clinically and with needle EMG confirmation, despite evidence of severe deep peroneal nerve palsy.

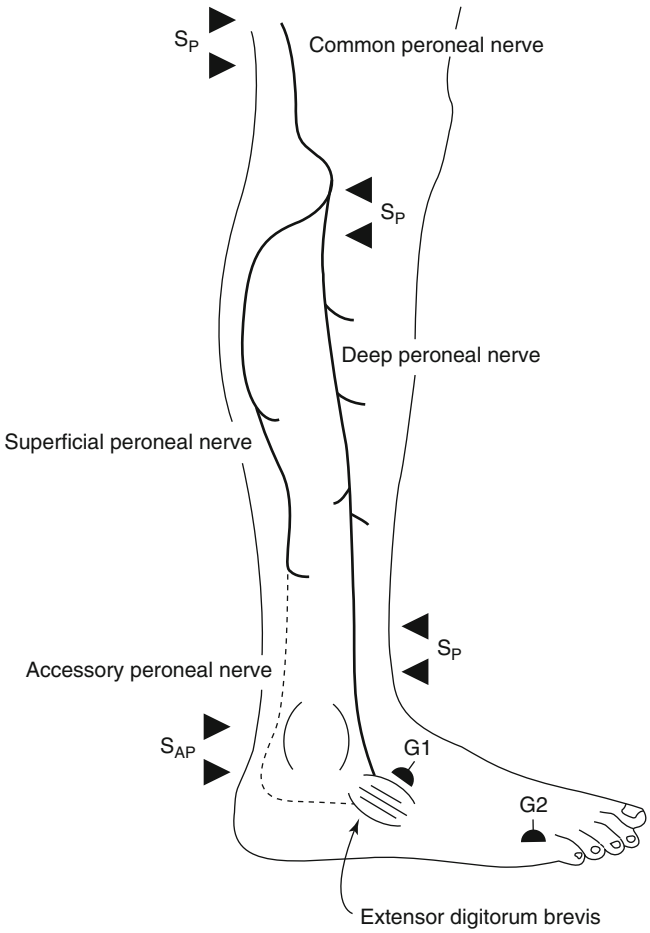


Fig. 7.43 Accessory peroneal nerve. The APN is derived from the distal superficial peroneal nerve and runs posterior to the lateral malleolus to supply the lateral portion of the extensor digitorum brevis muscle. During routine peroneal motor studies, recording the extensor digitorum brevis, the peroneal nerve is stimulated (S_P) at the ankle, below-fibular neck, and at the lateral popliteal fossa. If an APN is present, the CMAP amplitude will be higher stimulating below the fibular neck and lateral popliteal fossa as compared to stimulating at the ankle. To demonstrate an APN, stimulation is performed posterior to the lateral malleolus (S_{AP}), while recording from the extensor digitorum brevis muscle, looking for a CMAP (*G1* active electrode, *G2* reference electrode) (Reproduced with permission from Preston and Shapiro [1])

Riche-Cannieu Anastomosis

The Riche-Cannieu anastomosis is a hand anomaly with communication between the recurrent motor branch of the median nerve and the deep branch of the ulnar nerve. This results in dual motor innervation of some of the intrinsic hand muscles such as the first dorsal interosseous, adductor

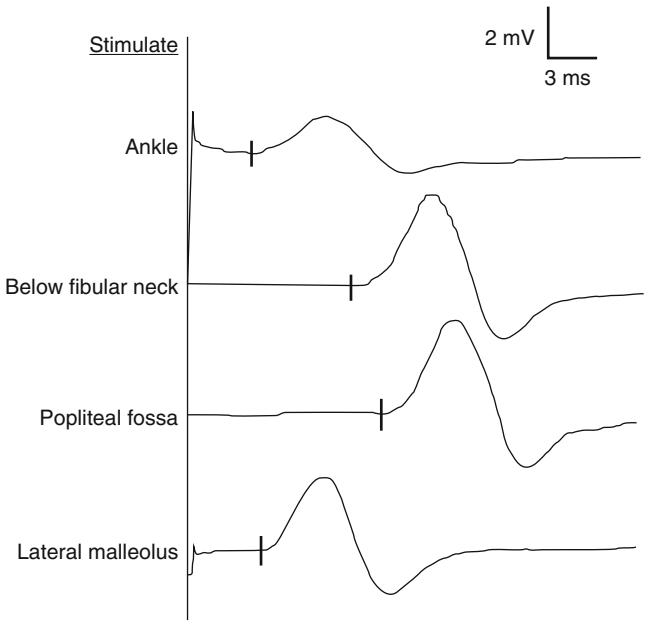


Fig. 7.44 Accessory peroneal nerve (APN). Routine peroneal motor study, recording the extensor digitorum brevis (EDB), stimulating at the ankle (*top trace*), below-fibular neck (*second trace*), and lateral popliteal fossa (*third trace*). The CMAP amplitude is higher stimulating below the fibula neck and popliteal fossa sites compared to stimulation at the ankle site. An APN is confirmed by stimulating posterior to the lateral malleolus and recording the EDB (*bottom trace*) (Reproduced with permission from Preston and Shapiro [1])

pollicis, and abductor pollicis brevis. Anatomical studies and surgical reports suggest that this anastomosis is common. However, this is not frequent apparent clinically or during nerve conduction studies. When prominent, this anastomosis is most evident during routine median motor nerve conduction studies. The median CMAP recording the abductor pollicis brevis is low in amplitude, stimulating wrist and antecubital fossa with normal distal latency, conduction velocity, and needle EMG. Stimulating the ulnar nerve at the wrist will evoke a robust CMAP recording abductor pollicis brevis. Care should be taken not to induce co-stimulation into the median nerve at the wrist. Also, when this anomaly is prominent, a severe or complete median or ulnar nerve lesion may be associated with relative sparing of some median innervated muscles or ulnar innervated muscles in the hand, respectively.

Nonphysiologic Factors

Electrode Impedance and Noise

All signals recorded during the NCSs and needle EMG are the result of differential amplification (Fig. 7.45), in which the difference between the signals at the active (G1) and reference (G2) electrodes is amplified and displayed. Therefore, if the same electrical noise is present at both the active and reference electrodes, it is subtracted out, and only the signal of interest is amplified (i.e., common mode rejection).

The best way to achieve identical electrical noise at each electrode is to ensure that the impedance at each electrode is identical (i.e., prevent electrode impedance mismatch). Impedance is an electrical term combining the effects of resistance to flow for a DC current and capacitance for an AC current. As per Ohm's law, the voltage (E), in this case the voltage from electrical noise, equals the current (I) induced from the electrical noise multiplied by the resistance (R) or impedance (E = IR). If the resistance or impedance is different at each electrode, then the same electrical noise will induce a different voltage at each electrode input. This difference is then amplified and displayed, often obscuring the signal of interest.

The most common cause of electrical noise in the EMG laboratory is 60-Hz interference generated from other electrical devices such as lights and computers. This noise interferes mostly with recording small potentials, such as SNAPs or fibrillation potentials. The best way to eliminate 60-Hz interference is for each electrode to appear identical to the amplifier (Table 7.7). To achieve this, one must use intact electrodes without frayed or broken connections and prepare the skin with either alcohol or acetone to remove dirt and oil. Conducting electrode jelly is then applied to the electrode before it is attached to the skin. The recording electrodes should be held firmly against the skin with tape or a Velcro band. Lastly, the closer the electrodes are to each other, the more likely any associated electrical noise will appear identical to a differential amplifier.

Stimulus Artifact

The stimulus artifact occurs in every NCS and serves a useful purpose by indicating when the shock occurred and from which point latencies are measured. However, the stimulus artifact may obscure the onset of the recorded potential if its trailing edge overlaps with that potential, leading to inaccurate measurements of both amplitude and onset latency (Fig. 7.46). This occurs most commonly when the recording electrode is placed at very short distance from the stimulating point. The following are recommendations for reducing stimulus artifacts:

- Place ground between stimulator and recording electrodes.
- Reduce electrode impedance mismatch between the recording electrodes.
- Use coaxial recording cables.
- Lower the stimulator intensity.
- Rotate the anode of the stimulator while maintaining the cathode.
- Increase the distance between stimulator and recording electrodes.
- Ensure that the stimulator and recording electrode cables do not overlap.

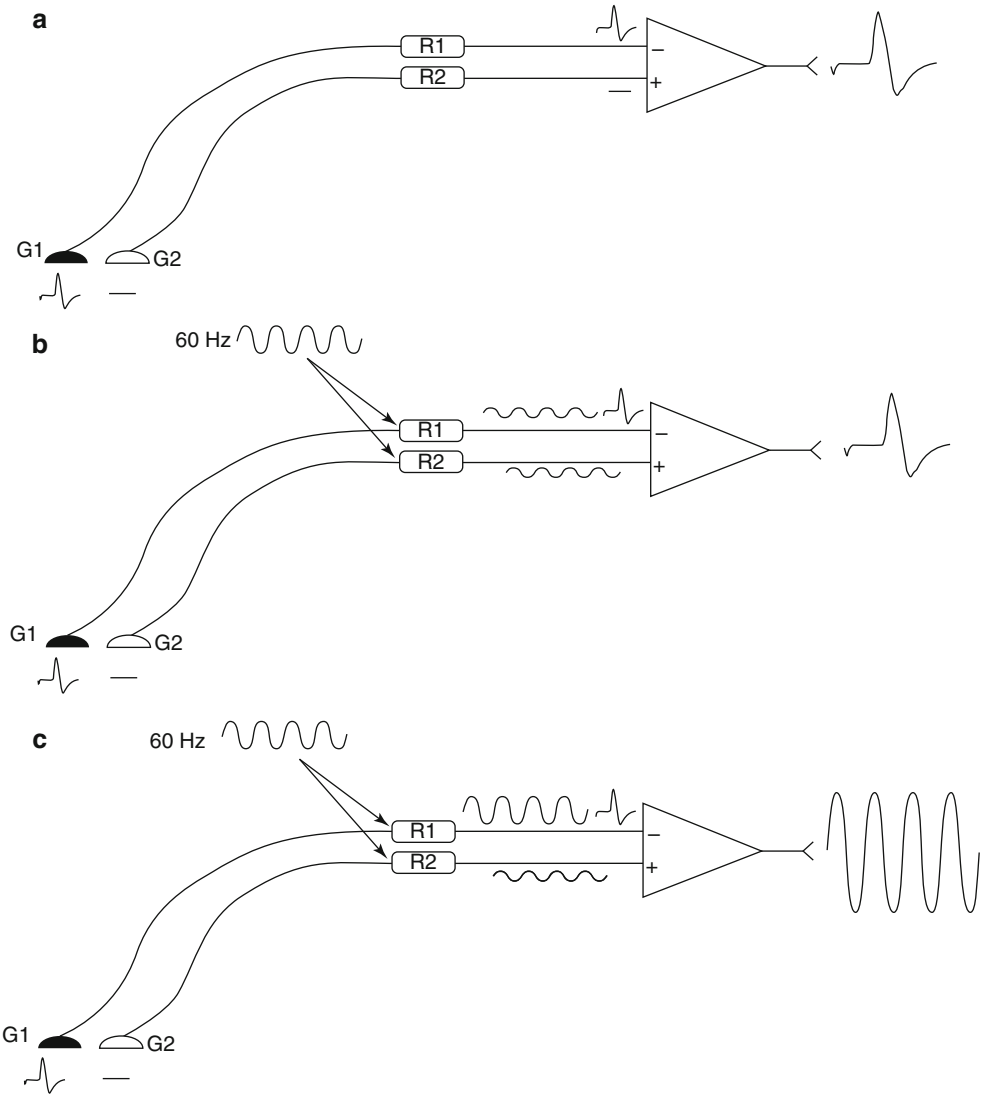


Fig. 7.45 Differentiation amplification and electrode impedance mismatch. All signals recorded in nerve conduction studies and EMG result from differential amplification. The signal present at the reference electrode (*G2*) is subtracted from the signal seen at the active electrode (*G1*) and amplified (**a**). Each recording electrode has its own impedance or resistance, modeled as R1 and R2 above, for the active and reference electrodes, respectively. If R1 and R2 are identical, any 60-Hz interference will induce a similar electrical noise at both inputs (**b**). This noise will then be subtracted out, and only the signal of interest will be amplified. However, if electrode impedances are mismatched (R1 > R2), then the amount of electrical noise will be different at the two inputs (**c**). Some of the electrical noise will then be amplified, often obliterating or obscuring the signal of interest (Reproduced with permission from Preston and Shapiro [1])

Table 7.7 Methods to reduce electrode impedance mismatch and 60-Hz interference

Active and reference recording electrodes should be the same type
Ensure all contacts are intact without any frayed or broken connections
Clean all dirt and oil from the skin with alcohol or acetone
Apply conducting electrode jelly between the skin and electrodes
Secure electrodes firmly to the skin with tape or velcro straps
Place ground between stimulator and recording electrodes
Use coaxial recording cables

From Preston and Shapiro [1], with permission

Filters

Every recorded potential during NCSs and needle EMG passes through a low- and high-frequency filter before being displayed. Filters help to reproduce the signal of interest and reject low- and high-frequency electrical noise. Low-frequency (high pass) filters exclude signals below a set frequency, while allowing higher-frequency signals to pass through. In contrast, high-frequency (low pass) filters exclude signals above a certain frequency, while allowing lower-frequency signals to pass through. Low-frequency noise (<10 Hz) results in wandering of the baseline (close to DC current), whereas high-frequency noise (>10 kHz) commonly obscures high-frequency potentials (e.g., SNAPs or fibrillation potentials). Hence, the high-frequency filter is set lower for sensory NCSs than for motor NCSs.

The use of filters has some disadvantages. Filtering does not completely exclude all signals above the high-frequency or below the low-frequency settings. Filtering also results in some loss or alteration of the signal of interest. For instance, as the low-frequency filter is reduced, more low-frequency signals pass through, and the duration of the recorded potential increases slightly. Likewise, as the high-frequency filter is lowered, more high-frequency signals are excluded, and the amplitude of the recorded potential usually decreases.

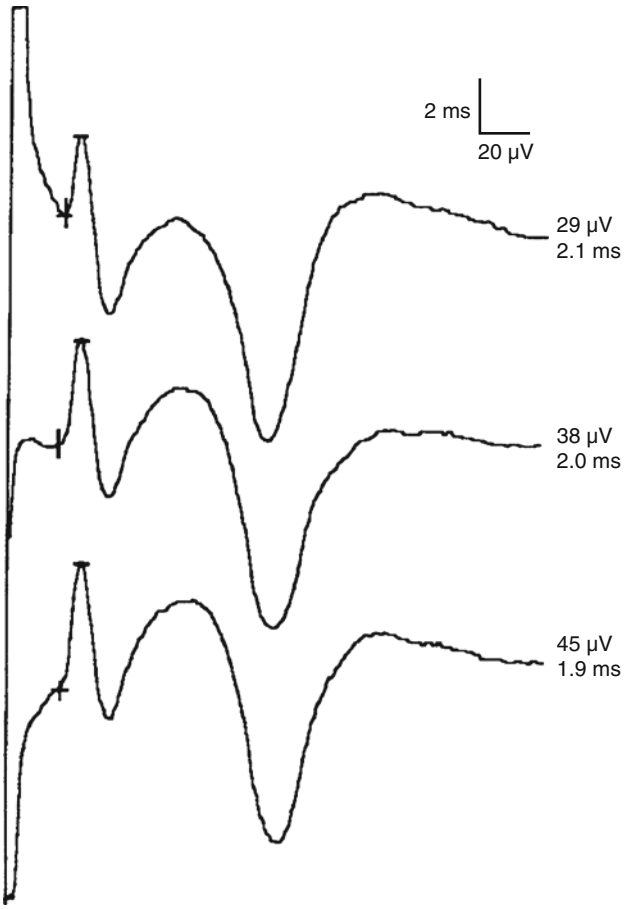


Fig. 7.46 Stimulus artifact and measurement error. Median antidromic sensory study, stimulating wrist, recording second digit. Stimulus artifact can be influenced by rotating the anode while maintaining the cathode in place. Large negative stimulus artifacts (*top*) may result in artifactually low amplitudes and prolonged latencies. Conversely, large positive stimulus artifacts (*bottom*) may result in artifactually large amplitudes and short latencies (Reproduced with permission from Preston and Shapiro [1])

Accordingly, all potentials should be obtained with standardized filter settings and only compared to normal values based on studies using the same filter settings. The recommended low and high filter settings for motor conduction studies are 10 and 10 kHz, respectively. For sensory conduction studies, the low- and high-frequency filter settings are 20 and 2 kHz.

Stimulator Position

When performing NCSs, the proper position of the stimulating cathode is to face the active recording electrode, and distance measurements should always be made between the cathode and the active electrode. If the cathode and anode of the stimulator are inadvertently reversed, there are two possible effects. First, although depolarization occurs under the cathode, hyperpolarization theoretically occurs at the anode. This hyperpolarization may create an anodal block, preventing the depolarization that occurs under the cathode from proceeding past the anode. The resultant SNAP or CMAP may then be reduced or absent. Second, the distal latencies prolong by approximately 0.3–0.4 ms, which represents the approximate time that it takes a normal nerve to traverse 2.5–3.0 cm, the typical distance between the cathode and anode of a stimulator. However, the proximal motor conduction velocities, which are calculated between a distal and proximal site, remain unchanged because the distal latencies are subtracted in velocity calculations. These erroneous findings on NCSs may be misinterpreted as a polyneuropathy or distal entrapment mononeuropathies.

Supramaximal Stimulation

All NCS measurements are based on the assumption that all axons are depolarized using supramaximal stimulation. To achieve such a stimulation, current intensity is slowly increased until a point is reached where the amplitude of the recorded potential no longer increases. At this point, the current is increased an additional 25 % to ensure that the potential does not change further. If it does not, then one can assume that supramaximal stimulation has been achieved.

If a nerve is not supramaximally stimulated at distal and proximal sites, a mistaken impression of axonal loss may result. If supramaximal stimulation is not achieved at a proximal stimulation site, where it had been so with a distal stimulation site, then the findings may be misinterpreted as evidence of conduction block. Conversely, a submaximal stimulation at a distal site with a supramaximal stimulation at a proximal site may erroneously suggest an anomalous innervation.

In addition to their effect on CMAP and SNAP amplitudes, submaximal stimulations at all stimulation sites result in inaccurate conduction velocities. Conduction velocity measurements assume that the same fibers (i.e., the fastest) are stimulated at distal and proximal sites. Without supramaximal stimulation, one may be erroneously measuring different fibers at different sites, resulting in invalid nerve conduction velocity measurements. Finally, latencies with submaximal stimulations are prolonged because the largest fibers have the highest threshold for stimulation and are evoked last.

Co-stimulation of Adjacent Nerves

As the stimulus current is increased to achieve supramaximal stimulation, the current may spread to excite nearby nerves, which may result in a spuriously large amplitude potential, caused by the inadvertent recording of additional nerve or muscle action potentials beyond the potentials of interest. Common sites of co-stimulation are median and ulnar nerves at the wrist, elbow, or axilla and the common peroneal and tibial nerve stimulations at the knee. Co-stimulation of adjacent nerves is unavoidable when stimulating proximal nerves at Erb's point (e.g., axillary or musculocutaneous nerves) or nerve roots (e.g., C8–T1 spinal roots).

Inadvertent co-stimulation of adjacent nerves, distally but not proximally, may be mistaken for conduction block. In contrast, if co-stimulation occurs proximally but not distally, one may erroneously diagnose an anomalous innervation in certain nerves. In addition, a true abnormal low-amplitude potential may become more "normal" if an adjacent nerve is co-stimulated.

To avoid co-stimulation of adjacent nerves, the examiner should watch the morphology of the waveform carefully, and for the resultant muscle twitch with each stimulation. If there is an abrupt change in waveform configuration or in muscle twitch pattern, especially at higher currents, co-stimulation of adjacent nerves may have occurred. For example, stimulation of the median nerve at the wrist results in a characteristic biphasic CMAP and twitch of the thumb and first two lumbricals. If current is increased to a point where the ulnar nerve fibers are inadvertently co-stimulated, the resultant CMAP becomes notched and the twitch abruptly changes to include the interossei and hypothenar muscles, both features of ulnar nerve stimulation.

If the question of co-stimulation is still not clear, one should simultaneously co-record muscles innervated by adjacent nerves, watching for a potential from the unintended muscle. If this occurs, then the stimulus intensity should be lowered until the unintended potential is no longer seen. For instance, when stimulating the median nerve at the wrist, the abductor pollicis brevis and abductor digiti minimi should be simultaneously recorded. With proper median nerve stimulation, no potential should be recorded from the abductor digiti minimi.

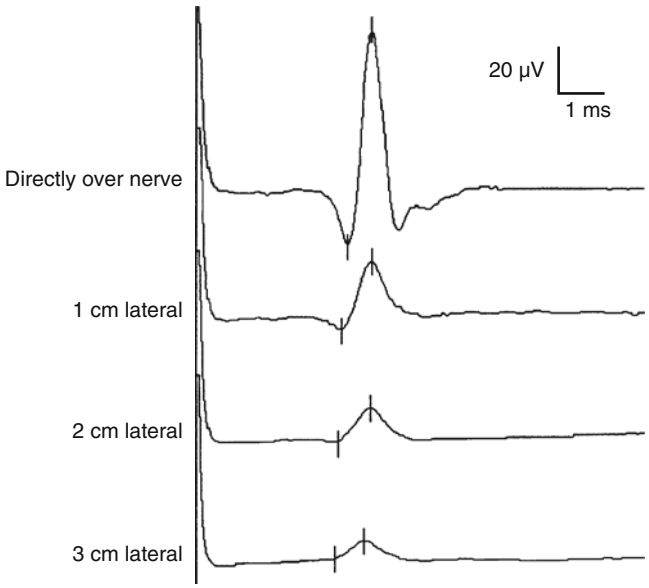


Fig. 7.47 Effect of distance between recording electrodes and nerve. Median mixed nerve study, stimulating wrist and recording antecubital fossa. If the recording electrodes are moved off the nerve, maintaining the same distance, the following changes occur: onset latency shifts to the left, peak latency remains relatively unchanged, and amplitude drops markedly. In nerve conduction studies, side-to-side comparisons between amplitudes are often made, looking for an asymmetry. One can easily appreciate that if the recording electrodes are placed lateral or medial to the nerve on one side and directly over the nerve on the other side, one might be left with the mistaken impression of a significant asymmetry in amplitude. When the location of the underlying nerve is not certain, it is important to try several recording electrode positions to ensure that the maximal amplitude is obtained (From Raynor et al. [21]. *Muscle Nerve* © 1997. Reprinted by permission of John Wiley & Sons, Inc.)

Recording Electrode Placement

Because muscle depolarization occurs first at the motor end-plate zone, the preferred montage for recording motor conduction studies is the belly-tendon method: the active electrode (G1) is placed over the center of the muscle belly, while the reference electrode (G2) is placed over the muscle's distal tendon which is presumably an electrically inert point in most motor studies. If the active recording electrode is not placed over the end plate, the volume-conducted depolarization potential first occurs at a distance from the recording electrode and is seen as an initial positive deflection. When the depolarization subsequently travels under the electrode, the potential then becomes negative. This incorrect placement results in two errors. First, the CMAP may not be maximized, giving the mistaken impression of a reduced amplitude. Second, if an initial positive deflection occurs, the latency is difficult to measure. Whenever an initial positive deflection is seen on a motor conduction study, the active electrode has most likely been placed off the motor end plate and should be moved until the positive deflection is no longer seen.

When performing a sensory or mixed NCS, a lower-amplitude nerve action potential is recorded not only when the nerve lies deep (as in orthodromic studies) but also when the recording electrode is inadvertently placed not directly (lateral or medial) over the nerve trunk. The amplitude of the potential decays dramatically with increasing distance from the nerve (Fig. 7.47) [21]. This occurs most frequently with conduction studies of anatomically variable sensory nerve trunks, including the sural, superficial peroneal, medial, and lateral antebrachial cutaneous nerves [22]. A small repositioning of the recording electrodes slightly medial or lateral to the initial recording position often markedly changes the amplitude of the potential. This assures that the highest-amplitude potential is evoked, especially for making side-to-side comparisons. In addition to its effects on amplitude, placing the recording electrodes lateral or medial to the nerve, the onset latency shortens, while the peak latency remains relatively unchanged. Although not intuitively obvious, these changes are due to the effects of volume conduction through tissue. In summary, recording electrodes placed at a distance from the nerve trunk result in a potential that is lower in amplitude and possibly spuriously fast.

Distance Between Active and Reference Recording Electrodes

Every potential recorded in a NCS is the result of the difference in electrical activity between the active and reference recording electrodes. For motor studies, the reference electrode is placed over the distal tendon, which is presumably electrically inactive, rendering the interelectrode distance not significant. However, for sensory and mixed studies, the active and reference electrodes are typically placed in a straight line over the nerve trunk. Accordingly, the nerve segment under the active electrode depolarizes first, followed by depolarization of the reference electrode. If the active and reference electrodes are too close, they may briefly become electrically active at the same time, resulting in a lower-amplitude potential. Taking into account the normal range of nerve conduction velocities, the preferred interelectrode distance between the active and reference recording electrodes for sensory and mixed nerve recordings is 3–4 cm, which ensures that depolarization will not occur under both electrodes simultaneously.

Distance Measurements

To compute a CV, it is assumed that the surface distance accurately represents the true underlying length of the nerve. In most circumstances, this assumption is correct. However, there are several notable exceptions, the most important being that of the ulnar nerve across the elbow. Surgical and cadaver dissection studies have shown that the ulnar nerve is slack and redundant when the arm is in the extended position. If surface distance measurements of the ulnar nerve are made in this position, the true length of the underlying nerve is underestimated. Thus, ulnar conduction studies performed with the elbow extended often result in artifactual slowing of conduction velocity across the elbow segment. When the elbow assumes a flexed position, the measured surface distance of the nerve across the elbow better reflects the true underlying length of the nerve, and a more valid measurement of nerve conduction velocity can be made [23].

Surface distance measurements of several other nerves are often inaccurate. These include the radial nerve at the spiral groove, the peroneal nerve around the fibular head, and the median and ulnar nerves between the axilla and Erb's point. In these situations, obstetrical calipers are recommended to more accurately approximate the true length of the underlying nerve.

Sweep Speed and Sensitivity

Both the sweep speed and sensitivity can markedly influence the recorded latency of SNAPs and CMAPs. As the sensitivity is increased, the onset latency decreases (Fig. 7.48). Conversely, as the sweep speed is decreased, latency measurements usually increase (Fig. 7.49). For this reason, all latency measurements on nerve conduction studies should be made using the same sensitivity and the same sweep speed.

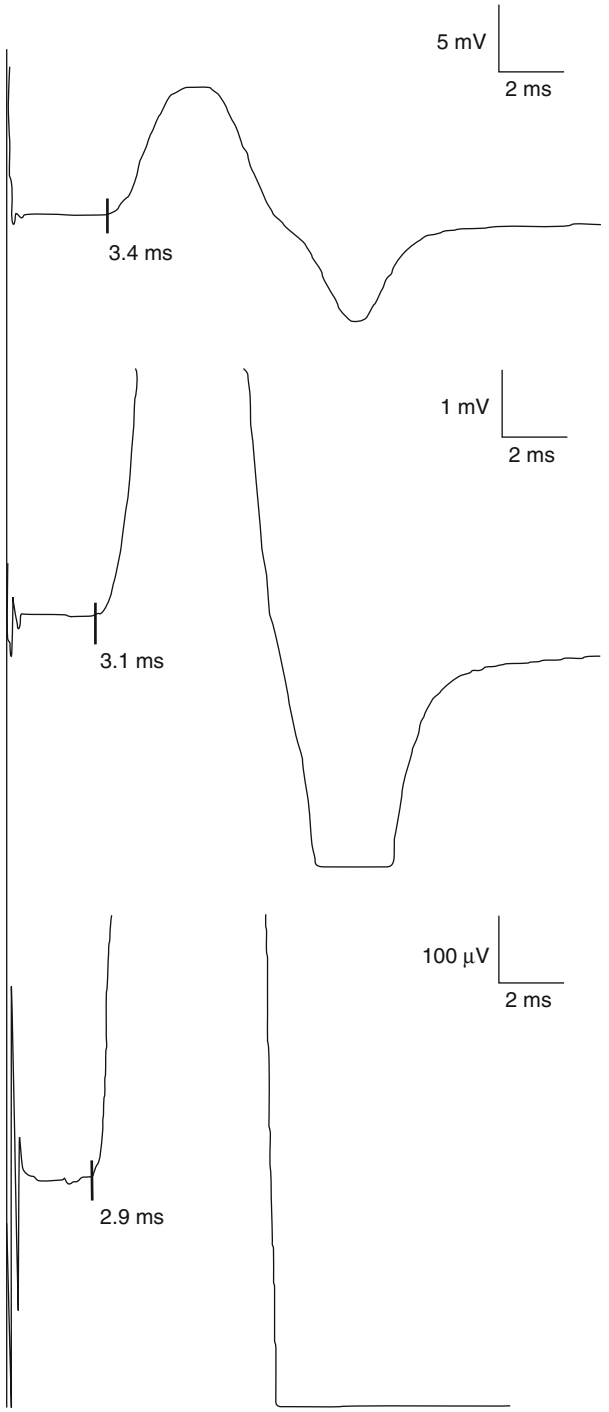


Fig. 7.48 Latency measurement and sensitivity. Median motor study, stimulating wrist, recording the abductor pollicis brevis, using varying sensitivities, with sweep speed held constant. Latency measurements should always be made using the same sensitivity. Note that as sensitivity is increased, latency measurement decreases (Reproduced with permission from Preston and Shapiro [1])

This is especially true within nerves, where potentials obtained with different sweep speeds or sensitivities at distal and proximal stimulation sites along the nerve can easily result in miscalculation of the conduction velocity.

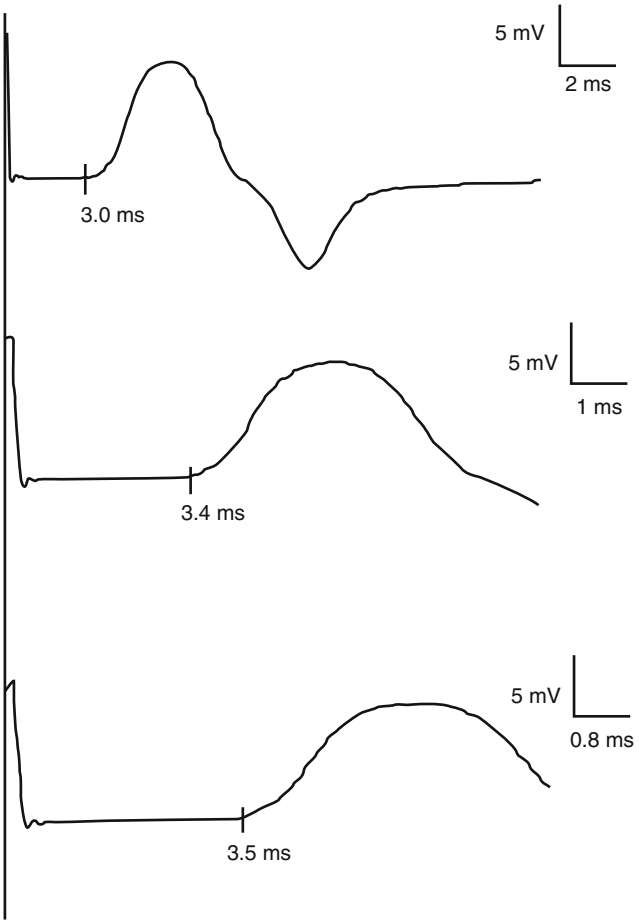


Fig. 7.49 Latency measurement and sweep speed. Median motor study, stimulating wrist, recording the abductor pollicis brevis, using varying sweep speeds, with sensitivity held constant. Latency measurements should always be made using the same sweep speed. Note that as sweep speed decreases, latency measurement usually increases (Reproduced with permission from Preston and Shapiro [1])

Late Responses

NCSs are most often used to assess distal nerve segments, because proximal surface stimulations, such as at Erb's point or the gluteal fold, are technically difficult. Needle, high-voltage, or magnetic stimulations may be used to study proximal nerve segments, although these techniques are also difficult to perform and not widely used. Two late responses, the F wave and H reflex, are commonly used in the EMG laboratory and are useful in assessing proximal nerve segments, but have several limitations (Table 7.8). Although both are usually thought as assessing the proximal nerve segments, they actually conduct through the entire nerve including the distal and proximal segments. However, they are most useful when the routine NCSs, which assess distal nerve segments, are normal. In these situations, when the late responses are abnormal, the findings imply a proximal lesion.

Table 7.8 F response and H-reflex comparison

	F response	H reflex
Afferent	Motor	Sensory (IA muscle spindle)
Efferent	Motor	Motor
Synapse	No	Yes
Nerves studied	All	Tibial-soleus (median-FCR, femoral-quads)
Stimulation	Supramaximal	Submaximal, long duration (1 ms)
Configuration	Usually polyphasic	Triphasic and stable
	Amplitude 1–5 % CMAP	At low stimulation intensity:
	Varies with each simulation	H is present without M
		As stimulation is increased:
		H and M increase
		At high stimulation:
		H decreases and M grows
Measurements	Minimal, maximal latency	Minimal Latency
	Chronodispersion	H/M Ratio (maximal H/maximal M amplitude)
	Persistence	
Major uses	Early Guillain-Barré syndrome	Early polyneuropathy
	C8–T1, L5–S1 radiculopathy	S1 radiculopathy
	Polyneuropathy	Early Guillain-Barré syndrome
	Internal control (entrapment neuropathy)	Tibial, sciatic, L–S1 plexus neuropathy
Normal values	≤32 ms median/ulnar[a]	≤34 ms[a]
	≤56 ms peroneal/tibial[a]	Leg height nomogram
	Compare to F estimate	Height nomogram
	Compare symptomatic to asymptomatic side	≤1.5 ms difference side to sideH/M Ratio ≤50 %
	Chronodispersion <4 ms (median/ulnar)	H-reflex amplitude <50 % difference side to side
	6 ms (peroneal/tibial) Persistence >50 %	
Miscellaneous	In normals, peroneal F waves may be absent or impersistent	Electrical correlate of the ankle jerk
	F responses may be absent in sleeping or sedated patients	Must be present if ankle jerk is present
	F responses may be absent with low-amplitude distal CMAPs	May be present even if ankle jerk is absent
	May be enhanced by Jendrassik maneuver	May be enhanced by Jendrassik maneuver

Adapted from Preston and Shapiro [1], with permission
[a]Assumes median height, normal conduction velocity, and distal latency

F Wave

The F wave is a late motor response which occurs after the CMAP (also referred to in this context as direct motor or M

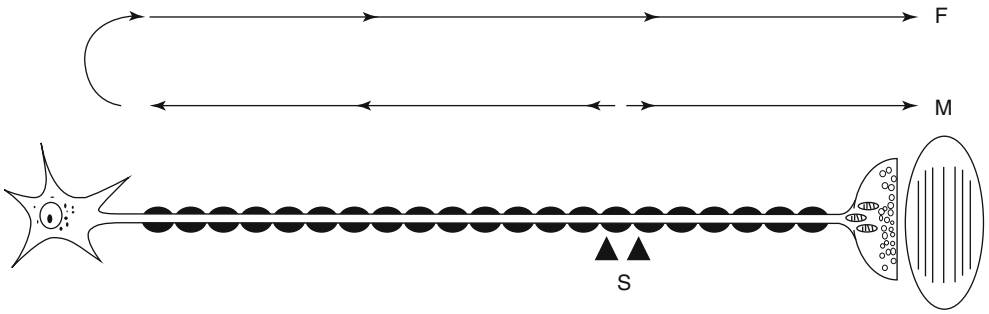


Fig. 7.50 F-response circuitry. When a nerve is stimulated distally (*S*), depolarization occurs both orthodromically and antidromically. The direct muscle response (*M*) occurs from orthodromic travel. The F response (*F*) is derived by antidromic travel to the anterior horn cell, backfiring of some anterior horn cells, and orthodromic travel back down the nerve past the stimulation site to the muscle (Reproduced with permission from Preston and Shapiro [1])

response). The F response derives its name from "foot," as it was first recorded from the intrinsic foot muscles. During a routine motor nerve study, the nerve action potential conducts in two directions, distally (orthodromically) to the NMJ to depolarize the muscle and proximally (antidromically) toward the spinal cord. The F response is triggered by the antidromic nerve action potentials which result in backfiring of a small population (less than 10 %) of anterior horn cells, which results in an orthodromic nerve action potentials toward the muscle (Fig. 7.50). The F response is not a true reflex, because its afferent and efferent loops are purely motor with no intervening synapse. The F response is actually a very small CMAP representing about less than 10 % of the muscle fibers (Fig. 7.51a).

F responses may be obtained easily from any motor nerve, with the exception of the peroneal nerve recording extensor digitorum brevis where F responses may be difficult to elicit even in normal individuals. F responses may also be absent or impersistent in sleeping or sedated subjects. If the stimulator is moved proximally, the latency of the CMAP increases as expected, but the F latency decreases because the action potential travels a shorter distance (Fig. 7.51b). However, with proximal stimulation, the F waves are often superimposed on the terminal CMAP and are more difficult to identify. Hence, they are best identified with distal stimulation.

F-Response Procedure

To obtain an F response, the equipment and recording setup are fundamentally the same as that for a routine distal motor conduction study. However, several technical adjustments need to be made to the EMG machine to record F responses. The gain is increased to 200 μV (as the amplitude of the F response is quite low), and the sweep speed is increased to 5 or 10 ms, depending on the length of the nerve being studied. Supramaximal simulation must be employed, and the stimulator is preferably turned around so the cathode is more proximal, to prevent a potential anodal block (see section "Stimulator Position").

Each F response varies slightly in latency, configuration, and amplitude because a different population of anterior horn cells backfires with each stimulation. As each F response varies in latency and amplitude, it is important to obtain at least ten F responses, preferably on a rastered trace. If F responses are absent or impersistent, one should first ensure that the nerve has been stimulated supramaximally. The Jendrassik (reinforcement) maneuver (e.g., making a fist with the contralateral hand or clenching teeth) before each stimulation can also be useful in helping to prime the anterior horn cells and elicit F waves.

Several measurements may be calculated from the wave including the minimal F-wave latency, maximal F-wave latency, F-wave chronodispersion (maximal minus minimal F-response latency) and F-wave persistence. The *minimal F-wave latency* is the most reliable and useful measurement and represents conduction of the largest and fastest motor fibers. The minimal F-wave latency is dependent on the length of the nerve studied; it is shorter in the arms than in the legs; similarly, taller subjects have longer F-wave latencies than shorter individuals. Because F responses are quite small, there is often some unavoidable error in placing the latency markers. It is best to place the latency marker on the F response at the point that it departs from the baseline, with either a positive or negative deflection. In addition, superimposing the rastered traces is often helpful to determine the minimal latency. Table 7.9 shows normal F-wave minimal latencies, commonly obtained in the upper and lower extremities. *F-wave chronodispersion* is the difference between the minimal (fastest) and maximal (slowest) F response (Fig. 7.52). In the upper extremities, normal chronodispersion is up to 4 ms and in the lower, up to 6 ms. *F-wave persistence* is a measure of the number of F waves obtained for the number of stimulations. Normal F-wave persistence is usually 80–100 % and always above 50 %. Occasionally side-to-side differences in F-wave persistence and chronodispersion help in identifying an abnormality.

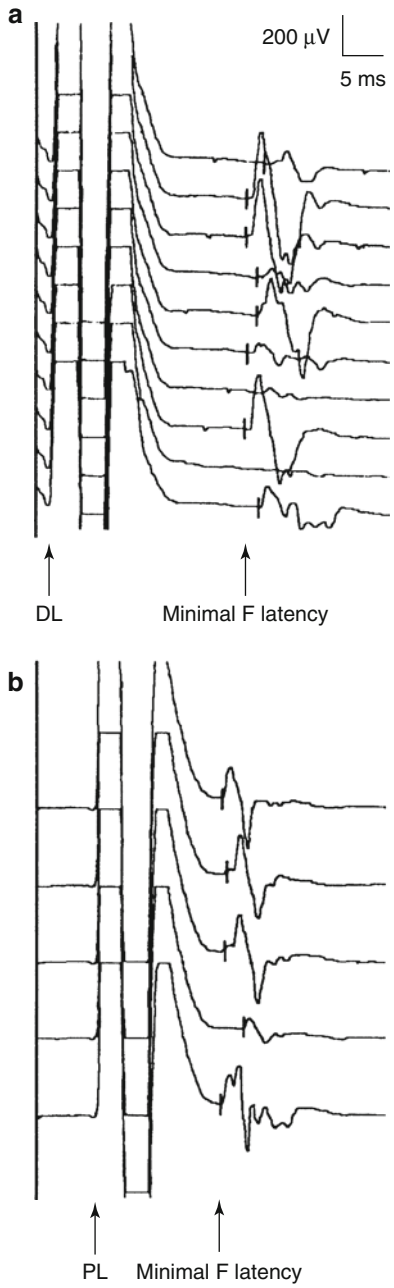


Fig. 7.51 Normal F responses: distal and proximal stimulation. Median F responses recording abductor pollicis brevis, stimulating wrist (**a**) and elbow (**b**). Note that with proximal stimulation, the proximal CMAP latencies increase as expected, but the F-response latencies decrease, due to the F response first traveling antidromically to the spinal cord (*DL* distal CMAP latency, *PL* proximal CMAP latency) (Reproduced with permission from Preston and Shapiro [1])

Table 7.9 Normal minimal values of F-wave latencies in adults, obtained with distal stimulations (wrist or ankle)

Distal	Recording muscle	Upper limit (ms)	Distance (cm)	Side-to-side difference (ms)
Median	Abductor pollicis brevis	<32	<73	<3
Ulnar	Abductor digiti minimi	<32	<73	<3
Peroneal	Extensor digitorum brevis	<57	<127	<4
Tibial	Abductor hallucis	<58	<128	<4

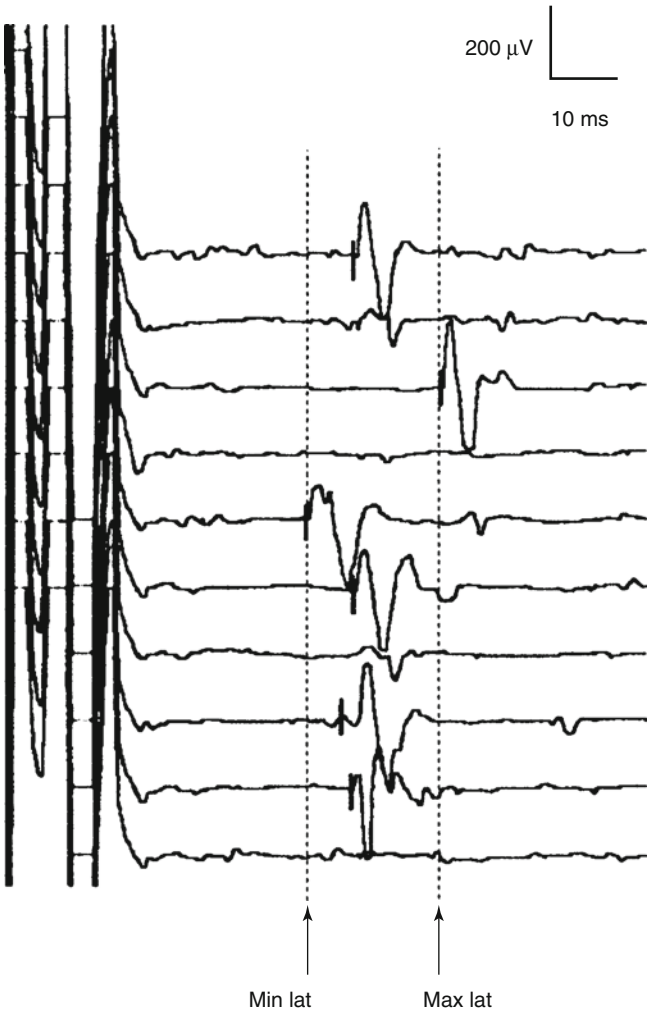


Fig. 7.52 F-response measurements. F responses, 10 rastered traces. Minimal latency is the shortest of the ten responses, representing the largest, fastest conducting fiber. Chronodispersion is the difference between the minimal and maximal latency F response. F-wave persistence is the number of F responses obtained per number of stimulations. In this case, F responses are absent in trace 4 and 10; persistence = 80 % (Reproduced with permission from Preston and Shapiro [1])

Although F responses are usually thought of as assessing the proximal nerve segments, they actually evaluate the entire nerve. A nerve with a prolonged distal motor latency due to a distal entrapment may have a prolonged F latency because the F response must pass through the distal segment of nerve as well. Also, in a generalized polyneuropathy associated with slowing of conduction velocity, the F-wave latency is slowed, reflecting the slowed conduction velocity of the entire nerve. The *F estimate* is a useful calculation to

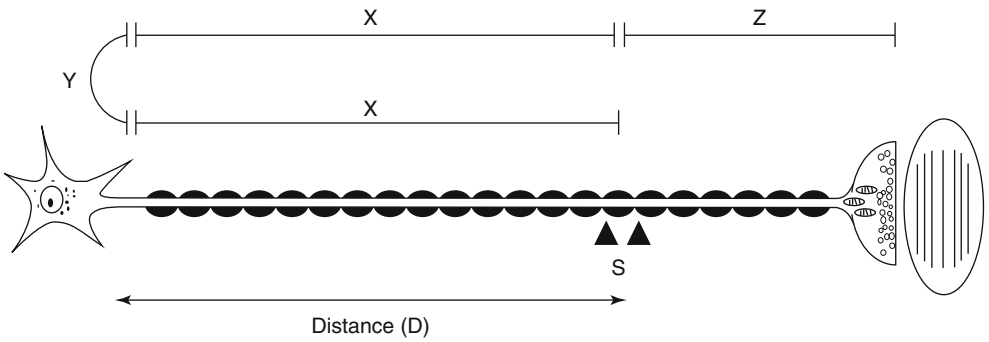


Fig. 7.53 F-estimate calculation. *X* = the time from the stimulation site (*S*) to the spinal cord; *Y* = turnaround time at the anterior horn cell; *Z* = time from the stimulation site to the muscle. Theoretic F estimate = 2*X* + *Y* + *Z*. *X* can be calculated by measuring the distance between the stimulation site and the spinal cord (*D*) which is then divided by the conduction velocity of the nerve. *Z* = distal latency. The turnaround time, *Y*, has been estimated experimentally as 1 ms. Thus, the F estimate = (2*D*/CV) × 10 + 1 ms + DL (a conversion factor of 10 is needed to obtain an answer in ms) (Reproduced with permission from Preston and Shapiro [1])

determine whether a prolonged F-wave latency is due to a lesion of the proximal nerve segment or merely reflects an abnormal distal motor latency or CV or an unusually tall patient. The F estimate determines the theoretic time it should take for the F response to occur, taking into account the distal motor latency, the CV, and the patient's height, as follows (Fig. 7.53). First, the time it takes for the nerve action potential to pass from the stimulation site to the anterior horn cells is estimated by dividing the distance between those sites by the motor nerve CV. The distance between the stimulation site and the spinal cord can be approximated by measuring from the xiphoid process to the stimulation site at the ankle for the peroneal and tibial motor studies and from the C7 spinous process to the stimulation site at the wrist for the median and ulnar studies. A brief turnaround time (approximately 1 ms) at the anterior horn cell is added to that time. Next, the time it takes the nerve action potential to conduct from the anterior horn cell to the stimulation site is again added (this equals the time it takes for the potential to travel up the nerve). Lastly, the distal motor latency is added (i.e., the time it takes the potential to travel from the stimulation site to the muscle).

Hence, the F estimate = (2*D*/CV) × 10 + 1 ms + DL, where *D* = distance from the stimulation site to the spinal cord (cm), CV = conduction velocity (m/s), DL = distal motor latency (ms), and constant 10 is the conversion factor to ms. Characteristically, the actual measured minimal F-wave latency is usually slightly shorter than the F estimate, because the conduction velocity used in the above equation is that of a distal nerve segment (forearm or leg), while the conduction velocity in the proximal nerve segments are slightly faster (due to a combination of larger nerve fiber diameter and warmer temperature). Thus, if the measured minimal F-wave latency is prolonged compared to the F estimate, this implies a delay in the proximal nerve segments, out of proportion to what can be expected for the distal motor latency, motor conduction velocity, and the height of the patient.

Clinical Applications of F Wave

Advantages

The F wave serves a useful purpose in testing the entire nerve circuit and can be used as a good internal control for other nerve conduction abnormalities. For instance, in most polyneuropathies, the F responses are slightly prolonged. In distal entrapment mononeuropathies, such as carpal tunnel syndrome, the F responses are typically prolonged. F responses may have their greatest utility in identifying early polyradiculopathy such as that occurring in Guillain-Barré syndrome. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP), the main subtype of Guillain-Barré syndrome, commonly causes acquired segmental demyelination of the spinal nerve roots. Early in Guillain-Barré syndrome, the routine motor nerve studies may be entirely normal, with prolonged or absent F responses, which implies proximal demyelination. This has been reported in 40–80 % of GBS patients early in the illness and may be the sole EDX abnormality in about ¼ of patients [24, 25].

F responses are generally absent in nerves where the CMAP amplitude is severely reduced due to significant axonal loss. As the F response is 1–5 % of the amplitude of the CMAP, there is a low chance of eliciting an F response from a nerve with such severe axonal loss.

Disadvantages

In theory, the F responses have their greatest utility in the diagnosis of radiculopathy or plexopathy. A prolonged F-wave latency in the context of normal nerve conduction velocity and distal latency may occur in proximal neuropathy, plexopathy, or radiculopathy, but this finding cannot be used to differentiate between these possibilities.

From a practical point of view, their usefulness in the diagnosis of radiculopathies is limited for several reasons:

1. The recorded muscles during motor NCSs are usually innervated by more than one root. Thus, in a single-level radiculopathy, the normal conduction through the

uninvolved root results in normal F-wave minimal latency despite a compressed neighboring root. For example, in L5 radiculopathy, recording a peroneal F wave from the extensor digitorum brevis muscle (innervated by L5 and S1 roots) is frequently normal, because of the normal S1 root. Likewise, with a severe C8 radiculopathy, the median and ulnar F waves are often normal because of the T1 innervation of the abductor pollicis brevis and abductor digiti minimi muscles.

2. Since minimal F-wave latencies are the most reproducible and clinically useful parameter, root compression resulting in motor axon loss can be associated with normal F-wave latencies, because the surviving axons are conducting normally. In order for the F responses to be absent or the minimal latency to be delayed, all or at least most of the nerve fibers must be involved. In these instances, F-wave persistence is usually abnormal and a more useful parameter.
3. If focal slowing occurs at the root segment of the motor axon, the delay in F-wave latency may be obscured, as its latency becomes "diluted" by the relatively long motor axon.
4. Since routine motor NCSs involve recording distal muscles, the F responses can only evaluate the roots and nerve that innervate these muscles. In the upper extremity, median and ulnar motor NCSs are recorded from abductor pollicis brevis and abductor digiti minimi, respectively, both innervated by the C8 and T1 nerve roots. In the lower extremity, peroneal and tibial F waves are obtained recording extensor digitorum brevis and abductor hallucis, supplied by the L5 and S1 nerve roots. Thus, due to this bias, F responses only have utility in assessing possible C8–T1 and L5–S1 radiculopathies. Lesions of the C5, C6, or C7 or L3 or L4 nerve root lesions will not show any F-wave abnormalities.
5. When radiculopathy predominantly affects sensory nerve root fibers (as often occurs with symptoms of pain and radiating paresthesias), the F response, which measures motor fibers only, is normal.

H Reflex

The H (Hoffmann) reflex is a true reflex with a sensory afferent segment, a synapse, and a motor efferent segment. Likewise, there are several other properties that differentiate the H and F responses (see Table 7.8). In newborns, the H reflex may be reproduced from any muscle. However, in adults, the H reflex can only be elicited consistently by stimulating the tibial nerve in the popliteal fossa, recording the gastroc-soleus muscle. An H reflex stimulating the femoral nerve recording the quadriceps muscle, or the median nerve recording the flexor carpi radialis muscle, is described but has significant limitations and so is not clinically useful.

Tibial H-Reflex Procedure

The H reflex involves the IA muscle spindle fibers as sensory afferents and the alpha motor neurons and their axons as efferents (Fig. 7.54). Several adjustments must be made to the EMG equipment to record an H reflex. Similar to changes made for the F response, the gain is increased to 200–500 μV, and the sweep speed is increased to 10 ms/div. Because a submaximal stimulus with a long duration selectively activates the IA fibers, the stimulus duration is increased to 1 ms. The recording montage consists of G1 placed over the soleus, two to three fingerbreadths distal to where it meets the two bellies of the gastrocnemius, and G2, the reference electrode, placed over the Achilles tendon. The tibial nerve is stimulated in the popliteal fossa with the cathode placed proximally at very low stimulus intensities. As the current is slowly increased, a triphasic H reflex first appears at a latency of 25–34 ms. If the H reflex is difficult to elicit, the Jendrassik maneuver can be used to prime the anterior horn cells. As the stimulus intensity is slowly increased, the H reflex continues to increase in amplitude and slightly decrease in latency, and a direct motor (M) potential with a short latency begins to appear. As the stimulus intensity is increased further, the M potential increases in amplitude while the H reflex decreases (Fig. 7.55). At supramaximal stimulation, the H reflex disappears, and the M potential is usually followed by an F wave which replaces the H reflex.

The explanation for these events is as follows: with very low stimulation intensity, the H reflex appears without the M potential, because only the IA afferents are selectively stimulated. As the IA afferents are stimulated, a sensory action potential conducts orthodromically to the spinal cord, crosses the synapse, and creates a motor potential that travels orthodromically down the motor axons to the muscle, generating the H reflex. As the stimulus intensity is increased, both the IA afferents and the motor axons are directly stimulated. At this point, the orthodromic motor fibers generate the M potential, while the antidromic potentials collide with the orthodromically traveling H-reflex potentials, resulting in a decrease in H-reflex amplitude. At supramaximal stimulation, the IA afferents and the motor axons are stimulated at high levels, and there is greater collision, resulting in disappearance of the H reflex which is often replaced by the F response.

Typically, the H reflex with the shortest latency is measured and compared to a set of normal controls for height or leg length (Figs. 7.56 and 7.57). Comparison to the contralateral side is often useful in assessing a unilateral lesion; any difference greater than 1.5 ms is considered significant. In addition, the maximal amplitude of the H response, often measured from peak to peak, is measured and compared to the contralateral side; a difference of more than 50 % in H-reflex amplitude is abnormal. The H response amplitude

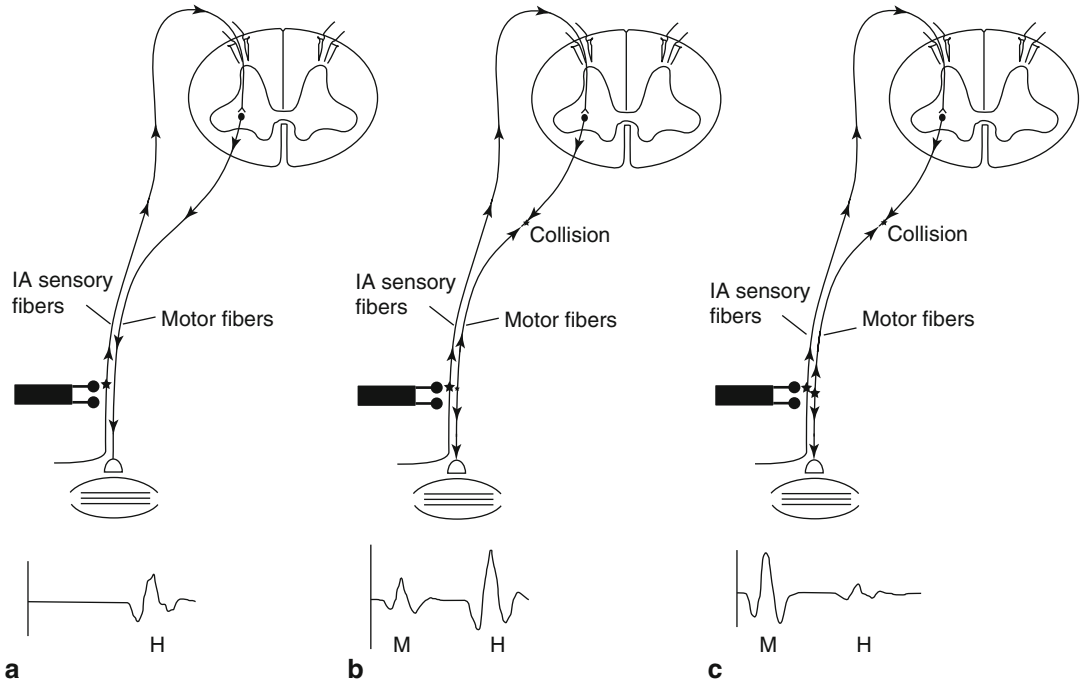
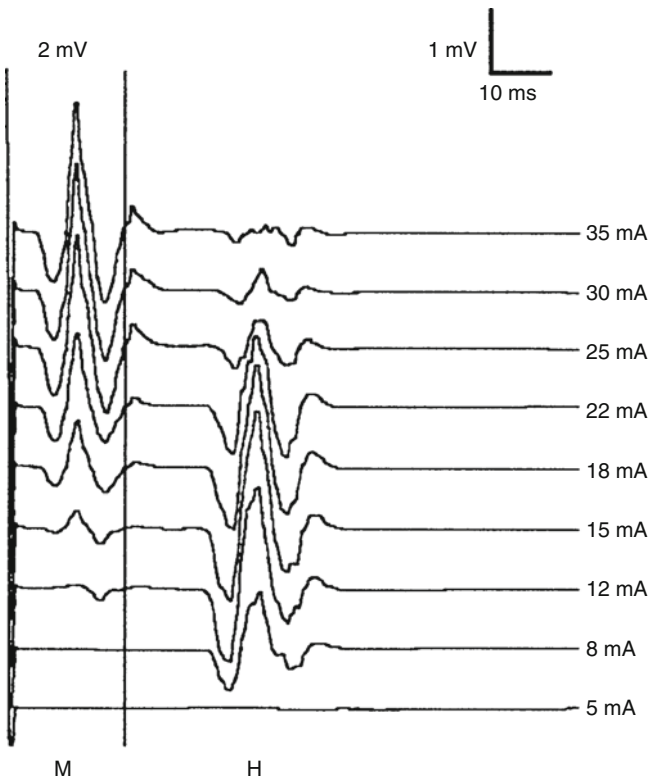


Fig. 7.54 H-reflex circuitry. The afferent loop is formed from IA sensory fibers and the efferent loop from motor axons, with an intervening synapse in the spinal cord. At low stimulation intensity (**a**), the IA sensory fibers are selectively activated, yielding an H reflex without a direct motor (*M*) potential. With increasing stimulation (**b**), more IA sensory fibers are activated, as are some of the motor fibers. The motor fiber stimulation results in a small M potential and some collision proximally of the descending H reflex by the antidromic motor volley. At higher stimulation (**c**), the selective activation of the IA sensory fibers is lost. Both sensory and motor fibers are stimulated at high levels. The motor stimulation results in an increasingly larger M potential. However, the H reflex decreases in size as there is greater collision proximally of the descending H reflex from the antidromic motor volley (Reproduced with permission from Preston and Shapiro [1])



may also be compared to the maximal amplitude of the M potential (measured peak to peak) to calculate an H to M ratio.

Clinical Applications of the Tibial H Reflex

The tibial H reflex is the electrical correlate of the Achilles tendon reflex (ankle jerk), mediated by the S1 arc reflex. The magnitude of ankle jerk correlates well with the amplitude of the tibial H wave, but not with the latency [28]. Any lesion which might decrease the ankle reflex might also reduce the H-reflex amplitude or prolong its latency. Thus, one may see an abnormal H reflex in polyneuropathy, proximal tibial and sciatic neuropathy, and lesions of the S1 nerve root. In addition, the H to M ratio is a crude assessment of anterior horn cell excitability. The H to M ratio often increases in upper motor neuron lesions.

Fig. 7.55 H reflex. Note that as low stimulation intensities, an H reflex is present without a direct motor (*M*) response. With increasing stimulation, the H wave grows and the M response appears. At higher stimulation, the M continues to grow and the H diminishes due to collision between the H-reflex and antidromic motor potentials (Reproduced with permission from Preston and Shapiro [1])

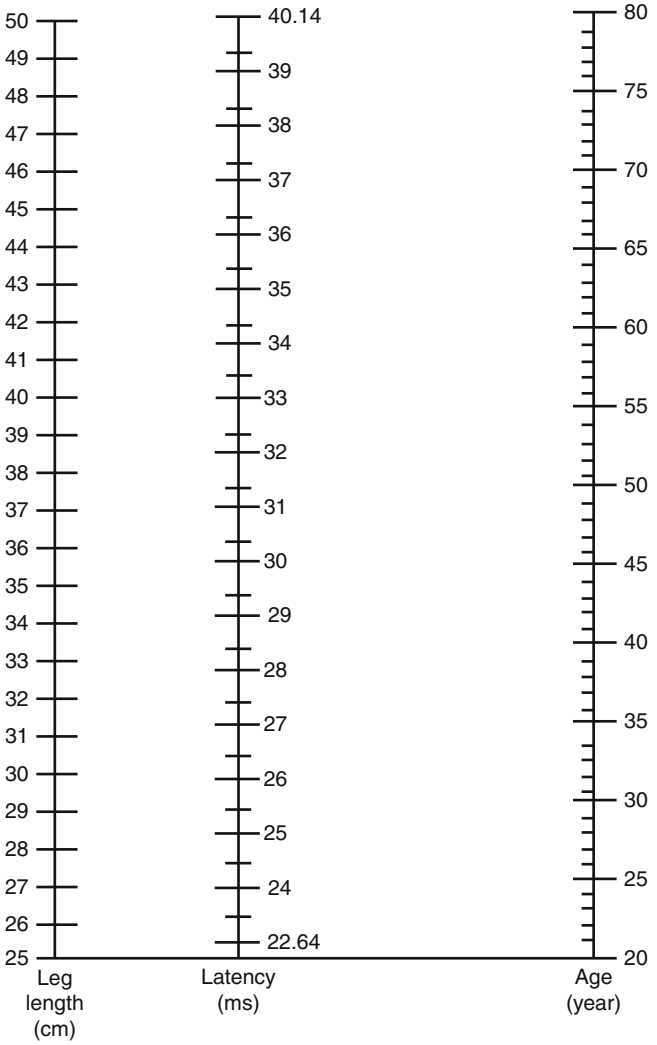


Fig. 7.56 H-latency reference values. Normal H latencies based on leg height and age. Leg height measured between the stimulation site in the popliteal fossa and the medial malleolus (Reprinted with permission from Braddom and Johnson [26])

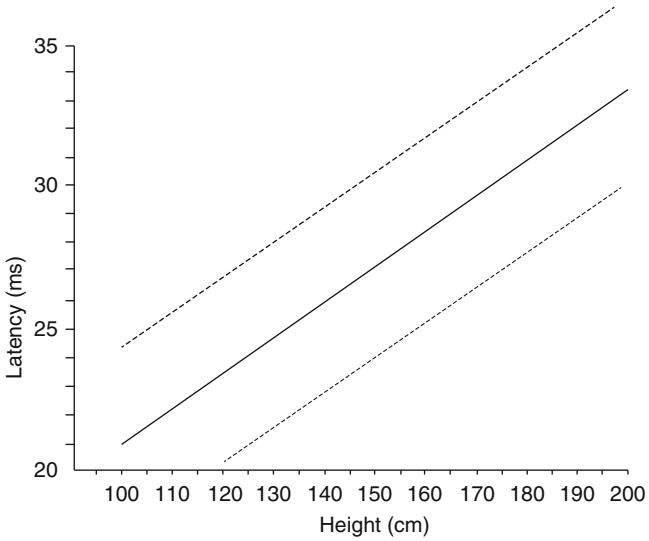


Fig. 7.57 H-latency reference values. Normal H-reflex latencies based on height (From Lachman et al. [27], courtesy of the BMJ Publishing Group)

It is generally accepted that the H-reflex amplitude and latency are potentially helpful in the diagnosis of S1 radiculopathy [29]. However, this has certain limitations:

1. An abnormal H reflex does not localize the lesion to the S1 root, because any pathological process along its long arc can result in an abnormal H reflex.
2. A normal H reflex does not exclude an S1 radiculopathy, because the H reflex is not always abnormal in definite cases of S1 radiculopathy.
3. The H reflex is commonly absent bilaterally in elderly patients or in patients with polyneuropathy.

Axon Reflex

The axon reflex (not a true reflex) is a late potential that is often recognized during the recording of F responses. The axon reflex is a small potential which typically occurs between the F response and the direct motor (M) response (Fig. 7.58a). In contrast to the F response which varies slightly in configuration and latency from stimulation to stimulation, the axon reflex has a fixed latency and configuration following successive stimulations. It is often useful to acquire these potentials on a rastered trace and then superimpose them. This easily shows that axon reflexes, unlike F responses, superimpose perfectly on one another (Fig. 7.58b).

Axon reflexes are typically seen in sprouted nerves, especially when a submaximal stimulus is given. An axon normally divides into its terminal divisions very close to the muscle, which is usually distal to the distal stimulation sites during motor NCSs. In diseased nerves, however, collateral sprouting may occur proximal to the distal stimulation site. As a nerve is stimulated, the proximally traveling (antidromic) action potential may conduct back down the branching nerve fiber to the muscle to generate an axon reflex, which occurs after the M potential but before the F response (Fig. 7.59). With supramaximal stimulation, the antidromic volley usually collides with the orthodromically traveling axon reflex, and the axon reflex is not seen. However, if all the distal nerve fibers have not been supramaximally stimulated, there may be no antidromic volley in the branching fibers to collide with the orthodromically traveling axon reflex, and the potential is free to travel back down the branching fiber to the muscle, creating the axon reflex. Axon reflexes are important to identify because they often suggest reinnervation along the nerve, and they may be confused with the F response. Rarely, the axon reflex follows rather than precedes the F response, if the regenerating collateral fibers are conducting very slowly.

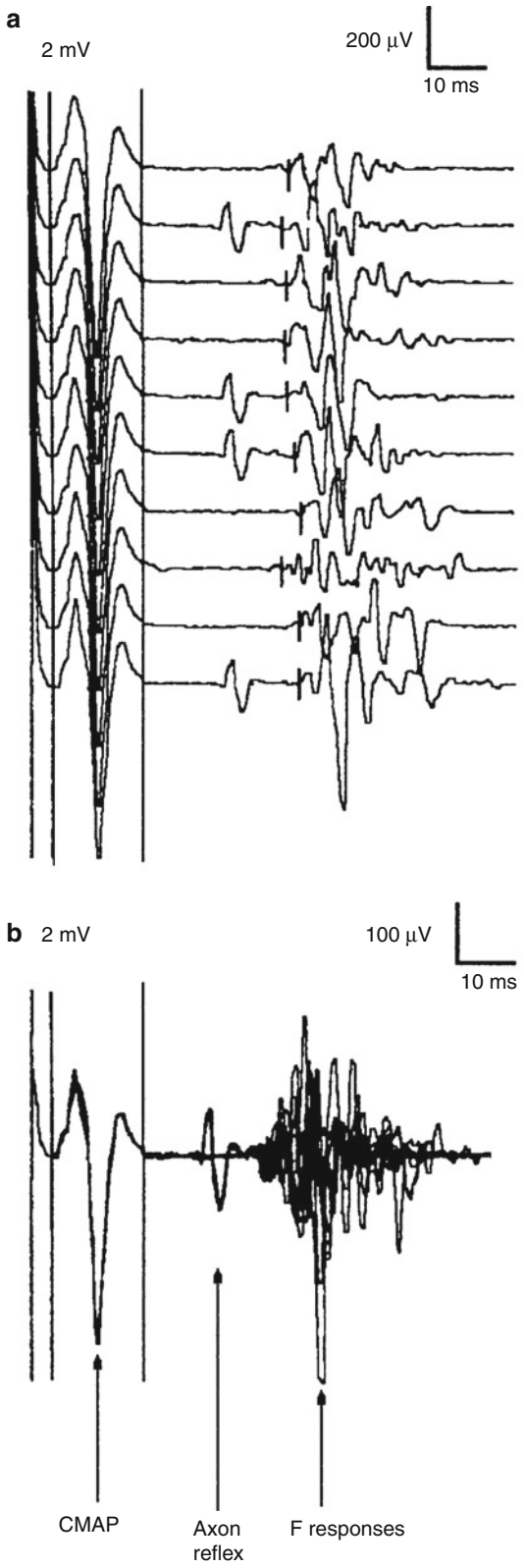


Fig. 7.58 Axon reflex. Tibial F responses, 10 rastered traces. Note that in (**a**) traces 2, 5, 6, 10, there is an additional potential, the axon reflex, that occurs between the CMAP and F response. When superimposed (**b**), the axon reflexes superimpose perfectly, in contrast to the F waves, which differ in configuration and latency in each trace (Reproduced with permission from Preston and Shapiro [1])

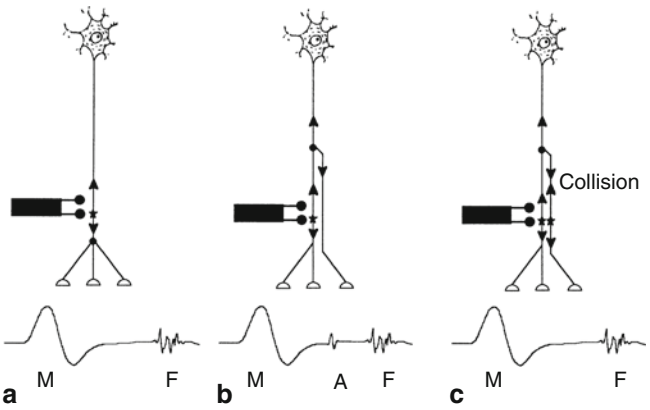


Fig. 7.59 Axon reflex circuit. (**a**) Normally, the axon divides into its terminal divisions close to the muscle. When stimulation occurs distally, orthodromic travel results in a direct motor (*M*) potential, while antidromic travel results in an F response as usual. (**b**) After denervation, collateral sprouts may grow from the more proximal axon to reinnervate denervated muscle fibers. The antidromic pulse may pass a collateral branching point to a nerve fiber and travel orthodromically back down the branching nerve fiber to the muscle to create the axon reflex. This occurs in the situation where all the distal nerve fibers have not been supramaximally stimulated, and there is no antidromic pulse to collide with the action potential traveling down the collateral fibers. Because the length of nerve traveled for the axon reflex is less than that traveled for the F response, the axon reflex usually occurs before the F. It is identified by its identical latency and configuration with each successive stimulation. (**c**) With supramaximal stimulation, the axon reflex is often eliminated, due to collision between the orthodromically traveling axon reflex and the antidromic volley from the reinnervated sprout (Reproduced with permission from Preston and Shapiro [1])

Blink Reflex

The blink reflex assesses the trigeminal (cranial nerve, [CN] V) and facial nerves (CN VII) and their connections in the pons and medulla. The blink reflex is the electrical correlate of the clinically evoked corneal reflex. Similar to the H reflex, the blink reflex represents a true reflex, with a sensory afferent limb, intervening synapses and a motor efferent. The blink reflex is useful in detecting abnormalities anywhere along the reflex arc, including the peripheral and central pathways. Accordingly, neuropathies of the facial or trigeminal nerves, as well as brainstem lesions, may cause abnormal blink reflexes.

Anatomy

The afferent limb of the blink reflex is mediated by sensory fibers of the supraorbital branch of the ophthalmic division of the trigeminal nerve (CN V_1) and the efferent limb by motor fibers of the facial nerve (CN VII). Similar to the corneal reflex, ipsilateral electrical stimulation of the supraorbital branch of the trigeminal nerve elicits a facial nerve (eye blink) response bilaterally. Stimulation of the ipsilateral supraorbital nerve results in an afferent volley along the trigeminal nerve to both the main sensory nucleus of V (midpons) and the nucleus of the spinal tract of CN V (lower pons

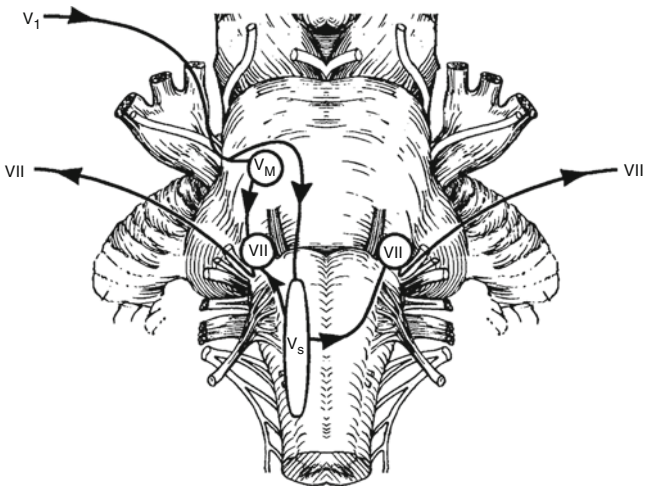


Fig. 7.60 Blink reflex anatomy. The afferent loop of the blink reflex is mediated by the first division of the trigeminal nerve (V_1), which synapses with both the main sensory nucleus of CN V (V_M) in the midpons and the nucleus of the spinal tract of CN V (V_S) in the medulla. The earlier R1 potential is mediated by a di-synaptic connection between the main sensory nucleus and the ipsilateral facial motor nucleus (VII). The later R2 responses are mediated by a multi-synaptic pathway between the nucleus of the spinal tract of CN V and both ipsilateral and contralateral facial nuclei (VII). The efferent pathway for both R1 and R2 is mediated via the facial nerve to the orbicularis oculi muscles (Modified from Chusid [30], with permission)

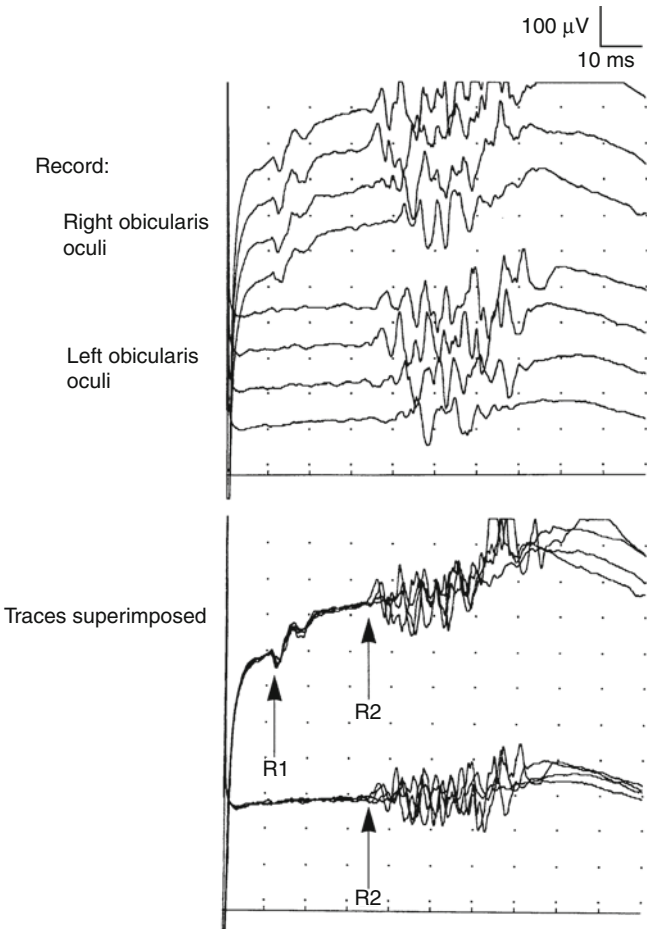


Fig. 7.61 Normal blink reflex. Stimulating right side, recording both orbicularis oculi muscles in a normal subject. On the ipsilateral side, an early R1 potential is present at 11 ms and a late R2 potential at 34 ms. The R1 is usually a bi- or triphasic potential and stable from stimulation to stimulation. The R2 potential is variable and usually polyphasic. On the contralateral side, only a late R2 potential is seen at 35 ms. To help determine the shortest R2 latencies, superimposing several traces is useful (Reproduced with permission from Preston and Shapiro [1])

and medulla) in the brainstem (Fig. 7.60). Through interneurons in the pons and lateral medulla, the nerve impulse next reaches the ipsilateral and contralateral facial nuclei, from which the efferent signal travels along the facial nerve bilaterally.

The blink reflex has two components, an early R1 and a late R2 response (Fig. 7.61). The R1 response is usually present ipsilateral to the side being stimulated, whereas the R2 response is typically present bilaterally. The R1 response is thought to represent the di-synaptic reflex pathway between the main sensory nucleus of V in the midpons and the ipsilateral facial nucleus in the lower pontine tegmentum. The R2 responses are mediated by an oligosynaptic pathway between the nucleus of the spinal tract of V in the ipsilateral pons and medulla, and interneurons forming connections to the ipsilateral and contralateral facial nuclei.

The earlier R1 response is usually stable and reproducible, with a bi- or triphasic morphology. Rarely, the R1 response cannot be reliably elicited on either side. The R2 response, on the other hand, is polyphasic, variable from one stimulation to another, and may habituate with repeated stimulations.

Blink Reflex Procedure

A two-channel recording system is required, and a small pediatric bipolar prong or bar electrode is best suited for stimulations. The sweep speed needs to be set at 5 or 10 ms/div. Initial sensitivity should be set at 100 or 200 µV/div. The filter settings are the same as for a motor conduction study (i.e., 10 Hz and 10 kHz). The patient should be lying supine on the examining table, in a relaxed state, with the eyes either open or gently closed. Surface recording electrodes are placed over the inferior orbicularis oculi muscles bilaterally. To record the CMAP from the orbicularis oculi muscle, the active recording electrode (G1) is best placed just lateral and inferior to the pupil at midposition. The corresponding reference electrodes (G2) are placed just lateral to the lateral canthus bilaterally. Alternatively, recording may be achieved with small concentric needle electrodes placed in the orbicularis oculi bilaterally. The ground electrode is placed either over the midforehead or chin. The supraorbital nerve (branch of the ophthalmic division of the trigeminal nerve) is stimulated ipsilaterally in the superior orbital fissure located in the medial supraorbital ridge and sometimes felt as a slight depression in the bony ridge over the eyebrow. The nerve is

easily stimulated with low currents; hence, an electrical pulse of 100 μs in duration is recommended, and the current is increased in small increments, usually 3–5 mA, until supramaximal stimulation is reached, typically at around 15–25 mA. The patient should be relaxed to eliminate any signal noise, which can obscure or confound one or both components of the blink reflex (especially R2). It is often helpful to use the speaker as an auditory feedback to the patient to help with muscle relaxation, and thereby reduce signal noise.

Once supramaximal stimulation is achieved, four to six responses are obtained on a rastered tracing and superimposed to determine the shortest response latencies. The R1 latency is fairly easy to measure, preferably at the point where the potential departs from the baseline, with either a positive or negative deflection (see Fig. 7.61). Measurement of the R2 latencies is more difficult as the potential varies in latency and morphology from stimulation to stimulation. With several traces superimposed, the shortest R2 latency is generally selected.

In a small number of individuals, stimulation of the infraorbital nerve, another branch of CN V_2, may result in a blink response. The reflex may also be elicited, with some difficulties, with a glabellar tap using a specially devised reflex hammer that automatically triggers the oscilloscope sweep. Mechanical stimulation over the forehead elicits usually an R1 response bilaterally.

Patterns of Abnormalities

For each blink response, the R1 and R2 latencies are compared to normal control values, as well as to the contralateral side. In healthy subjects (Fig. 7.62a), the absolute R1 latency is <13 ms, the ipsilateral R2 latency <41 ms, and the contralateral R2 latency <44 ms. For side-to-side comparisons, the difference between the R1 latencies should be less than 1.2 ms, the difference in ipsilateral R2 latencies should be <5 ms, and the difference in contralateral R2 latencies should be <7 ms. In healthy individuals, electrical stimulation elicits an R1 response on the side ipsilateral to the stimulation, and R2 responses bilaterally. The R1 latency reflects conduction time along the fastest fibers of the afferent sensory fibers of the ipsilateral trigeminal nerve to the main sensory nucleus

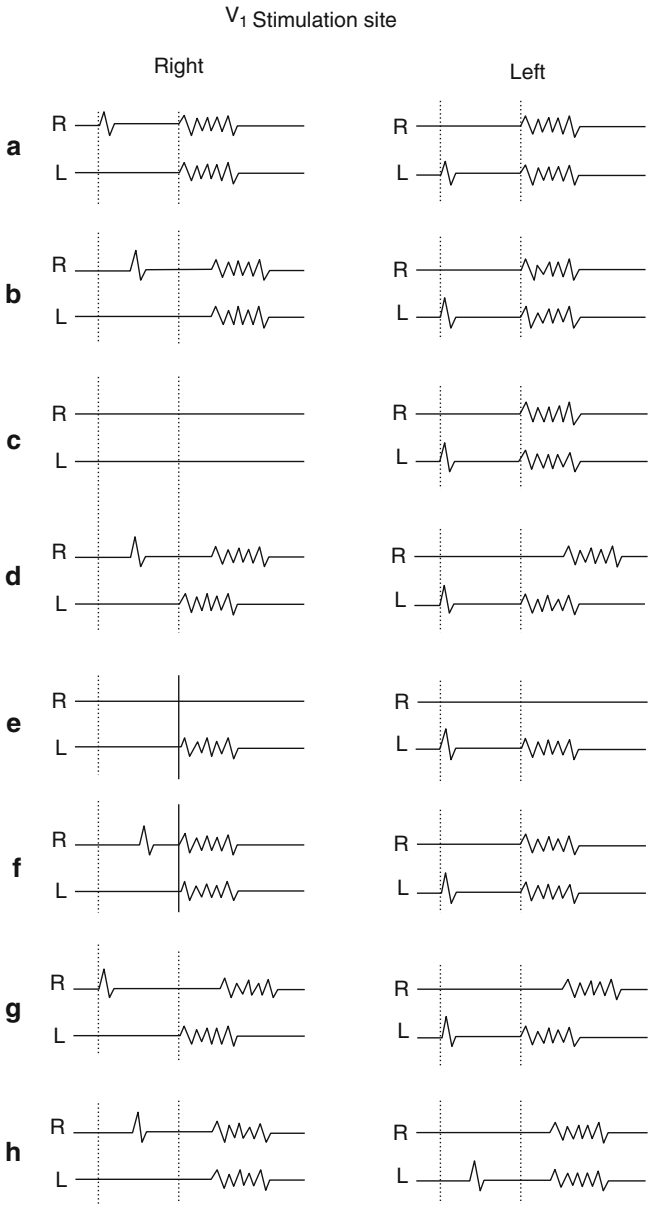


Fig. 7.62 Blink reflex patterns of abnormalities. (**a**) Normal pattern. Recording both orbicularis oculi muscles, stimulating the supraorbital nerve on each side results in an ipsilateral R1 (early) and bilateral R2 (late) potentials. (**b**) Incomplete right trigeminal lesion. Stimulating the affected right side, there is a delay of all potentials, including the ipsilateral R1 and R2 and contralateral R2. Stimulating the unaffected side results in all normal potentials. (**c**) Complete right trigeminal lesion. Stimulating the affected right side, all potentials are absent. Stimulating the unaffected side results in all normal potentials. (**d**) Incomplete right facial lesion. Stimulating the affected side results in delay of the ipsilateral R1 and R2, but a normal contralateral R2. Stimulating the unaffected side results in a normal ipsilateral R1 and R2, but a delayed contralateral R2. In this pattern, all potentials on the affected side are abnormal, regardless of which side is stimulated. (**e**) Complete right facial lesion. Stimulating the affected side results in absent ipsilateral R1 and R2 potentials, but a normal contralateral R2. Stimulating the unaffected side results in a normal ipsilateral R1 and R2, but an absent contralateral R2. (**f**) Right midpontine lesion (main sensory nucleus V and/or lesion of the pontine interneurons to the ipsilateral facial nerve nucleus). Stimulating the affected side results in an absent or delayed R1, but an intact ipsilateral and contralateral R2. Stimulating the unaffected side results in all normal potentials. (**g**) Right medullary lesion (spinal tract and nucleus V and/or lesion of the medullary interneurons to the ipsilateral facial nerve nucleus). Stimulating the affected side results in a normal R1 and contralateral R2, but an absent or delayed ipsilateral R2. Stimulating the unaffected side results in normal ipsilateral R1 and R2 potentials, but a delayed or absent contralateral R2. (**h**) Demyelinating peripheral polyneuropathy. All potentials of the blink response may be markedly delayed or absent, reflecting slowing of either or both motor and sensory pathways (Reproduced with permission from Preston and Shapiro [1])

of V, across di-synaptic pathways in the pons to the facial nerve nucleus, and along the efferent motor fibers of the ipsilateral facial nerve. The R2 latency is a measure of conduction time along the fastest fibers of the afferent pathway of the ipsilateral trigeminal nerve to the nucleus of the spinal tract of V, across multiple synapses in the pons and lateral medulla to both the ipsilateral and contralateral facial nerve nuclei, and along the efferent pathways of the facial nerves bilaterally.

Many different patterns of abnormalities can occur depending on the site or sites of the lesion(s). The major abnormal patterns consist of the following:

- *Unilateral Trigeminal Lesion* (Fig. 7.62b, c): Stimulating the symptomatic side, all potentials (ipsilateral R1 and R2, contralateral R2) are delayed in latencies or absent. However, normal ipsilateral R1 and R2 and contralateral R2 are evoked with stimulation of the asymptomatic side. In this situation, the abnormal potentials correlate with the stimulation side.
- *Unilateral Facial Lesion* (Fig. 7.62d, e): Stimulating the symptomatic side evokes delayed or absent ipsilateral R1 and R2 potentials, but a normal contralateral R2. Stimulating the asymptomatic side results in a normal ipsilateral R1 and R2, but a delayed or absent contralateral R2. In this pattern, the abnormal potentials correlate with the recording side.
- *Unilateral Midpontine Lesion* (*Main Sensory Nucleus of CN V*) *or Lesion of the Pontine Interneurons to the Ipsilateral Facial Nerve Nucleus*, *or Both* (Fig. 7.62f): Stimulating the affected side results in an absent or delayed R1, but an intact ipsilateral and contralateral R2. Stimulating the unaffected side results in all normal potentials, including R1 and ipsilateral and contralateral R2.
- *Unilateral Medullary Lesion* (*Spinal Tract and Nucleus of CN V*) *or Lesion of the Medullary Interneurons to the Ipsilateral Facial Nerve Nucleus*, *or Both* (Fig. 7.62g): Stimulating the affected side results in a normal R1 and contralateral R2, but an absent or delayed ipsilateral R2. Stimulating the unaffected side results in normal ipsilateral R1 and R2 potentials, but a delayed or absent contralateral R2. With a more extensive lesion in the medulla involving medullary interneurons to the contralateral facial nerve, stimulating either supraorbital nerve results in a normal R1, but delayed or absent ipsilateral and contralateral R2 potentials.
- *Peripheral Neuropathy* (Fig. 7.62h): Axonal neuropathies rarely affect the latencies of the blink reflexes, as typical axonal distal dying back neuropathies are unlikely to affect the fibers that mediate the blink reflex, which are proximal. However, in demyelinating neuropathies, all potentials of the blink response may be markedly delayed, reflecting slowing of either or both motor and sensory pathways.

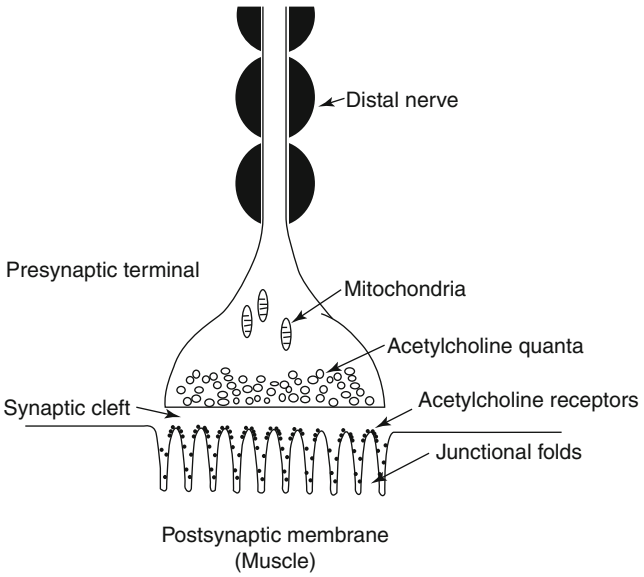


Fig. 7.63 Normal neuromuscular junction anatomy (Reproduced with permission from Preston and Shapiro [1])

Repetitive Nerve Stimulation

Repetitive nerve stimulation (RNS) is a useful EDX test in evaluating patients with suspected neuromuscular junction (NMJ) disorders. RNS is indicated whenever there is a clinical suspicion of an NMJ disorder such as myasthenia gravis (MG), Lambert-Eaton myasthenic syndrome (LEMS), or botulism. Knowledge of normal NMJ physiology and the effects of RNS on the NMJ and its associated muscle fiber in normal subjects and in patients with NMJ disorders is useful in understanding these responses.

Physiology

The NMJ is an electrical-chemical-electrical link between nerve and muscle (Fig. 7.63), with *acetylcholine* (ACH) as the neurotransmitter. ACH molecules are packaged as vesicles in the presynaptic terminal, in discrete units known as *quanta*, with each quantum containing approximately 10,000 molecules of ACH. Each quantum (vesicle) released results in a 1 mV change of postsynaptic membrane potential. This occurs spontaneously during rest and forms the basis of *miniature end-plate potential* (*MEPP*). The quanta are located in three separate stores: (1) *a primary or immediately available store* consisting of approximately 1,000 quanta, located beneath the presynaptic nerve terminal membrane and immediately available for release; (2) *a secondary or mobilization store* that consists of approximately 10,000 quanta that can resupply the primary store after a few seconds; and (3) *a tertiary or reserve store* consisting of more than 100,000 quanta that exists a distance from the NMJ (in the axon and cell body).

When a nerve action potential depolarizes the presynaptic terminal, *voltage-gated calcium channels* (*VGCCs*) open,

allowing an influx of calcium. The infusion of calcium results in the release of ACH from the presynaptic terminal. The greater the calcium concentration inside the presynaptic terminal, the more quanta are released. Normally, calcium diffuses out of the presynaptic terminal for approximately 100–200 ms.

When released, ACH diffuses across the synaptic cleft and binds to acetylcholine receptors (ACHRs) on the postsynaptic muscle membrane. The postsynaptic membrane is composed of numerous junctional folds, effectively increasing the surface area of the membrane, with ACHRs clustered on the crests of the folds. The binding of ACH to ACHRs opens ion channels, resulting in a local depolarization, the end-plate potential (EPP), which is proportional to the amount of ACH that binds to the ACHRs. If the EPP depolarizes the muscle membrane above *threshold*, an all-or-none muscle fiber action potential (MFAP) is generated and propagated through the muscle fiber. Under normal circumstances, the number of quanta (vesicles) released following a single nerve action potential at the presynaptic terminal is about 60. This results in an EPP which always rises above threshold and results in an MFAP. The amplitude of the EPP above the threshold value needed to generate an MFAP is called the *safety factor*, which is estimated to be 7–20 mV.

Following closure of the nicotinic receptor, ACH is released in the synaptic cleft and subsequently hydrolyzed by *acetylcholinesterase* into choline and acetate. Choline is taken back up into the presynaptic terminal and resynthesized to acetylcholine. ACH is finally repackaged into vesicles in order to protect the molecules from hydrolysis (by the presynaptic acetylcholinesterase).

Basic Concepts

RNS in normal subjects and patients with NMJ disorders is better understood after discussing the following facts:

1. The number of quanta released after a nerve action potential depends on the number of quanta in the immediately available store and the probability of release (i.e., $m = pn$, where m = the number of quanta released during each stimulation, p = the probability of release (effectively proportional to the concentration of calcium and typically about 0.2 (or 20 %) in normal conditions), and n = the number of quanta in the immediately available store [typically approximately 1,000 at baseline in normal conditions]).
2. The mobilization store starts to replenish the immediately available store after 1–2 s.
3. The rate at which motor nerves are stimulated dictates whether calcium plays a role in enhancing the release of ACH. Because calcium diffuses out of the presynaptic terminal in 100–200 ms, a slow rate of stimulation (more than every 200 ms) implies that the subsequent stimulus arrives long after calcium has dispersed. Thus, with an interstimulus interval of >200 ms, or a slow RNS rate of <5 Hz, the role of calcium in ACH release is not enhanced. In contrast, with rapid RNS (i.e., an interstimulus interval of <100 ms, or stimulation rate >10 Hz), calcium influx is greatly enhanced, the probability of release of ACH quanta increases, and more quanta are released.
4. The CMAP is the summation of all MFAPs in a muscle, obtained after supramaximal stimulation of the motor nerve. In the EMG lab, all measurements during RNS are made on the CMAP only.

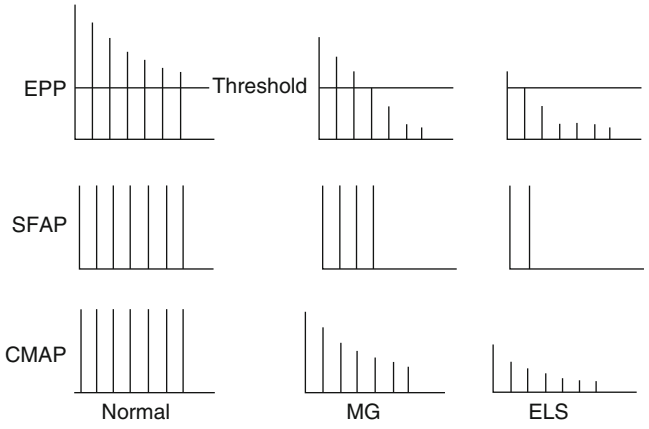


Fig. 7.64 Slow repetitive stimulation effect on end-plate potential (*EPP*), single-fiber action potential (*SFAP*), and compound muscle action potential (*CMAP*) in normal health, myasthenia gravis(*MG*), and Lambert-Eaton myasthenic syndrome (*LEMS*) (Adapted from Oh [31])

Slow Repetitive Stimulation

During slow RNS (<5 Hz, usually 2–3 Hz) in healthy subjects, ACH quanta are progressively depleted from the primary store, and subsequently fewer quanta are released with each successive stimulation. The corresponding EPP falls in amplitude, but because of the normal safety factor, the EPP remains above threshold to ensure generation of an MFAP with each stimulation (Fig. 7.64, left column). After the first few seconds, the secondary (i.e., mobilization) store begins to replace the depleted quanta with a subsequent rise in the EPP.

The effect of slow RNS on the EPP, MFAP, and CMAP is better understood with the following 3-Hz RNS example:

Stimulus	n	m	EPP	MFAP	CMAP
1	1,000	200	40	+	Normal
2	800	160	32	+	No change
3	640	128	26	+	No change
4	512	102	20	+	No change
5	640	128	26	+	No change

In this example, there are initially 1,000 quanta in the immediately available store (n), and with each stimulation, 20 % of the quanta are released. If the EPP is above 15 mV (threshold in this example), an MFAP is generated. Note the

normal depletion of the immediately available store (*n*), the subsequent decline in number of quanta released (*m*), and the corresponding fall in the EPP from the first to fourth stimulation. During the second stimulation, only 160 quanta are released instead of the initial 200, due to the fact that the number of quanta in the immediately available store has dropped to 800 (1,000 minus the 200 released during the first stimulation) and subsequently 20 % of the 800 are released. At the fifth stimulus, however, sufficient time has elapsed for the secondary or mobilization store to begin to resupply the primary store. The number of quanta in the immediately available store increases with a corresponding increase in the number of ACH quanta released and a higher EPP. At all times, the EPP stays above threshold (15 mV), resulting in the consistent generation of an MFAP (Fig. 7.64, left column). In the EMG laboratory, these findings translate to normal baseline CMAPs with no change in amplitude, because action potentials are generated in all muscle fibers.

In *a postsynaptic disorder*, such as MG, where the safety factor is reduced (fewer ACHRs resulting in less binding of ACH), the baseline EPP is reduced but usually still above threshold. Slow RNS will cause depletion of quanta and may drop the EPP below threshold, resulting in the absence of an MFAP (Fig. 7.64, center column). This is better understood with the following 3-Hz RNS example:

Stimulus	*n*	*m*	EPP	MFAP	CMAP
1	1,000	200	18	+	Normal
2	800	160	14	–	Decrement
3	640	128	11	–	Decrement
4	512	102	9	–	Decrement
5	640	128	13	–	Plateau

In this example, the number of quanta in the immediately available store (*n*), the number of quanta released (*m*), and the depletion of quanta with slow RNS are all normal. However, the response to the quanta (i.e., the EPP) is abnormal. Whereas in healthy subjects, the release of 200 quanta generated an EPP of 40 mV, in this case, the same number of quanta generates an EPP of only 18 mV. In MG, this occurs as a result of fewer ACHRs and, accordingly, less binding of ACH. The reduced safety factor, in conjunction with the normal depletion of quanta, results in subsequent EPPs falling below threshold and their corresponding MFAPs not being generated. Thus, the number of individual MFAPs declines and this provides the basis for a decremental CMAP response to slow RNS, as seen in the EMG lab. As the number of individual MFAPs declines, a decrement of the CMAP amplitude and area occurs (Fig. 7.64, center column). This decrement reflects fewer EPPs reaching threshold and fewer individual MFAPs contributing to the CMAP. Often, after the fifth or sixth stimulus, the secondary stores are mobilized and no further loss of MFAP occurs. This results in stabilization or sometimes slight improvement of the CMAP after the fifth or sixth stimulus, giving the characteristic U-shaped decrement.

In *a presynaptic disorder*, such as LEMS, the calcium concentration in the presynaptic terminal is reduced, due to an antibody attack on the VGCCs. Thus, the probability of release (*p*) dramatically falls, with a decrease in the number of quanta released. A slow (3 Hz) RNS may be modeled as follows:

Stimulus	*n*	*m*	EPP	MFAP	CMAP
1	1,000	20	4	–	Low
2	980	19.6	3.9	–	Decrement
3	960	19.2	3.8	–	Decrement
4	940	18.8	3.7	–	Decrement
5	920	18.4	3.6	–	Plateau

In this example, the number of quanta in the immediately available store (*n*) is normal, but the number of ACH quanta released (*m*) is low, due to the reduced probability of release (*p*). Hence, the baseline EPP is low, often not reaching threshold, and many muscle fibers do not fire (Fig. 7.64, right column). With successive stimulations, there is further depletion, though not as marked as in normal or postsynaptic disorders; because so few quanta are released, the subsequent amount of depletion cannot be as great. In this example, as the EPP is below threshold at baseline, an MFAP is never generated (see Fig. 7.64, right column). Thus, the baseline CMAP is low in amplitude, because many muscle fibers do not reach threshold due to inadequate release of quanta after a single stimulus. With slow RNS, there is also further decrement of the CMAP, because subsequent stimuli result in further loss of MFAPs. Note that in some presynaptic disorders, the baseline EPP may be low, but still above threshold, resulting in a reduced safety factor. In this situation, action potentials may be generated initially in large numbers of muscle fibers but then fail to be generated as the EPP falls below threshold with slow RNS. This results in a borderline (rather than low) amplitude baseline CMAP which decrements with slow RNS.

Rapid Repetitive Stimulation

If RNS is rapid enough (>10 Hz, usually 30–50 Hz), so that new calcium influx occurs before the previously infused calcium has diffused back out, then calcium continues to accumulate in the presynaptic terminal, causing an increased probability of quanta release (*p*). This, along with increased mobilization of quanta from the secondary store, usually leads to an increased number of quanta being released and a correspondingly higher EPP. However, in normal subjects, the result is the same as with any other EPP above threshold: an all-or-none MFAP. Thus, in normal subjects, CMAPs generated following rapid RNS do not change significantly in amplitude or area (Fig. 7.65, left column).

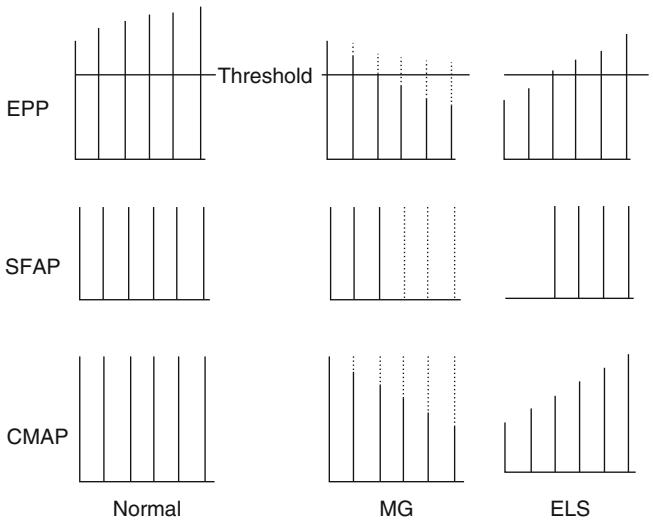


Fig. 7.65 Rapid repetitive stimulation effect on end-plate potential (*EPP*), single-fiber action potential (*SFAP*), and compound muscle action potential (*CMAP*) in normal health, myasthenia gravis, and Lambert-Eaton myasthenic syndrome (*LEMS*) (Adapted from Oh [31])

The physiology of rapid RNS in patients with *postsynaptic disorders* is more complex. In these patients, the EPP will also increase, but because the EPP is usually above threshold at baseline, the result will still be the generation of an MFAP and no subsequent change of CMAP amplitude (Fig. 7.65, center column, *dotted lines*). However, if the EPP has been lowered, such as after slow RNS, the decreased EPP may be repaired or improved with rapid RNS. In severe postsynaptic blockade (e.g., during myasthenic crisis), the increased quantal release cannot compensate for the marked NMJ block resulting in a drop in EPP amplitude and fewer MFAPs being generated, along with an associated CMAP decrement (Fig. 7.65, center column, *solid lines*).

Presynaptic disorders are distinctly different. Because the EPP is abnormally low at baseline, and often below threshold, rapid RNS may increase the EPP above threshold so that an MFAP is generated where one had not been present previously (Fig. 7.65, right column). Hence, the number of individual MFAPs increases. This provides the basis for an incremental CMAP response to rapid RNS seen in the EMG laboratory. As the number of individual muscle fiber action potentials increases, an increment of the CMAP amplitude and area occurs. This increment reflects more EPPs reaching threshold and more individual MFAPs contributing to the CMAP.

Exercise Testing

Maximal voluntary exercise can be used to demonstrate many of the same effects as rapid RNS, because motor units fire at their maximal firing frequency, typically 30–50 Hz. Both result in higher-amplitude EPPs.

In *healthy subjects*, brief intense exercise may lead to a slight increase in CMAP amplitude, known as *pseudofacilitation*. After brief exercise, EPPs are facilitated. However, because they are above threshold at baseline, the same number of MFAPs is generated. Although there is no increase in the actual number of MFAPs that summate to create the CMAP, brief maximal exercise causes the muscle fibers to fire more synchronously. This pseudofacilitation results in an increase in CMAP amplitude, but usually with a decrease in CMAP duration, and little change in the CMAP area. In general, postexercise increments of CMAP amplitude from pseudofacilitation do not exceed 50 % of baseline in normal subjects (see below).

In *postsynaptic disorders*, maximal exercise, just like rapid RNS, results in higher EPPs. Because the EPP is usually above threshold at baseline, the result is the same: the generation of an MFAP. Exercise likewise may repair or improve a low EPP which has developed during slow RNS. If the EPP has dropped below threshold, then subsequent exercise may increase the EPP back to above threshold. In *presynaptic disorders*, exercise, like rapid RNS, can often facilitate low EPPs. If the baseline EPP is below threshold, exercise may increase the EPP above threshold so that an MFAP is generated where one had not been present previously.

The effects of rapid RNS or voluntary exercise described above occur with *brief* periods of exercise or rapid RNS and are best achieved following 10 s of exercise [32]. This process, known as *postexercise* (*or post-tetanic*) *facilitation*, can be demonstrated on the CMAP in patients with NMJ disorders (Fig. 7.66). Following 10 s of maximal voluntary contraction, increased mobilization of quanta and accumulation of calcium occur, resulting in greater numbers of quanta released and a higher EPP. This postexercise facilitation can be demonstrated in two situations. First, in presynaptic disorders such as LEMS associated with reduced release of quanta and subthreshold EPPs at baseline, brief exercise can facilitate EPPs above threshold, giving rise to muscle fiber action potentials that were not present previously. Accordingly, an increment of the CMAP amplitude and area occurs. Second, brief exercise can repair EPPs that have been lowered by slow repetitive simulation. If the EPPs are facilitated above threshold, muscle fiber action potentials will be generated that were not present previously. Accordingly, a decrement of the CMAP amplitude and area that has developed during slow RNS may be lessened or "repaired" (see Fig. 7.66a, b).

The phenomenon of *postexercise* (*or post-tetanic*) *exhaustion* is less well understood. Immediately after a prolonged exercise or rapid repetitive stimulation (usually 1 min), EPPs typically increase initially, as described above, but then subsequently decline over the next several minutes, usually falling below baseline. In normal subjects with a normal safety factor, the EPP never falls below threshold. However, in patients with impaired NMJ transmission, slow repetitive

stimulation performed 2–4 min after a prolonged exercise may result in a greater decline of the EPP, such that the EPP does not reach threshold and its MFAP is not generated.

To demonstrate postexercise exhaustion, the muscle is maximally exercised for 1 min. Slow RNS is then performed immediately after, and at 1, 2, 3, and 4 min later. In healthy subjects with a normal safety factor, the EPP never falls below threshold, and the CMAP amplitude and area remain stable. However, in patients with impaired NMJ transmission, the decrement in CMAP amplitude and area to slow RNS becomes more marked 2–4 min after prolonged exercise (see Fig. 7.66c–e). If this occurs, 10 s of maximal voluntary exercise can then be used to repair the decrement toward normal (see Fig. 7.66f).

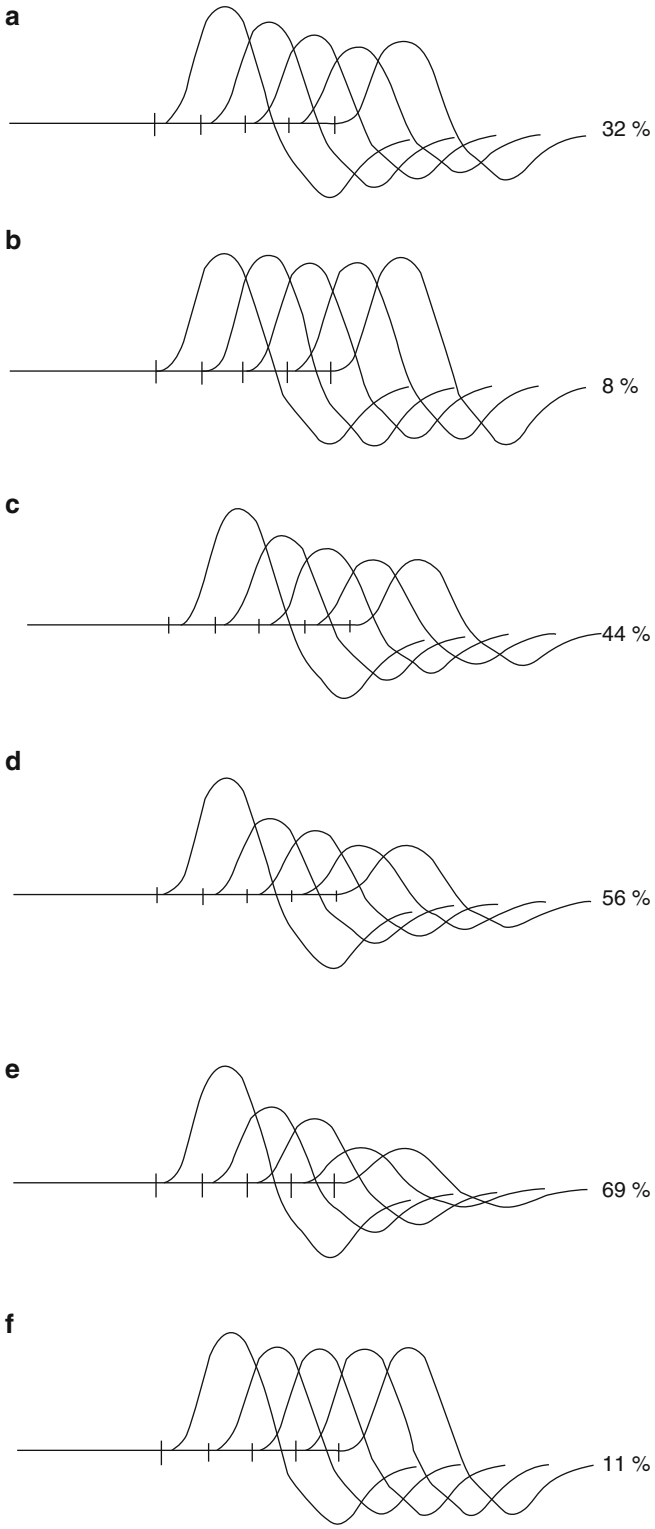


Fig. 7.66 Postexercise facilitation and exhaustion. 3-Hz RNS in a patient with myasthenia gravis. (**a**) Decrement of CMAP amplitude at rest; (**b**) postexercise facilitation: decrement of CMAP immediately following 10 s of maximal voluntary exercise. Decrement has repaired toward normal; (**c**, **d**, **e**) postexercise exhaustion: decrements of CMAP 1, 2, and 3 min after 1 min of maximal voluntary exercise. Decrement becomes progressively more marked over the baseline decrement. (**f**) Postexercise facilitation after a decrement: immediately following another 10 s of maximal voluntary exercise, the decrement, which has worsened as a result of postexercise exhaustion, repairs toward normal (Reproduced with permission from Preston and Shapiro [1])

Technical Factors in Repetitive Nerve Stimulation

Close attention to technical factors is critical when performing RNS. Technical factors, if not appreciated and closely controlled, may result in either factitious decrements or increments and the mistaken impression of an NMJ disorder.

Movement Artifacts

The greatest technical problem with RNS is failure to immobilize the recording electrode over the muscle properly. If the position of the recording electrode moves in relationship to the muscle during stimulation, CMAP configuration may change. The recording electrodes and the stimulator should be secured with tape or a Velcro strap if possible. When stimulating distal nerves such as the median or ulnar nerves, the limb may also be secured to a pad or board. Unfortunately, securing the stimulator and limb to prevent movement is not possible when testing proximal nerves.

Submaximal Stimulation

Submaximal stimulation can create a host of problems, including artifactual CMAP decrements and increments.

Limb Temperature

In NMJ disorders, a CMAP decrement may be diminished if the limb is cold. The reason for this is not completely known, but may be related to decreased functioning of the enzyme acetylcholinesterase when cold, effectively making more ACH available to bind at the ACHRs. Patients with MG note worsening symptoms in warm weather, perhaps because the acetylcholinesterase is more active. RNS should always be performed with the temperature at least 33 °C at the recording site.

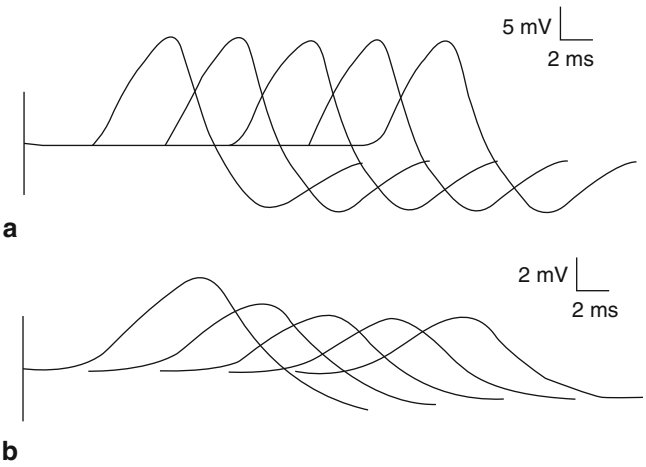


Fig. 7.67 3-Hz RNS of proximal and distal nerves in patient with myasthenia gravis. (**a**) Normal decrement (4 %) in the ulnar nerve. (**b**) Markedly abnormal decrement (42 %) in the spinal accessory nerve. In myasthenia gravis, the yield of an abnormal decrement is greater with proximal nerves. Note also the U-shaped decrement (Reproduced with permission from Preston and Shapiro [1])

Acetylcholinesterase Inhibitors

It is best to advise patients to refrain from taking acetylcholinesterase inhibitors (e.g., pyridostigmine) for 4–6 h, and preferably 12–24 h, before the EDX study if not medically contraindicated. These agents make more ACH available to bind at the ACHRs and may mask a decrement.

Nerve and Muscle Selection

RNS can be performed using any motor nerve. The nerves most commonly used are the ulnar, median, musculocutaneous, axillary, spinal accessory and facial nerves, recording abductor digiti minimi, abductor pollicis brevis, biceps, deltoid, and upper trapezius, respectively. Because weakness in MG patients is predominantly ocular, bulbar, and proximal, the yield of detecting abnormalities increases with the use of more proximal nerves (Fig. 7.67). Unfortunately, there are more technical difficulties stimulating proximal nerves because of pain and movement artifacts. Of the proximal nerves, the spinal accessory nerve recording the upper trapezius is often preferred. The spinal accessory nerve is quite superficial, just posterior to the sternocleidomastoid muscle, and can usually be supramaximally stimulated with a relatively low current. Shoulder movement can be reduced by gentle but firm downward pressure on the shoulder or arm.

The facial nerve can also be used for RNS, recording the nasalis, orbicularis oculi, or other facial muscles (REF check). However, the facial CMAP amplitudes are small at baseline, and one cannot immobilize the muscle and prevent possible electrode movement. Hence, small changes from the baseline CMAP, for example, from electrode movement or failure to perform supramaximal stimulation, are much more likely to confound facial RNS, creating possible false-positive results.

Stimulation Frequency

The optimal frequency for slow RNS is 2 or 3 Hz. The frequency for slow RNS must be kept low enough to prevent calcium accumulation, but high enough to deplete the quanta in the immediately available store before the mobilization store starts to replenish it. For rapid RNS, the optimal frequency is 30–50 Hz. However, brief maximal voluntary exercise can substitute for rapid RNS in cooperative subjects. Exercise testing has the distinct advantage of being painless, whereas rapid RNS is quite painful and often difficult to tolerate. Only in the event of an uncooperative patient (e.g., an infant, a patient in coma) should rapid RNS be used.

Number of Stimulations

A train of 5–10 pulses is preferable for slow RNS. The number of pulses should be kept low to reduce patients' discomfort, but must be counterbalanced by the need to have enough pulses to detect a decrement. When the mobilization store begins to resupply the immediately available store (usually after the fifth or sixth stimulus), the decrement stops or the CMAP begins to improve. This results in a so-called *U-shaped decrement*, which is highly characteristic of NMJ disorders (Fig. 7.67). For rapid RNS, which should only be done in patients who cannot perform brief maximal voluntary exercise, a stimulus train of 5–10 s should be given. This is the length of time often required to see the maximal incremental response from increased mobilization of quanta and calcium accumulation.

Decrement and Increment Calculation

The decrement is usually calculated by comparing the lowest CMAP amplitude (or area) to the baseline CMAP (first CMAP of the RNS train). With slow RNS, the lowest CMAP is usually the third or fourth. By the fifth or sixth stimulation, the decrement plateaus or begins to improve, due to the mobilization store resupplying the immediately available store, (i.e., the U-shaped decrement). The CMAP decrement is expressed in a percentage and calculated as follows:

$$\%\ \text{Decrement} = \frac{\text{Amplitude}\left(\text{Baseline CMAP}\right) - \text{Amplitude}\left(\text{Lowest CMAP}\right)}{\text{Amplitude}\left(\text{Baseline CMAP}\right)} \times 100$$

Normal subjects should have no decrement. Any decrement greater than 10 % is defined as abnormal. The 10 % cutoff allows for inherent technical factors which are often encountered. However, any reproducible decrement is probably abnormal.

CMAP increments are calculated by comparing the highest CMAP amplitude or area with the baseline CMAP and expressed as a percentage as follows:

$$\%\ \text{Increment} = \frac{\text{Amplitude}\left(\text{Highest CMAP}\right) - \text{Amplitude}\left(\text{Baseline CMAP}\right)}{\text{Amplitude}\left(\text{Baseline CMAP}\right)} \times 100$$

With 10 s of maximal voluntary contraction, the calculation is simple and consists of comparing the CMAP obtained after brief exercise with the baseline CMAP. With rapid RNS, the highest CMAP, usually the last one obtained after 5–10 s, is compared with the baseline (first) CMAP. In healthy subjects, pseudofacilitation may cause an increment up to 50 %. The increment in LEMS is often higher than 200 % and is often more pronounced than in patients with botulism which is usually associated with more than 100 % increment. Increments of 50–100 % may also be encountered in cases of botulism with severe presynaptic NMJ blockade.

Decrement in Non-neuromuscular Junction Disorders

Although a decremental response with RNS occurs predominantly in primary disorders of the NMJ, decrements may be seen in severe neurogenic disorders, such as amyotrophic lateral sclerosis. Generally, any condition associated with prominent denervation and reinnervation, and newly formed NMJs (which are immature and unstable), may show a decrement to RNS. In addition, some myopathies, including the myotonic disorders and the metabolic myopathies (e.g., McArdle's disease), may also show a decrement to RNS. This underscores that RNS should not be used in isolation. For every patient, a clinical history and neurologic exam, NCSs and needle EMG need to be performed, so that if a decremental response occurs with RNS, it can be interpreted in the proper context.

Repetitive Nerve Stimulation Protocol

A recommended RNS protocol in the EMG laboratory for patients with suspected NMJ disorders is detailed in Table 7.10.

Electrophysiologic Findings in Neuromuscular Disorders

Focal Neuropathic Lesions

Neuropathic lesions result from loss or dysfunction of peripheral nerve fibers, their primary nerve cells, or both. They represent the bulk of disorders encountered in the EMG laboratory and include mononeuropathies, plexopathies, and radiculopathies and polyneuropathies, as well as disorders primarily affecting the motor neurons or the dorsal root ganglia. Focal peripheral nerve lesions may primarily affect the axon, resulting in axonal loss, or the myelin, resulting in segmental demyelination.

Table 7.10 Protocol for evaluating disorders of the NM

1. Warm the extremity (33 °C)
2. Immobilize the muscle as best as possible
3. Perform routine motor nerve conduction studies first to insure that the nerves are normal
4. Perform RNS at rest. After making sure that the stimulus is supramaximal, perform 3 Hz at rest for 5–10 impulses, repeated 3 times, 1 min apart. Normally, there is <10 % decrement between the first and fifth response
5. If >10 % decrement occurs and is consistently reproducible: (a) Have patient perform maximal voluntary exercise for 10 s (b) Immediately repeat 3 Hz RNS postexercise to demonstrate postexercise facilitation and repair of the decrement
6. If <10 % decrement or no decrement: (a) Have patient perform maximal voluntary exercise for 1 min, and perform 3 Hz RNS immediately, and at 1, 2, 3, and 4 min after exercise to demonstrate postexercise exhaustion (b) If a significant decrement occurs, have patient perform maximal voluntary exercise again for 10 s, and immediately repeat 3 Hz RNS to demonstrate repair of the decrement
7. Perform RNS on one distal and one proximal motor nerve. Always try to study weak muscles. If no decrement is found with a proximal limb muscle, a facial muscle can be tested, keeping in mind technical considerations
8. If the CMAP amplitude is low at baseline, have the patient perform 10 s of maximal voluntary exercise, then stimulate the nerve supramaximally immediately postexercise looking for an abnormal increment (>50–100 % from baseline). If the patient exercises for more than 10 s, or the nerve is not stimulated immediately postexercise, a potential increment may be missed
9. Always perform concentric needle EMG of proximal and distal muscles, especially clinically weak muscles. Any muscle with denervation or myotonia on needle EMG may demonstrate a decrement on RNS, which does not signify a primary disorder of the NMJ

From Preston and Shapiro [1], with permission

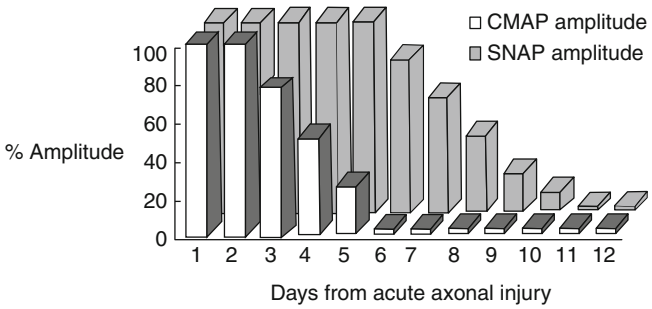


Fig. 7.68 Effect on CMAP and SNAP amplitude after Wallerian degeneration (From Katirji [33], with permission)

Axonal Loss Lesions

After axonal loss lesions (e.g., partial transection of a nerve), the distal segment of the nerve undergoes Wallerian degeneration. With the completion of Wallerian degeneration, the degenerated axons do not contribute to the SNAP and CMAP amplitudes, which decrease or become absent at all stimulation sites. This axon-loss pattern is the most common pattern encountered in the EMG laboratory.

Immediately after an axonal loss lesion, the nerve segment distal to the lesion can conduct action potentials, despite being effectively disconnected from its proximal segment and despite loss of function. With stimulation and recording distal to the site of the lesion, the CMAP and SNAP amplitudes follow two different courses (Fig. 7.68). The CMAP amplitude is normal for 2–3 days and declines rapidly to reach its nadir in 5–6 days. However, the SNAP amplitude is unaffected for 5–6 days and then drops to reach its nadir in 10–11 days [34]. The difference between the decline of the SNAP and CMAP amplitudes following axon-loss nerve lesions is likely related to early transmission failure of the neuromuscular junction which affects only the CMAP amplitude. This is supported by the fact that mixed nerve action potentials follow the time course of SNAPs, both recorded directly from nerve trunks [35].

Therefore, early after a peripheral nerve injury, and as long as some fibers are still conducting distal to the lesion, stimulating the nerve distal and proximal to the lesion results in a conduction block pattern (Fig. 7.69). This "axonal" conduction block (sometimes called *pseudo conduction block*) mimics conduction block encountered with focal segmental demyelination (see section on "Demyelinating Lesions"). In contrast to segmental demyelinating lesions, a repeat NCS after completion of Wallerian degeneration will prove that the lesion is due to axonal loss by revealing a drop in the CMAP amplitude with both distal and proximal stimulation. It should be noted that the identification of "axonal" conduction block in the early days of axonal loss is extremely helpful in localization, particularly in closed nerve injury, where the exact site of trauma is not clear on clinical grounds. This is why it is important to obtain NCSs as early as possible following a suspected acute peripheral nerve lesion. Waiting for the completion of Wallerian degeneration results in low-amplitude CMAPs regardless of stimulation site and does not allow for precise localization of the injury site.

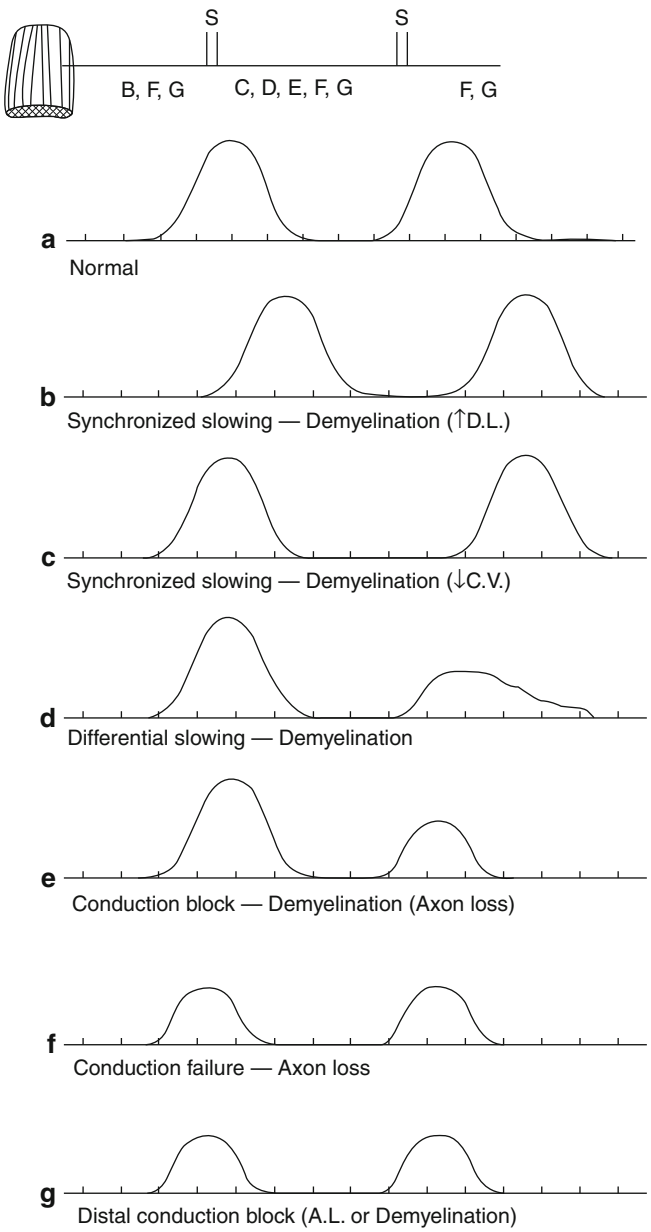


Fig. 7.69 Motor nerve conduction study changes seen with different types of focal pathophysiology located along various nerve segments both proximal and distal to the nerve stimulation sites. The *uppermost drawing* illustrates where lesions are situated to produce the abnormalities seen (*S* stimulation sites, *D.L.* distal latency, *C.V.* conduction velocity, *A.L.* axon loss) (From Wilbourn and Ferrante [36])

In contrast to the significant effect of partial axon-loss lesions on SNAP and CMAP amplitudes, these lesions are often associated with relative preservation of conduction velocities and distal latencies. This is due to the random distribution of conduction velocities of nerve fibers, which

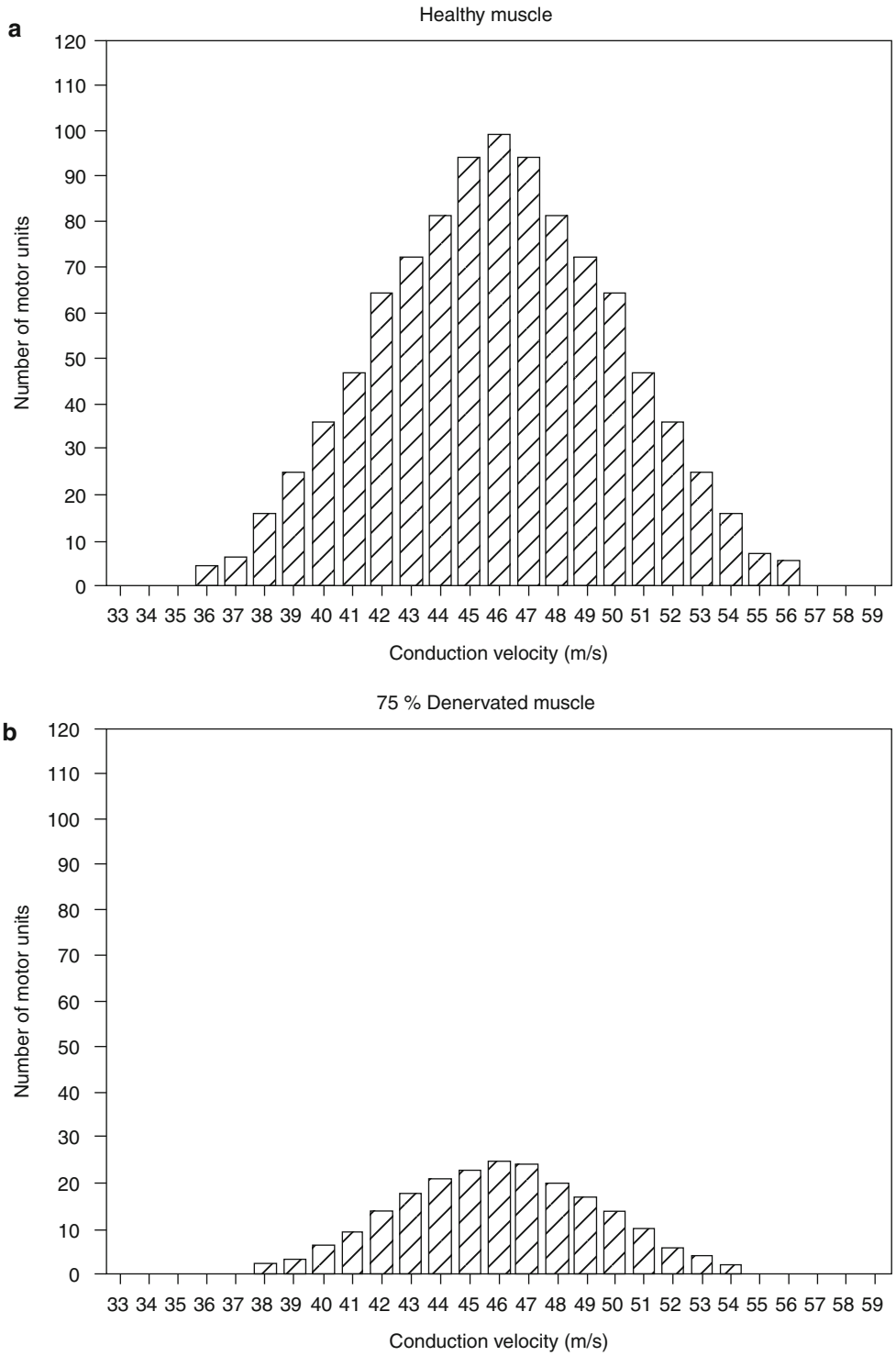


Fig. 7.70 Computer simulation of the effect on the distribution of conduction velocities in (**a**) healthy muscle and (**b**) with 75 % loss of the motor units (From Osselton et al. [37], with permission)

results in survival of some of the fast-conducting fibers (Fig. 7.70). Sometimes, particularly when axonal loss is severe, the largest and fastest conducting axons are lost, resulting in a slight slowing of conduction velocity (CV) and distal latency (DL). This, however, never reaches values in the demyelinating range (i.e., CV <75 % lower limit of normal (LLN); DL >130 % upper limit of normal [ULN]).

On needle EMG, decreased recruitment of MUAPs occurs in weak muscles immediately following the lesion. No abnormal spontaneous activity or change in MUAP morphology is seen acutely; these changes develop over time. Within the next several weeks, fibrillation potentials develop. The time it takes for fibrillation potentials to appear depends on the length of nerve between the muscle and the lesion,

Table 7.11 Time-related changes in axonal loss

	Immediate	Hyperacute <4 days	Acute >1 week <3–6 weeks	Subacute >3–6 weeks <2–3 months	Subacute-chronic >2–3 months < many months/years	Chronic > Several months/years
Clinical	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal	Normal/abnormal
Nerve conductions	Normal	Normal	Abnormal	Abnormal	Abnormal	Normal/abnormal
MUAP recruitment	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased
Spontaneous activity	Normal	Normal	Normal	Abnormal	Abnormal	Normal
MUAP morphology	Normal	Normal	Normal	Normal	Reinnervated	Reinnervated

From Preston and Shapiro [1], with permission

developing first in proximal muscles and proceeding distally. In general, fibrillation potentials appear in denervated proximal muscles in 10–14 days but do not become fully developed in distal muscles until 3–5 weeks.

EDX studies often can determine the severity of the axonal loss. Because of the mosaic distribution of the muscle fibers of individual motor units, loss of few axons may be best diagnosed by detecting fibrillation potentials in denervated muscles. Hence, *the presence of fibrillation potentials is the most sensitive sign of axonal loss*. In contrast, it requires more substantial axonal loss before SNAP or CMAP amplitudes decrease. The SNAP amplitude is more sensitive to axonal loss than the CMAP. Thus, in mild axon-loss lesions, fibrillation potentials on needle EMG may be the only finding. In moderate lesions, the SNAP amplitude may also decline, but the CMAP is often normal. With advancing severity, the SNAP is often absent and the CMAP is low in amplitude. In complete lesions, both are absent.

In the chronic stages, reinnervation follows denervation, which typically takes several months. Reinnervation may occur by collateral sprouting from surviving axons (in partial lesions only) or by proximal-to-distal regeneration of axons from the site of the lesion. "Nascent" MUAPs are the earliest signs of proximal-to-distal axonal regeneration. These MUAPs are very low in amplitude and extremely polyphasic, with normal or increased duration. They are often unstable and associated with decreased MUAP recruitment. As reinnervation proceeds, particularly if collateral sprouting plays a major role, MUAPs become polyphasic and longer in duration and higher in amplitude, reflecting increased numbers of muscle fibers per motor unit. If reinnervation is successful, fibrillation potentials disappear months to years later, leaving only large reinnervated MUAPs with decreased recruitment on needle EMG as a permanent sign of axonal injury. If successful reinnervation occurs, as occurs in partial lesions, CMAP and SNAP amplitudes may improve and even reach normal values after several months or years.

Thus, the time course of focal peripheral nerve lesions with axonal loss (i.e., acute, subacute, chronic) can usually be determined by the combined findings on NCSs and needle EMG (Table 7.11).

Demyelinating Lesions

In pure demyelinating lesions, the pattern of abnormalities is different from axonal loss lesions and depends on the degree of demyelination. Because myelin is essential to maintain the saltatory fashion of nerve conduction, its disruption may result in focal slowing or conduction block.

Focal slowing occurs when the fastest conducting fibers of a nerve segment are demyelinated, usually by widening of the nodes of Ranvier (paranodal demyelination). Focal slowing may affect any segment of a nerve, thus manifesting by slowing of distal latency or conduction velocity (see Fig. 7.69). Prolongation of late responses (F waves and H reflexes) may only imply focal slowing of proximal nerve segments if distal latencies and conduction velocities are normal. If the focal slowing affects different groups of fibers more than others, desynchronized slowing occurs, resulting in excessive temporal dispersion (also referred to as *differential slowing*). Excessive temporal dispersion is defined as greater than a 20 % increase in CMAP duration between distal and proximal stimulations for the median, peroneal, and ulnar nerves and greater than a 30 % increase for the tibial nerve [38]. Note that pure conduction slowing alone does not result in weakness, because the nerve action potentials eventually reach their destination, though not as fast. Slowing may result in depressed or absent myotatic reflexes and a perception of altered sensation. Also, if focal slowing is the only abnormality (i.e., without demyelinative conduction block or axonal loss), the entire needle EMG, including MUAP recruitment and morphology, remains normal.

Conduction block occurs when there is segmental demyelination resulting in loss of one or more internodal segment (internodal demyelination). To demonstrate a conduction block, the lesion of the affected nerve must be bracketed by two stimulation points, one distal and the second proximal to the lesion. Distal to the conduction block, the nerve conducts normally. However, with proximal stimulation, the nerve action potentials cannot traverse the area of demyelination resulting in a drop (or complete loss) of CMAP. This finding is similar to the pseudo conduction block encountered with acute axonal loss lesions (less than 4–5 days from injury), in which distal nerve conductions remain normal. However,

Table 7.12 Electrodiagnosis of conduction block

Definite in any nerve[a]
1. 50 % drop in CMAP amplitude with ≤15 % prolongation of CMAP duration
2. 50 % drop in CMAP area
3. 30 % drop in area or amplitude over a short nerve segment (e.g., radial across the spiral groove, ulnar across the elbow, peroneal across the fibular head)
Possible in median, ulnar, and peroneal nerves only
1. 20–50 % drop in CMAP amplitude with ≤15 % prolongation of CMAP duration
2. 20–50 % drop in CMAP area

Note: All amplitudes, areas, and durations reflect negative-peak areas, amplitudes, and durations

[a]Caution should be taken in evaluating the tibial nerve, where stimulation at the knee can be submaximal, resulting in 50 % or at times >50 % drop in amplitude, especially in overweight patients

unlike axonal loss lesions, the underlying axon remains intact and Wallerian degeneration never occurs. Hence, in demyelinating conduction bock, the distal CMAP does not decrease with time, as occurs with acute axon loss. Clinically, acute conduction block due to segmental demyelination of sensory and motor fibers results in sensory loss and weakness, respectively. The presence of conduction block implies that the clinical deficit (weakness and/or numbness) is secondary to demyelination and recovery may occur rapidly with remyelination.

Conduction block can be used to localize the lesion in compressive or entrapment mononeuropathies (e.g., ulnar neuropathy at the elbow, radial neuropathy at the spiral groove, or common peroneal neuropathy at the fibular head). Evaluation of the amplitudes and areas of the distal and proximal CMAPs is essential for the diagnosis of conduction block. Because there is substantial difference in the degree of CMAP amplitude and area reduction and CMAP duration prolongation with proximal stimulation among the various intact nerves and between healthy individuals, the criteria for conduction block continue to be debated [38–41]. Suggested working criteria are shown in Table 7.12.

On needle EMG, the recruitment pattern is decreased in a demyelinating conduction block because of a reduction in the number of conducting motor units. Because there is no Wallerian degeneration, however, no denervation or subsequent reinnervation occurs. Hence, MUAP morphology is normal and there are no fibrillation potentials. *Thus*, *reduced recruitment of MUAPs is the only abnormality on needle EMG in a pure demyelinating lesion with conduction block.* However, pure demyelinating lesions are rare. Most demyelinating lesions are accompanied by some degree of axonal loss. Hence, it is not uncommon to record fibrillation potentials, sometimes abundantly, in lesions where the NCSs suggest a purely demyelinative conduction block. This is due to the loss of a few, often clinically insignificant, number of axons in the midst of the demyelinating process.

Nonlocalizing Mononeuropathy

A nonlocalizing mononeuropathy is a familiar pattern in the EMG laboratory. This occurs primarily in axon-loss mononeuropathies examined after the completion of Wallerian degeneration. NCSs and needle EMG are normal throughout, except in the distribution of a single nerve. Sensory or motor nerve conductions, or both, may be abnormal depending on whether the involved nerve is a sensory, motor, or mixed nerve and on the severity of the lesion. In a nonlocalizing axon-loss lesion, the findings on NCSs reveal decreased CMAP or SNAP amplitudes, or both, with normal or slightly slowed distal latencies and conduction velocities. On needle EMG, neurogenic changes are limited to muscles innervated by the involved nerve distal to the site of the lesion. The mononeuropathy can only be localized at or proximal to the most proximal abnormal muscle identified on the needle EMG. Because there are usually no demyelinating findings on NCSs, such as focal slowing or conduction block, the lesion cannot be localized accurately. Common nonlocalizing mononeuropathies encountered in the EMG laboratory are axon-loss ulnar mononeuropathy or common peroneal mononeuropathy. Although the lesion is often across the elbow or fibular neck, respectively, the ulnar or peroneal conduction studies in these cases only show evidence of axonal loss, without slowing or conduction block.

Localizing Mononeuropathy

In a localizing mononeuropathy, NCS and needle EMG abnormalities are also limited to a single nerve. Definite localization is determined by electrophysiologic evidence of focal slowing or conduction block, or both, due to demyelination at the site of the lesion. Occasionally, axon-loss mononeuropathies may be localizing when examined by NCSs in the first 4–5 days by revealing a conduction block pattern similar to demyelination conduction block (see previous). Mixed lesions with low distal CMAPs and SNAPs with demyelinative conduction block or focal slowing, or both, are not uncommon. Localizing mononeuropathies are frequently seen in entrapment neuropathies in which the predominant underlying primary pathophysiology is demyelination (e.g., carpal tunnel syndrome, ulnar mononeuropathy across the elbow, radial mononeuropathy at the spiral groove, peroneal neuropathy at the fibular neck).

Radiculopathy

Radiculopathy is one of the most frequent patterns seen in the EMG laboratory. Because the lesion is at the level of the root (i.e., proximal to the dorsal root ganglia), sensory NCSs are always normal. Motor conductions are also generally

normal, although CMAP amplitudes may be low in severe radiculopathy, when the muscle(s) used for recording is innervated by the involved nerve root. With routine NCSs, this only occurs in the median and ulnar motor studies in C8–T1 radiculopathies, and in the peroneal and tibial motor studies in L5–S1 radiculopathies.

Because each nerve root innervates a segment of paraspinal muscles and several limb muscles, usually by way of several different peripheral nerves, a radiculopathy is recognized on needle EMG by neurogenic abnormalities in muscles that share the same nerve root innervation (i.e., myotomal pattern). Abnormalities are usually expected in distal and proximal limb muscles innervated by the same nerve root, but by different nerves. In addition, abnormalities in the paraspinal muscles are useful, but not required, in helping to recognize a radiculopathy. Similar to other axonal loss lesions, it is important to remember that the specific neurogenic abnormalities vary, depending on the time course of the radiculopathy (see previous).

In summary, two criteria are necessary to establish the diagnosis of radiculopathy. The first is denervation in a segmental myotomal distribution (i.e., in muscles innervated by the same roots via more than one peripheral nerve), with or without denervation of the paraspinal muscles. At least two muscles, and preferably more, should reveal evidence of denervation (fibrillation potentials, decreased recruitment or abnormal MUAP morphology, or both). The second criterion is a normal SNAP in the corresponding dermatome. For example, in a C7 radiculopathy, the flexor carpi radialis (median innervated C7 muscle) and triceps (radial innervated C7 muscle) may be abnormal on needle EMG, with or without the cervical paraspinal muscles, with the median SNAP (recording middle finger) being normal. The only exception to this rule is in some rare cases of L5 radiculopathy, wherein the superficial peroneal SNAP may be absent or reduced in amplitude (less than 50 % of the contralateral superficial peroneal SNAP). Although the reason behind this finding is not completely understood, it is thought that the L5 dorsal root ganglion is actually located proximal to the intervertebral foramen in a small percent of individuals, causing it to be susceptible to external intraspinal compression, for example, from a disk herniation [3].

Polyradiculopathy

The polyradiculopathy pattern is seen when multiple nerve roots are involved. This pattern may occur in diabetes, cervico-lumbosacral stenosis, or when multiple nerve roots are infected (e.g., from cytomegalovirus) or infiltrated (e.g., by tumor, granulomatous tissue). Similar to an isolated radiculopathy, sensory NCSs are always normal. Motor NCSs may show changes consistent with axonal loss if the recorded muscles are in the distribution of the abnormal nerve roots. On needle EMG, there are neurogenic changes in the limb muscles in the distribution of multiple myotomes with or without involvement of the paraspinal muscles. The EDX findings in polyradiculopathy are not fundamentally different from those of motor neuron disease. However, this differentiation is usually easily made on clinical grounds, as patients with motor neuron disease have no radicular pain and sensory manifestations and often have upper motor signs.

Generalized Disorders

Polyneuropathies

Peripheral polyneuropathies are recognized by characteristic widespread abnormalities on NCSs and neurogenic findings on needle EMG. A common pattern is the symmetric stocking-glove polyneuropathy in which abnormalities are length dependent. Because longer nerves are preferentially affected on NCSs and needle EMG, abnormalities are more prominent distally, worse in the legs than the arms, and more prominent in distal than proximal segments. The vast majority of polyneuropathies, especially those due to toxic, metabolic, or genetic factors, result in symmetric EDX findings. Side-to-side comparisons are often useful. Polyneuropathies may be demyelinating, axonal, or a combination of both. Symmetric polyneuropathies can result from either axonal loss or demyelinative lesions. Any significant asymmetry should make one question the diagnosis of an axonal symmetric stocking-glove polyneuropathy.

Symmetric Axonal Polyneuropathy

Axonal polyneuropathies are associated with a characteristic pattern on NCSs, provided that the polyneuropathy has been present long enough for Wallerian degeneration to have occurred (i.e., >10–11 days). In general, CMAP and SNAP amplitudes are low, with normal or only slightly slowed distal latencies, late responses, and conduction velocities (Fig. 7.71). These changes are always more marked in the lower extremities. Likewise, needle EMG reveals evidence of axonal loss that is more prominent distally than proximally and more pronounced in the lower than upper extremities. As with axonal loss lesions in general, the needle EMG findings depend on how long the polyneuropathy has been present. Although reduced recruitment of MUAPs develops in weak muscles acutely, fibrillation potentials typically develop within weeks, and reinnervated MUAPs become apparent within several weeks to months. Different patterns also develop based on the temporal profile of the illness. For example, if the process is relatively active and progressive, a combination of fibrillation potentials with reduced recruitment of reinnervated MUAPs will be seen, most prominent distally. If, on the other hand, the polyneuropathy is chronic

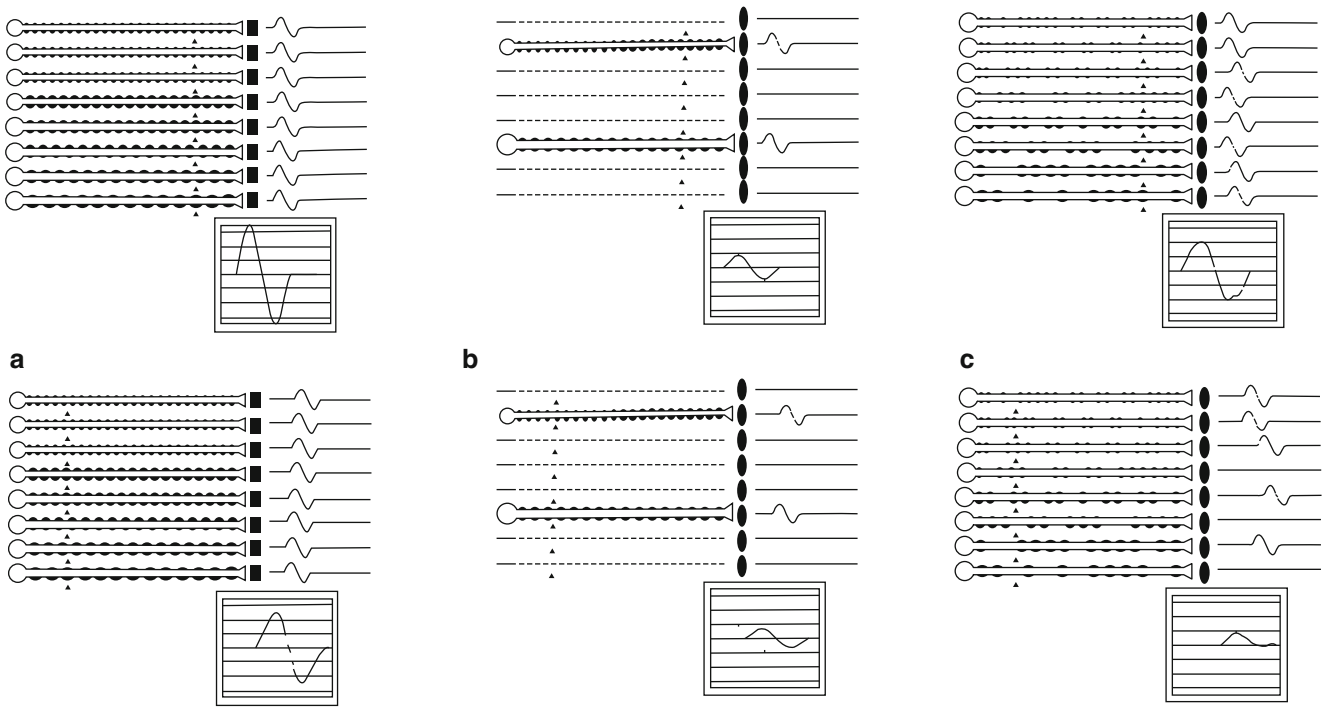


Fig. 7.71 Computerized model of peripheral motor nerve in normal nerve (**a**), axonal degeneration (**b**), and segmental demyelination (**c**) (Adapted from Albers [42], with permission)

and only very slowly progressive, reinnervation may completely keep pace with denervation. In such cases, there may be little or no fibrillation potentials, and the sole findings on needle EMG is reduced recruitment of reinnervated MUAPs.

Asymmetric Axonal Polyneuropathy

The presence of any significant asymmetry in an axonal polyneuropathy may have important diagnostic significance. In some cases, an asymmetric or a non-length-dependent pattern can be seen in typical, symmetric axonal polyneuropathies with superimposed mononeuropathies, plexopathies, or radiculopathies. For example, a diabetic patient with a distal symmetrical polyneuropathy may develop a diabetic amyotrophy (radiculoplexopathy) resulting in markedly asymmetric findings. More important, however, is that an asymmetric pattern may suggest underlying multiple mononeuropathies. Multiple mononeuropathies, as those occurring in mononeuritis multiplex, are a unique pattern in which individual peripheral nerves are affected in a stepwise manner. This pattern is most often seen in the context of an underlying vasculitic neuropathy. If the pattern is not recognized initially, as more nerves are affected, a confluent pattern of nerve involvement will develop, difficult to differentiate from a typical distal polyneuropathy. In these cases, asymmetrical EDX findings may be important clues to the true underlying mononeuritis multiplex pattern.

Demyelinating Polyneuropathy

Although axonal changes are present in all chronic polyneuropathies, few are due to primary demyelination. Demyelinating polyneuropathy is an important pattern to recognize. The differential diagnosis of such is narrowed further by the finding of uniform slowing versus nonuniform slowing and conduction blocks.

In demyelinating neuropathies, in which the process is uniform, all nerve segments are equally affected, often worse in the lower extremities. Consequently, demyelination results in marked slowing of conduction velocities (<75 % LLN), distal latencies, and late responses (>130 % ULN). This particular pattern of demyelination, symmetric uniform slowing without conduction block, is the pattern seen in the inherited demyelinating polyneuropathies (i.e., Charcot-Marie-Tooth disease type I).

The presence of conduction blocks has special diagnostic significance, as it helps to differentiate acquired from inherited demyelinating conditions. Conduction blocks at nonentrapment sites characteristically occur in acquired demyelinating neuropathies, such as Guillain-Barré syndrome or chronic inflammatory demyelinating polyneuropathy (CIDP), but are not seen in the inherited demyelinating neuropathies (e.g., Charcot-Marie-Tooth type I). One rare exception to this conduction block rule is in patients with hereditary neuropathy with sensitivity to pressure palsies (HNPP), an inherited demyelinating neuropathy, in which conduction blocks may occasionally accompany focal slowing at nonentrapment sites.

In summary, the cardinal feature of demyelinating polyneuropathies is marked slowing with relative preservation of CMAP amplitudes (see Fig. 7.71). In an inherited demyelinating neuropathy, there is symmetry comparing side-to-side and uniform conduction velocity slowing without conduction block. Also, the absence of conduction block at noncompressive sites is the key feature that separates inherited from acquired demyelinating polyneuropathies. In contrast, acquired conditions (e.g., CIDP) often have asymmetric nerve conductions when comparing side to side, even when there is no apparent clinical asymmetry. In addition, conduction block and excessive temporal dispersion at nonentrapment sites always mark the polyneuropathy as acquired, as they are not seen in inherited demyelinating neuropathies.

Anterior Horn Cell Disease

As the sensory system is spared in motor neuron disease, sensory conduction studies are usually normal. Motor NCSs may also be normal, but more often are low in amplitude consistent with axonal loss. No demyelinating features are seen on motor NCSs, an important feature because some demyelinating motor neuropathies can mimic motor neuron disease. However, these disorders are associated with conduction blocks and other signs of demyelination on NCSs. On needle EMG, the findings in motor neuron disease are similar to polyradiculopathy: neurogenic abnormalities are seen in the paraspinal muscles and in the distribution of multiple nerve roots. In addition, craniobulbar and thoracic paraspinal muscles may also be abnormal. Abnormalities in these latter areas are especially important, as they are not involved in cervical-lumbar spondylosis (i.e., cervico-lumbosacral polyradiculopathy), a common condition sometimes confused with motor neuron disease.

Myopathies

Myopathies result from loss or dysfunction of muscle fibers. The EDX of myopathy is usually based on needle EMG abnormalities alone. Sensory NCSs are normal, unless there is an associated neuropathy. Motor conduction studies are also normal in most cases, because distal muscles are often used to record during routine motor NCSs. These muscles are spared in most myopathies, which have a predilection for proximal muscles. In myopathies that are diffuse (e.g., critical illness myopathy), in their terminal stages (e.g., advanced Duchenne muscular dystrophy), or affect distal muscles preferentially (e.g., myotonic dystrophy type I), CMAP amplitudes may be decreased, but with normal latencies and conduction velocities.

On needle EMG, myopathy is usually diagnosed by changes in MUAP morphology and recruitment. In many myopathies, there is dropout or dysfunction of individual muscle fibers, which effectively decreases the size of the motor unit. In myopathy, MUAP morphology becomes short in duration, low in amplitude, and polyphasic. These changes result from dropout of individual muscle fibers and less synchronous firing of the remaining fibers. MUAP recruitment is usually normal, as the number of motor units remains intact. However, because each motor unit has fewer fibers than normal, it can generate less force. Consequently, more MUAPs than usual must fire to generate a particular amount of force. This results in a pattern of *early recruitment*, whereby an inappropriately large number of motor units must fire to generate a small amount of force. In severe myopathies where every muscle fiber in many motor units is lost, the number of motor units effectively decreases. This results in decreased recruitment which may be confused with a neurogenic disorder.

The analysis of spontaneous activity is also important in evaluating myopathic patterns. Certain myopathies are associated with abnormal spontaneous activity, including fibrillation potentials, myotonic discharges, or complex repetitive discharges (CRDs). Only a limited number of myopathies are associated with fibrillation potentials or myotonic discharges (Table 7.13). Fibrillation potentials in myopathies are due to segmental muscle fiber degeneration which results in effective denervation of some segments of muscle fibers (see Fibrillation Potentials).

A chronic myopathy with fibrillation potentials and denervating features is one of the most difficult patterns to recognize. Following denervation of muscle fibers in myopathies, some reinnervation normally occurs. In chronic conditions, this can lead to complicated needle EMG patterns, where both myopathic (short duration, low amplitude, and polyphasic) and neuropathic (long duration, high amplitude, and polyphasic) MUAPs are seen, often in the same muscle. In some cases, recruitment, which is usually normal or early in myopathy, may actually be reduced. However, the degree of neurogenic MUAP changes (large, long, and polyphasic) often appears out of proportion for the mild reduction in recruitment pattern, which is an important clue to a possible chronic myopathy.

Neuromuscular Junction Disorders

NMJ disorders often present in a similar fashion to myopathies, with proximal muscle weakness. They may be mistaken for myopathies on EMG as well, especially if repetitive nerve stimulation (RNS) is not performed. NMJ disorders result in different patterns on NCS-EMG, depending on whether the pathophysiology is presynaptic or postsynaptic. In all NMJ disorders, sensory conduction studies are normal. Motor NCSs always yield normal distal latencies, conduction velocities, and late responses.

In postsynaptic disorders (e.g., myasthenia gravis), CMAP amplitudes are usually normal, and slow RNS results in a decremental CMAP response (>10 %). Several minutes after exercise, the decrement becomes more marked (post-tetanic

Table 7.13 Needle electromyography findings in myopathies

Normal	Myopathic MUAPs with fibrillation potentials	Myopathic MUAPS only	Fibrillation potentials only	Myopathic MUAPs and myotonia	Myotonia only
Metabolic myopathies	*Inflammatory myopathies*	*Muscular dystrophies*	*Inflammatory myopathies*[b]	*Myotonic dystrophies*	*Myotonia congenita*
McArdle's disease	Polymyositis	FSH	Polymyositis	Myotonic dystrophy (I and II)	Thomsen's disease
Tarui's disease	Dermatomyositis	Limb girdle	Dermatomyositis	*Muscle channelopathies*	Becker's disease
Brancher deficiency	Inclusion body myositis	Oculopharyngeal	Sarcoid myopathy	Paramyotonia congenita	*Other myotonic disorders*
Debrancher deficiency	Sarcoid myopathy	Congenital	HIV-associated myopathy	Hyperkalemic periodic paralysis[a]	Atypical painful myotonia
CPT deficiency	HIV-associated myopathy	*Congenital myopathies*	*Others*	*Others*	Myotonia fluctuans
Carnitine deficiency	*Muscular dystrophies*	Central core	Acute rhabdomyolysis	Acid maltase deficiency	
Adenylate deaminase deficiency	Duchenne	Nemaline rod	Chloroquine	Myotubular myopathy	
Mitochondrial myopathies	Becker	*Endocrine myopathies*		Colchicine	
Kearns-Sayre syndrome	Distal	Steroid(severe)			
MELAS	*Others*	Hypothyroid			
MERRF	Critical illness myopathy	Hyperthyroid			
Endocrine myopathies	Myotubular myopathy	Hyperparathyroid			
Steroid (mild)	Parasitic infections (trichinosis)	*Toxic myopathies*			
Hypothyroid		Alcohol			
Hyperthyroid		Emetine			
Hyperparathyroid					
Cushing's					
Others					
Fiber-type disproportion					
Periodic paralysis[a]					

Source: Adapted from Katirji [43], with permission
CPT carnitine palmitoyltransferase deficiency, *McArdle's disease* myophosphorylase deficiency, *Tarui's disease* phosphofructokinase deficiency, *MELAS* mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, *MERRF* myoclonic epilepsy and ragged-red fibers, *HIV* human immunodeficiency virus, *FSH* facioscapulohumeral muscular dystrophy
[a]Between attacks
[b]Early or mild

exhaustion). As weakness and fatigue in myasthenia gravis affect extraocular, bulbar, and proximal muscles, decremental responses are more often seen with stimulation of more proximal nerves. It should be noted that slow RNS decrement correlates with disease severity and muscle weakness but is not a good objective measure of fatigue [44]. Single-fiber EMG is a more useful technique in assessing fatigue in patients with MG (see Chap. 8).

Presynaptic disorders (e.g., LEMS and botulism) have a different pattern. In these disorders, CMAP amplitudes are usually reduced at rest. There is a marked incremental CMAP response (typically >200 % in LEMS and >100 % in botulism) following rapid (30–50 Hz) RNS or brief (10 s) maximal voluntary exercise. Slow RNS also generally reveals a decremental CMAP response.

On needle EMG, abnormal spontaneous activity is not a common feature in NMJ disorders. However, in botulism or severe myasthenia gravis, NMJ blockade may be so severe that muscle fibers are effectively denervated, often resulting in fibrillation potentials. MUAP morphology in NMJ disorders is usually normal, including the recruitment pattern. However, the needle EMG may demonstrate unstable MUAPs, which vary in configuration (i.e., amplitude and phases) from potential to potential. If the severity of the disorder is such that blocking occurs, individual muscle fibers may drop out, thereby reducing the number of muscle fibers per motor unit. This results in short-duration, low-amplitude, polyphasic MUAPs, often accompanied by early recruitment, findings usually associated with myopathy.

Central Nervous System (CNS) Disorders

Patients with CNS lesions (i.e., brain and spinal cord) often present with weakness and numbness. They may have increased reflexes and muscle tone and other signs that mark the lesion as central. In an acute event, however, reflexes and muscle tone may be decreased, making it difficult to differentiate a central from a peripheral lesion. For example, in patients with new upper extremity weakness and numbness following open heart surgery, the differential includes a traction lesion of the lower trunk of the brachial plexus versus a stroke from a cardiac embolus. Acutely, both conditions may be associated with depressed reflexes and decreased muscle tone, along with weakness and numbness of the hand. In this type of situation, the EMG can easily differentiate between the two. In CNS disorders, motor and sensory nerve conduction studies are normal. There are no fibrillation potentials or reinnervation on needle EMG, and MUAP morphology remains normal. However, on voluntary contraction, the interference pattern is not full and often has an erratic or sputtering pattern of slow-firing MUAPs. This is due to decreased activation (i.e., reduced firing frequency), while the number of available MUAPs (i.e., the recruitment) remains appropriate for the level of activation.

Another CNS lesion that often creates confusion is a segmental lesion of the spinal cord. Muscles innervated below the level of the lesion display the typical CNS pattern of decreased activation. However, at the segmental level of the lesion, the anterior horn cells may be affected, leading to a lower motor neuron pattern in the muscles innervated by that segment. For example, in a patient with cord compression at C5–C6 resulting in quadriplegia, needle EMG of leg muscles and of muscles innervated by segments below the site of the lesion shows decreased activation. However, EMG of C5–C6 muscles (e.g., deltoid and biceps) shows decreased recruitment and active denervation or reinnervation, depending on the time course of the lesion. Muscles partially innervated by these segments (e.g., pronator teres, a C6–C7 muscle) show a combination of decreased activation and decreased recruitment, as well as other neuropathic changes.

Other Important Electrodiagnostic Patterns

Sensory Loss with Normal Sensory Nerve Action Potentials

When performing sensory NCSs, the electromyographer is occasionally presented with an apparent paradox: the SNAP is normal, yet the patient has clear sensory loss in the distribution of the normal SNAP that is being recorded. It is important to remember that there are only three possible explanations for this situation, provided the study is technically accurate (Fig. 7.72):

1. *The Lesion Is Proximal to the Dorsal Root Ganglion*. This includes structural lesions of the nerve roots, spinal cord, or brain, as well as psychiatric or factitious disorders. Because the dorsal root ganglion and peripheral nerve are intact, sensory responses remain normal on conduction studies.
2. *There Is a Proximal Demyelinating Lesion*. Because Wallerian degeneration does not occur with demyelination, the underlying axon remains intact. Thus, if the nerve is stimulated and recorded distal to the lesion, the distal segment continues to conduct normally and the SNAP will be normal, although effectively disconnected from its proximal segment.
3. *There Is a Hyperacute Axonal Lesion*. Immediately following an axonal lesion, the distal nerve continues to conduct normally for the first several days, before Wallerian degeneration occurs. During this time, if the nerve is stimulated and recorded distal to the lesion, it will conduct normally. This underscores the need for the electromyographer to know the temporal course of the clinical history before interpreting a study.

Low-Amplitude CMAPs with Normal SNAPs

A pattern of diffusely low CMAP amplitudes with normal SNAPs suggests a pure motor loss. Often, distal latencies,

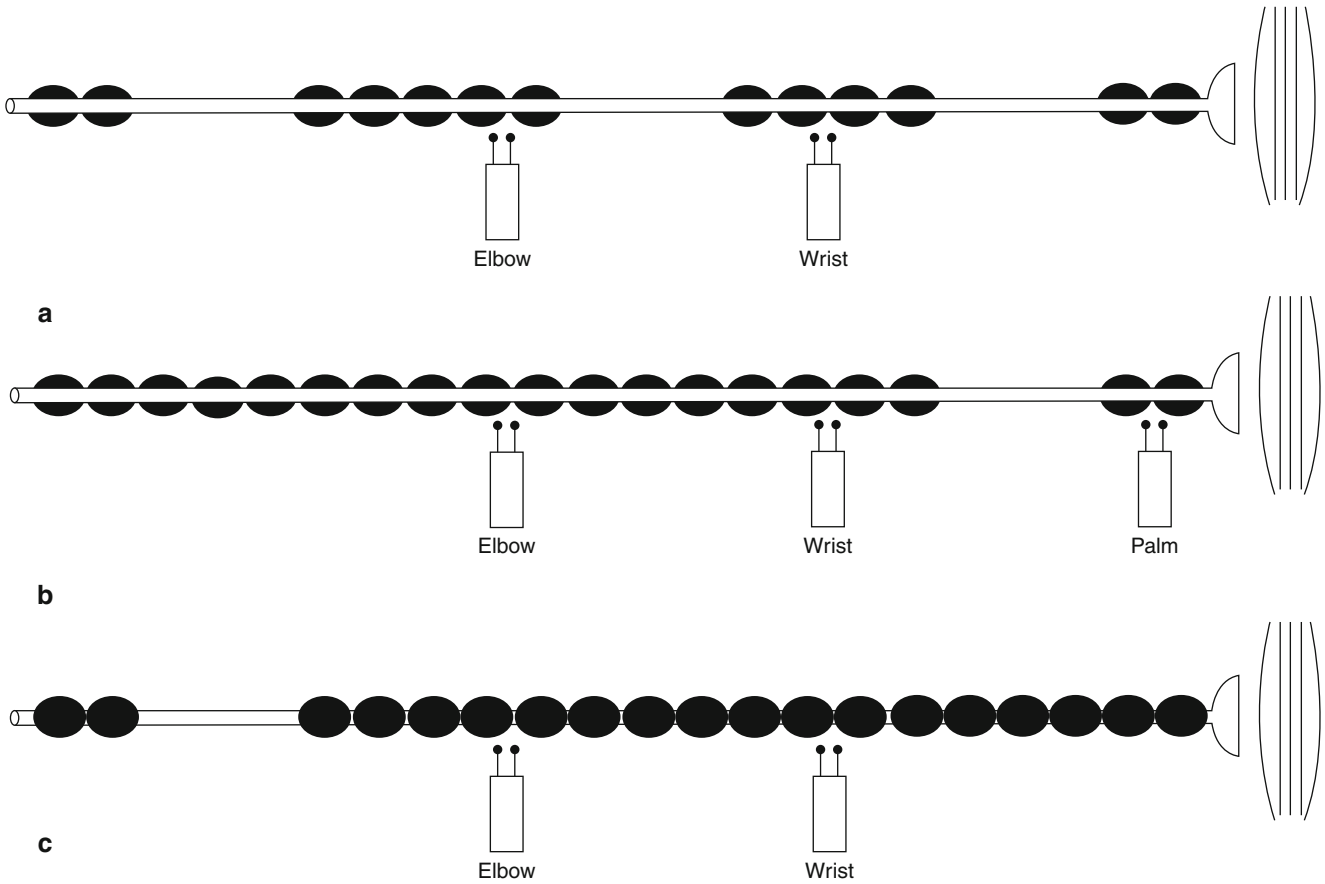


Fig. 7.72 Sensory loss and normal sensory nerve action potentials (SNAPs). When confronted with a patient with sensory loss, yet normal SNAPs in the distribution of the sensory loss, there are three possible explanations. (**a**) The lesion is proximal to the dorsal root ganglion (DRG). Because the DRG and peripheral nerve remain intact, SNAPs will be normal. This occurs in lesions of the brain (structural and psychiatric) and spinal cord, as well as lesions of the nerve roots. In nerve root lesions, Wallerian degeneration occurs centrally into the spinal cord and peripherally to the level of the DRG, leaving the DRG intact. (**b**) Proximal demyelination. Because demyelination leaves the underlying axon intact, subsequent Wallerian degeneration does not occur. If demyelination is proximal to the stimulation and recording sites, the SNAPs will be normal. (**c**) Hyperacute axonal injury. All peripheral axonal injuries result in abnormal SNAPs following Wallerian degeneration. If sensory studies are performed distal to the injury, and earlier than 4–7 days, before Wallerian degeneration has occurred, the SNAPS will also be normal (Reproduced with permission from Preston and Shapiro [1])

conduction velocities, and late responses are normal. This pattern may be seen in the following situations:

1. Anterior horn cell disease, such as amyotrophic lateral sclerosis
2. Polyradiculopathy, such as cervico-lumbosacral polyradiculopathies
3. Pure motor axonopathy (polyneuropathy) as seen with acute motor axonal neuropathy
4. Presynaptic NMJ disorders, such as LEMS
5. Myopathy (distal, diffuse, or terminal), such as critical illness myopathy, distal myopathies, or advanced Duchenne muscular dystrophy

Rapid RNS or postexercise CMAP evaluation should exclude LEMS. The needle EMG can be used to differentiate the neurogenic disorders (motor neuron disease, polyradiculopathy, axonopathy) from the myopathic ones (NMJ and myopathy). The differentiation between motor neuron disease and polyradiculopathy is difficult by EDX criteria but easily made clinically since polyradiculopathy is often associated with sensory manifestations or pain.

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Single-Fiber EMG

8

James M. Gilchrist and Dinesh G. Nair

Introduction

Single-fiber electromyography (SFEMG) is the use of a special needle electrode to record electrical signals from single muscle fibers in vivo. The technique was originally developed by Drs. Erik Stalberg and Jan Ekstedt to study muscle fatigue. Their initial work was published as doctoral theses in 1966 [1] and 1964 [2], respectively. Dr. Stalberg has since become the primary proponent and researcher of SFEMG, and there is little regarding SFEMG he has not investigated, written about, or clarified. His textbook, now in its third edition, *Single Fiber Electromyography* [3], is the definitive monograph on the subject. The clinical and research utility of SFEMG has far outstripped the original intent of Drs. Stalberg and Ekstedt. SFEMG has become an important tool for assessing neuromuscular transmission and measuring reinnervation. It is the most sensitive clinical measure of dysfunctional neuromuscular transmission and an accurate electrical correlate of fiber-type grouping.

Basic Principles

The theoretical construct underlying SFEMG is the selective recording of a limited number of single muscle fiber action potentials (MUAP) from one motor unit. This requires a needle electrode with different specifications from a concentric or monopolar needle electrode. Single muscle fiber action potential amplitudes decrease exponentially with distance from the recording electrode. The motor unit action potential (MUAP) amplitude recorded by a needle electrode is therefore dominated by the nearest few muscle fibers, whereas MUAP duration correlates with the ultimate territorial spread of the motor unit. This amplitude differential between close and distant muscle fiber potentials is distorted, in part from the needle electrode itself, thus diminishing the amplitude gradient between closest and furthest fibers. This is particularly true for concentric needle electrodes which have a recording surface larger than individual muscle fibers. A smaller electrode will emphasize the amplitude difference between close and distant fiber potentials and, therefore, increase the near to far muscle fiber potential amplitude ratio. A smaller recording surface will also restrict the number of recordable muscle fiber potentials. In addition, muscle fiber potentials adjacent to the recording electrode will have high amplitudes and short duration and relatively more high frequency components compared to more distant potentials. Single muscle fiber action potential (MFAP) amplitude decreases exponentially with distance from the recording electrode. By using a high-pass filter of 500 Hz, much of the amplitude of distant muscle fiber potentials will be attenuated while preserving that of the near potentials. High-pass filtering and a small electrode recording surface, with the addition of bipolar recording, can then record and discriminate a single MFAP from the summated MUAP of which it is a part [3].

It therefore is logical that the caliber and the recording surface of a SFEMG needle are significantly smaller than of a concentric needle electrode (Fig. 8.1). A SFEMG recording surface is 25 μm in diameter with an effective recording area of 300 μm^3 [3], as compared with a concentric needle electrode which records from approximately 1 cm^3. Any needle point may mechanically deform muscle fibers, which would alter the muscle fiber potential and lead to potentially inaccurate waveforms and measurements. To avoid this, the active SFEMG electrode port is not at the end of the needle but rather 3–5 mm proximal to, and on the opposite side from, the beveled tip of the needle. The cannula serves

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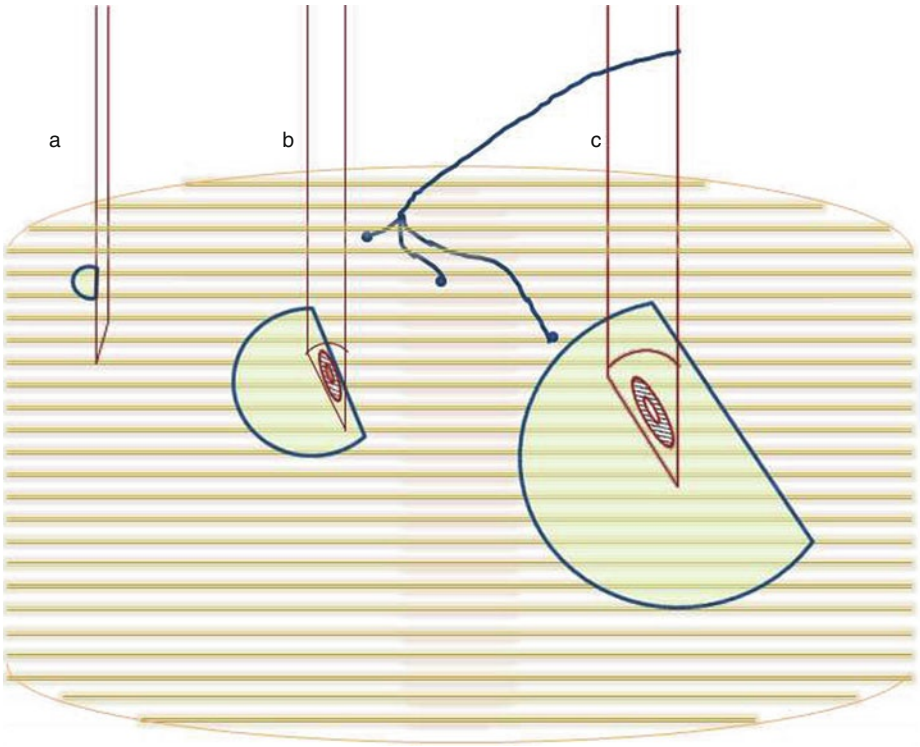

Needle	Width (∝m)	Area (mm^2)
a. SFEMG	25	0.0005
b. CNE facial	80	0.019
c. CNE	150	0.07

Fig. 8.1 Relative size and recording area of the SFEMG needle in comparison with two types of concentric needles. The recording area and the number of muscle fibers for each needle are approximate and not exactly to scale

as the reference electrode. Single-fiber EMG needles used for fiber density and jitter measurement contain a single electrode. Multielectrode single-fiber EMG needles are also possible and are useful for measurement of muscle fiber propagation velocity and volume conduction.

The small recording area of a SFEMG needle means it can only record signals from muscle fibers in its immediate vicinity, which limits the choice to 5–7 fibers at any time. Given the normal random distribution of muscle fibers within motor units, the 5–7 fibers within the SFEMG electrode recording area may be members of 5–7 different motor units. By using an amplitude threshold to trigger the oscilloscope trace on the closest muscle fiber potential (the potential with the sharpest rise time and the greatest amplitude), muscle fiber potentials from other motor units will be excluded from the oscilloscope screen. By counting the number of single muscle fiber potentials seen with each MUAP firing, one can determine the number of muscle fibers from that MUAP within the small recording territory of the SFEMG needle electrode. For the most part it should be one or two. By sampling 20 different sites in a muscle, an average number of single muscle fiber potentials per recording site can be calculated. This is called *fiber density*. In conditions with loss of random distribution of MUAP muscle fibers, such as reinnervation, fiber density will increase.

In those instances where two or more fiber potentials from a single MUAP are recorded, an interpotential interval (IPI) can be calculated. By recording multiple consecutive firings of the muscle fiber potentials, one can determine consecutive IPIs and, therefore, calculate the difference between consecutive IPIs. Comparison of consecutive differences will illustrate the variation between IPIs. This variation is called *jitter*. Jitter is most accurately determined by calculating a mean consecutive difference (MCD) [4] using the formula

$$\mathrm{MCD} = \frac{[\mathrm{IPI}_1 - \mathrm{IPI}_2] + \ldots + [\mathrm{IPI}_{n-1} - \mathrm{IPI}_n]}{n-1}$$

where IPI = interpotential interval.

Jitter is believed to derive from variation in the time it takes the neuromuscular junction end plate potential (EPP) to reach threshold for action potential generation at the postsynaptic membrane [5]. In disorders with disturbed neuromuscular transmission, there will be an increased variation in the time taken to attain an EPP capable of reaching threshold. This will lead to increased jitter (Fig. 8.2). Therefore, abnormal jitter is an indicator of abnormal neuromuscular transmission.

In those instances where an EPP fails to reach threshold for action potential generation, one of the muscle fiber potentials in the pair will be absent. This is called *impulse blockade* (Fig. 8.2c). It is another indicator of abnormal neuromuscular transmission, usually indicating a more severe disturbance than increased jitter alone. Impulse blocking, often referred to simply as blocking, is usually intermittent, with the affected fiber potential appearing and disappearing

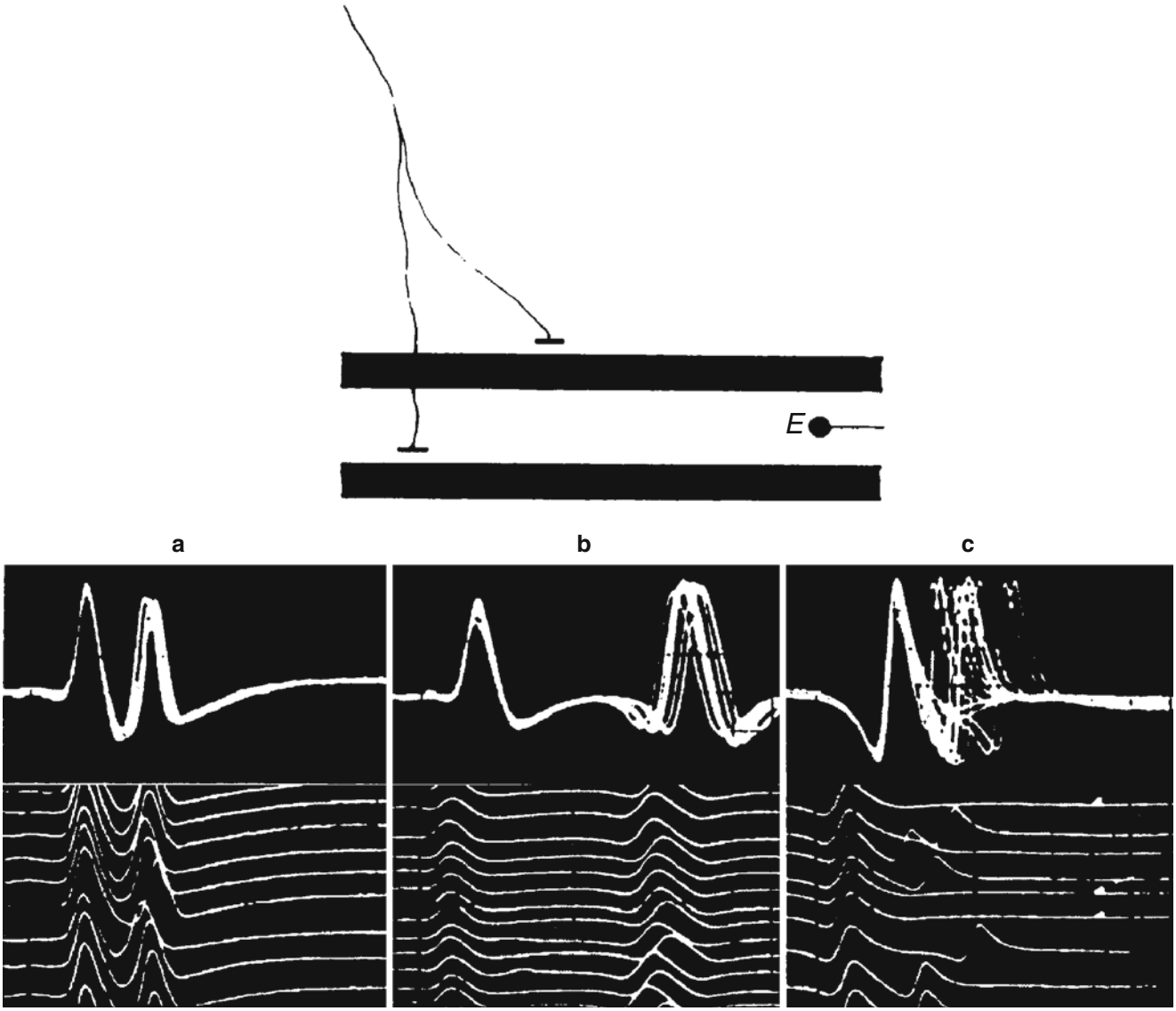

Fig. 8.2 Jitter as recorded using voluntary SFEMG technique. The electrode (*E*) is between two single muscle fibers. (**a**) Recording from a normal muscle, rastered traces on the *bottom*, superimposed traces on *top*. (**b**) Recording with increased jitter, indicating one or both of the motor end plates is abnormal. (**c**) Recording with increased jitter and blocking. Calibration 500 μs (Reproduced with permission from Stalberg [6])

in an unpredictable pattern. In my experience, blocking is uncommonly seen with jitter less than 100 μs.

SFEMG electrodes are expensive, get dull, develop increased impedance with use, and must be sterilized for reuse, which does not entirely eliminate concern for infections. Disposable concentric needle electrodes (CNE) provide an easy and probably acceptable alternative for single-fiber electrodes. The relatively larger recording uptake area of the CNE compared to the SFEMG electrode (see earlier part of this chapter for details and Fig. 8.1) creates different challenges, which in part can be allayed by increasing the low-frequency filter and using more restrictive selection of APs for analysis. The larger needle also causes a larger shunting effect of the electric field around the muscle fiber, and the recorded AP amplitude is smaller than when recorded using an SF electrode. The spikes obtained with a CNE do not represent a single-fiber AP but are rather a summation of action potentials from more than one fiber. Therefore, CNE cannot be used to measure fiber density.

Methodology

SFEMG for fiber density or jitter determination is performed by inserting a SFEMG needle into the muscle to be studied. A ground electrode should be nearby. The electrode is connected to an electromyograph machine with an amplitude threshold trigger and delay line. Filter settings should be set

at 500 Hz for the high-pass filter and 10–20 kHz for the low-pass filter. Selected single muscle fiber potentials should have a peak-to-peak amplitude of at least 200 μV with a rise time of 300 μs. The waveform should remain constant through consecutive recordings. For jitter analysis, at least 50 consecutive recordings should be made to allow for a statistically valid calculation. Paired fiber potentials with very short IPIs should have at least a 100 μV "notch" between them to count as two separate potentials.

When using a CNE for jitter analysis, the cutoff of the high-pass filter needs to be increased above 500 Hz in order to suppress activity of distant muscle fibers and decrease their contribution to the low-frequency components of the signal [7, 8]. If increased beyond 1,000 Hz, spikelike signal components appear, a phenomenon called ringing, and the amplitude of the signal further decreases. Also, summation of signals with similar latency may produce changes in individual waveforms and even result in a polyphasic MUAP, resulting in imprecise measurements. Hence, it is suggested that the best low-frequency filter setting for a CNE is likely 1,000 Hz [8]. In order to optimize the recording, a small CNE (30 G) with a recording area of 0.019 μm^2, often referred to as the facial electrode (Fig. 8.1), is recommended.

There are two commonly used methods for activation of muscle fibers when using SFEMG in a clinical setting. The first method is *voluntary*, in which the patient activates the muscle fiber (Fig. 8.2). This is the most commonly used method despite some drawbacks. The motor unit firing rate is dependent on the patient and may not be amenable to change or variation. The patient may not be able to cooperate in maintaining a constant firing rate (e.g., parkinsonian tremor) or may not be able to cooperate at all (child, comatose patient, patient with severe weakness). The second method is *axonal stimulation* (Fig. 8.3). This is performed by installing a monopolar needle electrode near the intramuscular nerve twigs and stimulating at a low current and constant rate [10, 11]. Disadvantages include a more technically complex procedure as you need to maneuver two needle electrodes, for stimulating and recording, while varying stimulation intensity to the appropriate level. Fiber density cannot be calculated, as the stimulated nerve twigs lead to muscle fibers from any number of MUAPs. In addition, direct muscle fiber stimulation may occur, leading to very low jitter, and if the nerve twig is not stimulated at the appropriate intensity (subliminal stimulation), jitter may be falsely increased. For the skilled electromyographer, stimulated SFEMG may be faster, as many single muscle fiber potentials can conceivably be analyzed at a time (Fig. 8.4). A primary advantage is that stimulation SFEMG requires no cooperation from the patient, and it is the preferred method in comatose or sedated patients, including children and the severely weak. Surface stimulation for SFEMG has also been done successfully [13].

One key difference in the two activation techniques is the number of end plates under study. In voluntary activation,

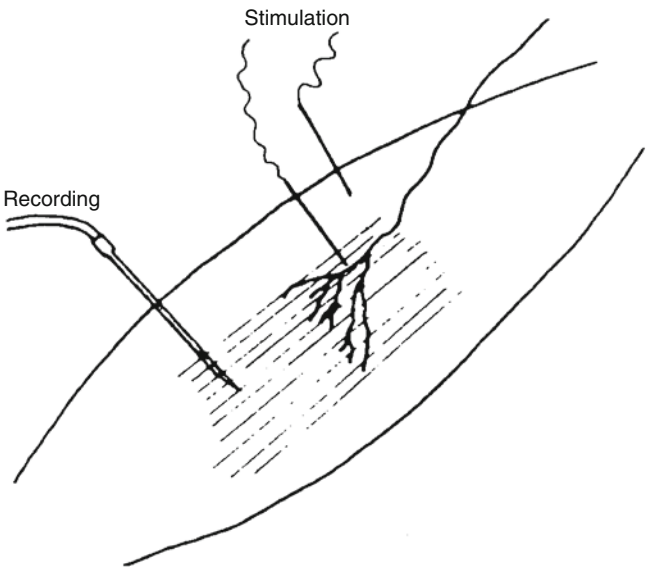

Fig. 8.3 Axonal stimulation SFEMG. The recording electrode is placed in the muscle, while the stimulating electrode is placed near the intramuscular nerve twigs (Reproduced with permission from Hilton-Brown et al. [9])

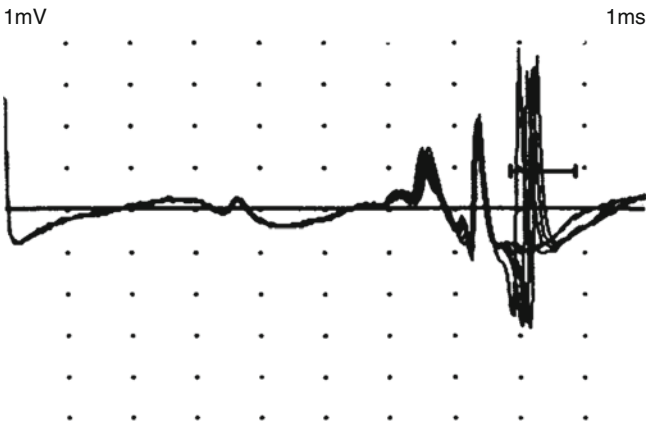

Fig. 8.4 Abnormal stimulated single-fiber electromyography of the extensor digitorum communis muscle. One of the advantages of stimulation single-fiber electromyography is the frequent recording of several muscle fiber action potentials (MFAPs). In this example, three separate MFAPs are recorded. The first MFAP shows a moderate amount of jitter (78 milliseconds [ms]), the second a normal amount of jitter (21 ms), and the third a large amount of jitter (165 ms), with blocking 30 % of the time (Reproduced with permission from Rivner and Swift [12])

jitter is calculated as the variation in IPIs between two muscle fiber potentials. As one of the potentials is time locked by the threshold trigger, all the variation of both end plates is expressed by the jitter of the other potential. In stimulation SFEMG, the IPI is measured as the latency between the stimulation and the single-fiber potential. Hence, only one end plate is involved.

Fiber density is easily calculated by hand, by averaging the number of single-fiber muscle potentials per recording site over 20 sites. Jitter can also be done by hand, but virtually

every EMG machine now manufactured has the capability for automatic measurement of jitter. All such programs should include methods for user intervention to delete extraneous or inaccurate data. Mean jitter should be calculated from 20 individual jitter measurements, and results are expressed as both the number and percentage of normal and abnormal fiber potential pairs and as mean jitter. The percentage of fiber potentials exhibiting impulse blockade, if any, is also an important measure of the health of neuromuscular transmission.

Normal values for fiber density and jitter are available from a multicenter international collaborative effort (Tables 8.1 and 8.2) [14]. Values differ between muscles and tend to increase with age, particularly over the age of 50 years. Fiber density values do not depend on the size of the muscle: a large biceps will have a fiber density comparable to a small biceps. As the values for jitter obtained by axonal stimulation are calculated on the basis of one end plate, the normal values are lower than those obtained by voluntary activation, theoretically by $1/\sqrt{2}$ or 71 % [10]. Normal values for axonal stimulation have been obtained for the EDC and the orbicularis oculi: they do not vary with age. The upper reference value for the EDC is 25 μs and for the orbicularis oculi is 20 μs [3]. The actual values were approximately 77 % of those obtained by voluntary activation.

The method used to record single-fiber activity with CNE is quite similar to that used for voluntarily activated SFEMG recordings. During voluntary contraction of the muscle, the electrode position is adjusted until two or more spikes are recorded. Jitter is measured between pairs of spikes. Axonal stimulation can also be used with CNE. The criteria for acceptable signals and normative values still remain untested, mainly due to variations in technique, filter settings, and needle size [3, 8]. Several studies have presented normative data for jitter using CNE [3], but the techniques, needle sizes, and filter settings were quite variable, and a larger database of normative values using standardized methods and equipment needs to be acquired. Thus, investigators should exercise caution before declaring a study to be abnormal, as several variables affect the criteria for identifying acceptable recordings [15]. Despite methodological concerns, however, the sensitivity and specificity of CNE SF studies appear to be comparable to studies using the SFEMG electrode [7, 8].

Table 8.1 Fiber density reference values: 95 % upper confidence limits

Muscle	10 years	20 years	30 years	40 years	50 years	60 years	70 years	80 years	90 years
Frontalis	1.67	1.67	1.68	1.69	1.70	1.73	1.76		
Tongue	1.78	1.78	1.78	1.78	1.78	1.79	1.79		
Sternocleidomastoid	1.89	1.89	1.90	1.92	1.96	2.01	2.08		
Deltoid	1.56	1.56	1.57	1.57	1.58	1.59	1.60	1.62	1.65
Biceps	1.52	1.52	1.53	1.54	1.57	1.60	1.65	1.72	1.80
Extensor digitorum communis	1.77	1.78	1.80	1.83	1.90	1.99	2.12	2.29	2.51
Abductor digiti minimi	1.99	2.00	2.03	2.08	2.16	2.28	2.46		
Quadriceps	1.93	1.94	1.96	1.99	2.05	2.14	2.26	2.43	
Tibialis anterior	1.94	1.94	1.96	1.98	2.02	2.07	2.15	2.26	
Soleus	1.56	1.56	1.56	1.57	1.59	1.62	1.66	1.71	

Table 8.2 Reference values for jitter measurements during voluntary muscle activation (μs): 95 % confidence limits for upper limit of mean jitter/95 % confidence limits for jitter values of individual fiber pairs

Muscle	10 years	20 years	30 years	40 years	50 years	60 years	70 years	80 years	90 years
Frontalis	33.6/49.7	33.9/50.1	34.4/51.3	35.5/53.5	37.3/57.5	40.0/63.9	43.8/74.1		
Orbicularis oculi	39.8/54.6	39.8/54.7	40.0/54.7	40.4/54.8	40.9/55.0	41.8/55.3	43.0/55.8		
Orbicularis oris	34.7/52.5	34.7/52.7	34.9/53.2	35.3/54.1	36.0/55.7	37.0/58.2	38.3/61.8	40.2/67.0	42.5/74.2
Tongue	32.8/48.6	33.0/49.0	33.6/50.2	34.8/52.5	36.8/56.3	39.8/62.0	44.0/70.0		
Sternocleidomastoid	29.1/45.4	29.3/45.8	29.8/46.8	30.8/48.8	32.5/52.4	34.9/58.2	38.4/62.3		
Deltoid	32.9/44.4	32.9/44.5	32.9/44.5	32.9/44.6	33.0/44.8	33.0/45.1	33.1/45.6	33.2/46.1	33.3/46.9
Biceps	29.5/45.2	29.6/45.2	29.6/45.4	29.8/45.7	30.1/46.2	30.5/46.9	31.0/48.0		
Extensor digitorum communis	34.9/50.0	34.9/50.1	35.1/50.5	35.4/51.3	35.9/52.5	36.6/54.4	37.7/57.2	39.1/61.1	40.9/66.5
Abductor digiti minimi	44.4/63.5	44.7/64.0	45.2/65.5	46.4/68.6	48.2/73.9	51.0/82.7	54.8/96.6		
Quadriceps	35.9/47.9	36.0/48.0	36.5/48.2	37.5/48.5	39.0/49.1	41.3/50.0	44.6/51.2		
Tibialis anterior	49.4/80.0	49.3/79.8	49.2/79.3	48.9/78.3	48.5/76.8	47.9/74.5	47.0/71.4	45.8/67.5	44.3/62.9

Findings in Neuromuscular Diseases

Disorders of the Neuromuscular Junction

Evaluation of neuromuscular transmission is the most common reason for performing SFEMG in most laboratories. The diagnosis of myasthenia gravis accounts for the bulk of such studies, and SFEMG can be very helpful in diagnosis and management. Less commonly, Lambert-Eaton myasthenic syndrome (LEMS), organophosphate intoxication, or botulism may be the referral diagnosis. Neuromuscular transmission is secondarily involved in anterior horn cell diseases, peripheral motor neuropathies, and myopathies, but those disorders will be discussed under more focused sections later.

SFEMG has been used in the diagnosis of myasthenia gravis since at least 1971, when Blom and Ringqvist examined 12 patients with MG [16]. Jitter and blocking improved after administration of anticholinesterase medication. Since then, there have been numerous studies of the sensitivity of SFEMG in diagnosing MG and comparisons to other diagnostic techniques. Sanders, Howard, and Massey published the largest series of SFEMG studies in MG by reporting the results on 788 patients [17, 18]. In their laboratories, the EDC was usually studied first; they found that the SFEMG of the EDC was abnormal in 85 % of all patients with MG at the time of initial examination. If the EDC was normal, and a second muscle was studied, 85 % of those patients had abnormal jitter studies. Thus, if two muscles were studied when the first was normal, SFEMG for jitter analysis was abnormal in 98 % of all patients with MG. This far exceeds the sensitivity of all other diagnostic tests for MG, as further illustrated by several comparative studies. Oh et al. [19] compared SFEMG of the EDC; repetitive nerve stimulation (RNS) of the ADQ, FCU, orbicularis oculi, trapezius, and deltoid; and acetylcholine receptor antibody testing in 120 patients with generalized MG. They found SFEMG to be the most sensitive at 92 % (testing just a single muscle), with RNS at 77 % (testing multiple muscles) and acetylcholine receptor antibody testing at 73 %. Gilchrist and Sanders [20] compared SFEMG of the ADQ, double-step RNS of the ADQ, and RNS of a proximal muscle in ten patients with normal RNS of the ADQ. SFEMG was abnormal in 90 %, RNS of the trapezius was abnormal in 3, and double-step RNS was abnormal in 3. In another study of patients with MG, SFEMG of any muscle in which at least one was abnormal had a yield of 99 %, SFEMG of the EDC was 89 %, RNS was 76 %, and acetylcholine receptor antibody was 80 % of patients with generalized MG [18]. SFEMG was sensitive regardless whether disease was generalized or ocular: the yield was 97 % even in ocular disease, if more than one muscle was studied.

The enhanced sensitivity of SFEMG makes physiologic sense: RNS will not be abnormal until at least 10 % of muscle fiber end plates undergo impulse blockade and, therefore, fail to generate or propagate a muscle fiber action potential. Muscle fibers with slowed and unstable neuromuscular transmission, but not so affected as to block, will count as normal. SFEMG not only can determine the fibers with impulse blockade but, by assessing jitter, allows those fibers with disturbed but still functional neuromuscular transmission to be measured. Support for this hypothesis comes from the study of Gilchrist et al. [21] in which RNS and SFEMG were done on the same muscle in 46 patients with MG. RNS was abnormal in 36 % of studies, SFEMG was abnormal in 86 %, and blocking was seen in 74 % of studies. All patients with decrement on RNS had abnormal jitter and all also had impulse blockade. No patient with decrement had a normal SFEMG exam, but there were many patients with normal RNS who had abnormal jitter.

SFEMG studies of jitter and impulse block also correlate well with the clinical severity of the disease [17, 22]. Sanders and Stalberg [18] found that changes in disease severity were accompanied by changes in SFEMG measurements. Mean jitter worsened by at least 10 % in two-thirds of patients whose disease worsened, and mean jitter improved by at least 10 % in 80 % of patients who clinically improved. Changes in jitter may therefore herald impending worsening or improvement but, more importantly, allow SFEMG jitter measurements to be used in the ongoing assessment of MG patients. Subjective fatigue often confounds the evaluation of fatigable weakness, rendering the patient's complaints of worsening difficult or impossible to accurately assess. Comparison of SFEMG jitter to prior studies allows a physiologic determination of worsening. Examples from my own practice include a patient with depression and MG: his complaints of worsening fatigue and weakness had to be discounted when his jitter studies remained stable or improved; another patient had ocular MG and severe mitral regurgitation and cardiomyopathy. His cardiologist felt his fatigue was due to his MG, but when his SFEMG jitter study was normal, a compelling case for cardiac asthenia was made.

The sensitivity of SFEMG to changes in neuromuscular transmission has led researchers to wonder whether it can predict progression of ocular myasthenia gravis to generalized disease [3, 23, 24]. The simple answer is no. Patients with purely ocular disease often have increased jitter in limb muscles, but neither its presence nor the degree of abnormality predicts which patients will go on to develop generalized myasthenia gravis.

SFEMG should be performed in a weak muscle if possible and, if normal, virtually excludes a diagnosis of MG. An abnormal SFEMG study by itself does not make the diagnosis of MG. Abnormal jitter remains a nonspecific finding and should be correlated with the history, examination, other diagnostic tests, and routine EMG. Its place in the diagnostic evaluation of MG is somewhat controversial. Some authors

consider SFEMG a last-ditch technique to make the diagnosis when MG cannot otherwise be confirmed, largely due to the relative unavailability of SFEMG [19]. I have found SFEMG to be better tolerated by patients than the Tensilon test or RNS, particularly of proximal muscles, and utilize it in preference to both. As mentioned above, I also consider baseline jitter studies useful as comparisons when difficult clinical questions arise later in the course. In those areas where SFEMG is not readily available, its use should be restricted to those patients whose diagnosis cannot otherwise be made. However, in centers with readily available SFEMG, it is the preferred electrodiagnostic method for confirming MG. Cholinesterase inhibitors can normalize jitter, and a normal exam on such drugs should be repeated off medications for at least 24 h if clinical suspicion of MG remains high [25]. Some practitioners use stimulation SFEMG routinely, finding it easier and quicker. I reserve stimulation for those patients who cannot cooperate, either due to age, infirmity, or level of consciousness. There is at least one study indicating voluntary SFEMG is more sensitive than stimulation SFEMG [26].

Ocular MG can be difficult to diagnose using other tests of myasthenia gravis, as AChR antibody has a low sensitivity in ocular MG, edrophonium test is not specific, and decrement during RNS is uncommonly observed in the ocular form of the disease. SFEMG of facial muscles in ocular myasthenia carries a sensitivity and specificity at least equal to that of generalized myasthenia gravis [27].

Over the last decade, muscle-specific tyrosine kinase (MuSK) antibody-positive myasthenia gravis (MuSK-MG) has been identified as a specific entity with unique clinical features and response to treatment, including resistance to anticholinesterases and usually requiring aggressive immunosuppression [28]. MuSK-MG patients, often women, present frequently with bulbar and facial weakness more so than limb weakness. As with acetylcholine receptor antibody-positive myasthenia gravis (AChR-MG), SFEMG is abnormal in MuSK-MG, though there is evidence that the neurophysiologic defect in neuromuscular transmission may not be as widely disseminated as in AChR-MG. Oh et al. [29] found SFEMG abnormalities in the EDC in 8/12 MuSK-MG patients, and Pasnoor et al. [30] reported SFEMG was abnormal in EDC in 18/21 cases, and in one patient whose EDC did not show abnormal jitter, the frontalis did. These results contrast with previous studies that reported a high diagnostic yield for SFEMG only when proximal muscles such as deltoid, frontalis, orbicularis oculi, and neck extensors [31, 32] were tested. Stickler et al. [31] reported that abnormal jitter by SFEMG in the EDC was relatively uncommon in MuSK-MG patients (59 %) compared to AChR-MG patients (91 %). Farrugia et al. [32] further addressed this by studying the different susceptibilities of the limb and facial musculature in both AChR-MG and MuSK-MG patients. In their study using concentric needle SFEMG, NM transmission abnormalities in the orbicularis oculi were found as frequently in the MuSK-MG patients (9/12) as in the AChR-MG patients (8/11) but were uncommon in the EDC in the MuSK group (1/13) compared to the AChR group (10/12). These results also bring up the interesting possibility that during development, MuSK may be differentially involved in postsynaptic differentiation and in agrin-induced clustering of ACh receptors at the end plate in facial and limb muscles. Taken together, results from previous studies highlight the importance of studying proximal muscles such as frontalis, orbicularis oculi, deltoid, or neck extensors with SFEMG in MuSK-positive patients, as SFEMG abnormalities are often not found in the EDC.

SFEMG jitter studies are also abnormal in LEMS, often more so than would be expected from the clinical picture. Large case series with SFEMG studies are not available, but virtually all patients reported have had markedly abnormal jitter and large percentages of blocking fibers [33–35]. Given the presynaptic nature of LEMS, a relationship between jitter and firing rate is expected. This relationship in reality is variable [33–36], but it is safe to say that a dramatic improvement in jitter and blocking with increasing firing rate is suggestive of a presynaptic defect in neuromuscular transmission.

Botulism arises from defective presynaptic release of acetylcholine caused by the toxin of *Clostridium botulinum.* Oh [37] reports SFEMG was abnormal in 95 % of 15 tested patients and in 100 % of patients with clinical weakness. Increased jitter and impulse blockade were seen, with decreasing abnormality at higher firing rates. SFEMG studies improved as the patient improved. Initially, fiber density was normal, but as botulism caused an irreversible block of acetylcholine release, patients improved by reinnervation and fiber density increased. Padua et al. [38] found similar abnormalities of SFEMG in each of seven cases of food-borne botulism. Studies after administration of botulinum toxin revealed increasing fiber density [39] and increasing jitter [40] over time, including muscles far removed from the injection site [40].

Anterior Horn Cells Disorders

Anterior horn cell disorders include amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), and polio and post-polio muscular atrophy. All cause loss of lower motor neurons and are characterized by muscle weakness and atrophy. ALS is a progressive disease also involving upper motor neurons. By the time patients become symptomatic, they have already lost approximately 50 % of their motor neurons in affected muscles. Polio is an acute disease with a prolonged recovery. Post-polio syndrome is a

controversial entity suggestive of late worsening and loss of motor neuron function. Spinal muscular atrophy is a genetic degenerative disease, again with a chronic course and controversy over whether it is truly progressive. All share similar electrodiagnostic and pathologic features indicative of a mix of acute denervation and compensatory reinnervation. Needle EMG shows large, polyphasic, and rapidly firing MUAPs, while fibrillations, positive waves, and fasciculations are widespread. Muscle pathology shows fiber-type grouping and group atrophy, often involving entire fascicles. At the time of diagnosis, fiber density and jitter will both be increased. The degree to which fiber density, jitter, and blocking are abnormal depends on the pace of denervation and reinnervation and the duration and severity of motor neuron loss (Fig. 8.5). Rapidly progressive loss of motor neurons, such as in ALS, creates a milieu of constant denervation and compensatory reinnervation with either failing terminal motor axons or immature regenerating axons, both being a source of increased jitter and impulse blockade [42]. However, the fiber density may have little time to increase in such a scenario. In SMA, a usually slowly progressive motor neuron disease, fiber density will be markedly increased due to extensive reinnervation, but jitter may be less abnormal [42]. Post-polio muscular atrophy cannot be distinguished from stable old polio by SFEMG exam [43], but nonetheless patients with old polio complaining of recent change in strength tend to have greater abnormalities of jitter and fiber density than those without new weakness [44]. Fiber density will be increased, along with increased jitter and, often, blocking. These abnormalities increase as a function of the time since onset of polio. The etiology of the long-term instability of the motor end plate is still a matter of controversy but likely reflects continuing immaturity of end plate function as individual terminal axons in overstretched motor units fail and then reinnervate, repeatedly.

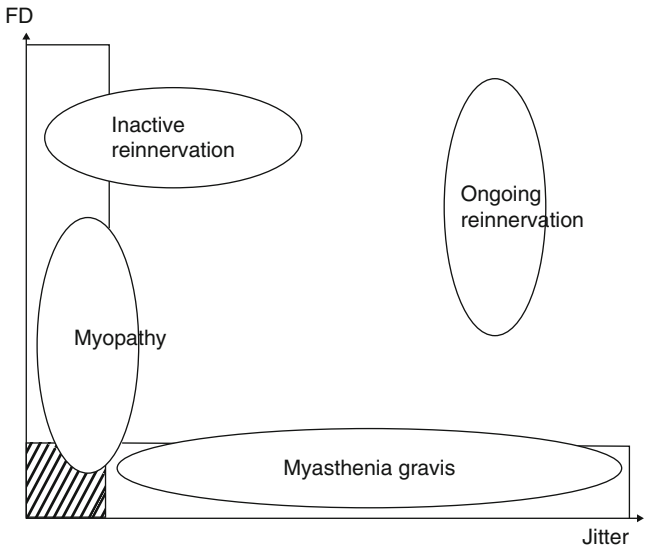

Fig. 8.5 The relationship between jitter and fiber density (*FD*) in myasthenia gravis, acute and chronic neurogenic disorders, and myopathies (Reproduced with permission Sanders and Stalberg [41])

Peripheral Nerve Disease

It comes as no surprise that peripheral neuropathy is associated with abnormalities of fiber density and jitter. Axonal degeneration leads to defective neuromuscular transmission with increased jitter and blocking from presynaptic failure, while immature end plates during reinnervation also have abnormal neuromuscular transmission, with resultant increased jitter and impulse blockade. Once reinnervation is complete, the fiber-type grouping which is typical of peripheral neuropathy results in abnormal fiber density. Jitter will be most abnormal in rapidly progressive neuropathies, reflecting the simultaneous loss of many presynaptic junctions (Fig. 8.5). Fiber density will be highest in chronic neuropathies with extensive reinnervation. SFEMG may even be abnormal in primary demyelinating neuropathies, indicating a degree of axonal degeneration.

Diabetic neuropathy has been the most studied of the peripheral neuropathies. Shields [45] found that abnormalities of fiber density and jitter were common in diabetics, even those without overt neuropathy. The degree of abnormality correlated with symptoms and signs of peripheral neuropathy. Bril et al. [46] also found a high incidence of SFEMG abnormalities in diabetic patients, with or without clinical neuropathy, and whether insulin dependent or not. The jitter increased as glycosylated hemoglobin increased, indicating SFEMG might be a sensitive measure of dynamic nerve changes in diabetic neuropathy [47].

Abnormalities of SFEMG have also been found in neuropathies due to uremia [48, 49], alcoholism [48], toxins [50], amyloidosis [51], Guillain-Barre syndrome (GBS) [52], chronic inflammatory demyelinating polyneuropathy (CIDP) [52, 53], and critical care multiorgan failure [54]. These abnormalities included increased fiber density (uremia, alcoholism, toxins, amyloidosis, GBS, CIDP) and jitter (critical illness neuropathy, alcoholism, CIDP). The only study to compare abnormalities among etiologies found that alcoholic polyneuropathy produced higher fiber densities than did uremic or diabetic neuropathy, despite (or because of) better nerve conduction velocities [48]. Jitter was only mildly abnormal in studies of alcoholic neuropathy and CIDP but was more abnormal in critical illness neuropathy, representative of its acute, monophasic nature.

Seventh cranial neuropathies have been studied using SFEMG as well. Takeda et al. [55] studied 36 patients with Bell's palsy (30 patients) or Ramsay-Hunt syndrome (6 patients). They found neuropraxic injuries with good

recovery and normal facial motor amplitudes had no abnormalities, while patients with facial motor nerve amplitudes less than 40 % of the unaffected side had increased fiber densities, consistent with axonal injury and collateral sprouting. Massey and Sanders [56] studied the frontalis muscle in a single patient serially over 3 years after an acute facial nerve injury. Fiber density and jitter were normal at onset; reached maximal abnormality at 37 days, coincident with the first clinical signs of recovery; and approached normal rapidly over the next 30 days, by which time the frontalis muscle had recovered completely. Even 34 months later, however, fiber density and jitter had not returned to baseline levels. This case illustrates how quickly collateral reinnervation can occur and how immature end plates with low safety factors can mature into normal neuromuscular transmission.

Muscle Disease

SFEMG can also be abnormal in muscle disease, particularly the destructive myopathies such as the muscular dystrophies and inflammatory myopathies (Fig. 8.5). The reasons for the abnormalities differ, however. Increased fiber density is less due to collateral reinnervation than to focal grouping of surviving muscle fibers, muscle fiber splitting, packing of muscle fibers from atrophy, and ephaptic recruitment of muscle fibers from other motor units [3]. Increased jitter is less common in muscle disease than nerve disease, and when seen is due to segmental denervation from muscle fiber necrosis and immature postsynaptic motor end plate function. Despite this, SFEMG can be useful in differentiating muscle from nerve disease. Shields found that SFEMG reliably confirmed the histopathologic diagnosis of either limb-girdle dystrophy (LGMD) or SMA and assisted in the differentiation of four patients with indeterminate diagnosis into one or the other category [57]. Fiber density is particularly helpful as it is usually lower in muscle disease than nerve disease. The anatomic distribution of jitter abnormalities may be more useful than the actual amount of increased jitter, which can overlap among neurogenic, neuromuscular transmission and myogenic disorders. Low jitter during voluntary SFEMG, i.e., less than 5 μs, indicates non-synaptic jitter and is seen with split fibers and ephaptically stimulated fibers [3]. Its presence is a sign of primary muscle disease.

Of the myopathies, the muscular dystrophies show the most abnormalities during SFEMG, and of the dystrophies, Duchenne dystrophy is the most abnormal [58]. Fiber density is frequently abnormal, often being greater than 3.0, which is in the range of peripheral neuropathy. Jitter is also often abnormal, being moderately increased in 20–40 % of patients with blocking in 5–10 %. Becker muscular dystrophy and LGMD are similarly affected but to a much less degree so that, as above, SFEMG can be used to distinguish them from a neurogenic process. Facioscapulohumeral dystrophy is very mildly abnormal by SFEMG, and myotonic dystrophy has abnormalities only slightly more interesting than that, being similar to LGMD. Oculopharyngeal muscular dystrophy may have increased jitter in an anatomic distribution, making differentiation from myasthenia gravis on a purely SFEMG basis impossible [59]. I have been fooled at least once and only made the correct diagnosis with further study of family members.

Mitochondrial myopathies are a diverse group, biochemically and clinically, and the results of SFEMG can be normal, mild to moderately abnormal, or, uncommonly, quite abnormal. Fiber density is slightly increased in a minority of patients and normal in the rest. One study of seven patients with Kearns-Sayre syndrome found normal jitter in all seven [60]. Other studies, including patients with chronic progressive external ophthalmoplegia, found increased jitter in most, with a range of abnormalities similar to that seen in myasthenia gravis, including the presence of blocking [59–62]. The difference in jitter results between the studies may be attributed to the latter groups having studied the frontalis muscle, whereas the Kearns-Sayre patients were studied only in an arm muscle.

Myotonia congenita demonstrates normal fiber density with 10 % of patients having slight increases in jitter. An interesting phenomenon is decreasing single-fiber action potential amplitudes during stimulation SFEMG [63]. One study [63] showed that Thomsen's disease patients had a rapid decrement between 40 and 70 % within 1 s of 20 Hz stimulation. Becker's disease patients had an even more profound decrement, often to zero, with 2 Hz stimulation for just 10–30 s. This decrement lessened with repeat trials, corresponding to the clinical improvement with warming up seen by these patients. Another channelopathy, hypokalemic periodic paralysis, showed no abnormalities of fiber density under the age of 40 [61] but increased fiber density over that age, corresponding with persistent myopathic findings on exam and histochemistry. Jitter was also increased in patients with persistent weakness, i.e., those patients with long-term disease and apparent permanent myopathy.

The SFEMG in patients with inflammatory myopathies is dependent upon the severity and stage of the disease but not on the cause or type of myositis. The abnormalities can be quite variable, but generally during the early stages of the disease, fiber density is only mildly increased whereas increased jitter and blocking are frequently encountered, due to either denervation of muscle fibers by segmental necrosis, immaturity of regenerating muscle end plates, or immature axonal sprouts [64]. As the disease enters a less progressive or arrested stage, the fiber density increases further and the jitter and blocking tend toward normal. The fiber density is highest in patients with the least atrophy and best return of strength, supporting the supposition their good result is due to effective reinnervation of new muscle fibers. Endocrine

myopathies, such as due to iatrogenic steroids, do not cause significant abnormalities of SFEMG [65]. As such, SFEMG may supplement needle electromyography in helping differentiate relapse or failure to respond to treatment in inflammatory myopathy from steroid myopathy.

Congenital myopathies are a mixed bag of SFEMG results. Central core disease [61], myotubular myopathy [3], and nemaline rod disease [61] have normal fiber densities, whereas type 1 fiber hypotrophy with central nuclei [61] has increased fiber density and, often, increased jitter and blocking, results which were not easily explainable by histochemical correlation [61].

Inborn errors of muscle metabolism show abnormalities to the degree that there are persistent structural muscle defects. In a case of late-onset McArdle's disease with proximal myopathy, fiber density and jitter were increased [66] and in acid maltase deficiency, which usually causes a permanent, progressive myopathy, fiber density was increased in more affected leg muscles [61]. Patients with myophosphorylase or phosphofructokinase deficiency have normal fiber density and jitter studies [61].

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Quantitative EMG Analysis

9

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Introduction

In a clinical neurophysiology laboratory, nerve conduction studies are performed in a very objective fashion. The signals are recorded using standardized techniques, including the size and placement of electrodes, filter settings, and temperature control. The waveforms are often marked using automated algorithms to assess the latencies and amplitudes. Measurements are compared against appropriate reference values that take into account differences in age, height, temperature, and other variables [1–3]. In contrast, the needle electromyography (EMG) examination is based on subjective assessment of the waveforms on the display screen and from their sound on an audio monitor. One masters waveform recognition only by extensive training and practice. The routine needle EMG examination may be divided into four steps.

First, the electrical activity in response to the needle insertion and movement is assessed. The amplitude and duration of these potentials depend in part upon the vigor and degree of needle manipulation by the operator. In normal muscle, this *insertional activity* appears as a short-duration burst. In pathologic states, the needle movement may trigger potentials in the form of fibrillation potentials (FP), positive sharp waves (PSW), complex repetitive discharges (CRD), or myotonia. These are discussed in detail in Chap. 7.

In the second step, the needle position is held fixed by the clinician and the patient relaxes the tested muscle. In normal muscle, no electrophysiologic activity is expected. For patients with neurogenic and myopathic diseases, one may observe FPs, PSWs, CRDs, etc. generated in a spontaneous fashion. This is called *spontaneous activity*. It is assessed and graded subjectively based on its presence and persistence at different tested sites.

Next, the patient is asked to slightly contract the muscle. Motor unit action potential (MUAP) discharges of a few different motor units (MUs) will fire. The MUAP is assessed, subjectively and objectively, by its configuration (amplitude, duration, peaks, and phases). The MU discharge pattern is assessed for its *firing rate* in relation to the level of voluntary activation of the tested muscle as well as the firing rates of the other MUs activated. Finally, the patient slowly increases the force of contraction to maximal effort. The needle EMG signal, called the *interference pattern (IP)*, is assessed by its sound, the number of spikes, and their amplitude.

Insertional and spontaneous activities are recognized quite easily by their characteristic sound and waveform pattern. The assessment of FP and PSW is of great importance in assessing denervation in patients with neurogenic disorders. When MUAP shape or firing rate is significantly different from normal, it can be recognized very easily. But if the muscle is minimally affected by the disease processes, the needle EMG findings on subjective assessment may be equivocal. In these instances, quantitative analysis (QA) can help recognizing mild abnormalities. Quantitative measurements can also be used to assess disease progression. Combined with muscle biopsy studies and computer simulations, QA has given us a better understanding of the relationship between the EMG signals and their signal generators.

Most clinical electromyographers practice what might be described as subjective EMG waveform analysis. They insert the needle electrode into the muscle to be studied, place the electromyograph on free run, and attempt to assess the signals as they are acquired, in what might be further described as passive, "subjective" analysis. Essentially no change in the signal occurs between the display screen on the electromyograph and the operator's retina. QA of the EMG signal

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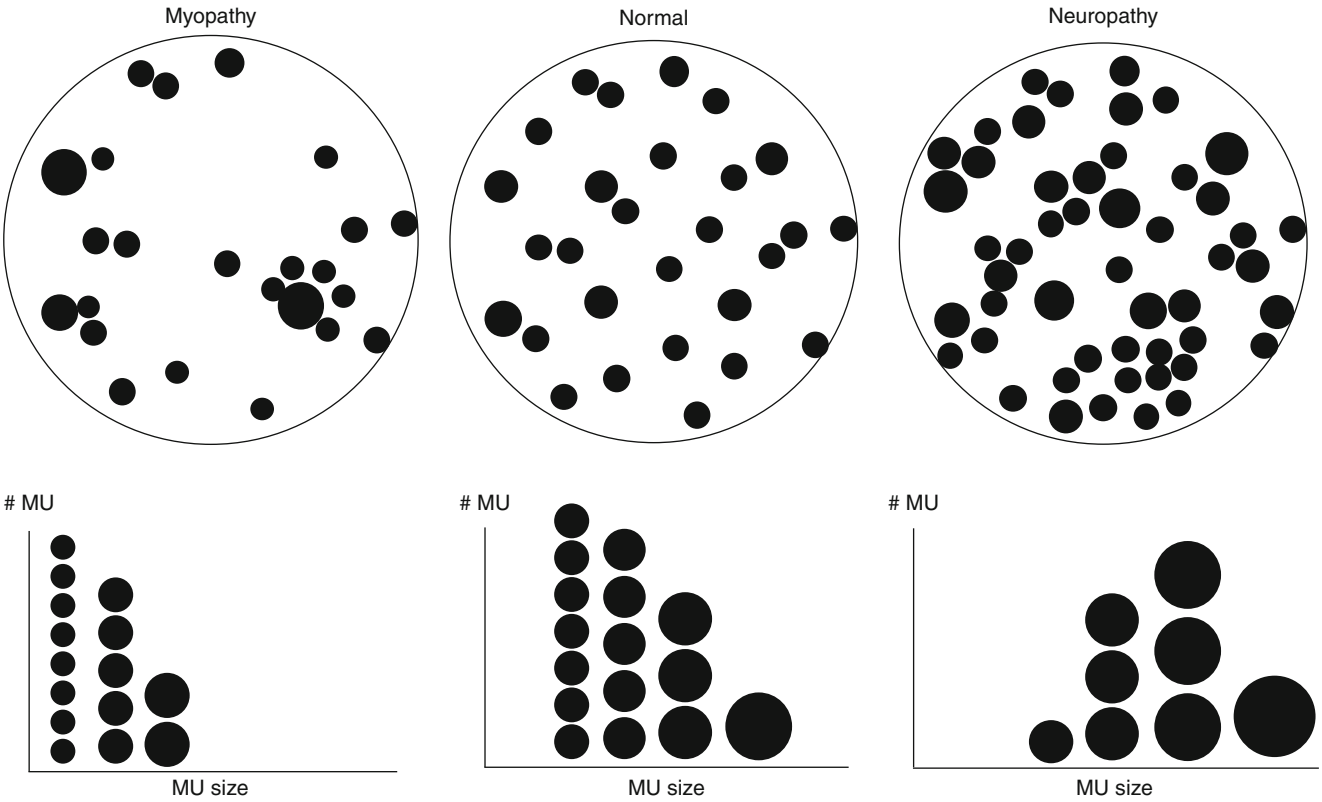


Fig. 9.1 The distribution of muscle fibers in a normal MU is shown schematically (*top row center*). The architecture of the same MU due to disease processes is shown for myopathy (*left*) and neuropathy (*right*). The concomitant change in the number and size of MU in the muscle is shown schematically below the MU schematic. In the *bottom row*, each *circle* represents one MU and its diameter reflects its size. See text for details

for many electromyographers implies long, tedious periods of signal acquisition followed by longer, labored times for analysis. Yet, it is in the fundamentals of quantitative EMG analysis that the impressions or gestalt for subjective assessment is grounded. One should not simply feel that the signal is not normal but rather have objective criteria for describing the signal as abnormal.

In this discussion of QA, the reader is encouraged to approach the EMG signal more objectively. The EMG signal should not simply be acquired in a passive manner but actively manipulated by the operator by changing the sensitivity setting, sweep speed, and low-frequency filter as needed to optimize the amount of information that can be derived from the signal. In other words, the operator should be interactive with the signal before final assessment. Practicing such quantitative procedures disciplines one to see and hear subtle abnormalities that would otherwise be missed. Additional recording techniques and manipulation of the EMG signal can easily be incorporated in the routine examination to document abnormalities. In other words, understanding QA improves the quality of the routine EMG examination by extracting more information from the signal at routine settings. We call this objective/interactive EMG [4].

The Motor Unit (MU)

A motor unit (MU) consists of all muscle fibers (MFs) innervated by one motor neuron (Fig. 9.1). The MFs of a MU are scattered through a large portion of the muscle cross section with no tendency to form groups. Most often, two MFs of the same MU are separated by more than 300 μm [5]. In large muscles such as the biceps brachii, the MFs of one MU may be distributed within a roughly circular territory of 5–10 mm diameter in a patchy mosaic pattern, such that MFs from the same MU are rarely contiguous or near one another. In a routine cross section of muscle at low power, only a few MFs from the same MU are likely to be visualized (approximately 2 MFs from the same MU for every 100 MFs seen) [6]. Thus, the MFs from more than 50 MUs may be visualized in a single low-power microscopic field. Larger MUs (i.e., those containing a greater number of MFs) have a larger MU territory. The end plates of a muscle may be distributed within a well-defined segment (typically at the midsection) along the long axis of the MFs [7]. This is called the end plate zone. Within the same MU, there is minimal variability in MF diameter. In the biceps brachii muscle, the mean MF diameter is 50–60 μm [8].

Based on metabolic properties, MFs may be divided into three groups: type I, type IIA, and type IIB. Type I MFs are fatigue resistant while type IIB MFs fatigue more easily. Type IIA MFs have intermediate characteristics. A MU contains MFs of only one type. In a normal muscle, a MF from a given MU is typically surrounded by MFs from other MUs, often with different MF types. Hence, on muscle biopsy, one obtains a random pattern of MF types without any tendency to form groups of MFs of the same type.

The MU size refers to the number and diameter of MFs in the MU (i.e., the number of MFs supplied by a single motor neuron or *innervation ratio*). The number and size of MUs vary among different muscles. Smaller muscles used in fine motor control and rapid movements (e.g., intrinsic hand muscles) tend to have smaller MUs, whereas larger muscles used in forceful activity (e.g., proximal limb muscles) have larger MUs [9]. A normal muscle contains more small, lower-threshold, fatigue-resistant MUs and fewer large, higher-threshold, rapid-fatiguing MUs (Fig. 9.1).

At minimal force of contraction, the smaller, type I MUs are activated first. These discharge at low rates. When MU firing rate increases, successive MU twitches will overlap and fuse to generate greater force from the same MU. This phenomenon is called *frequency modulation*. With further increase in force of contraction, more MUs are activated. This is called *recruitment*. A muscle uses a combination of these two processes to generate and maintain the desired force level. In many muscles, most MUs are recruited at moderate activation. Thus, maximal effort is primarily achieved through frequency modulation. Other muscles may recruit MUs until near maximal effort.

To reiterate, the MUs recruited at minimal effort are relatively small (i.e., type I), have few MFs, and are also fatigue resistant. When force is increased, the larger, type II MUs are recruited and tend to fatigue easily. This orderly recruitment of MUs based on their size is referred to as the *size principle* [10]. It should be noted that in using selective electrodes, i.e., concentric needle (CN) and monopolar needle (MN) electrodes, where the signal does not represent the electrical activity of the whole MU (i.e., the action potentials of all of the MFs from the MU), the MU size may not be proportionate to the relative size of the MUAP. In routine clinical EMG, patients activate their muscle by performing graded, low effort, isometric muscle contraction. For the purposes of this chapter, unless otherwise noted such as when discussing IP, this pattern of volitional activation should be assumed.

Disease Processes

In patients with neurogenic disease, the primary disease process affects the "neurogenic" portion of the MU resulting in the loss of that MU. This can occur due to loss of the motor neuron (e.g., polio, motor neuron disease) or the loss of its axon (e.g., trauma, diabetic distal symmetric axonal polyneuropathy). The denervated MFs atrophy and are recognized by their spontaneously generated action potentials: FP and PSW. Hence, assessment of insertional and spontaneous activity is essential to the electrodiagnostic examination. Also, the denervated MFs belonging to the lost MU can no longer be activated in voluntary contraction. Meanwhile, the surviving MUs in the immediate neighborhood generate collateral axon branches to reinnervate the denervated MFs. The net effect is a reduced number of MUs with an increase in MU size by virtue of the increased number of MFs innervated by that MU within its MU territory. In remodeling of the MU in reinnervation, the size of the MU territory per se is not increased, only a relative increase in the number of MFs within it (Fig. 9.1).

The MFs of the surviving MUs are no longer distributed randomly, such that the MFs of the MU are spatially isolated by MFs from other MUs, as in the normal state. Reinnervated MFs change their metabolic properties to conform to that of the motor neuron reinnervating it. On histological sections, small groups or clusters of MFs of the same metabolic type are seen. Thus, reinnervation is most characteristically recognized on muscle biopsy by MF type grouping [8]. Some MF loss may also be compensated for by MF hypertrophy. Denervated MFs on muscle biopsy are seen as small, angular, atrophic MFs. In the end stage of a chronic neurogenic process when large reinnervated MUs are being lost and further reinnervation is failing, the biopsy may show large groups of atrophic MFs corresponding to the loss of large reinnervated MUs. FP and PSW in such instances may be smaller in amplitude reflecting the smaller diameter of these angular, denervated MFs. These may be missed on routine instrument settings. It may be helpful to increase the low-frequency filter (e.g., to 100–500 Hz) and thus increase the sensitivity to better detect these FPs.

In patients with myopathy, the main disease process is the loss of MFs, thereby affecting the "myogenic" portion of the MU. Nonfunctional, affected MFs lost from MUs may be seen scattered throughout a cross section of muscle as small angulated MFs. High-resolution microscopy can reveal changes in the internal structures of the MFs, e.g., presence of chained nuclei. It is important to remember that in some myopathic processes, the predominant structure affected is the contractile mechanism; hence, the electrical signal may be relatively unaffected despite symptoms. Histologically, the response of the MFs to the myopathic process is variable. While MFs may typically atrophy, others may become hypertrophic. The latter, however, is not typically seen in polymyositis. Overall, this results in highly increased variability in MF diameter which is readily appreciated on muscle biopsy (Fig. 9.1) [8]. Hypertrophic MFs may eventually split into two or more smaller MFs. These will obviously be clustered together. Reinnervation may occur following segmental necrosis of a MF, isolating that segment from its end plate. New innervation may also occur in the process of innervating regenerated

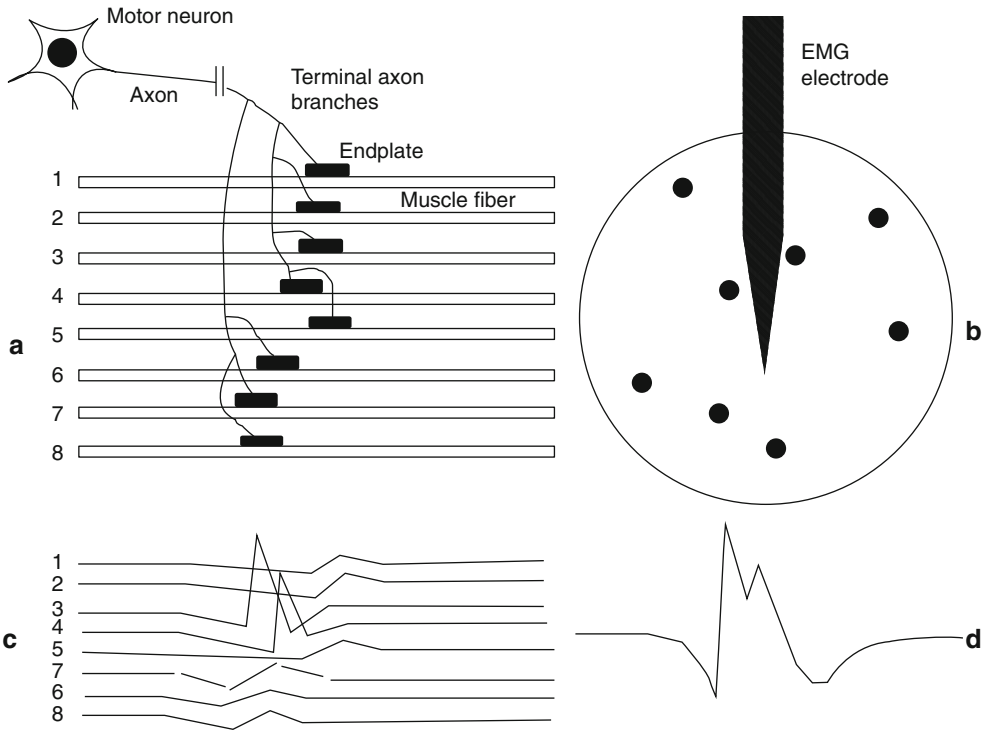


Fig. 9.2 The MU is described in (**a**). The muscle fiber distribution is shown in (**b**) along with a monopolar needle electrode. The individual muscle fiber APs (**c**) are summated to obtain the MUAP (**d**)

satellite cells forming new "nascent" MFs or innervating component MFs resulting from split hypertrophied MFs [11]. With severe loss of MFs, entire MUs may be lost and may slightly reduce the number of MUs. Thus, MU remodeling in myopathic processes affects not only the size of the MFs but also their distribution within the MU territory [12].

Muscle biopsy allows the most direct observations of MU abnormalities. A disadvantage is that it is invasive and expensive. In contrast, the EMG examination allows one to make inferences on changes in the MUs based on measurements of the signals recorded. It is therefore important to recognize the relationship between the EMG parameters and their generators, i.e., MFs and MUs. Although this is an indirect approach, EMG is relatively noninvasive and should complement the muscle biopsy. Other benefits of the EMG examination are that it can be performed in several muscles to confirm consistency in observations and can be repeated serially in the same muscle if needed. Thus, one may assess the topographic distribution of disease (e.g., distal, proximal, diffuse) as well as clinical progression. Needle EMG examination is also often used to select a muscle that is most suitable for muscle biopsy.

Motor Unit Action Potential (MUAP)

The MUAP is the quintessential building block of the EMG signal recorded during voluntary contraction (Fig. 9.2). When the motor neuron discharges, an action potential (AP) propagates through the axons and its terminal branches to reach the end plate, also called the neuromuscular junction or synapse. The arrival of the AP releases acetylcholine (ACh) from the nerve terminals in the end plate. The ACh diffuses through the synaptic cleft and binds to the receptors in the postsynaptic membrane. This produces a local depolarization called the end plate potential (EPP). When the EPP reaches a threshold level, a MF AP is generated that propagates bidirectionally toward the tendons. The AP initiates a chain of events leading to contraction of the MF.

An EMG electrode records the MF AP in the extracellular space (Fig. 9.2b). The extracellularly recorded MF AP, recorded away from the end plate region but along the length of the MF, has a triphasic waveform (Fig. 9.2c). The initial positive deflection represents the AP propagating toward the electrode. As the AP passes in front of the electrode, the main positive–negative deflection is recorded. When the AP propagates away from the electrode, the potential returns to the baseline. If the electrode is placed immediately over the end plate area, the initial positive defection will not be recorded. The potential will have a biphasic waveform with an initial negative deflection [13, 14].

The extracellular potential waveform also depends on the distance between the recording electrode and the MF. At a short distance, the potential has a short rise time and high amplitude (Fibers 3 and 4 in Fig. 9.2). The sound of the potential is described as "crisp" or "sharp." The potential recorded from a distant fiber has low amplitude with a high rise time. Such a potential sounds "dull" on the audio monitor. Regardless of the distance, near and far MFs have similar initial and terminal slow components of the potential (Fig. 9.2c).

The MF APs are dispersed (i.e., asynchronous) as they pass the electrode. This results from a variety of anatomic factors: (1) The nerve AP arrives at the end plate at different times due to differences in the length of terminal axon branches and their AP propagation velocity (Fig. 9.2a). (2) The time required for

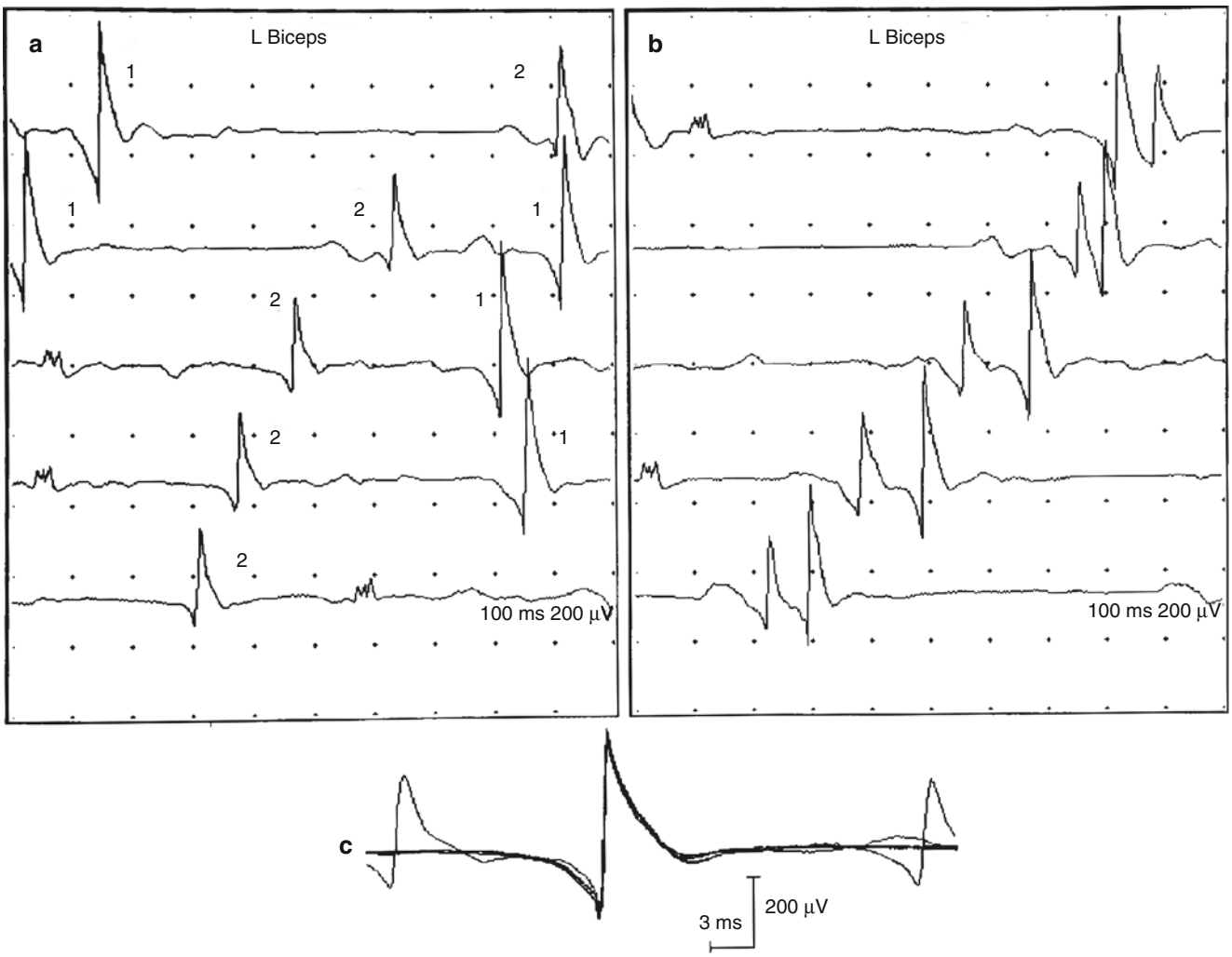


Fig. 9.3 Concentric needle EMG recording from the biceps muscle of a normal subject is shown in a free-running display mode (**a**, **b**). Five consecutive sweeps are presented. The traces are drawn from *top* to *bottom*. In (**a**), discharges of two different MUAPs are identified and labeled. Another portion of the same recording is shown in (**b**) where the two MUAPs superimpose each other. The resulting waveforms appear polyphasic with long duration. However, these waveforms are not seen in a recurrent fashion. Hence, they are not used for analysis. In (**c**), an amplitude triggered delay line is used to time lock the discharges of the larger MUAP on the screen. Five consecutive discharges are superimposed. The discharges of the smaller MUAP appear randomly in the traces. The MUAP features can be assessed after averaging these discharges. Even without the averager, we can easily assess its amplitude, duration, and phases

AP transmission across the neuromuscular junction is quite small but may vary from one discharge to another: This forms the basis for the jitter measurements in single-fiber EMG [5]. (3) The end plates are at different distances from the electrode. Thus, the APs travel varying distances to reach the electrode (Fig. 9.2a). (4) Finally, the AP propagation velocity varies among the MFs. Large MFs conduct APs faster than the smaller MFs [15]. The resulting variations in arrival times for the MF AP at the electrode is termed the "temporal dispersion."

The MUAP is the sum of all extracellularly recorded potentials of all MF APs within the MU (Fig. 9.2d). It is obvious that its shape depends on the MU architecture, i.e., number, size, and distribution of MFs, end plate zones, etc., and is altered in disease processes (Fig. 9.1). These changes in turn alter the MUAP waveform and form the basis for analysis in the needle EMG examination.

The MU abnormalities can be assessed using three different techniques: MUAP waveform measurements, MU firing rate analysis, and analysis of interference pattern recording at different force levels. We will now review these techniques.

MUAP Waveform Analysis

Recording Techniques

The needle is inserted in the muscle, while the subject exerts minimal effort. The needle position is adjusted to record "sharp" and "crisp" EMG activity. This usually coincides with increased amplitude and reduced rise time of the EMG signals. MUAPs can be extracted using a variety of techniques. In the manual method (Fig. 9.3a), a

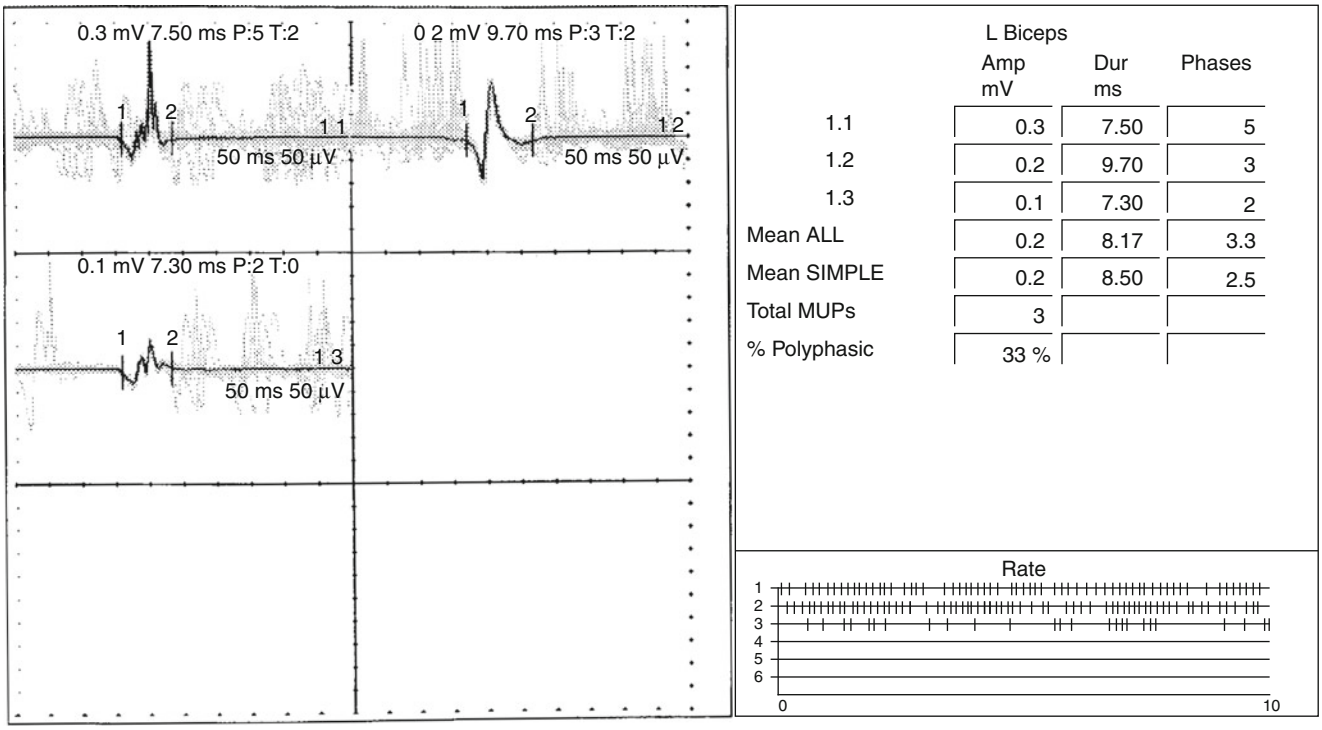


Fig. 9.4 A multi-MU analysis program was used to analyze CNEMG recording from the biceps muscle of a normal subject. From the 10 s epoch, the algorithm identified three different MUAPs. Their discharges are shown as if using an amplitude trigger and delay line. The dark trace is the averaged MUAP. The *vertical tick marks* labeled *1* and *2* are the beginning and end points of the MUAP. The amplitude, duration, and phases are measured automatically and tabulated to the right. The discharge pattern of each MUAP is shown in the *lower right corner*. The horizontal line represents time from 0 to 10 s. Each *vertical tick mark* is one MU firing. The gaps in the firing pattern represent MUAP superimpositions that were not resolved by the algorithm. It should not be misinterpreted as irregular MU firing. This analysis required the computer less than 1 s

500 ms EMG epoch is "frozen" on the display for visual assessment. A waveform occurring in a recurrent fashion is a MUAP. This is very easy when the signal contains discharges of a single MU. When two or more MUs are discharging, their MUAPs may superimpose by chance (Fig. 9.3b). The resulting waveform will not repeat consistently in the EMG record and should be therefore excluded from analysis. As a rule of thumb, one should see a waveform at least three times before calling it a MUAP [16]. The MUAP waveform is quantified manually. This technique can be easily performed on most modern systems.

A trigger and delay line device displays the EMG activity only when it exceeds a user-defined voltage level. If this level is adjusted so that only one MUAP crosses it, the EMG signals will be displayed only when that MUAP occurs. As a result, the MUAP waveform appears time locked in the display area (Fig. 9.3c). Activity from other low-amplitude MUAPs appears randomly. This makes it easier to assess characteristics of the triggering MUAP. On many instruments, one can average such time-locked discharges to improve the signal-to-noise ratio. After obtaining a relatively noise-free baseline, the MUAP measurements may be performed manually or automatically.

As computers and software have become more powerful, many have developed algorithms to decompose the EMG signal into the discharges of its constituent MUAPs (Fig. 9.4). Since several MUs are simultaneously acquired and analyzed, the method may also be called the "multi-motor unit analysis (MMA)" [17, 18] or "decomposition" [19, 20]. Because of minimal analysis time and a yield of one to four different MUAPs from each tested site, it is possible to analyze 20 MUAPs within only a few minutes, including muscles that are considered difficult to study, e.g., paraspinals [21].

The shape of the MUAP may vary depending on where it is recorded within the MU [6, 14]. Therefore, there is some risk that two presumably different MUAPs may actually represent signals from the same MU. To reduce the chance of this possibility, the following sampling technique is suggested. The needle electrode is inserted perpendicular to the long axis of the MFs. After recording the MUAPs at one site, the needle is inserted deeper along the same axis by 5–10 mm to the next recording site. This linear track is called a *corridor*. The rationale for moving 5–10 mm is to try to move away from a previously sampled MU's territory. With practice using the basic manual technique, it is possible to obtain two and rarely three MUAPs from one site, and each corridor of needle insertion typically yields 3–5 MUAPs. To avoid

unnecessary skin insertions, the needle electrode is withdrawn after recording from the deepest or most distal site in the muscle to just outside the muscle (i.e., still subcutaneous). The electrode is then angled 30–60 ° to one side of the original corridor yet remaining perpendicular to the long axis of the MFs, and a new corridor is explored. Since there is a greater risk of MU territory overlap in the superficial portion of this secondary corridor, recording MUAPs should initially start at a slightly deeper site. This process may be repeated using another corridor on the opposite side of the initial corridor. One usually obtains 20 or more MUAPs by investigating different corridors from different skin insertions. Stålberg and coworkers have shown differences in MUAP features when recorded from superficial and deeper portions of the muscle; hence, there should be some attempt not to bias the sampling to only superficial versus deeper portions of the muscle [13, 22].

When selecting a new skin insertion site, the needle is moved in a direction perpendicular to the long axis of the MFs. Inserting the electrode proximal or distal to the previous site along the long axis of the muscle (and therefore the MFs) will assure a high likelihood of sampling the same MUs but at a different site along the length of the MF. If the needle is angled less than 90° to the long axis of the MFs, then less efficient sampling of MUs occurs because fewer MFs are being traversed per unit length of the needle electrode. Sampling in the end plate zone should be avoided because it tends to be painful.

Use of a 50 mm CN or MN electrode offers the most flexibility in sampling (particularly in larger muscles) and has the same electrode diameter as its more commonly used counterpart, the 37 mm electrode. Recording areas on the CN and MN electrodes differ. The recording area on a 37 or 50 mm CN is the same regardless of length and the same applies for the 37 and 50 MN electrodes. Some of the shorter, 25 mm CN electrodes (i.e., the so-called facial CN needle electrode) have a smaller recording surface than the longer CN electrodes. This is important as amplitude values may differ between these electrodes.

Measurements

The technique of MUAP quantification was pioneered by Buchthal and coworkers beginning in the 1950s [23]. Those investigators measured the *amplitude* between the maximum negative to maximum positive peaks, i.e., peak-peak (Fig. 9.5). The MUAP onset occurs when it first deviates from the baseline. The MUAP terminates when the potential returns to the baseline and remains at that level until the next MUAP discharge. The time interval between these events is the total MUAP *duration*. The visual assessment of duration depends on the display sensitivity. At a setting of 1 mV/div

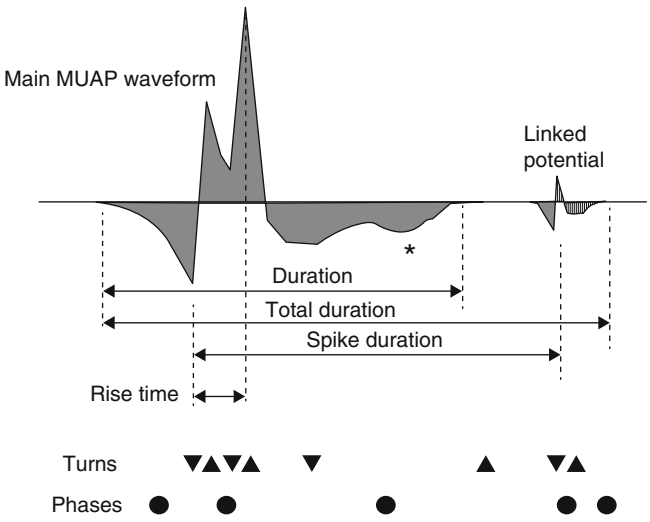


Fig. 9.5 A schematic is used to explain different features of the MUAP waveform. The *circles* and *triangles* project on to the phases and turns. The peak indicated by *asterisk* occurs when the APs reach the tendon. The amplitude of this potential in this schematic is less than the threshold for turns measurements. Therefore, those peaks do not generate turns. See text for details

or higher, the MUAP appears to have shorter duration. At a setting of 50 μV/div or less, the duration appears longer, perhaps also due to some baseline shifts. Hence, the duration is best assessed using a display setting of 100–200 μV/div. A *phase* occurs when the signal deviates from and then returns to the baseline. The number of phases can be quickly assessed by counting the baseline crossings in the MUAP and adding one. A MUAP is called simple when it has four or less phases. A *polyphasic MUAP* has five or more phases. Buchthal and colleagues measured the mean amplitude of all MUAPs and computed the percentage of polyphasic MUAPs in normal muscles. The mean duration was computed after excluding the polyphasic MUAPs.

With access to computers, algorithms have been generated to make automated measurements of the MUAP. Many such methods use "amplitude deviation from baseline" and/or "signal slope" criteria to detect the MUAP onset and end [18, 22]. Furthermore, the signal must cross the baseline by a threshold amplitude (e.g., 20 μV) before it is considered a phase. This will exclude spurious phases generated by noise near the baseline. A turn occurs at the peak of the MUAP. To exclude peaks generated by noise, the amplitude must change by a threshold value (40–100 μV) between successive turns. A *serrated MUAP* has more than five turns. A *complex MUAP* is either polyphasic or serrated [24]. Zalewska and Hausmanowa-Petrusewicz described the "irregularity factor" which also quantifies the complexity of the MUAP waveform [25].

The MUAP rise time is usually measured from the maximum negative peak to the maximum positive peak that precedes it. This definition may be unsatisfactory for

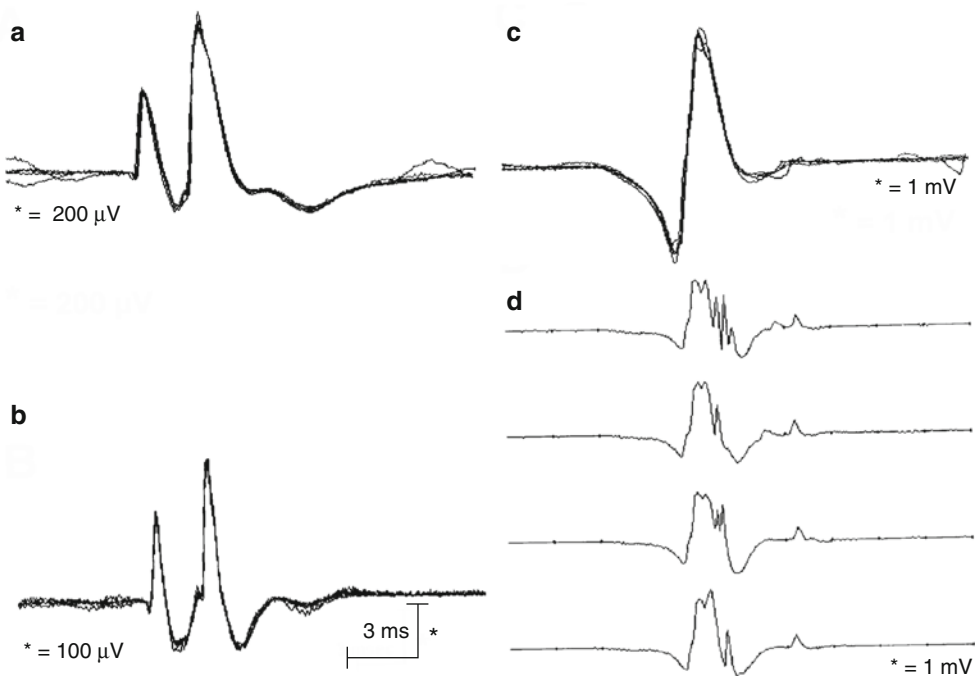


Fig. 9.6 Consecutive discharges of a stable (**a**, **b**) and unstable (**c**, **d**) MUAP are shown. The filter settings are 3–10,000 Hz in **a** and **c**, 500–10,000 Hz in **b** and **d**. The successive discharges superimpose extremely well for the stable MUAP (**a**, **b**). For the MUAP in **c**, the waveform appears significantly variable when the filter settings are changed (**d**). The amplitude calibration is indicated below the traces

polyphasic MUAPs (Fig. 9.5). Thus, MUAP rise time is not used in assessment of MUAP abnormalities.

Sometimes, a MUAP may be divided into two or more time-locked sections that are separated by baseline. In these recordings, the portion with the greatest duration or amplitude may be considered the main body of the MUAP. The remaining portions are called "linked" or "satellite" potentials. Although relatively easy to hear on the audio portion of the signal, these may easily be missed unless trigger/delay techniques are used. When such potentials occur, duration measurements can be tricky. Including the linked potentials may yield a very long-duration values that are "inconsistent" with the expected values or other measurements in the same muscle. One usually measures the duration from the main body of the MUAP only or may exclude these potentials from the analysis. The spike duration is usually measured between the first and last peaks of the MUAP. When linked potentials occur (Fig. 9.5), the spike duration may be longer than the duration of the main body of the MUAP [22].

The *MUAP area* is measured between the rectified signal waveform and baseline. The MUAP ratio, computed as area/amplitude, quantifies the MUAP "thickness" on visual assessment [26]. The MUAP size index is obtained by mathematically normalizing the MUAP ratio to its amplitude [27]. The mean values of these features are used for analysis.

When the MUAP waveform configuration is relatively constant during successive discharges, it is called a *stable MUAP* (Fig. 9.6a, b). An *unstable MUAP* reveals a significant change in the waveform from one discharge to another (Fig. 9.6c, d) that results from abnormalities of neuromuscular transmission. "Jiggle" is a quantitative measurement of this change [28]. Stability is a subjective measurement which should be assessed from potentials that are within 3–4 ms of the trigger point. Potentials that are farther away from the trigger point may appear unstable due to other phenomena, such as velocity recovery function [15]. The percentage of unstable MUAPs may be computed. MUAP instability can be better appreciated when the low frequency of the band-pass filter of the EMG instrument is set to 500 Hz or higher. This was originally described as the "Blanket principle" [29].

Assessment Strategies

Buchthal and coworkers defined reference values for the mean amplitude, mean duration, and percentage of polyphasic MUAPs in normal subjects (Tables 9.1 and 9.2) [30]. Durations that differ by more than 20 % from the normal mean are considered abnormal. Many investigators have used a similar approach and described upper and lower normal limits of amplitude and duration [20, 24].

Analysis based on mean values is quite different from subjective MUAP assessment. By visual inspection, one can easily recognize rare MUAPs that are quite abnormal in normal subject (e.g., a MUAP with eight phases). Stålberg and coworkers referred to these MUAPs as "outliers" [31]. If such MUAPs are seen occasionally, they are taken as a statistical anomaly and ignored. However, if such outlier MUAPs occur with greater frequency, then we would suspect an underlying disease process. To mimic this approach, Bischoff and coworkers defined normal limits of amplitude and duration for individual MUAPs [17]. A study is considered

Table 9.1 Mean values of MUAP duration (ms) in normal muscles are tabulated

Age (years)	Deltoid	Triceps	Biceps	Ext dig comm	Abd dig quinti	Abd poll brev	Vast med	Vast lat	Rect fem	Gastroc	Tib ant	EDB
0	7.8	9.0	7.7	7.1	6.2	6.2	7.9	9.7	8.7	7.2	9.5	7.2
3	8.3	9.6	8.2	7.6	6.8	6.8	8.4	10.3	9.2	7.7	10.1	7.7
5	8.6	9.9	8.5	7.8	7.3	7.3	8.7	10.7	9.6	8.0	10.5	8.0
8	9.0	10.3	8.9	8.2	7.9	7.9	9.1	11.2	10.0	8.4	11.0	8.4
10	9.3	10.6	9.1	8.4	8.3	8.3	9.3	11.5	10.3	8.6	11.2	8.6
13	9.6	11.0	9.4	8.7	8.7	8.7	9.6	11.8	10.6	8.8	11.6	8.8
15	9.8	11.2	9.6	8.8	9.0	9.0	9.8	12.1	10.7	8.9	11.7	8.9
18	10.0	11.4	9.8	9.0	9.2	9.2	10.0	12.3	11.1	9.2	12.1	9.2
20	10.2	11.6	10.0	9.2	9.2	9.2	10.2	12.6	11.3	9.4	12.3	9.4
25	10.5	11.9	10.3	9.5	9.2	9.2	10.5	13.0	11.6	9.7	12.7	9.7
30	10.7	12.0	10.6	9.8	9.3	9.3	10.8	13.4	12.0	10.0	13.1	10.0
35	11.1	12.1	10.9	10.0	9.3	9.3	11.1	13.7	12.3	10.2	13.4	10.2
40	11.3	12.2	11.1	10.2	9.3	9.3	11.3	14.0	12.6	10.4	13.6	10.4
45	11.4	12.3	11.2	10.3	9.4	9.4	11.4	14.1	12.7	10.5	13.8	10.5
50	11.6	12.4	11.4	10.5	9.4	9.4	11.6	14.4	12.9	10.7	14.0	10.7
55	11.8	12.5	11.6	10.7	9.4	9.4	11.8	14.6	13.1	10.9	14.3	10.9
60	12.1	12.6	11.9	11.0	9.5	9.5	12.1	15.0	13.5	11.2	14.7	11.2
65	12.1	12.7	12.2	11.2	9.5	9.5	12.4	15.4	13.7	11.5	15.0	11.5
70	12.4	12.8	12.4	11.4	9.5	9.5	12.6	15.6	14.0	11.7	15.3	11.7
75	12.8	12.8	12.6	11.6	9.5	9.5	12.8	15.9	14.2	11.8	15.5	11.8
80	13.0	12.8	12.8	11.8	9.5	9.5	13.0	16.1	14.4	12.0	15.7	12.0

Data from Buchthal [30]
Note the increase in duration with age and identical values for different muscles

Table 9.2 MUAP amplitude (μV) measurements in muscles of normal adult subjects are summarized

Muscle	Mean	SD	Range
Deltoid	212	147	150–304
Triceps	340		
Biceps	180		120–390
Ext dig comm	210	115	
Abd dig quinti	350		
Abd poll brev	260		
Vast med	230		150–360
Vast lat	260		210–370
Rect fem	170		130–215
Gastrocnemius	160	95	
Tib ant	220		
Ext dig brev	460		

Data from Buchthal [30]

abnormal when the mean values are outside the normal range or when more than 10 % MUAPs have measurements outside the individual normal limits (Table 9.3). Those investigators found a similar diagnostic sensitivity using either criterion of abnormality. Furthermore, they did not find a significant change in MUAP duration with age for subjects less than 60 years old [17, 31, 32].

The advantage of outlier-based analysis is that the third abnormal MUAP (i.e., >10 % when the sample size is 20 MUAPs) may occur within the first 2 or 3 min of the examination. At this time, the study has already reached diagnostic significance, and one may terminate the MUAP analysis in that muscle. However, a large sample of MUAPs must be obtained if the goal of the examination is to assess disease progression. The outlier approach, although new to MUAP analysis, is used quite successfully in single-fiber EMG and macro EMG [5, 33].

Findings in Normal Subjects

In normal subjects, large muscles tend to have a long-duration MUAPs (Tables 9.1 and 9.3). MUAP duration increases with age after the sixth decade. MUAP amplitude is often high in small distal muscles (Tables 9.2 and 9.3). This variation reflects the differences in the MU size and architecture among normal muscles. One must recognize this difference (Tables 9.1 and 9.3) not only in quantitative analysis but also in the routine needle EMG examination.

The reference values depend upon the technique of recording. Using an amplitude trigger delay line always selects the highest amplitude MUAP in the signal (Fig. 9.3). Hence, the mean MUAP amplitude values will be higher compared to other techniques [18, 24]. The amplitude is higher when the examiner makes a conscious effort to reduce the MUAP rise time to less than 500 μs. Slight needle movements can significantly affect the MUAP amplitude and rise time;

Table 9.3 Reference values for individual and mean values of MUAP features are tabulated. These investigators did not find age-dependent variation in normal subjects until the sixth decade of age

	Amplitude (μV)			Duration (ms)			Thickness		
Muscle	Mean ± SD	Minimum	Maximum	Mean ± SD	Minimum	Maximum	Mean ± SD	Minimum	Maximum
Deltoid	550 ± 110	162	1,531	10.4 ± 1.3	4.2	18.4	1.56 ± 0.22	0.65	2.94
Biceps	436 ± 115	1,788	1,414	9.9 ± 1.4	4.2	16.4	1.46 ± 0.2	0.56	2.09
First dorsal interos	752 ± 247	188	2,301	9.4 ± 1.3	4.0	18.0	1.38 ± 0.22	0.49	2.61
Vastus lat	687 ± 239	172	1,954	11.7 ± 1.9	4.6	21.6	1.72 ± 0.23	0.60	3.11
Anterior tibialis	666 ± 254	194	1,572	11.4 ± 1.2	4.6	18.4	1.67 ± 0.23	0.58	2.81

Data from Bischoff et al. [17]

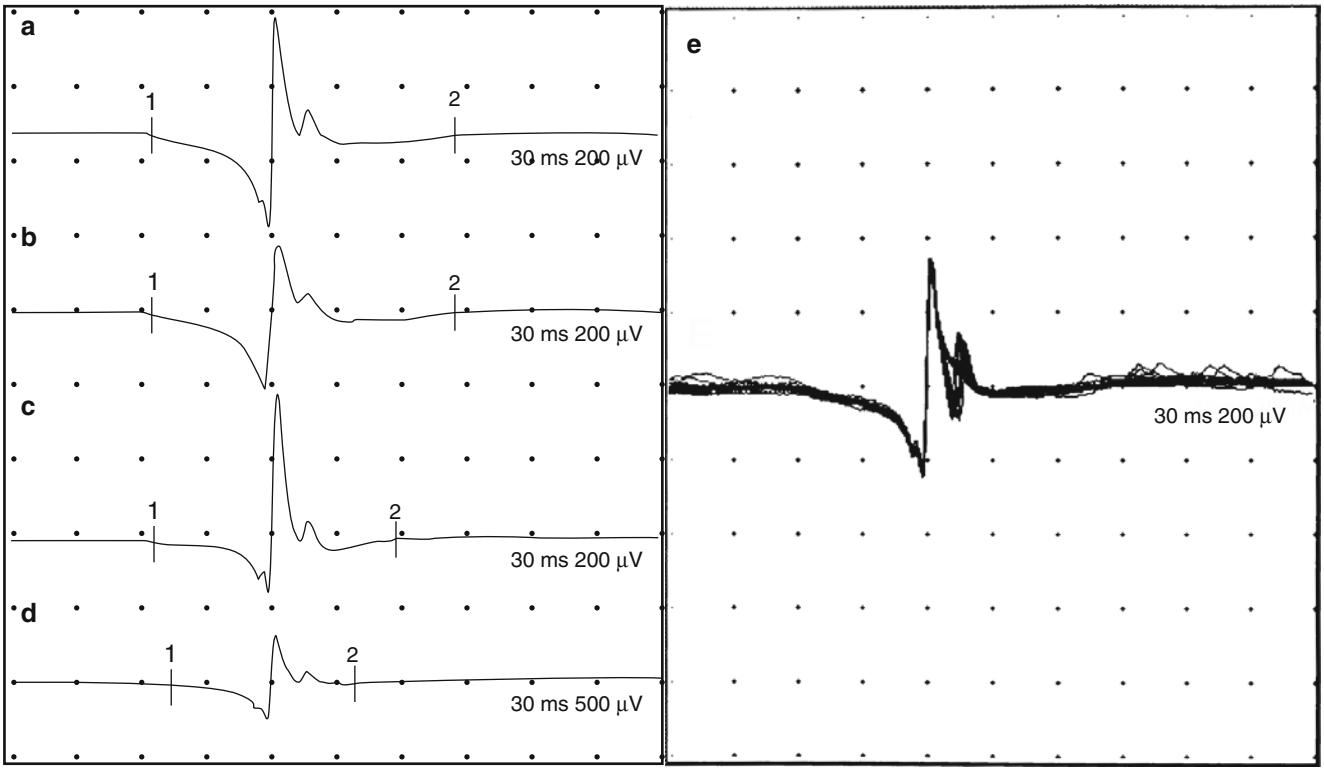


Fig. 9.7 The change in MUAP waveform and its assessment due to technical factors is illustrated. The *vertical tick marks* labeled *1* and *2* represent the onset and end of the MUAP by subjective assessment. See text for details

however, the duration remains relatively constant [34]. Hence, the MUAP duration is considered a "robust" MUAP feature. The duration values also appear quite similar among different methods. This results from two factors. The duration is far less sensitive to electrode position within the MU compared to the amplitude. Secondly, many algorithms developed for duration measurements were deliberately tuned to match measurements by Buchthal and coworkers [30].

MUAP measurements are also affected by technical factors (Fig. 9.7). Averaging unstable MUAPs will reduce the amplitude of different peaks. In Fig. 9.7e, the individual MUAP discharges demonstrate jitter and blocking of one muscle fiber in the MU. On averaging the discharges, that component appears with reduced amplitude (Fig. 9.7a). Reducing the high-frequency setting (e.g., 10,000 Hz in (a) to 2,000 Hz in (b)) decreases the MUAP amplitude and increases its rise time. The smaller peaks are attenuated. Increasing the low-frequency setting (e.g., 3 Hz in (a) to 100 Hz in (c)) reduces the MUAP duration. Subjective duration assessment depends upon the display setting. Reducing the display gain (e.g., changing from 200 μV/div in (a) to 500 μV/div in (d)) will give the perception of a short duration to the same MUAP. Automated measurements may be also incorrect due to poor signal-to-noise ratio.

Monopolar needle EMG usually gives MUAPs with higher amplitude and a greater incidence of polyphasic

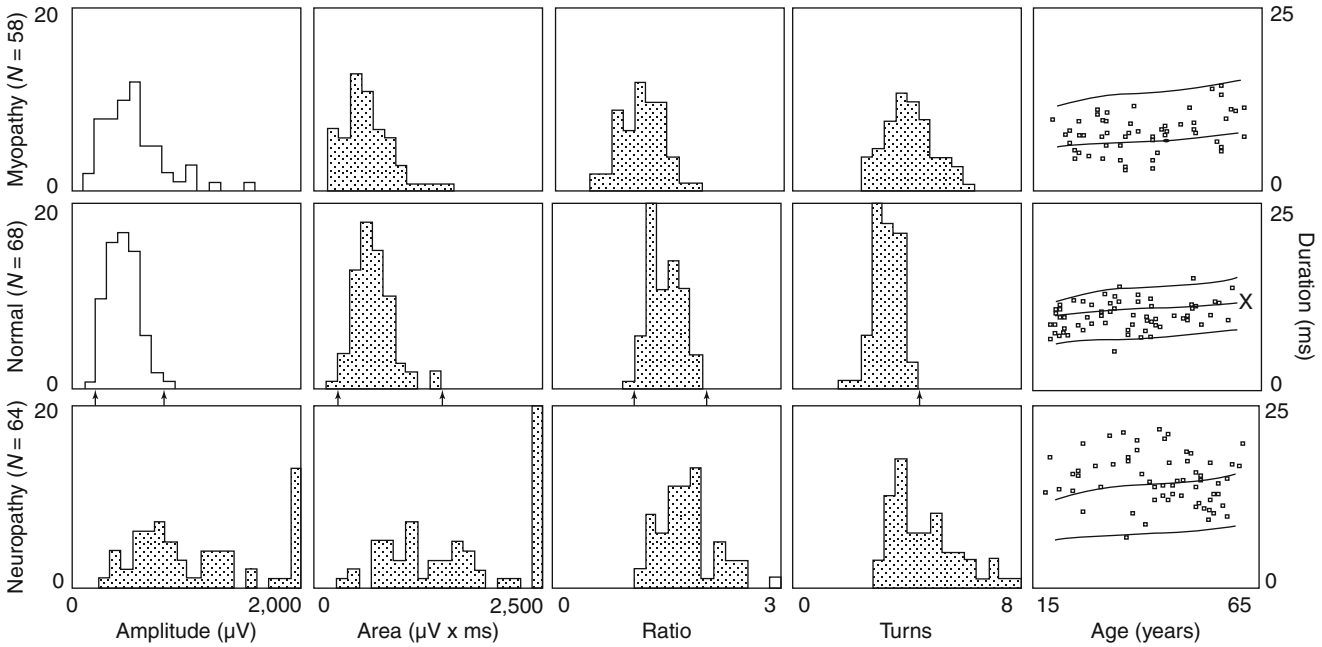


Fig. 9.8 Amplitude triggered delay line and averager was used to record MUAPs from the biceps muscle. The mean values of amplitude, area, area/amplitude ratio, turns, and duration of simple MUAPs were computed. The histogram of these measurements in normal subjects is shown in the *middle row*. The *arrows* indicate the upper and lower normal limits. The duration values are plotted against the patient's age. The *horizontal line* indicated by *X* depicts the slight trend in the mean MUAP duration with age. The other *two horizontal lines* indicate upper and lower normal limits. These limits were used to assess MUAP recordings from the biceps muscle of patients with myopathy (*top row*) and neuropathy (*bottom row*). Observe the typical patterns and also some less recognized abnormalities. See text for details (Reproduced with permission from Stewart et al. [24])

waveforms [35–38]. In our hands, monopolar and concentric needle MUAPs have similar duration. However, some investigators found a longer duration for monopolar recordings [35]. If the temperature is reduced, the MUAP duration and amplitude increase.

Findings in Patients with Nerve and Muscle Diseases

As described earlier, the absolute values of the MUAP measurements vary considerably among different laboratories. However, the pattern of abnormalities on MUAP analysis is quite similar for different research groups [13, 24, 39–42]. In patients with neuropathy, the mean amplitude, mean duration, percentage of polyphasic MUAPs, and incidence of unstable MUAPs are increased. In contrast, the MUAP mean duration and amplitude are reduced in patients with myopathy. The incidence of polyphasic MUAPs is also increased, and unstable MUAPs may be seen. In patients with neuromuscular junction diseases, the MUAPs show prominent instability which is the sine qua non for such diseases as myasthenia gravis. In severely affected muscles of patients with neuromuscular junction diseases, the MUAP duration may be reduced. These are the classical patterns of MUAP abnormality that are used routinely in the day-to-day needle examination. QA also reveals many other patterns and combinations of abnormalities that do not fit the above criteria. With QA, subtle changes in the MU architecture and MUAP waveforms may be seen that are often not appreciated.

- The MUAP duration is increased in patients with neuropathy and decreased in patients with myopathy. Because of this contrasting pattern, this feature is useful for differential diagnosis. Changes in duration are considered "specific" to the underlying disease process. In patients with myopathy, one may record complex long-duration MUAPs with linked potentials and also short-duration simple MUAPs in the same muscle. Together, they may give a normal mean MUAP duration. In some cases, one may incorrectly infer a neurogenic disease process based on the complex and long-duration MUAP. Therefore, we exclude the polyphasic MUAPs from the calculations of mean MUAP duration. This increases the diagnostic sensitivity of the technique [42, 43, 43a, 44, 45].
- Increased MUAP amplitude is usually associated with a neurogenic disease process. QA reveals that some patients with myopathy also have a mild increase in amplitude. In our studies [24, 42], the mean MUAP amplitude in myopathy was never greater than twice the upper limit in our normal subjects (Fig. 9.8). Since a mild increase is seen in both patient groups (i.e., myopathy and neuropathy), this finding is considered a nonspecific abnormality. When

amplitude is significantly increased (more than twice the upper normal limit), we consider this as a specific abnormality indicating a neurogenic disease process.

- When the amplitude is increased in patients with myopathy, the waveform appears "thin" by visual assessment. This gives a reduced area/amplitude ratio (Fig. 9.8). This observation is a specific abnormality for myopathy, since the ratio is normal or increased in patients with neuropathy. Thus, the MUAP "thickness" is useful for differential diagnosis when the MUAP amplitude is mildly increased (Fig. 9.8) [26].
- The incidence of polyphasic MUAPs is increased in all patient groups. In myopathic processes, this is primarily due to increased variation in MF diameter [13]. In neurogenic processes, this is considered to be a result of collateral reinnervation of denervated MFs by surviving motor neurons. Therefore, this is a nonspecific finding on MUAP analysis.
- Although MUAP duration differentiates between myopathic and neurogenic disease processes, it is not a diagnostically sensitive feature. When the muscle is minimally involved based on muscle strength assessment, duration values may be normal. In those patients, one may find abnormalities in other MUAP features. In our experience, an increased incidence of polyphasic MUAPs is the earliest abnormality by QA [24, 42]. When the muscle is moderately or severely affected, the duration is likely to be abnormal. This implies that we should sample moderately weak muscles and select muscles that demonstrate MUAP duration abnormalities for biopsy studies.
- It is not uncommon to record high-amplitude and long-duration MUAPs in muscles that are apparently not weak or involved in the disease process. This reflects an earlier insult to the MUs and a full recovery by collateral reinnervation. During reinnervation, the newly formed end plates are immature and demonstrate poor efficacy of neuromuscular transmission which result in unstable MUAP waveforms. When the end plates mature, the MUAPs are stable. Thus, MUAP stability is useful to assess whether reinnervation is complete and makes a distinction between an acute and chronic disease process [5, 29]. Theoretically degenerating end plates would also have inefficient neuromuscular transmission and therefore unstable MUAPs. However, degeneration takes only a few days compared to several weeks for reinnervation. Hence, unstable MUAPs are attributed mainly to ongoing reinnervation even in progressive motor neuron diseases.
- In a slow progressive neurogenic disease, reinnervation may adequately compensate for MU loss. Previous studies suggested that in a slow chronic neurogenic process, approximately 1/3–1/2 of motor neurons (and therefore MUs) may be lost before clinical weakness is manifest. In such instances, high-amplitude MUAPs are readily noted. Amplitude measurements are easy to perform even when the signals are displayed in a free-running sweep. This is the parameter of choice to investigate chronic neurogenic changes in the muscle.
- The aforementioned patterns of abnormalities are seen in muscles with minimal to moderate weakness. In severely weak muscles, one may observe atypical MUAP waveforms. Following a severe trauma such as when all motor axons are severed from the nerve trunk, all MUs in the muscle may be lost. As the nerve regenerates and forms new "nascent" MUs (as opposed to collateral sprouting when axonal loss within a muscle is patchy), the MU size will be initially small. Their MUAPs will have low amplitude, reduced duration, and a polyphasic waveform. In many respects, they appear similar to the MUAPs seen in patients with myopathy. Therefore, we recommend that one should describe and interpret the MUAP waveform instead of characterizing them as "myopathic" or "neurogenic." While the reinnervation continues and the MUs are rebuilt, the MUAP waveform is unstable. This potentially implies a good prognosis, i.e., ongoing reinnervation. In contrast, stable MUAPs indicate that MU remodeling, and hence reinnervation, is complete, although the degree of clinical recovery may be variable.

Based on the above considerations, we recommend that one should describe and interpret the MUAP waveform rather than characterizing them as "myopathic" or "neurogenic." To apply labels to MUAPs that imply an etiology or causation is to oversimplify MUAP analysis and in turn potentially mislead the referring physician in their evaluation of the patient.

Computer simulations indicate that the CN MUAP amplitude depends upon the number and size of fibers within 500 μm of the recording tip [46]. The MUAP amplitude is greatly affected by the size and distance to the closest MF. Therefore, slight changes in the needle position can significantly affect MUAP amplitude. This explains the great variability of MUAP amplitude among different recording techniques. Furthermore, a single MF close to the recording tip may result in normal MUAP amplitude.

The number of phases and turns depends upon the temporal dispersion of the APs of MFs within one mm of the recording electrode. The dispersion is affected by action potential propagation in terminal nerve branches and in the MFs as described earlier (Fig. 9.2). When there is an increased number of MFs from a single MU in this area, we have a better chance of observing their temporal dispersion. However, it is quite possible that the potentials will summate to produce large amplitude simple MUAPs. In contrast, if there is a severe loss of MFs, this area may contain just one fiber that gives a simple small waveform.

MUAP duration depends on MFs that are up to 2.5 mm from the recording tip. This represents a significant portion of the MU territory. In a large muscle, such as the biceps

Table 9.4 The MUAP abnormalities are related to underlying disease processes

MUAP abnormality	Myopathy	Neuropathy
Increased amplitude	MF hypertrophy	MF hypertrophy
	Slight MF grouping due to reinnervation, regeneration, and split MF	MF grouping due to reinnervation
	Synchronous MU firing (tremor)	Synchronous MU firing (tremor)
		Synchronous MU firing due to ephaptic transmission in nerves
Reduced amplitude	Loss of MF	Atrophy of MF
	Atrophy of MF	Unstable waveform
	Fibrotic tissue attenuates potential	Fibrotic tissue attenuating potential
Increased phases and turns	Increased temporal dispersion due to	Increased temporal dispersion due to
	Slow conduction in atrophic MF	Slow conduction in new collateral nerve branches
	Fast conduction hypertrophic MF	Slow conduction in newly reinnervated MF that are atrophic
	Increased variability of MF diameter (atrophy and hypertrophy)	Fast conduction in hypertrophic MF
	Synchronous MU firing (tremor)	Synchronous firing of MUs (tremor)
		Synchronous MU firing due to ephaptic transmission in nerves
Increased duration	Increased temporal dispersion (see above) giving long-duration polyphasic waveform	Increased number of fibers in MU after reinnervation
	Synchronous MU firing (tremor)	Increased temporal dispersion (see above)
		Synchronous MU firing (tremor)
Reduced MUAP duration	Loss of MF	Newly formed MUs
	MF atrophy	MF atrophy
		Poor neuromuscular transmission fails to elicit MF AP
Unstable MUAPs	Formation of new end plates after necrosis	Formation of new end plates during reinnervation
	Changes in MF AP propagation velocity during successive MUAP discharges (velocity recovery function)	Abnormal AP propagation in terminal axon branches
		Velocity recovery function

When MUs fire synchronously due to tremor, the resulting waveforms appear to have long-duration and complex waveform. A closer inspection may reveal that the waveform does not replicate and hence does not qualify as a MUAP

brachii which has a rough MU area of 5–10 mm in diameter, MUAP duration reflects about 25–50 % of MU territory. Hence, change in the MUAP duration reflects changes in the MU size. When the temporal dispersion is significantly increased, one may record long-duration MUAPs with linked (satellite) potentials. In such MUAP, a single MF AP may significantly change the duration, which does not reflect the actual MU size (Fig. 9.5) [47]. Therefore, one is justified to exclude these from duration analysis to increase the diagnostic sensitivity of the technique [42, 45]. MUAP duration is relatively constant when the needle electrode position is changed slightly within the MU territory that occurs naturally in MUAP recordings. This makes the MUAP duration a robust feature for assessment.

Based on computer simulations [46, 47], the relationship between disease processes and MUAP abnormalities is summarized in Table 9.4.

The above relationship also applies to monopolar needle electrodes. Note that the spike component of the CN MUAP is generated by only those fibers that are in front of the needle tip. Hence, the recording area is semicircular. In contrast to the concentric needle, the monopolar electrode has a spherical uptake area for the amplitude and spike component of the MUAP (Fig. 9.9) [48, 49]. The uptake area for the duration is circular for both electrodes [50], which explains similar values of MUAP duration for these electrodes.

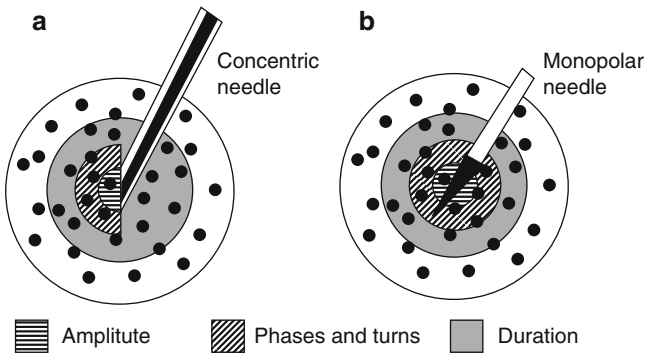


Fig. 9.9 The distribution of muscle fibers in the cross section of the MU is shown schematically. In (**a**), the *semicircles* around the concentric needle tip enclose fibers that define the MUAP amplitude and spike component. The uptake area for duration is *circular*. These relationships are based on computer simulations. The uptake area for monopolar MUAP features is shown in (**b**)

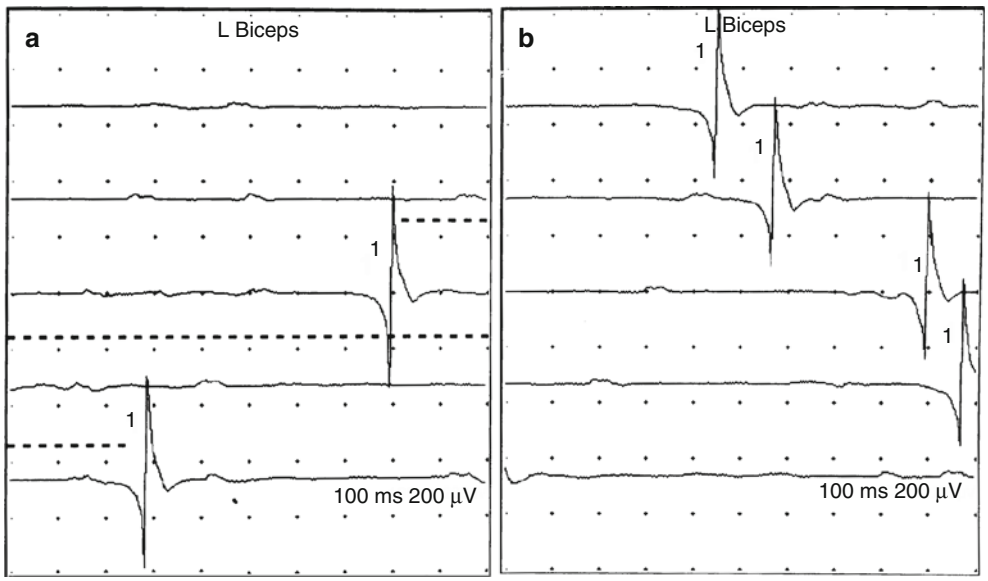


Fig. 9.10 CNEMG signals were recorded from the biceps muscle of a normal subject. Five consecutive sweeps of 100 ms duration are shown. The traces are drawn from *top* to *bottom*. In (**a**), there is no EMG activity in the first three traces. As the subject gradually increased the force, recruitment of a MU is inferred from its MUAP discharges. The inter-discharge interval (IDI, *dotted line*) is 150 ms which corresponds to an onset frequency of 6 Hz. In (**b**), the MU firing rate is increased due to further increase in force. The 500 ms epoch contains four MUAP discharges. Multiplying by 2, we estimate the firing rate of 8 Hz. The continuation of this recording is shown in Fig. 9.11

MU Firing Rate Analysis

How to Measure the Firing Rate

The MU firing rate is equal to the number of MU discharges in a 1 s time interval and is measured in Hertz (Hz). The first step in MU firing rate analysis is to identify a MUAP and its discharges. Thus, all techniques of MUAP waveform analysis can be adapted to firing rate analysis. In the manual method, a 500 ms epoch is "frozen" on the display screen (Figs. 9.3, 9.10, and 9.11). Such epochs usually contain adequate MUAP discharges to identify and validate the MUAP waveform. The number of discharges of a MUAP in the epoch is multiplied by two to obtain the MU discharges in 1 s epoch, i.e., the MU firing rate (Fig. 9.10).

The time interval between successive MUAP discharges is called the *inter-discharge interval (IDI)*. The IDI is measured in milliseconds (ms). It is inversely related to the firing rate by the following formula

$$\text{Firing rate (Hz)} = \frac{1{,}000}{\text{IDI}}, \text{ OR } \quad \text{IDI (ms)} = \frac{1{,}000}{\text{Firing rate}}$$

When the sweep duration is 100 ms and successive sweeps are shown in a raster fashion, MU firing rate can be estimated by very simple rules. If the MU firing rate is 10 Hz, the IDI will be 100 ms which equals the duration of one sweep. The MUAP will appear at roughly the same location on successive sweeps (MUP #2 in Fig. 9.11a). If the rate is less than 10 Hz, the IDI is more than 100 ms. The discharges are separated by more than one sweep. The successive discharges will appear to shift to the right in the recording (first four traces in Fig. 9.10b). On some sweeps, the MUAP may not be seen at all (last trace in Fig. 9.10b). Conversely, when the rate exceeds 10 Hz, the MUAP will appear to shift left (Fig. 9.11, MUAP #1). On some occasions, the MUAP discharge is seen twice on a sweep (Fourth trace in Fig. 9.11b). When the firing rate is 20+ Hz or more, each sweep will contain two MUAP discharges. At 30+ Hz, each sweep will contain 3 MUAP discharges and so on.

Manual analysis of MU firing rate is quite easy when the signal contains discharges of just one MU (Fig. 9.10b). When more MUs are discharging, their MUAPs superimpose. This makes MUAP identification and firing rate analysis tedious and time consuming (Fig. 9.3b). Automated methods can analyze an epoch that contains discharges of several MUAPs in just a few seconds [18, 19]. These methods use the IDI values to compute the MU firing rate. Unfortunately, the algorithm may fail to resolve the MUAP superimpositions. When a MUAP discharges are missed, the algorithm will calculate IDI values that are roughly integer multiples (e.g., twice, three times) of the true IDI value (Fig. 9.4). This will increase the mean IPI and artifactually yield lower rates. The median value is less affected by the spuriously high or low values. Hence, the median IDI value may be optimal in aforementioned formula to compute firing rate.

Recording Technique

The MU firing rate varies with the force of contraction. Even when the subject maintains a relatively constant effort, the IDI changes slightly from one discharge to another. Therefore, different protocols have been developed to study the MU firing rate that gives different physiologic information [1, 51–53].

In the traditional methods of MUAP analysis, the subject exerts a relatively constant effort. The average firing rate of each MU during the analysis epoch is measured. The

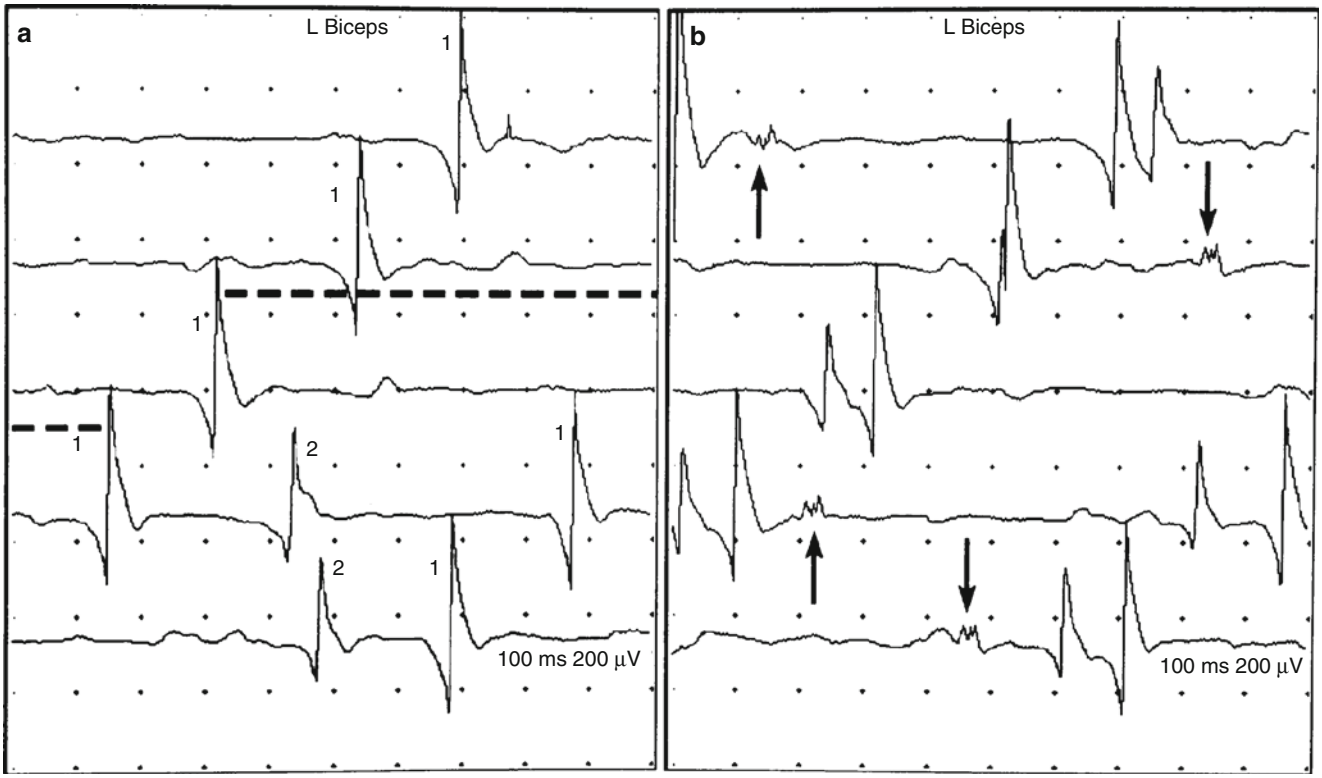


Fig. 9.11 This is a continuation of the recording in Fig. 9.10. When the force was further increased, the firing rate of the first recruited MU (#1) increased, and a new MU (#2) was recruited. This is detected from its MUP discharges in the fourth and fifth trace (**a**). The two discharges of MU #2 are seen roughly at the location on the sweep, which gives it an onset frequency of roughly 10 Hz. The *dotted line* indicates the recruitment interval of roughly 80 ms. This corresponds to a recruitment frequency of 12.5 Hz. In (**b**), the force of contraction is increased further. Careful examination reveals discharges of three MUAPs in this recording. The third MUAP (indicated by *arrows*) has low amplitude and serrated waveform. The MUs are discharging at 12 Hz or less. This gives a recruitment ratio of 3 for this recording. Waveforms in (**b**) appear polyphasic with long duration due to superimposition of the MUAPs

recruitment ratio is obtained by dividing the rate of the fastest discharging MU by the number of MUs [1].

The dynamic change in MU firing rate is investigated when the subject gradually increases the force of contraction. At rest, the EMG contains no MU activity. When the force is gradually increased, one MU will be recruited and its discharges recorded by the needle electrode. The MU firing rate when it begins to discharge is called its *onset frequency* (Fig. 9.10a). When the force is further increased, the MU firing rates increase (Fig. 9.10b), and eventually, a second MU will be recruited (Fig. 9.11a). The EMG will contain discharges of two MUAPs. The firing rate of the first MU just before the recruitment of the second MU is called the *recruitment frequency* (Fig. 9.11a) [53].

The instantaneous variability of a single MU discharge rate may be calculated from the IDI values. In a simple method, the mean and standard deviation values of firing rate are used to compute the coefficient of variation. In a more elegant method [54], successive IDIs are correlated (a data point (X, Y) is constructed where X and Y are successive IDI values, and a plot of these (X, Y) is constructed to study the correlation between Y and X).

The changes in the MU firing rate of all discharging MUs are investigated by a technique called *precision decomposition* [55, 56]. A special electrode is used to record three-channel EMG activity when the subject gradually increases force to moderate levels and then relaxes the tested muscle. Almost every discharge of several different MUs is identified. The instantaneous firing rate and the force of contraction are plotted against time to study their relationship (Fig. 9.12).

Findings in Normal Subjects

At minimal effort, the average MU firing rate varies among muscles. The MU onset frequency is usually 6–10 Hz (Fig. 9.10). The recruitment frequency varies significantly among different muscles [53] (Table 9.5). It probably reflects the difference in the force generation mechanism among the muscles. Muscles requiring for fine control (e.g., facial muscles) use frequency modulation to adjust force. Hence, they often have higher range of discharge frequency. In contrast, the larger muscles used for forceful activity rely on recruitment of motor units. Their motor units have smaller

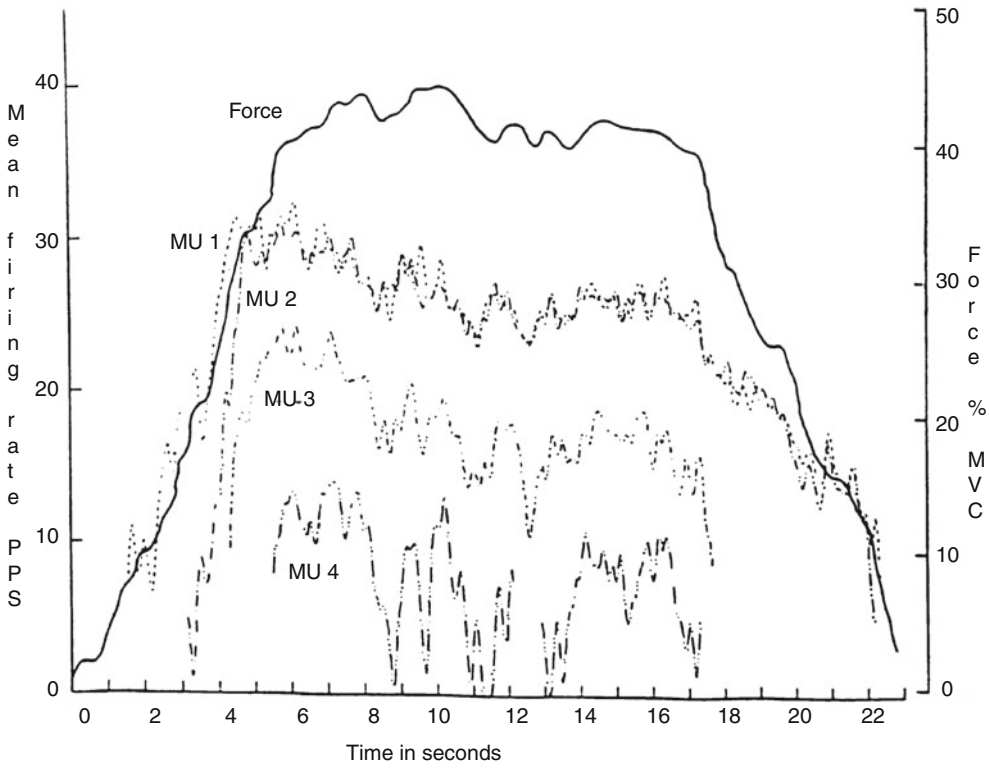


Fig. 9.12 Results of precision decomposition from the first dorsal interosseus muscle of a normal subject are shown. The time is indicated along *X* axis. The *Y* axis shows change in the force of contraction and firing rate of individual MUs. Observe the orderly recruitment of MU. When the force is reduced, the MUs are released, i.e., stop discharging, in reversed order of recruitment. The last recruited MU is released first. The first recruited MU is last to stop firing. The firing rate of these normal MUs at high force levels is 25+ Hz which is well above the commonly observed rate of 10–15 Hz. Finally, the rate changes in parallel for all MUs (Reproduced with permission Stashuk and Deluca [56])

Table 9.5 Onset and recruitment interval/frequency in normal muscle

	Onset		Recruitment	
Muscle	Interval (ms) mean (standard deviation)	Frequency (Hz)	Interval (ms) mean (standard deviation)	Frequency (Hz)
Frontalis	102 (29)	9.8	46 (16)	21.7
Orbicularis oris	79 (19)	12.7	34 (10)	29.4
Deltoid	116 (23)	8.6	84 (16)	11.9
Biceps	124 (21)	8.1	86 (14)	11.6
Pronator teres	132 (38)	7.6	88 (19)	11.4
First dorsal interosseous	142 (39)	7.0	98 (21)	10.2
Multifidus	152 (33)	6.6	102 (20)	9.8
Vastus lateralis	126 (30)	7.9	88 (18)	11.4
Tibialis anterior	124 (26)	8.1	90 (13)	11.1

Table constructed using data from Petajan and Phillips [51]. The rates are computed using the mean interval value

range of firing rate. The recruitment ratio is less than 5 and corresponds to 3 MUs discharging at less than 15 Hz (Fig. 9.11b) [1].

In normal muscles, successive IDIs exhibit a negative correlation [54]. It corresponds to the subjective observation that a long IDI is followed by a short IDI and vice versa. We can often hear this pattern when double discharges occur in MUAP recordings. Precision decomposition demonstrates MU firing at 25+ Hz in normal muscles (Fig. 9.12). Although individual MU firing rates differ, all MUs change their rate in parallel. In other words, when one MU increases the firing rate, other recruited MUs also discharge faster [56]. This is called the *central drive.*

Findings in Patients with Nerve and Muscle Diseases

In patients with neuropathy (Fig. 9.13), routine MUAP analysis at minimal effort shows increased MU firing rate. Recruitment frequency is increased. This corresponds to the usual visual assessment of single fast-firing MU (Fig. 9.13a). The recruitment ratio is increased and corresponds to two MUs firing at more than 15 Hz (Fig. 9.13b). These observations are described as *reduced recruitment* on the routine EMG. The term "reduced" expresses the lack of other MU activity in the recording. In patients with upper motor neuron lesions, MU firing rate is reduced [20]. The IDI shows

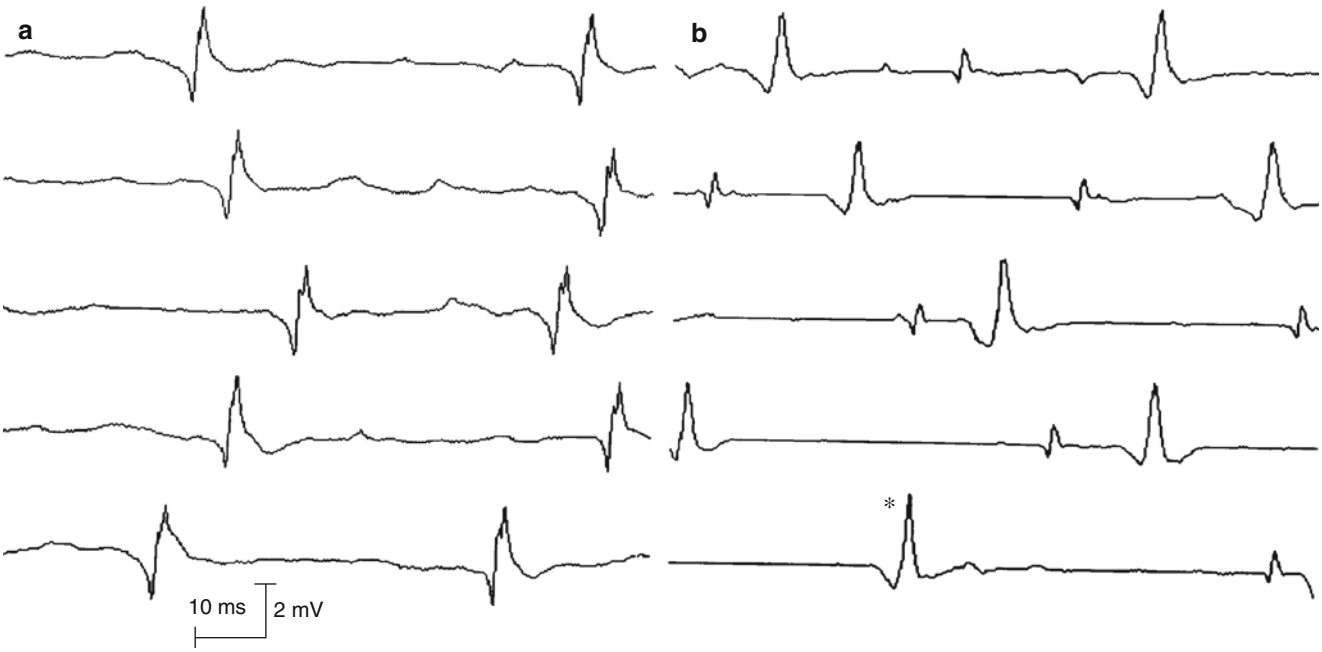


Fig. 9.13 CNEMG recordings from the biceps muscle of a patient with neuropathy are shown in raster mode. Traces are drawn from *top* to *bottom*. In (**a**), two discharges of a MUAP are seen on each sweep. This gives it a firing rate of 20+ Hz. There is no other MU activity seen. This indicates increased recruitment frequency. In (**b**), discharges of two MUs are seen. The eight discharges of each MU in a half-second epoch give them a firing rate of more than 15 Hz. This corresponds to increased recruitment ratio. The waveform indicated by * represents a superimposition of both MUAPs

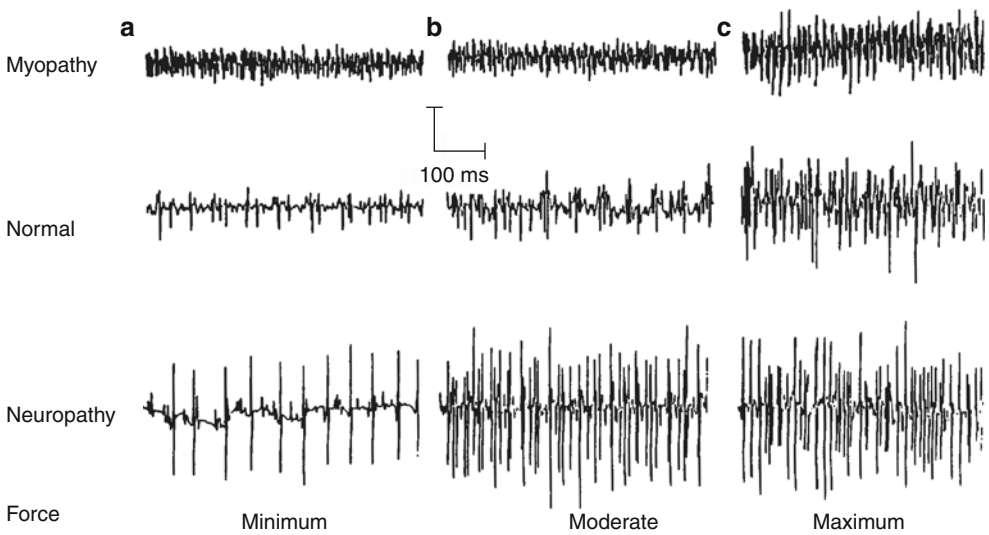


Fig. 9.14 EMG IP was recorded at minimal (**a**), moderate (**b**), and maximal (**c**) effort of the biceps muscle in a patient with myopathy (*top row*), a normal subject (*middle*), and a patient with neuropathy (*bottom*). Observe the increased recruitment at minimal effort in the patient with myopathy. At maximal effort, the pattern is full with reduced amplitude. In neuropathy, the amplitude is increased with reduced number of spikes (Reproduced with permission from Nandedkar [4])

considerable variability from one discharge to another. The plot of sequential IDIs may not show a negative correlation.

In patients with myopathy, routine MUAP analysis also shows a slightly higher MU firing rate. Several MUs discharge even at minimal effort (Fig. 9.14). This offsets the higher firing rate and may give a reduced recruitment ratio. This observation is described as *increased* or *early* recruitment of MUs. These terms refer to the greater than expected number of discharging MUs for force of contraction [3]. Recruitment frequency may be increased in some recordings [43a].

Disease Processes and Firing Rate

The technique of precision decomposition is relatively new. However, it should give valuable information about motor control in neuromuscular diseases. In normal subjects, one can visually assess the MU firing rate only at a minimal force of contraction. Precision decomposition reveals that normal MUs do discharge at rates of 25+ Hz at higher forces of contraction (Fig. 9.12). Therefore, the high MU firing rate per se seen in patients with neuropathy is not an abnormality of

MU discharge frequency. Rather, it reflects the loss of MUs and allows us to view the surviving MUs discharging at a higher rate. The greater the loss of MUs, the easier it will be to recognize fast-firing MUs. Reduced MU firing rate and higher variability are characteristic of an upper motor neuron lesion.

Recruitment of a MU is easily recognized when the MUAP has a high-amplitude spike component. As discussed earlier, this is defined by the few muscle fibers closest to the recording electrode. If there is a significant loss of MFs, the MUAP spike component will have a lower amplitude. We may then fail to fully recognize the MU recruitment (Fig. 9.11b). This results in higher values of recruitment frequency in some recordings of patients with myopathy [43a, 53].

Assessment Strategies

The MU firing rate analysis requires identification of individual MUAP discharges. When the signal contains discharges of three or more MUAPs, this process can be time consuming and laborious. Hence, in our opinion, firing rate analysis is not quite suitable for patients with myopathy. In patients with neuropathy, loss of MUs makes it easier to assess the MU firing rate. Increased recruitment frequency is easily recognized when a single MU discharges at 20+ Hz. This results in two discharges of the same MUAP on every sweep of 100 ms duration (Fig. 9.13a). Recruitment ratio abnormalities must be assessed with caution. To show that a muscle is normal, one must demonstrate three MUs in the recording. (In a normal muscle, one can easily record two MUs firing at 12 Hz which would correspond to an increased recruitment ratio.) In contrast, to demonstrate increased ratio, it is adequate to show one or two MUs firing at more than 15 Hz (Fig. 9.11b).

Variability of firing rate is best assessed by the sound of the EMG signal when the patient tries to maintain a steady force of contraction.

MUAP Assessment at High Force: Analysis of Interference Pattern

At minimal force of contraction, the EMG may contain discharges of a single MU. The MUAP waveform and its firing rate can be easily assessed. As the force of contraction is increased, the firing rates of the MUs also increase, and new MUs are recruited. At moderate to high activation, the EMG becomes a complex signal in which individual MUAPs can no longer be readily recognized. Therefore, the MUs recruited at higher force cannot be easily studied using the earlier described technique. To reflect the summation and cancellation of individual MUAP waveforms (i.e., phase interaction), this signal is called the *interference pattern (IP)*. The term "interference" usually refers to undesired signals derived from external sources, e.g., the main power supply. However, in this context of EMG assessment, the term is well recognized. The IP signal contains information about the number of MUs, their firing rate, and their waveform characteristics. These characteristics are assessed indirectly from measurements of the IP signal. Because of the complexity of the signal, the manual methods of analysis are rather simplistic. All quantitative methods require automation by computers. These techniques also use different features of the signal for assessment. These are discussed individually.

Subjective Assessment at Maximal Effort

Buchthal and coworkers proposed a simple technique to assess IP signals recorded at maximal effort using two features: *fullness* and *envelope amplitude* (Fig. 9.14) [30, 40]. In a full pattern, the signal baseline is completely obscured by MUAPs. In a discrete pattern, one can recognize individual MUAPs even at maximal effort. The signal usually contains discharges of just one or two MUs. To measure amplitude, one draws an imaginary line connecting together the positive peaks and a similar line connecting the negative peaks. The amplitude difference between these lines is the envelope amplitude. Solitary peaks are excluded from envelope measurements. The criteria for abnormality are as follows (Fig. 9.14):

- If the IP is full in a weak or wasted muscle and the envelope amplitude is reduced, the abnormalities are consistent with myopathy.
- A discrete pattern with increased amplitude is consistent with a neurogenic disease process.

The normal envelope amplitude varies among different muscles but is usually greater than 1.5–2 mV. This assessment is subjective and hence numerical measurements of the same signal made by different operators may differ slightly. Furthermore, the criteria should not be used if the patient fails to exert maximal force (e.g., due to pain and discomfort, somatoform disorders).

Frequency Domain Measurements

The sound of EMG signals has a high pitch in patients with myopathy. Walton demonstrated this shift using an audio spectrometer [57]. With access to computers, spectrum analysis is relatively easy [58]. The basic concept is as follows: Any signal can be represented as a sum of harmonically related sinusoids of different amplitudes and phases. The power in each sinusoid is proportional to the square of its amplitude. A plot of power versus the frequency of the

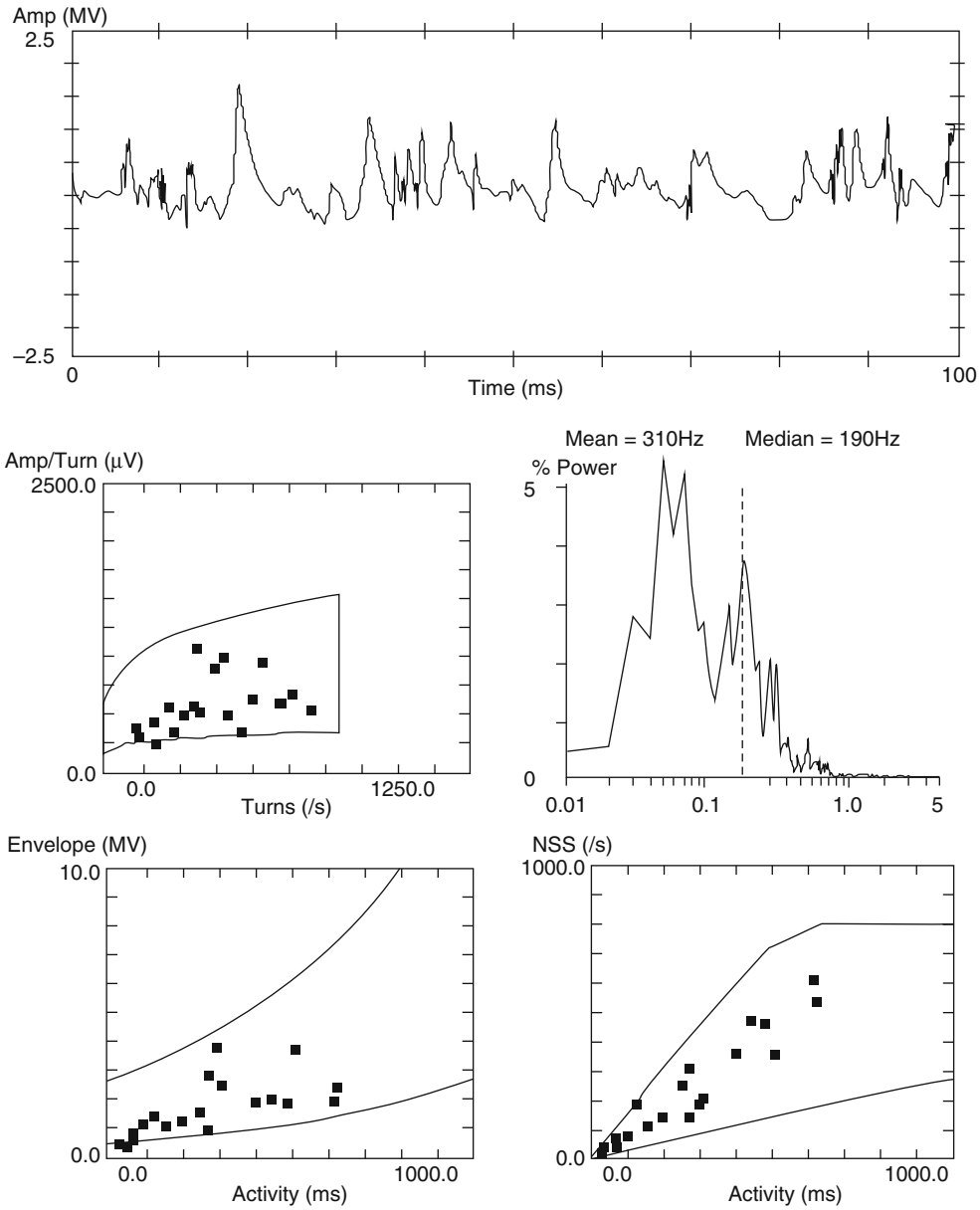


Fig. 9.15 Different techniques of IP analysis are demonstrated from IP recordings in a normal subject. An EMG signal is shown at the *top*. The power spectrum of this signal is shown below to its *right*. The results of "turns and amplitude" analysis are shown to *left* in the *middle*. The *bottom* two plots describe findings on EQUIP analysis. These three plots contain more than 90 % of the data points in the tested muscle. See text for details (Reproduced with permission from Sanders et al. [61])

sinusoid is called the power spectrum (Fig. 9.15). To accommodate a wide range of frequencies and power, logarithmic scales may be used. The calculation of the power spectrum is often facilitated by the fast Fourier transform (FFT). The spectrum is quantified by the sum of power in all sinusoids. This is also called the *total power*. The frequency that contains 50 % of the power below it and 50 % power above it is called the *median frequency*. The *mean frequency* is computed by summating the product of frequency and power and then dividing the sum by the total power. A shift to high frequencies will give higher numerical values of the mean and median frequencies. Changes in signal amplitude will affect the total power.

Power spectrum analysis offers a very high-resolution technique to measure energy in narrow bands of frequency. This is often not necessary. Therefore, one may use broadband filters to measure power in a few frequency ranges, e.g., low, mid, and high. The power in these bands is normalized to measurements in normal subjects. Therefore, in a normal muscle, the resulting values are close to unity. If the spectrum shifts to right, the normalized power will be greater than one for the high-frequency band and less than one for the low-frequency band. Opposite pattern will result when the spectrum shifts to low frequency [59].

In patients with neuropathy, the power spectrum shifts to low frequencies giving a low pitch sound. The mean and median frequencies are reduced (Fig. 9.16). Conversely in patients with myopathy, the spectrum shifts to high frequency. The mean and median frequencies are increased

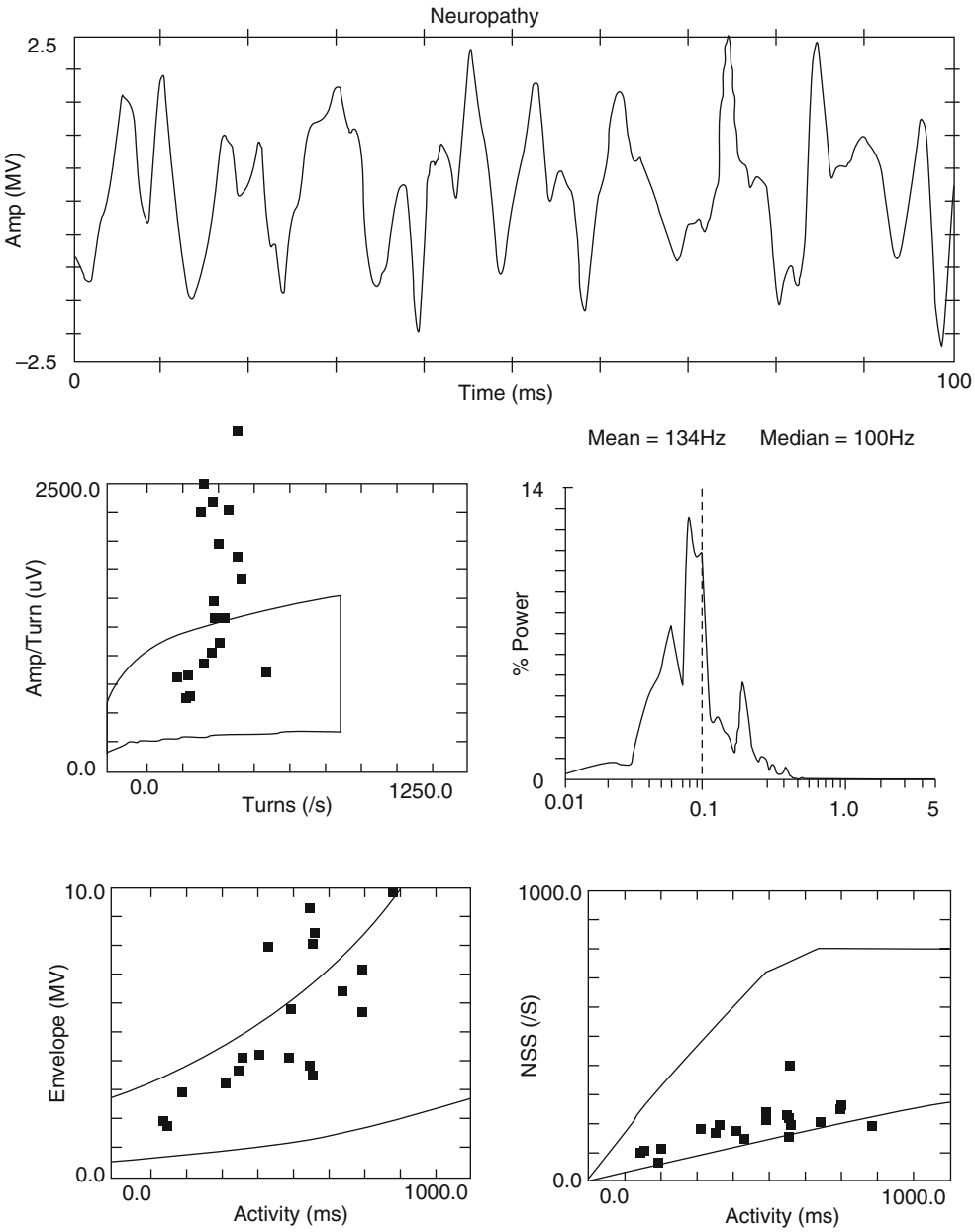


Fig. 9.16 Different techniques of IP analysis are demonstrated from IP recordings in a patient with neuropathy. An EMG signal at the *top* shows reduced number of spikes. The mean and median frequencies are reduced compared to Fig. 9.15. The turns and amplitude plot shows data points outside and on the *upper side* of the normal cloud. EQUIP also shows increased amplitude and reduced NSS values (Reproduced with permission from Sanders et al. [61])

(Fig. 9.17). Reduced signal amplitude will give less power. With fatigue, the spectrum shifts to low frequencies, and the total power is increased [60].

Turns and Amplitude

The computation of spectrum is a rather abstract way of quantifying the IP signals. If the spectrum shifts to high frequency, we expect the signal to contain more peaks. To exclude peaks generated by noise, Willison defined a "turn" of the IP signal (Fig. 9.18a) [61, 62]. A turn occurs at a peak of the signal. If a turn occurs on a positive going peak, then the immediately following and preceding turns occur on negative going peaks and vice versa. Finally, successive peaks are separated by at least 100 μV difference. The number of turns (NT) is used to quantify the IP. The mean amplitude change between successive turns (MA) is used to assess the amplitude changes.

The NT and MA values depend on the force of contraction (Fig. 9.18b). NT increases with force until it is about 50 % of maximum. With further increase in force, the NT increases mildly or may even decrease slightly. The MA increases with force at all levels of activation. Since the IP measurements depend on the force, the recordings are performed when the subject exerts a standard force. Signals are recorded from different sites, and the mean values of IP measurements are compared against normal.

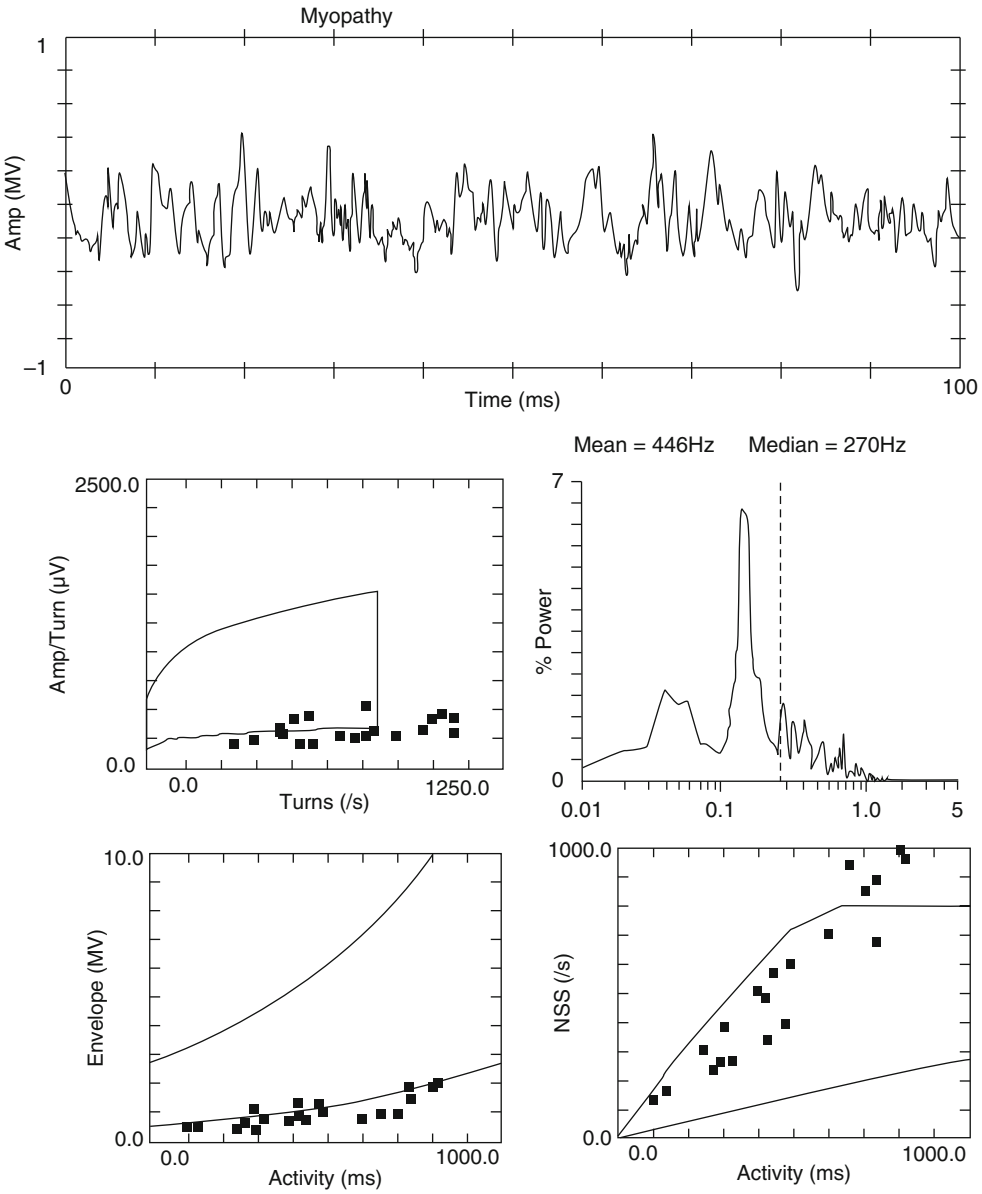


Fig. 9.17 Different techniques of IP analysis are demonstrated from IP recordings in a patient with myopathy. An EMG signal at the *top* shows increased number of spikes and reduced amplitude. The mean and median frequencies are increased compared to Fig. 9.15. The turns and amplitude plot shows data points outside and on the lower side of the normal cloud. EQUIP also shows reduced amplitude and increased NSS values (Reproduced with permission from Sanders et al. [61])

Willison, Hayward, and coworkers used a fixed load, e.g., 2 kg for biceps, and demonstrated increased NT in patients with myopathy [63–65]. The MA was increased in patients with chronic partial denervation. Fuglsang-Frederiksen and coworkers standardized the force to 30 % of patient's maximal effort [66–68]. Besides abnormalities of MA and NT, they also found reduced NT/MA ratio in patients with neuropathy and increased NT/MA ratio in patients with myopathy. Patients with myopathy also had a higher incidence of short-duration intervals between successive turns. The diagnostic sensitivity of IP analysis was similar to MUAP waveform analysis. When used together, they increased the overall diagnostic sensitivity.

This approach to IP analysis has several limitations. It requires force monitoring and hence additional hardware. In many muscles, force cannot be measured easily. Finally, it requires patient cooperation. Smyth analyzed IP in children who were referred for EMG. The force of contraction was not measured. The mean ratio of NT to MA was computed from several different sites with different levels of activation. Later, those children with no evidence of a neuromuscular disease were defined as the reference population [69]. Analysis based on the mean gave a modest diagnostic yield in the patient group [70]. Gilchrist and coworkers also demonstrated usefulness of the mean NT/MA ratio without force monitoring in adult subjects [71].

Stålberg and coworkers also ignored the force of contraction but used a novel way to assess the abnormalities [72]. Their analysis, now called *turns and amplitude (TA)*, is performed as follows: The IP signal is recorded from six to ten different sites. At each site, the signal is analyzed at three to four different force levels that range from minimal to

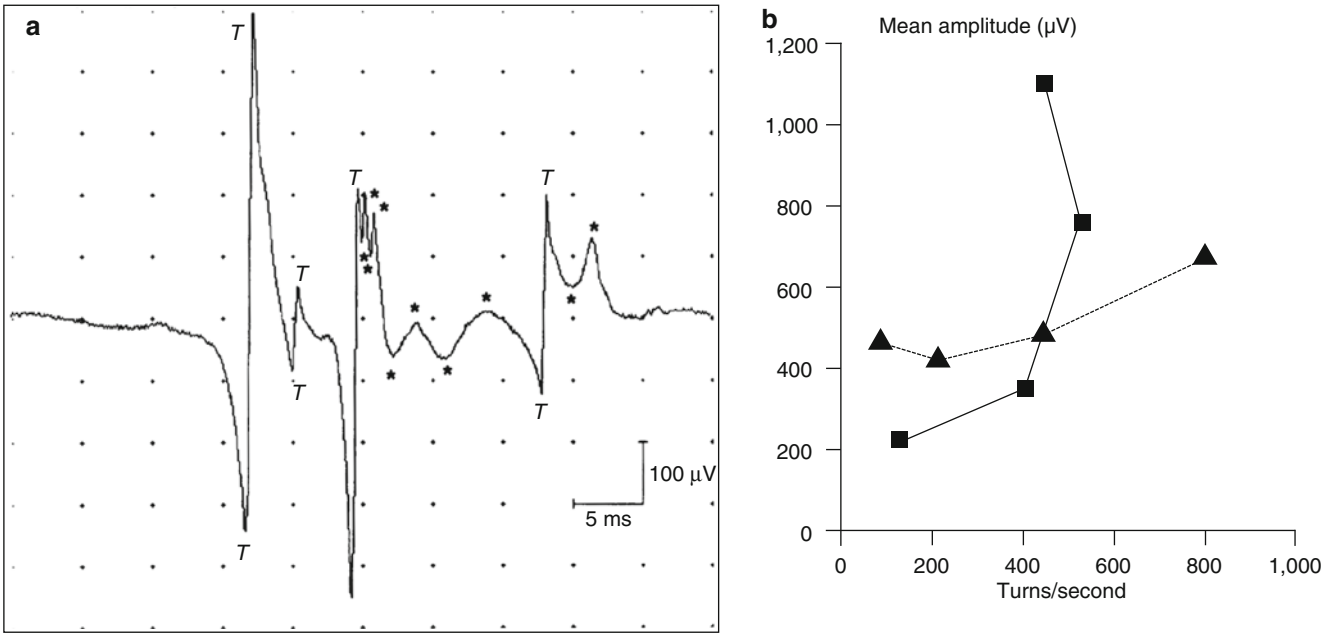


Fig. 9.18 In (**a**), 50 ms epoch of EMG signal is used to identify the turns (indicated as *T*) based on 100 µV amplitude threshold level. Peaks indicated by * did not qualify as turns. They include small peaks in the MUAP and also peaks generated by noise and baseline fluctuations. In (**b**), IP signals were recorded from two sites in the biceps muscle of a normal subject when the force of contraction was mild, moderate, submaximal, and maximal. A plot of mean amplitude (MA) versus number of turns (NT) is constructed. Data points from each site are connected by *straight lines*. Note the change in NT and MA with the force of contraction

maximum. The force is varied when the patient matches the resistance offered by the clinician. A plot of MA versus NT is created. An area on this plot is defined which contains more than 90 % of data points in normal subjects. The boundary of this area is called the *normal cloud* (Fig. 9.15). A typical investigation acquires 20 data points. Hence, the study will be abnormal when three data points are outside the normal cloud. This can occur within the first 2 or 3 min. If so, the test has now reached diagnostic significance and may be stopped. In patients with neuropathy, the data points fall on the upper side of the normal cloud (Fig. 9.16). In contrast, some data points occur below or to the right of the normal cloud in patients with myopathy (Fig. 9.17).

The IP quantification described so far is quite different from the subjective assessment that is based on IP fullness, amplitude, and sound. To mimic this assessment, Nandedkar and coworkers defined three IP parameters that were derived from the turns [73, 74]. *Activity* defined the number of milliseconds from a 1 s signal that contained "spiky" MUAP activity. When activity was more than 500 ms, the IP appeared full by visual assessment. The amplitude was measured from the envelope of the signal [75]. The *number of small segments (NSS)* measured the frequency of short-duration low-amplitude portions between successive turns. This quantifies the high-frequency component that is heard but not recognized easily by visual inspection. When the force of contraction is increased, activity and amplitude increase. NSS also increases initially and then remains constant or decreases slightly at high force. Signals were recorded from different sites and at different force levels. Two plots were constructed along with their normal clouds: envelope amplitude versus activity and NSS versus activity (Fig. 9.15). In patients with neuropathy, the data points fell above the amplitude-activity cloud. The activity was less than 500 ms in many patients indicating a reduced pattern. NSS values fell below the cloud indicating reduced high-frequency components (Fig. 9.16). In contrast, patients with myopathy showed a full pattern with activity values well in excess of 500 ms. The amplitude data fell below the normal cloud indicating reduced values. The NSS are increased and fall above the normal cloud. This corresponds to a high pitch sound of the IP (Fig. 9.17).

Many other modifications to the NT and MA analysis were described and are reviewed by Fuglsang-Frederiksen [76] and Gilai [77]. However, it is beyond the scope of the current discussion to review their details.

Interference Pattern Features and MUAP Waveform

When force of contraction is increased, the number of MU discharges increases due to recruitment and increased firing rates. Therefore, the NT, activity, and NSS increase with force. Some of the newly recruited MUs have MFs close to the recording surface. Hence, they will have large amplitude MUAPs. This will increase the envelope amplitude and MA. Recruitment of

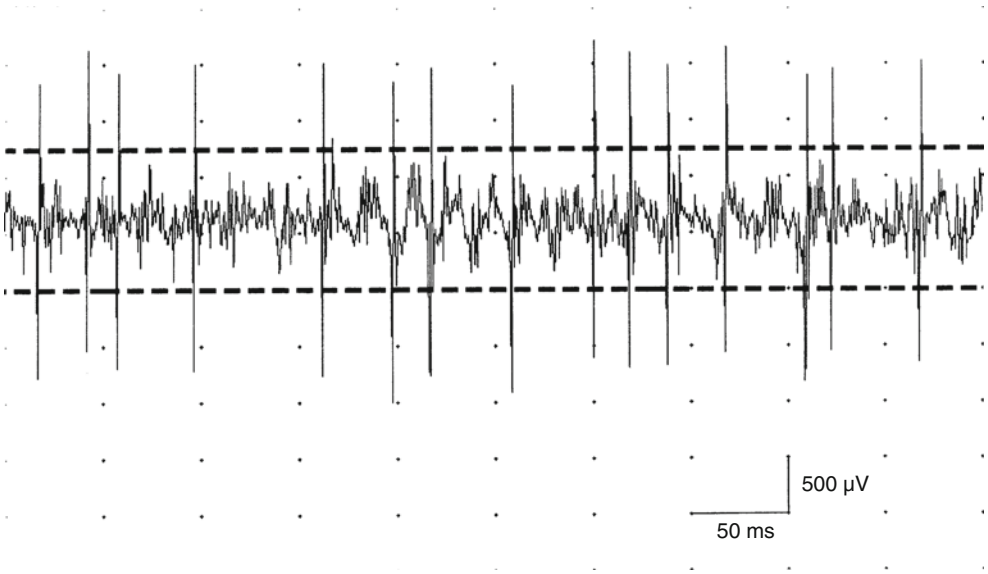


Fig. 9.19 The IP was recorded at maximal effort of the biceps muscle in a patient with myopathy. The spikes exhibit a bimodal distribution of amplitude. Majority of the spikes have low amplitude. However, the signal also contains discharges of a high amplitude, thin MUAP that appears to discharge quite rapidly. See text for details

high-amplitude MUAPs is recognized quite easily by visual assessment. Some newly recruited MUs may not have MFs close to the recording electrode. Their MUAPs will have a low amplitude (Fig. 9.11b), and their recruitment is recognized from an increase in NT, NSS, and activity. When several MUs are discharging, their MUAPs will superimpose each other. Their waveforms may interfere to generate higher amplitude signals. Computer simulations, however, indicate that the chance summation of several MUAPs to produce high-amplitude signal is rather low [73]. Therefore, the envelope amplitude mainly reflects the upper limits of the highest amplitude component MUAPs. Simulations indicate that summation of one large and one small MUAP often results in a signal that is very similar to the larger MUAP. Smaller MUAPs are masked and cannot contribute to the turns (Fig. 9.13b). Therefore, NT and NSS may decrease slightly at maximal effort.

Interference Pattern Features and Disease Processes

In normal muscles, the intramuscular needle may record from over 10–15 different MUs that are near the needle tip. In patients with neurogenic disease, the interference pattern is reduced due to loss of MUs. If the IP is discrete and contains MUAPs from only one or two MUs, this implies a significant MU loss.

The IP pattern may be spuriously reduced when the patient fails to exert the desired force due to pain and discomfort. However, this should not cause confusion. In normal subjects, the MUAP waveform and MU firing rate at minimal effort will be normal. In patients with neurogenic diseases, the MUAP waveform is altered as described earlier. Furthermore, the MUs appear to fire at higher rates (Fig. 9.13).

In patients with only upper motor neuron disease, the number of MUs may be normal, but the patient cannot activate them. The MUAP waveform may also be normal. The abnormality in these recordings is mainly the reduced and variable MU firing rate which is typically slowed for level of effort [20]. Obviously, one needs to combine different approaches in MUAP analysis to identify the underlying abnormality [61].

As stated previously, the EMG envelope amplitude is increased in patients with neurogenic diseases due to increased MUAP amplitude following reinnervation. In patients with myopathy, the amplitude is reduced due to loss of MFs and MF atrophy. In some patients with myopathy, one may record an IP that contains mainly low-amplitude MUAPs but also high-amplitude spikes (Fig. 9.19). These spikes are generated by discharges of a single MUAP when the needle electrode is close to a hypertrophied MF. These spikes appear thin by visual assessment, which is a specific finding in myopathy. Because of their high amplitude, they can be easily recognized when they discharge at higher rates. These fast-firing high-amplitude MUAPs should not be misinterpreted as evidence of neuropathy [43].

The high pitch sound in myopathy reflects the short-duration, short rise time, and polyphasic MUAPs. In neuropathy, the long-duration simple MUAPs with long rise time give a dull sound. In the very early stages of reinnervation, MUAP amplitude and duration may be normal, but the waveform is polyphasic and unstable. This may impart a high pitch sound to the IP signal.

Practical Considerations

The IP assessment at maximal effort is usually performed as part of the routine needle EMG examination. The criteria

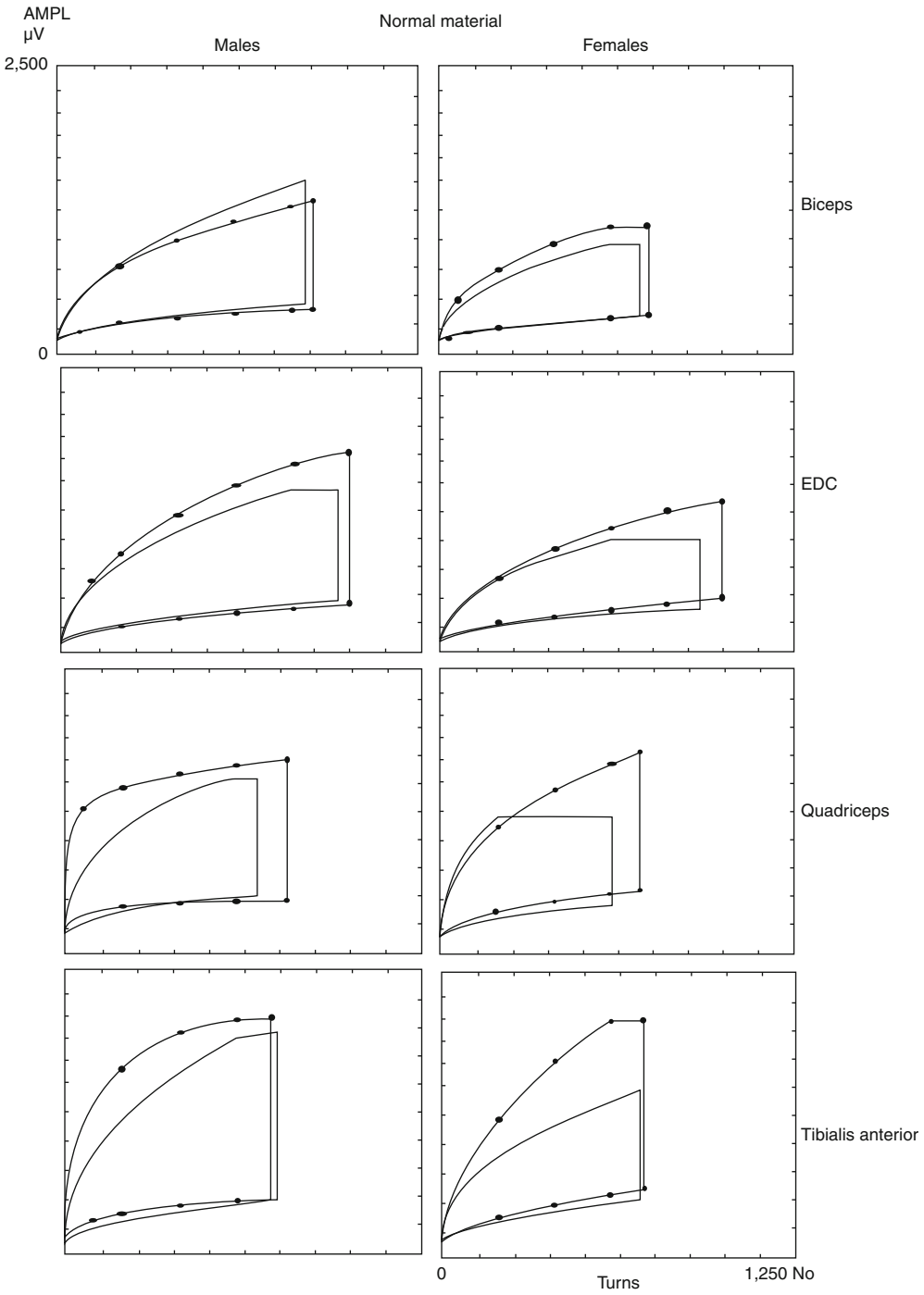


Fig. 9.20 Normal clouds for four different muscles in male (*left*) and female (*right*) subjects. The *lines* connecting the *symbols* define the cloud for subjects over 60 years. The other cloud is for subjects below 60 years. A concentric needle was used in this study (Reproduced with permission from Stålberg et al. [72])

described by Buchthal can be quite helpful in this analysis [30, 40] and should be used only when the patient exerts maximal effort.

The techniques based on spectrum analysis require special software on the EMG instrument. The measurements are not intuitive like time domain features (e.g., amplitude). We are not aware of well-defined reference values for different muscles.

The techniques of TA or EQUIP also require special software. The technique of IP recordings is relatively simple compared to MUAP analysis. The quantitation requires little time. Hence, the test can be performed "online" and completed within 5 min. The contrasting pattern of data distribution in neuromuscular diseases makes it useful in electrodiagnosis. The diagnostic yield is similar to MUAP analysis, but the sensitivity is increased when both analyses are used. The only significant limitation of these techniques is the relative paucity of reference values. The normal clouds vary among different muscles. The clouds also depend on the needle electrode type (concentric versus monopolar), patient age (below or above 60 years), and gender (Fig. 9.20) [72].

The maximal force generation (manual resistance versus a strain gauge) also affects the cloud boundaries for high turns values [78]. Hence, at present, these methods have limited clinical usefulness.

Motor Unit Number Estimation

Loss of motor units is a key feature in patients with a neurogenic process. Therefore, it has always been of long-standing interest to estimate the number of MUs in a muscle, which McComas and coworkers pioneered in the early 1970s [79]. Due to technical problems encountered with the method, interest in MU counting declined. With access to fast computers, there has been a renewed interest in *motor unit number estimation (MUNE)*.

Principle of MUNE

MUNE is a three-step process. First, the *compound muscle action potential (CMAP)* of the tested muscle is recorded using standard motor nerve conduction techniques (Fig. 9.21a). The premise is that the CMAP represents the sum of MUAPs of all MUs in the muscle recorded by the surface electrode. Next, the same surface electrode is used to estimate single *surface-recorded MUAP (SMUAP)* amplitudes (Fig. 9.21b). Finally, to obtain the number of MUs, the CMAP amplitude is divided by the SMUAP amplitude (Fig. 9.21c). MUNE techniques differ mainly in the second step. Furthermore, one may use CMAP and SMUAP area in lieu of amplitudes for computations.

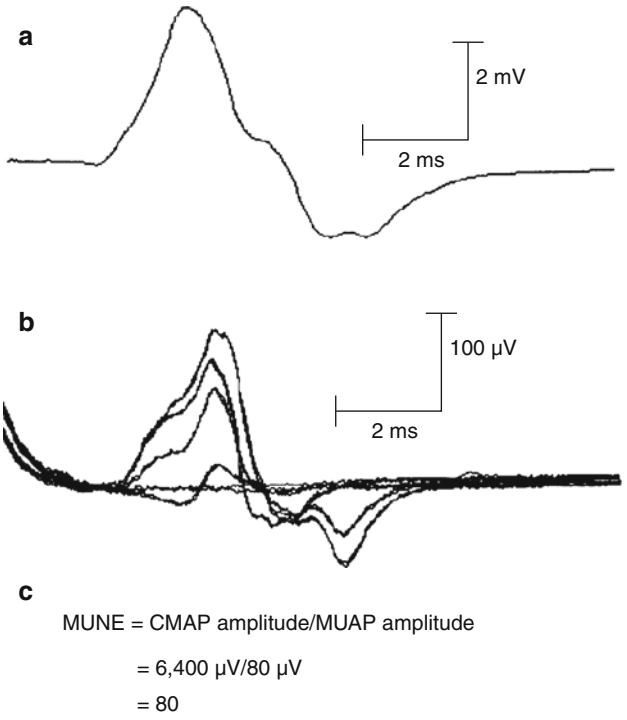


Fig. 9.21 The principles of MU counting technique are illustrated using the method described McComas. In (**a**), the CMAP of the abductor pollicis brevis muscle is recorded by supramaximal stimulation of the median nerve at the wrist. Its peak-peak amplitude is 6.4 mV. In (**b**), the responses recorded by incremental stimulation are shown. In each case, two trials are superimposed. The largest response represents a sum of 4 surface EMG MUAPs. Dividing its peak-peak amplitude by 4 gives the average MUAP contribution to the CMAP, i.e., 80 µV. In (**c**), their ratio is computed to obtain the MU count of 80. Ideally, the mean MUAP amplitude should have been estimated from 10 MUs

Estimation of SMUAP

McComas and coworkers used a so-called incremental stimulation technique to estimate single SMUAP amplitude [79–83]. This method uses a standard motor nerve conduction setup, by recording the muscle action potential when the stimulus intensity is increased. At very low stimulus intensity, none of the axons are stimulated. As stimulus intensity is increased, a stage is reached when an axon will depolarize and generate an AP. The SMUAP of that MU is then recorded. When the intensity is varied slightly, that axon will either be stimulated or not stimulated. Hence, the response contains either the SMUAP or the baseline. No intermediate response is observed. This is called the "all or none" phenomenon (Fig. 9.22). The signal represents one SMUAP.

When the intensity is increased further, the response will not change until another axon is stimulated (Fig. 9.21b). The response represents a sum of two SMUAPs. When the intensity is changed slightly, we record either the baseline, the first SMUAP, or a sum of the two SMUAPs. No intermediate response is seen. When the intensity is increased further, the response changes in a stepwise fashion whenever another axon is stimulated (Fig. 9.21b). The procedure is continued until about ten steps are recorded. The last response represents the sum of all ten SMUAPs. Dividing the amplitude of the last response by the number of steps gives individual SMUAP amplitudes.

This method is conceptually simple but has several pitfalls. If the newly stimulated axon gives a very small SMUAP, we may fail to recognize its stimulation. This will overestimate the SMUAP amplitude and yield a smaller MU count. In some instances, two axons may have a very similar stimulation threshold. The evoked response will then exhibit three different possible waveforms that correspond to stimulation of the first axon, the second axon, or both axons. If this is interpreted as stimulation of three axons, we will underestimate SMUAP amplitude and get a larger MUNE. This phenomenon is called *alternation.* By subtracting the successive incremental responses, we obtain the SMUAP amplitudes of the stimulated MUs. By adding these SMUAPs in different

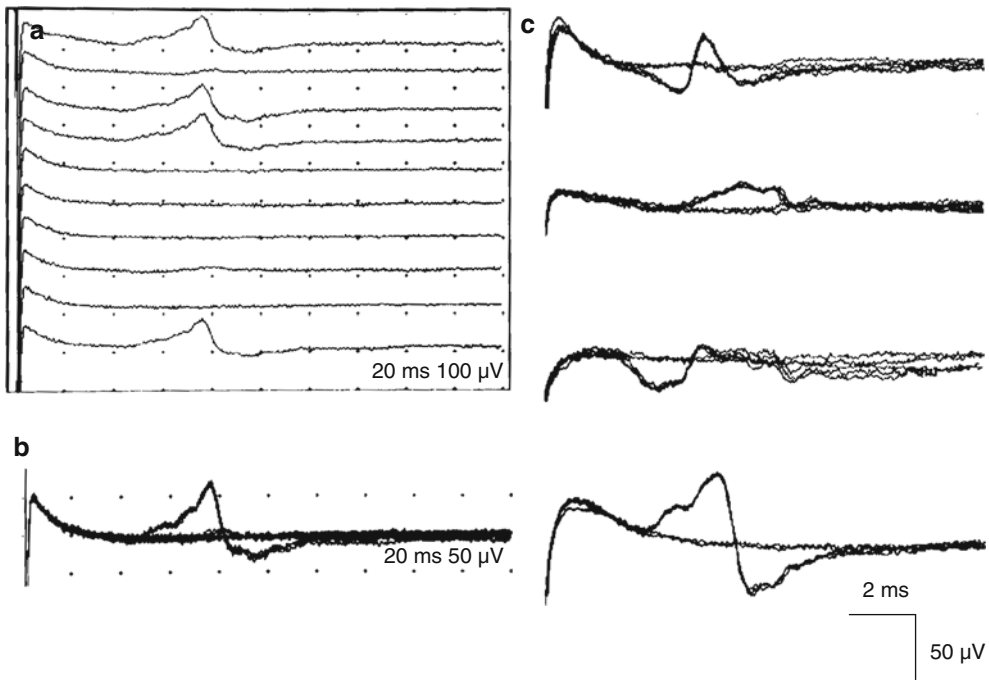


Fig. 9.22 The muscle action potential was recorded from the abductor pollicis brevis muscle when the median nerve was stimulated at the wrist. Results of ten stimuli are shown in (**a**) raster and (**b**) superimposed fashion. At this low setting of stimulus intensity, the response contains either the baseline or small amplitude potential. When present, this potential has the same shape as seen by superimposing the traces. No intermediate waveform configurations are seen making this an "all or none" phenomenon. The SMUAP recorded from different stimulation sites, i.e., multipoint, are shown in (**c**)

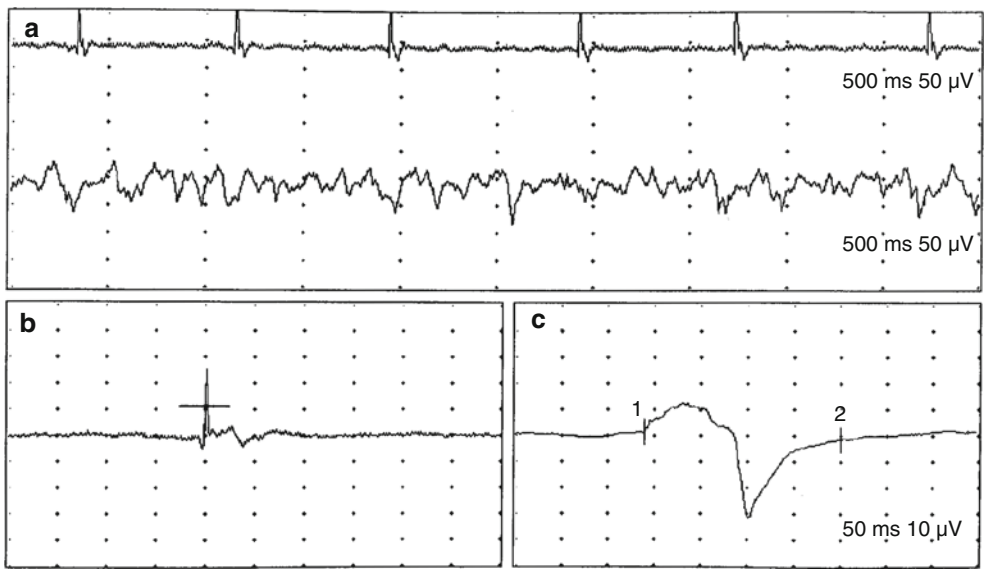
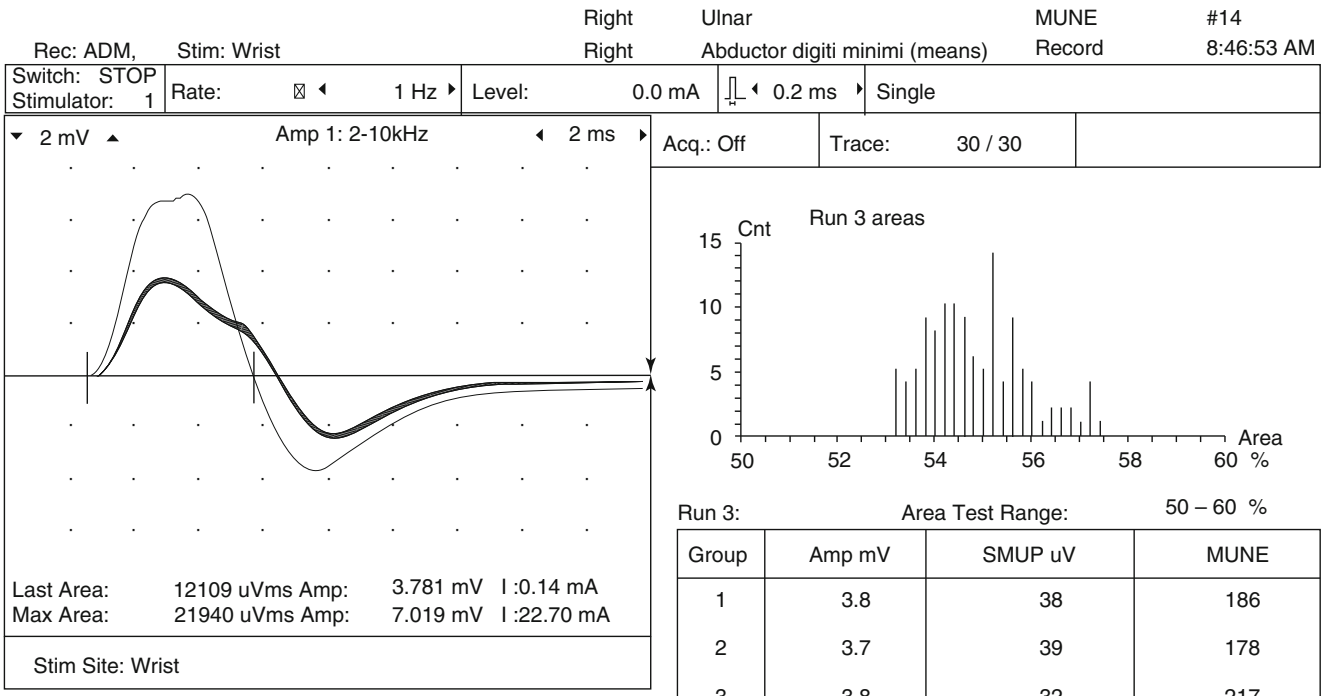


Fig. 9.23 In (**a**), EMG signals are recorded simultaneously using a surface and an intramuscular needle electrode. The needle EMG signals are used to identify and trigger from a single MU discharges (**b**). The time-locked and delayed surface EMG signals are averaged to obtain the MUAP (**c**). This procedure is similar to the macro EMG recordings

combinations, alternation can be resolved [84]. Needless to say, this requires special analysis and software.

In the *multipoint stimulation (MPS) method*, the stimulus intensity is increased to identify only the first stimulated MU (Fig. 9.22a, b) [85]. This allows one to avoid the technical pitfalls of the incremental stimulation method. The stimulator is then placed at a different position along the nerve to record another SMUAP and so on (Fig. 9.22c). It may be possible to get perhaps two or three different SMUAPs from each stimulation site by careful comparison of the evoked responses (Fig. 9.21b). Many such derivatives of the MPS have been developed, e.g., motor unit number estimation based on stochastic activation (MUESA) [86] and adaptive MPS [87]. In another technique, the nerve is stimulated at submaximal intensity to record a few hundred F waves. Repeating F waves are considered to be individual SMUAPs [88].

SMUAPs may also be recorded without using electrical stimulation. In a two-channel recording technique, called *spike-triggered averaging (STA)* [89–91], an intramuscular needle electrode is used to identify activity from a single MU (Fig. 9.23). This is used to trigger the display sweep and the averager. The delayed surface EMG signals are averaged to obtain the SMUAP. The position of the needle is



Est. Mune: 114 waSMUP(uV); 61

All Runs: MUNE(tested+untested) = 172

Run	N	Level %	SMUP uV	MUNE
1	270	22–30	78± 8	8
2	180	35–45	67± 7	10
3	120	53–57	37± 2	8
4				
	570	23%tested	61± 12	26
	None	77% untested	37	146

Run 3: Area Test Range: 50 – 60 %

Group	Amp mV	SMUP uV	MUNE
1	3.8	38	186
2	3.7	39	178
3	3.8	32	217
4	3.8	39	181
5			
6			
7			
8			
9			
10			
Avg:	3.8	37± 2	189

Fig. 9.24 Signals recorded from the hypothenar muscle at submaximal stimulus intensity demonstrate variability of amplitude. Responses from 30 stimuli are superimposed (*top left*). The largest amplitude signal is the compound muscle action potential. The area distribution from 120 stimuli (i.e., 4 runs) is shown as histogram (*top right*). The variability is used to estimate the mean MUAP amplitude and hence estimate the MU count (Table in *bottom right*). The results of three such runs are shown in the table in *bottom left*

then changed to record from another MU. The STA technique has been modified in several ways. Fang and coworkers used a separate surface electrode instead of the intramuscular needle to identify individual MU activity [92]. DeKoning et al. used the macro electrode instead of surface electrodes for the recordings [93]. Stein and Yang measured the force generated by the MU and the muscles to estimate the MU count [94].

Other than the incremental stimulation technique, all methods record individual SMUAPs. When two SMUAPs are summated, the amplitude of this combined SMUAP is less than the sum of their individual SMUAP amplitudes. This results from phase cancellation of their SMUAP waveforms. In other words, a MU contributes less amplitude to the final CMAP amplitude than its individual SMUAP amplitude recorded by the above techniques. Using an averaged SMUAP amplitude gives a smaller MU count. To include phase cancellation, one may summate the waveforms by aligning them at their onset point. The amplitude of the resulting response is divided by the number of constituent SMUAPs to estimate a "phase-corrected" SMUAP amplitude [88]. This adjusted calculation is then used for MUNE. It is important to recognize that individual SMUAPs have different latencies within the CMAP. In the neural network-based method, the CMAP is synthesized by summating the SMUAPs by offsetting their onset points. The number of SMUAPs required for the synthesis of the CMAP is the MUNE [92].

At submaximal intensity, some axons may not depolarize with each stimulus. As a result the evoked response varies

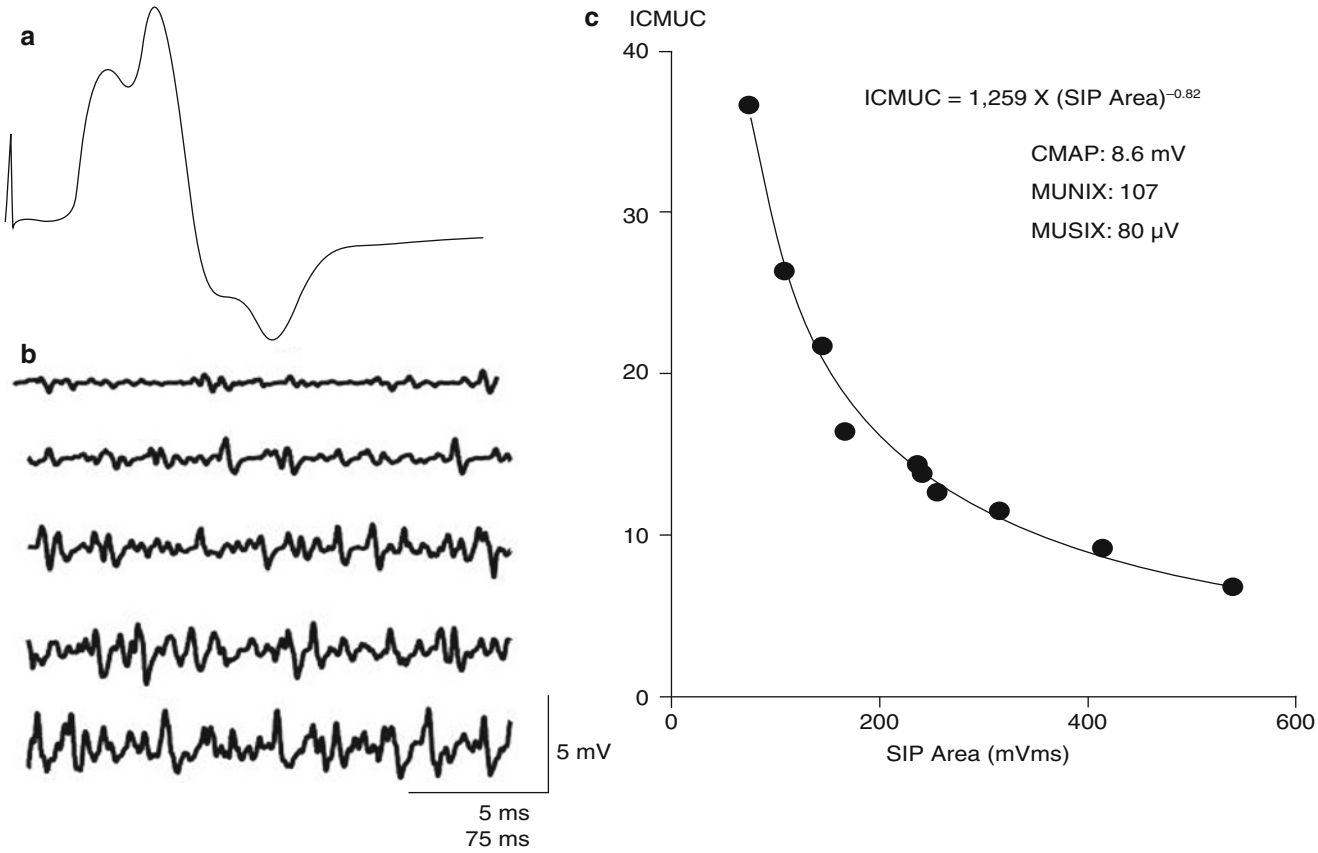


Fig. 9.25 The MUNIX method is illustrated with recordings from a healthy subject. The abductor digiti muscle was tested. (**a**) CMAP, (**b**) SIP at different force levels. Only 5 of 10 recordings are shown. (**c**) The data is analyzed to compute MUNIX and MUSIX

from one discharge to another (Fig. 9.24). Daube assumed a Poisson distribution for the number of stimulated axons at submaximal intensity [95]. The nerve is stimulated 30 times at submaximal intensity. Collectively, the 30 responses are called a "group." The variance of the evoked response amplitude (or area) is used to estimate the individual SMUAP amplitude (or area). The technique does not give individual SMUAP waveforms. The number of MUs is estimated. The process is then repeated until the coefficient of variation of MUNE from the groups is less than 10 % or ten groups are acquired (Fig. 9.24, Table in bottom right). This completes a run at the selected level of stimulation. One may perform additional runs by using another stimulus intensity level (Fig. 9.24, Table in bottom left). Shefner and coworkers have modified the technique by combining the results from the different runs. This increased the reproducibility of the technique [96].

Motor unit number index (MUNIX) is a newer technique that computes an index which reflects the number of motor units [97]. The CMAP is recorded using the standard nerve conduction methods (Fig. 9.25a). The same electrodes are used to record the surface EMG interference pattern (SIP) at different isometric force levels ranging from slight to maximum (Fig. 9.25b). A mathematical model is used to compute MUNIX as follows. First, the so-called ideal case motor unit count (ICMUC) is computed for each SIP signal by the following formula:

$$\text{ICMUC} = (\text{CMAP power} / \text{CMAP area}) \times (\text{SIP area} / \text{SIP power})$$

Next, the relationship between ICMUC and SIP area (used as in indicator of force) is modeled by a power regression as below:

$$\text{ICMUC} = A \times (\text{SIP area})\alpha$$

In Fig. 9.25c, each data points shows the area and ICMUC value for each SIP epoch. The solid line shows the power regression line. It shows a very good fit to the data. Once the parameters A and α are computed from the recordings, MUNIX is computed as

$$\text{MUNIX} = A \times (20)\alpha$$

The "motor unit size index (MUSIX)" is computed by dividing MUNIX in to the CMAP amplitude. It is an estimate of average surface-recorded motor unit potential amplitude

Table 9.6 The MUNE findings in different muscles of normal subjects and patients with neurogenic diseases are summarized

Muscle	Group	Technique	Age	# Subjects	MUNE	Reference
Ext dig brev	Control	Incr stim	–	151	210±65	McComas [80]
			–	39	197±49	Ballantyne et al. [84]
		STA	–	6	87	Nandedkar et al. [91]
		MUESA	–	23	84±37	Slawnych et al. [86]
	Polio	MUESA	–	42	35±34	
	ALS	Incr stim	–	21	42±37	Armon et al. [99]
Thenar	Control	Incr stim	–	115	342±89	McComas [80]
		Incr stim	–	10	170±62	Stein and Yang [94]
		STA (force)	–	10	130±39	
		STA	–	10	135±27	
		MUESA	–	29	107±55	Slawnych et al. [86]
		F wave	33±11	18	287±103	Stashuk et al. [88]
		F wave	68±3	15	195±34	
		MPS	–	33	219±77	
		AMPS	19–39	24	353±120	Wang et al. [87]
		AMPS	41–58	18	258±64	
		AMPS	60–87	17	194±74	
		F wave	–	54	253±107	
		Neural net	–	5	222±98	Fang et al. [92]
	ALS (baseline)	MPS	36–76	21	57±50	Felice [100]
	ALS (baseline) (1 year later)	MPS	37–77	21	19±20	
	ALS	Incr stim	–	21	40±52	Armon et al. [99]
	Polio	MUESA	–	41	55±50	Slawnych et al. [86]
	Spinal cord injury	Incr stim	–	12	63±11	Yang et al. [101]
Biceps	Control	STA	<60	30	911±254	Brown et al. [90]
		STA	>60	10	479±220	

Table 9.7 The number of estimated MUs, using the statistical method of Daube, is summarized

Level	Median-thenar	Ulnar-hypothenar	Peroneal-EDB	Tibial-abductor hall
5–10 %	210/90	285/105	154/52	310/195
15–20 %	185/85	223/110	137/45	250/167
40–50 %	153/70	154/70	135/38	195/154
70–90 %	175/85	213/115	105/35	202/115
Multipoint	234/95	256/115	158/58	285/187

Data from Daube [95]
The level represents the evoked potential as a percentage of the compound muscle action potential at supramaximal stimulation. Each cell of the table shows mean/minimum normal MU count. Note the higher number of MUs estimated at low level of stimulation

which reflects MU size. In Fig. 9.25c, the MUNIX is 108 and MUSIX is 87 μV.

Findings in Normal Subjects and Patients with Neuromuscular Diseases

McComas and coworkers investigated the MU count in the extensor digitorum brevis muscle and reported a mean count of 210 MUs in healthy subjects [80]. In normal healthy subjects, the MU count was reduced and attributed to the normal aging. In patients with neurogenic diseases, the MU count was reduced, as expected. Surprisingly, they also found a reduced MU count in patients with muscular dystrophy. This led them to propose a neurogenic basis for muscular dystrophy [80]. Panayotopoulos and coworkers demonstrated that small MUs may be missed in the incremental stimulation method [98]. This in turn would yield a reduced MU count in dystrophy. While neurogenic processes may be seen in patients with dystrophy, the primary disease process is still consistent with a myopathic process.

The aforementioned MUNE techniques have been used primarily to study healthy subjects and patients with neurogenic diseases [83–97, 99–103]. The findings are summarized in Tables 9.6, 9.7, and 9.8. The data in healthy subjects shows significant difference among estimates made by

Table 9.8 MUNIX and MUSIX values in healthy subjects. The 5–95 % range is shown

Muscle	MUNIX	MUSIX (μV)
Abductor pollicis brevis (thenar)	78–247	44–92
Abductor digiti minimi (hypothenar)	95–242	48–98
Biceps	83–293	37–50
Tibialis anterior	69–195	39–63
Abductor hallucis	69–420	42–121

Adapted from Neuwirth et al. [103]

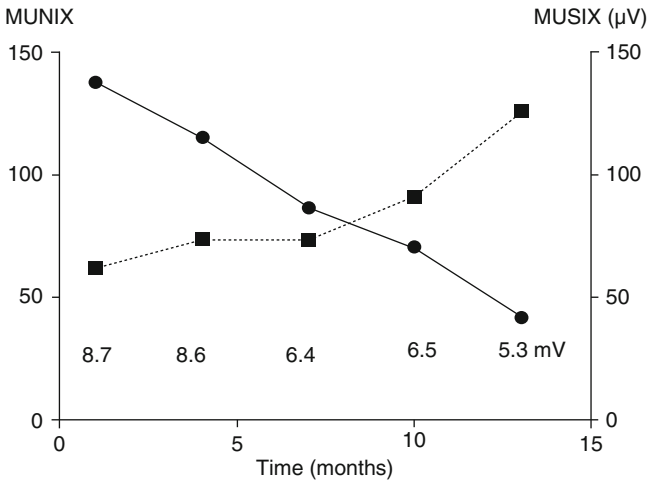


Fig. 9.26 Serial MUNIX studies in a patient with amyotrophic lateral sclerosis. The MUNIX and MUSIX are plotted against time. The CMAP amplitude is also listed for each study. The MUNIX decreased more than CMAP amplitude indicating disease progression

different techniques. In the statistical method, the estimates also depend on the choice of stimulation range (Table 9.7). In general, the number of motor units is slightly reduced in older subjects. In patients with neuropathy, the number of motor units is reduced depending on the severity of the disease. A serial MUNIX study demonstrates the process of MU loss and reinnervation (Fig. 9.26). In this patient, the MUNIX decreased by 70 % over the study period. Due to reinnervation, the MUSIX almost doubled. However, reinnervation of all denervated muscle fibers was not possible, and hence, the CMAP amplitude decreased by 30 %.

Limitations of MUNE

Perhaps the development of so many techniques of MUNE has occurred due to inherent limitations and pitfalls of each method. We have already considered the problems with small SMUAPs and alternation phenomenon with the incremental stimulation method. The multipoint stimulation technique and its derivatives can be tedious to acquire a large sample of SMUAPs. Furthermore, it does not adequately account for phase cancellation of the SMUAPs comprising the CMAP. The statistical method uses variability in the signal for analysis. When variations occur due to abnormalities of neuromuscular transmission, the MUNE values may remain high and normal despite MU loss. In general, stimulation-based methods for SMUAP recognition are limited to muscles where the nerve supplying the muscle is easily accessible for repeated stimulation, e.g., distal hand and foot muscles. Large proximal muscles have not yet been studied extensively using these methods.

SMUAP identification based on needle EMG recordings is conceptually simple. It can be performed in any muscle as long as a CMAP can be recorded, e.g., large proximal muscles. On the negative side, it is invasive and also fails to account for phase cancellation. The techniques based on multichannel surface recordings are noninvasive [92], but the neural network algorithm for MUNE is not readily available. The MUNIX method is being tested for proximal and distal muscles [103]. It requires very little time to perform. But it does require patient cooperation. Furthermore, it is not very intuitive. Many MUNE methods are not commercially available and not automated. This makes the technique time consuming.

The surface electrodes record mainly from the fibers that are within 2 cm of the skin surface [104]. This is sufficient to include small muscles such as the thenar, hypothenar, and extensor digitorum brevis muscles. However, in large muscles, like the biceps, the electrode records much smaller SMUAPs amplitudes from deeper MUs. This perhaps explains the larger MUSIX in distal hand muscles (Table 9.8). Using the deep MUs to estimate SMUAP in the spike-triggered averaging method will give a much higher MU count.

Finally, all methods are based on recording the CMAP [105]. Any variability in CMAP can affect the MUNE, the MU size estimation, or both. To assess the disease progression, it is necessary to study the MUNE and MU size together (e.g., Fig. 9.26). In serial studies, changes in CMAP due to technical factors, e.g., electrode placement, electrode size and geometry, skin temperature over the studied muscle, and limb and digit position (i.e., MF length), may affect results [106]. Therefore, in our serial MUNIX studies, we always display the recordings from previous and current investigation in superimposed manner at the time of the study. This is not possible on many commercially available systems. In demyelinating diseases, some axons may require very high stimulus intensity for depolarization. If one fails to excite them, the CMAP is underestimated. This may result a reduced MU count.

Clinical Utility

The MUNE is of interest mainly in patients with neurogenic disorders. It is hoped that MUNE will be useful to study

disease progression in degenerative diseases like amyotrophic lateral sclerosis. That could allow one to utilize MUNE as a surrogate marker in studying the effectiveness of the new therapies. However, at this point of time, MUNE methods remain mainly in the research domain. Currently, the loss of MUs is assessed indirectly in the routine electrodiagnostic studies, e.g., from reduced pattern at maximal effort (Fig. 9.14).

Other EMG Techniques

The MU architecture and resultant remodeling in neuromuscular diseases may also be studied using special techniques, such as single-fiber EMG (SFEMG) and macro EMG. The fiber density measurements on SFEMG are most sensitive in detecting reinnervation changes. Jitter analysis is most sensitive in demonstrating abnormalities of the neuromuscular junction. SFEMG is very nonspecific since jitter abnormalities may be found in a variety of neuromuscular diseases [107]. Macro EMG electrode records from the entire MU. Hence, macro MUAP amplitude and area depend on the MU size. They demonstrate increased MU size in patients with neuropathy. In patients with myopathy, MU size is normal or reduced [12]. Thus, macro EMG may be used for differentiating between myopathic and neurogenic disease processes. However, it is diagnostically less sensitive than other methods, reflecting the lesser selectivity of this electrode. While the macro electrode records from the entire MU, the SFEMG electrode records mainly from MFs that are within 300 μm of the recording electrode. This makes it the most selective of readily available recording electrodes. As described in Fig. 9.9, concentric and monopolar electrodes have an intermediate uptake area (and thus intermediate selectivity). This is a fortuitous coincidence which offers the sensitivity and specificity that enhances and is needed in clinical electrodiagnosis. By combining these different techniques, we can better understand the pathophysiology and progression of neuromuscular diseases [39, 44, 108].

Using Quantitative Analysis

Quantitative analysis in needle EMG examination is not performed in many clinical EMG laboratories. This is largely due to the time required for the study, availability of reference values, diagnostic sensitivity and specificity, special instrumentation, etc. We agree that every patient does not need quantitative analysis. But knowledge, understanding, and skills used for quantitation can be used in the routine EMG examination performed in every patient. This is particularly useful when the signals have atypical characteristics. We will illustrate this using two examples.

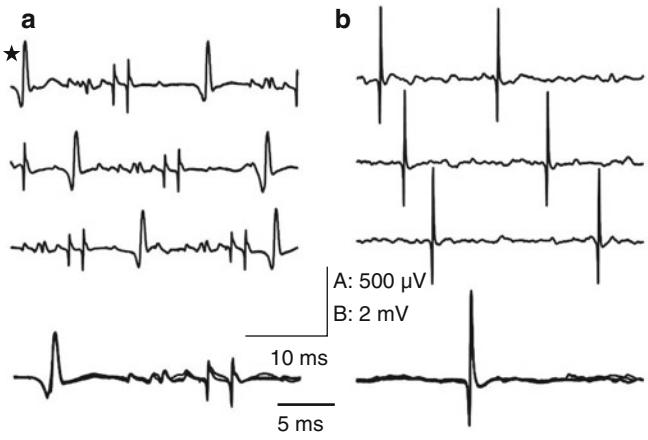


Fig. 9.27 Atypical MUP recordings in (**a**) neuropathy and (**b**) myopathy. In (**a**), discharges of a complex potential give appearance of increased recruitment. In (**b**), large amplitude fast-firing MUAP suggests possibility of a neurogenic disease. Note the different amplitude calibrations in (**a** and **b**). Also the sweep speed is different for free-running versus triggered sweeps. See text for details

The signals recorded, using a free-running sweep, are shown in the top portion of Fig. 9.27a. The subject was exerting low force of contraction. By a quick glance, one can see several small MUAPs in this signal that suggests "early" recruitment as seen in myopathy. However, the sound of the EMG signal was not what one would expect from discharges of multiple MUs. It sounded more like a complex repetitive discharge. The signal was, however, not generated spontaneously. When the amplitude trigger and delay line were used, we find that the signal contains discharges of a single, long-duration, complex MUAP with linked potentials. Polyphasic potentials are nonspecific abnormality as they can be seen in patients with myopathy and neuropathy. Next, we recognized that the potential appears twice on each sweep. This is easily seen by following one part of the potential marked by an asterisk on the top trace. The sweep duration is 100 ms. The two discharge per sweep give this potential a firing rate of roughly 20 Hz. There is no other active MU. Hence, this represents reduced recruitment. The polyphasic MUAP waveform can be due to reinnervation. Therefore, we feel quite comfortable in considering this as evidence of a neurogenic process.

The signals in the free-running display of Fig. 9.27b also have a MUAP discharging at 20 Hz. There appears to be no other MU activity. Finally, the amplitude of this MUAP is increased compared to normal. This appears to suggest a neurogenic abnormality. However, the MUAP appears very thin (i.e., lack of expected area or "thickness" in the main spike). Using trigger and delay line, one can demonstrate that it has a very short duration (less than 5 ms). This reduced duration is specific for myopathy. Note that the display setting is 2 mV/div. At this instrument setting, smaller amplitude MUAPs may not be visually detected. If there were no other MUAPs, the baseline would be smooth. But the "rough"

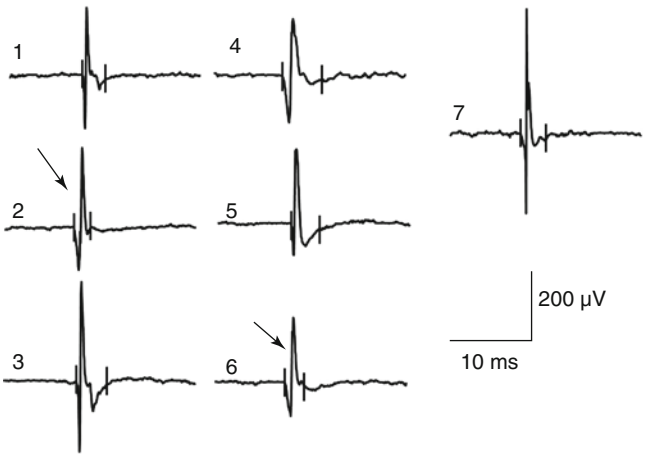


Fig. 9.28 Multi-MUP analysis is used to document short-duration MUPs in a patient with myopathy. *Arrows* indicate MUAPs with reduced duration, i.e., outliers

baseline seen, however, indicates that there are low-amplitude MUAPs. Indeed, smaller amplitude MUAPs are more easily seen when the display sensitivity is changed to the customary 100 μV/div setting for analysis. Such high MUAP amplitude can occur if the recording electrode is close to a hypertrophic MF (Table 9.4). Therefore, this atypical MUAP signal is still consistent with myopathy.

The modern multi-motor unit analysis or decomposition methods are very fast. One can easily acquire over 25 MUAPs in less than 5 min. A single 5–10 s epoch is analyzed in a fraction of a second. Therefore, these algorithms can also be used to document abnormal waveforms. Figure 9.28 shows 7 MUPs recorded from two different sites in the vastus lateralis muscle. The short duration is recognized quite easily. The waveform looks "thin." The MUAPs with duration less than 5 ms are indicated by the arrows. Note that these MUAPs are abnormal using the limits shown in Table 9.3. The process of analysis added only a minute or two to the examination, and it provided very objective evidence of abnormality.

Single-fiber EMG is the most sensitive test to detect abnormalities of neuromuscular transmission. When jitter is significantly increased and there is blocking, one can also visualize this as a variable MUAP waveform on routine EMG study. One can demonstrate this quite easily using the trigger and delay line and enhancing it by increasing the low-frequency filter to single-fiber EMG settings (e.g., 500 or 1,000 Hz) (Fig. 9.6). When unstable potentials are found on the routine EMG examination in a patient suspected of a neuromuscular junction disease, SFEMG jitter analysis may not add much for diagnosis. After one has experienced the audio quality of increased jitter on SFEMG, one becomes more sensitive to the sound of an unstable MUAP at both routine and increased low-frequency filter settings. In patients with neuropathy, unstable potentials indicate ongoing compensatory reinnervation which is a good sign for recovery.

Quantitative analysis may be useful for monitoring diseases [109]. New methods are being developed to quantify severity of the disease using combined analysis of many different MUAP measurements [110, 111]. Serial MUAP studies show decrease in CN MUAP duration and also the macro EMG amplitude [44]. SFEMG jitter may be used to follow patients with neuromuscular junction diseases [107]. Macro EMG MUAPs may be used to follow changes in MU size in neurogenic diseases [39]. MUNE can be used to study the MU loss and compensatory reinnervation [81, 102]. The MU size and the MU count may be used to define the exercise program for patients with old poliomyelitis [112].

Quantitative analysis measures many different features of the EMG signal, e.g., amplitude, duration, and phases. The normal limits of each feature are defined such that there is only a slight chance (often <2–3 %) that the measurements in healthy subjects are outside the normal range. As more and more measurements are made, there is a greater chance that at least one feature has abnormal values. This occurs not due to pathology but due to inherent statistical analysis. Therefore, one should not overestimate isolated mild abnormalities. Having marked abnormalities on a specific feature (e.g. duration) and/or abnormalities on two or more features is more consistent with a pathologic muscle [113].

Each laboratory should develop its own reference values. This is not always possible. When using published reference values [17, 114], the examiner should perform studies in a few healthy subjects to confirm their suitability and reproducibility for their particular laboratory. Attention should also be paid to instrumentation and accessories. As example, the so-called facial needle electrode is used extensively in routine EMG examination since it has a smaller diameter and may cause less pain. However, this electrode also has a smaller recording surface. Hence, it tends to record slightly higher amplitude MUAPs compared to the longer needle electrodes with slightly larger diameter [115]. Furthermore, its length limits the evaluation of larger muscles or in large individuals.

Conclusion

The shape of the MUAP depends on the MU architecture. The MUAP features give complementary information about remodeling of the MU due to disease processes. MU firing rate is useful to study loss of MUs and upper motor neuron lesions. IP analysis gives information about the number of MUs and their waveforms. It also allows the study of high force threshold MUs. Collectively, these techniques offer useful information about the underlying disease processes. By understanding and including quantitative EMG techniques and principles in the routine EMG examination, we may better document abnormalities and extract more information about the severity, duration, activity, and prognosis of the disease. MUNE

techniques are an exciting development in electrophysiologic testing. However, these methods are in an evolutionary stage. When the MUNE techniques are improved, they may be of great value in monitoring disease progression. While quantitative analysis of the EMG signals may appear esoteric and time consuming, it is nevertheless critical to understand their principles in order to perform competent routine EMG.

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Testing of Autonomic Function

10

Kamal R. Chémali and Thomas C. Chelimsky

Introduction

In recent years, objective testing of the autonomic nervous system (ANS) has acquired a new dimension. After being generally underrecognized, disorders of the ANS now constitute a major component of neurological dysfunction and neuromuscular diseases in particular. For example, peripheral neuropathy due to diabetes mellitus (DM), which accounts for a large number of neuromuscular consultations, is frequently associated with dysautonomia. Several recent studies concluded that diabetic cardiac autonomic neuropathy contributes to arrhythmia or silent myocardial infarction and is the major predictor of death ahead of coronary artery disease and by far outweighing the prognostic value of the somatic peripheral neuropathy [1–5]. One study established a correlation between the presence of ANS dysfunction and a poor response of DM to insulin treatment [6]. These reports led several experts to argue for a systematic detection of dysautonomia in DM through the use of autonomic testing [7]. Furthermore, in nondiabetic patients who suffered a myocardial infarction, decrease in heart rate variability increases arrhythmic complications and mortality [8]. A large prospective long-term study demonstrated the value of markers of cardiac autonomic tone in identifying infarct survivors at risk for malignant ventricular tachyarrhythmias and sudden death [9]. As much as large (myelinated) fiber neuropathy is well detected by conventional electrodiagnostic studies and electromyography [10], small-fiber (unmyelinated or thinly myelinated) neuropathy often cannot be detected by this technique [11] and requires autonomic testing for diagnosis [12]. Thus, the unique early involvement of small fibers in diabetic peripheral neuropathy cannot translate into early diagnosis without the help of the autonomic laboratory.

Since autonomic dysfunction may remain asymptomatic for a long period of time, it is of utmost importance not only to test the ANS qualitatively, i.e., to determine whether autonomic dysfunction is present or absent, but also to quantitate the deficit and to localize the site of the lesion within the ANS. With this perspective, testing the ANS becomes an indispensable part of the evaluation of many secondary neuromuscular diseases but also of primary diseases affecting the peripheral nervous system where dysautonomia or distal pain is a major component of the clinical picture.

Autonomic testing, alone or in combination with other tests such as skin biopsy, should ideally be able to (1) establish the presence or absence of small-fiber involvement in the diagnosis of a neuropathy, distinguish subtypes of neuropathy (e.g., pandysautonomic, cholinergic, adrenergic, or sympathetic), and localize the process as pre- or postganglionic; (2) assess cardiovascular risk factors associated with certain disorders, such as in DM, and evaluate the risk for syncope and sudden death; (3) diagnose syndromic or central autonomic disorders such as the postural orthostatic tachycardia syndrome (POTS), multiple system atrophy, or diffuse Lewy body disease (presenting with isolated end-organ failure, such as impotence, constipation, incontinence, or orthostasis); and (4) delineate the role of the ANS in focal disorders associated with pain as seen in the complex regional pain syndrome (CRPS) also referred to as reflex sympathetic dystrophy.

Basic Principles and Anatomy

Autonomic homeostasis depends on a state of equilibrium between the effects of the two major components of the ANS, the parasympathetic nervous system (PSNS) and sympathetic nervous system (SNS), upon the organs they innervate.

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Since each of these systems follows a separate well-defined pathway, little, if any, neuronal interaction occurs between them. Rather, their competitive antagonism occurs at the level of the effector organs. Therefore, most autonomic tests aim at monitoring the response of the effector organ to different maneuvers or stimuli. Test combinations should be selected for optimal dissection of the ANS into its different components and evaluation of as many of its branches as possible. In focal disorders, testing the ANS also allows more precise localization of the geographic distribution of the autonomic disturbance and the site of the lesion.

Basic Anatomy of the Autonomic Nervous System

Every neural system, however simple or complex, comprises of an input (the afferent limb), some decision-making component (an integrator), and an output (the efferent limb). For autonomic function, the afferent limb consists of information regarding the state of the particular end organ of interest conveyed through visceral afferent nerve fibers. This portion of the circuit is often not termed "autonomic" but rather "visceral afferent." Strictly speaking, according to this framework, the autonomic system begins with the central nervous system (CNS) integrators, and proceeds outward, to include the efferent connections, classically divided into parasympathetic and sympathetic branches. The two branches differ in the site at which the signal exits the CNS; the parasympathetic branch is craniosacral, while the sympathetic is thoracolumbar. Acetylcholine activates nicotinic receptors at the ganglia for both systems. The postganglionic segment innervates the end organ through a cholinergic muscarinic connection for the parasympathetic branch and a noradrenergic connection for the sympathetic branch.

The Parasympathetic Nervous System

General Concepts

The PSNS is responsible for maintenance of homeostasis when the organism is at rest. The PSNS is divided into two major segments: preganglionic and postganglionic. The preganglionic segment refers to first-order neurons whose cell bodies lie in the CNS. This includes the brainstem nuclei, such as the Edinger-Westphal nucleus, the salivary nucleus, the dorsal motor nucleus, and the nucleus ambiguus, and the ventral horns and intermediolateral columns of the sacral segments (S2–S4) of the spinal cord. The cranial preganglionic axons travel along cranial nerves III, VII, IX, and X and synapse in parasympathetic (PS) ganglia, in the vicinity or within the target organs, with short second-order neurons that innervate these organs. The sacral preganglionic axons travel with the pelvic nerve to the inferior hypogastric plexus. Most synapse on PS ganglia within the target organs and some on neurons in the myenteric and submucosal plexuses of the enteric nervous system, also with short second-order neurons.

Parasympathetic Ganglia and Effector Organs

Preganglionic fibers arising from the brainstem synapse in the following PS ganglia (Fig. 10.1):

- The *ciliary ganglion* receives PS fibers arising within the Edinger-Westphal nucleus in the midbrain and traveling with the oculomotor nerve (III). Postganglionic fibers innervate the pupillary constrictor and ciliary muscle.
- The *pterygopalatine ganglion* receives PS fibers arising within the lacrimal nucleus in the pons and traveling with the facial nerve (VII). Postganglionic fibers innervate lacrimal glands and palatal, pharyngeal, and nasal mucous glands.
- The *submandibular ganglion* receives PS fibers arising within the salivary nucleus in the pons and traveling with the facial nerve. Postganglionic axons innervate submandibular and sublingual glands and mucous glands of the oral cavity.
- The *otic ganglion* receives PS fibers arising in the inferior salivary nucleus in the medulla and traveling with the glossopharyngeal nerve (IX). Postganglionic fibers innervate the parotid glands and mucous glands of the oral cavity.
- The *visceral ganglia* receive PS fibers arising in the dorsal motor nucleus of X and nucleus ambiguus in the medulla and traveling with the vagus nerve (X). Postganglionic fibers innervate the bronchi and lungs, the heart, the gastrointestinal tract from the esophagus to the descending colon, the liver, the gallbladder, the pancreas, the kidneys, and the intestines.
- Fibers arising from the *sacral spinal cord* (*S2–S4*) travel with the pelvic nerve and synapse in the pelvic plexus (inferior hypogastric), where pre- and postganglionic sympathetic and parasympathetic fibers intermingle. Postganglionic fibers innervate the bladder, descending colon, rectum, and genitalia.

The enteric nervous system, which innervates the gastrointestinal tract, pancreas, and gallbladder, is considered a third and separate division of the ANS [13–16]. Its neurons are interconnected in a complex meshwork forming two major plexuses: the myenteric (Auerbach's) plexus and the submucous (Meissner's) plexus. This system is particularly sensitive to fluctuations of the chemical environment of the gut and to variations in the tension of the gut wall and reacts autonomously to establish homeostasis. However, even though this system can act independently, it is largely controlled by CNS reflexes through both the PSNS and the SNS [13].

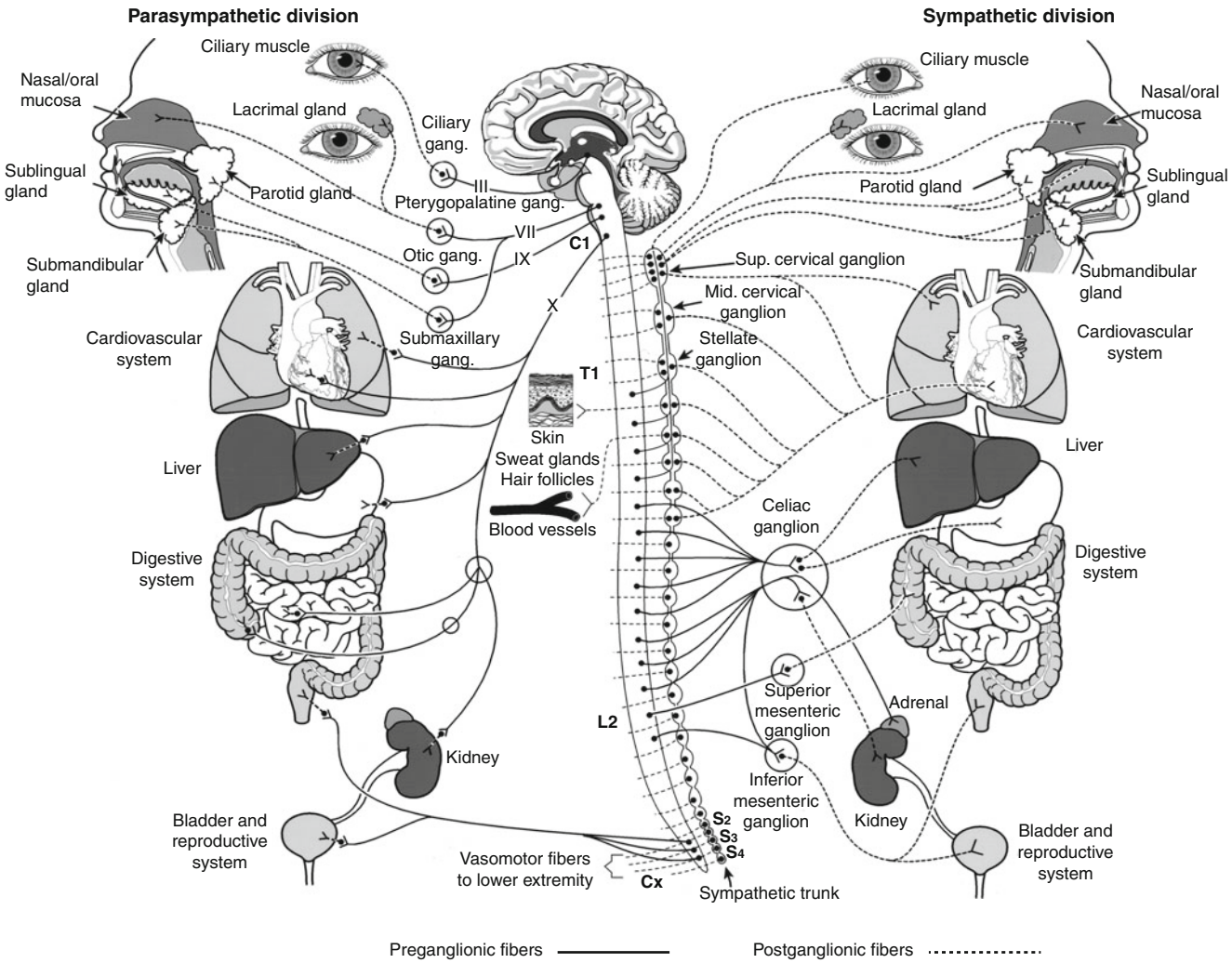

Fig. 10.1 The efferent parasympathetic and sympathetic autonomic systems (Copyright Cleveland Clinic foundation 1999)

The Sympathetic Nervous System

This division of the ANS is mainly responsible for the reestablishment of homeostasis, disturbed by exposure of the organism to external challenges and stimuli. As the PSNS, it arises in the CNS and makes its way to the periphery to innervate target organs. It is also divided into preganglionic and postganglionic compartments.

The sympathetic fibers originate from the hypothalamus, which may be divided into three functional zones: periventricular, medial, and lateral. Each of these zones is formed of nuclei which give rise to neurons that project to autonomic centers in the brainstem: the periaqueductal gray matter in the midbrain, the parabrachial region in the pons, and the intermediate reticular formation of the medulla (ventrolateral medulla). Projections from these structures terminate primarily in the sympathetic preganglionic neurons located in the T1–L2 segments of the intermediolateral cell column of the spinal cord (lamina VII) [17]. These neurons have short myelinated axons that leave the spinal cord through the ventral roots and exit, close to where the ventral root meets the dorsal root to form the spinal nerve, via white rami communicantes to project to the 22 pairs of paravertebral sympathetic trunk ganglia which lie close and parallel to the vertebral column (Figs. 10.1 and 10.2). Here, the preganglionic axons synapse with postganglionic neurons whose long unmyelinated axons travel through gray rami communicantes and join the ventral ramus where they travel along peripheral spinal nerves and innervate target organs (Fig. 10.2). Some preganglionic fibers pass through the paravertebral sympathetic ganglia and branches of the splanchnic nerves to synapse on neurons of the prevertebral (or collateral) ganglia, which include the coeliac ganglion and the superior and inferior mesenteric ganglia. These ganglia innervate the gastrointestinal system and other abdominal organs such as the kidneys, pancreas, and liver. They also provide the major sympathetic innervation to the bladder and external genitalia [16]. One exception is the adrenal medulla, which receives

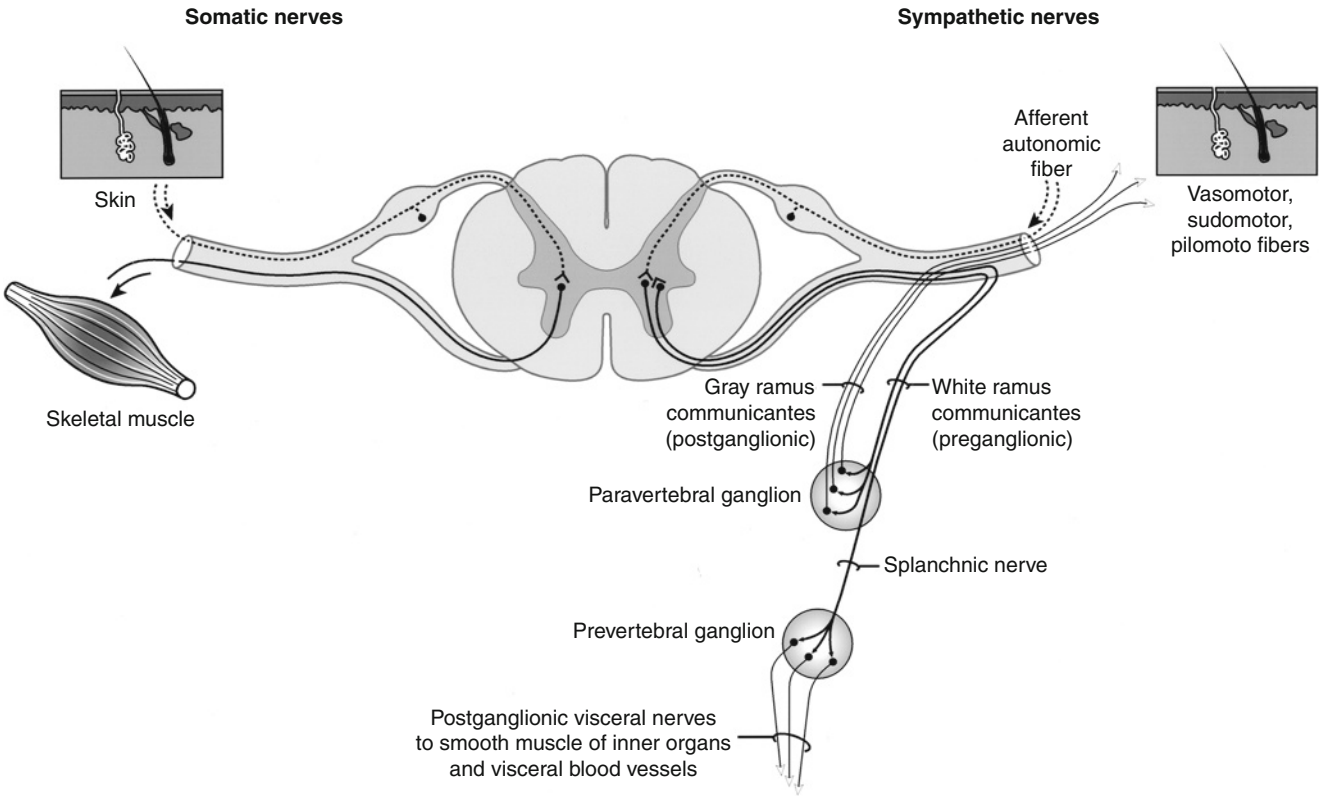

Fig. 10.2 The course of the sympathetic outflow fibers from the spinal cord and roots

only preganglionic fibers, with the medulla being equivalent to a ganglion. Although there is a lot of cross-innervation, it would be fair to presume that fibers originating from T1 segment innervate the head, fibers from T2 the neck, fibers from T3 to T6 the thorax, fibers from T7 to T11 the abdomen, and fibers from T12, L1, and L2 the pelvis and the legs [18].

Cholinergic and Adrenergic Neurons

Acetylcholine is the neurotransmitter for all preganglionic neurons (sympathetic and parasympathetic) and for the parasympathetic postganglionic neurons. For practical purposes, one can simplify the system and conceive the ganglionic acetylcholine receptors as nicotinic and target organ cholinergic receptors as muscarinic, although, in reality, there is a mixture of both at each level. Norepinephrine (noradrenaline) is the transmitter in the postganglionic neurons of the sympathetic nervous system. One exception is sympathetic nerve fibers to the sweat glands, which display acetylcholine as a postganglionic transmitter. Dozens of peptides also modulate synaptic transmission at the autonomic ganglia or act as co-transmitters, but so far, these transmitters do not play a major role in autonomic testing. Some of the most important are substance P, which is mainly found in the intestine where it may play a role in the myenteric reflex. Vasoactive intestinal polypeptide (VIP) is concentrated in the sacral cord and other parts of the CNS and might be co-released with acetylcholine at cholinergic muscarinic junctions, while neuropeptide Y is co-released with norepinephrine. Somatostatin is released in the hypothalamus. Calcitonin gene-related peptide (CGRP) is widely distributed throughout the central, peripheral, and autonomic systems and seems to play a major role in non-cholinergic and non-adrenergic vasodilation [18].

Effects of the Autonomic Nervous System on Target Organs

Cardiovascular System

Activation of sympathetic nerves increases heart rate and contractility of the ventricles and the atria. It causes vasoconstriction of all blood vessels with the exception of some arteriovenous anastomoses in the skin and skeletal muscle vessels, which receive cholinergically mediated sympathetic vasodilators. Activation of the parasympathetic system decreases heart rate and contractility of the atrium only.

Sweat Glands

Sweat secretion is under the control of sympathetic postganglionic fibers with acetylcholine as principal terminal neurotransmitter. However, other neurotransmitters are localized in the periglandular nerves, including catecholamines

[19–22], VIP [23, 24], CGRP, atrial natriuretic peptide (ANF), galanin [25], oxytocin, and ATP [26, 27]. The exact role of these substances in sweat excretion is not fully understood.

Pupils

Activation of the peripheral sympathetic innervation of the radial smooth muscle of the pupil produces dilation of the pupil. Dilation also occurs by central inhibition of the Edinger-Westphal nucleus, via fibers originating from the posterior thalamus. The postganglionic nerves release norepinephrine on to alpha-adrenergic receptors on the dilator pupillae [28]. Constriction of the pupil occurs when it is exposed to light or with near vision. Both reflexes are mediated by the activation of parasympathetic preganglionic neurons whose cell bodies lie in the Edinger-Westphal nuclei. Because afferent impulses are carried to these nuclei by crossing fibers on both sides, illumination of one eye produces constriction of both pupils. Postganglionic nerves release acetylcholine and activate muscarinic receptors on the sphincter pupillae [28].

Bladder

Activation of the sympathetic fibers to the bladder is mediated by norepinephrine, which elicits relaxation of the detrusor muscle and contraction of the trigone, which includes the internal sphincter (bladder neck), and exerts primarily inhibitory effects on synaptic transmission in parasympathetic ganglia. Activation of the parasympathetic fibers utilizes acetylcholine, ATP, and NO as neurotransmitters. Acetylcholine promotes contraction of the detrusor muscle and inhibits release of norepinephrine from sympathetic terminals, ATP promotes bladder contraction, and NO elicits relaxation of the urethral smooth muscle [29].

Salivary Glands

Sympathetic activation produces only weak serous secretion of the submandibular gland, while parasympathetic activation produces copious serous secretions of all salivary glands.

Gastrointestinal System

Sympathetic activation decreases the motility of the gastrointestinal tract by inhibiting the contraction of the longitudinal and circular smooth muscles and causes contraction of the sphincters. In contrast, parasympathetic activation increases the motility of the gastrointestinal tract through the contraction of the longitudinal and circular muscles and relaxes the sphincters.

Autonomic Tests

Although many tests have been devised to assess autonomic function over the last 50 years, certain ones have retained utility, while others have faded. Both economic forces and simple expediency have led autonomic laboratories across the USA to increasingly adopt a fairly standard battery of tests. These include the cardiac response to deep breathing, Valsalva maneuver or handgrip, the cardiovascular response to tilt table test, and one of the several different ways to measure sweat function (axon reflex testing by capsule, direct sweat testing by capsule, thermoregulatory sweat testing, or sweat droplet quantitation using a Silastic imprint).

Testing the ANS in our laboratories includes the following: (1) a measure of cardiac parasympathetic function through the cardiac response to deep breathing; (2) a measure of cardiac sympathetic and parasympathetic functions as well as vasomotor sympathetic function through the Valsalva maneuver; (3) an analysis of the separate arteriomotor and venomotor systems through the tilt table test; (4) a quantitative axon reflex sweat testing (QSART), assessing postganglionic sympathetic cholinergic sudomotor function; and (5) the thermoregulatory sweat test (TST) which is recommended in situations where the first four tests provide ambiguous results. The three tests of cardiovascular function combined with one of the tests of sudomotor function form a commonly used and powerful screen of the ANS, because it evaluates four organ systems (cardiac, arteriomotor, venomotor, and sudomotor) and three physiologically distinct systems (sympathetic adrenergic, sympathetic cholinergic, and parasympathetic cholinergic) and assesses the risk for the most severe complication of autonomic dysfunction, syncope.

Pupillometry has come into greater use recently, as equipment now permits non-pharmacologic analysis of the function of the different ANS branches. This test holds promise, and the evolution of its use will eventually determine its role in autonomic testing.

Finally, direct quantitation of sudomotor fibers was made possible by the development of skin biopsy techniques, which demonstrate both somatic and autonomic sudomotor small-caliber unmyelinated C fibers.

From a practical perspective, interpretation of autonomic studies utilizes each of the tests in a specific way (Tables 10.1, 10.2, and 10.3). The three cardiovascular tests (heart rate variability to deep breathing, the Valsalva maneuver, and the tilt table test) provide a system view, determining which autonomic branches are affected, parasympathetic, sympathetic, or both. In contrast, the sudomotor tests provide information about neuraxis localization, both through the presence or absence of the QSART response and the pattern of the thermoregulatory sweat test (Table 10.3). Tilt table testing also assesses the risk of syncope. When assessing heart rate changes, and determining whether a particular effect is primarily sympathetic or parasympathetic, it should be kept in mind that the parasympathetic system (given a normal heart and sinus node) acts between the heart rates of 40 and 100 beats per minute (bpm), whereas the sympathetic system acts

Table 10.1 Neural pathways of autonomic reflexes

Test	Stimulus	Afferent limb	Central integrator	Efferent limb	Effector organ
Deep breathing	6 deep breaths during 1 min	Vagus nerve, baroreceptors, glossopharyngeal nerve	NTS; hypothalamus	Vagus nerve	Heart
Valsalva maneuver	Forceful (40 mmHg) expiration for 15 s	Glossopharyngeal and vagus nerves	NTS; hypothalamus	Vagus nerve; sympathetic efferents	Heart, blood vessels
Response to standing	Standing up from a supine position	Baroreceptor and muscle	NTS; hypothalamus	Vagus nerve; sympathetic efferents	Heart, blood vessels
Sustained handgrip	30 % of maximal handgrip power for 5 min	Muscle afferent; central command	Cortex; hypothalamus	Sympathetic efferents; vagus nerve	Blood vessels, heart
QSART	Acetylcholine iontophoresis	Axon of postganglionic sympathetic sudomotor nerve	None	Branching axon of postganglionic sudomotor nerve	Sweat glands
TST	Heat	Pre- and postganglionic sudomotor nerves, intermediolateral columns, bulbospinal pathways	Hypothalamus	Sympathetic efferents, pre- and postganglionic sudomotor fibers	Sweat glands
Pupillometry	Brief light	Optic nerve	Edinger-Westphal nucleus	Parasympathetic efferents within oculomotor nerve	Constrictor of the pupil

Modified from Low: Clinical Autonomic Disorders
NTS nucleus tractus solitarius, *QSART* quantitative sudomotor axon reflex test, *TST* hermoregulatory sweat test

Table 10.2 Specific information regarding particular autonomic functions derived from cardiovascular autonomic tests

	Parasympathetic cardiac	Sympathetic cardiac	Sympathetic arteriomotor	Sympathetic venomotor	Syncopal risk
Test 1	Cardiac response to *deep breathing* reduced for age	Blunted heart rate increase during *Valsalva phase II*	Diastolic BP drops with *tilt*	Pulse pressure drops *during tilt*	Mean BP < 70, or drops >70 mmHg *during tilt*
Test 2	Blunted heart rate reduction during *Valsalva phase IV*	Cardioacceleration during *tilt* blunted (if BP drops)	Diastolic BP drops with *Valsalva phase II*		BP drop accompanied by HR drop at *end of tilt* (vasodepressor syncope)

Table 10.3 Findings of sweat tests in autonomic disorders

Sweat test	Postganglionic lesion	Preganglionic lesion
Quantitative sudomotor axon reflex test (QSART)	Abnormal with distal > proximal reduction in sweat output	Normal
Thermoregulatory sweat test (TST)	Abnormal with peripheral (stocking-glove) pattern	Abnormal with central (reverse stocking-glove) pattern

between 85 and 160 bpm. Outside the overlap zone between 85 and 100 bpm, the particular branch responsible for an action is clear. In the low range, the parasympathetic system is excited or inhibited to reduce or increase heart rate, and in the high range, the sympathetic system is inhibited or excited for the same effects.

Assessment of the complex regional pain syndrome (CRPS) requires a search for asymmetry with the uninvolved limb, rather than a search for impaired function in comparison to established norms. As a guide in the diagnosis of CRPS, we utilize asymmetry in sudomotor nerve fibers and intraepidermal nerve fiber density on skin biopsy at the zones of maximal allodynia and at the exact contralateral areas of the uninvolved limb [30, 31], asymmetry in resting sweat output and QSART output across two sites in the affected limb compared to the unaffected limb, and asymmetry in resting skin temperature to assist in determining probable response to a sympathetic block [32].

Autonomic testing is indicated (1) to establish a specific ANS diagnosis, such as multiple system atrophy, autonomic neuropathy, or CRPS; (2) to determine whether the ANS is involved in a particular disorder and, thereby, guides the diagnostic process, such as in patients with polyneuropathy or polyradiculopathy of unknown cause, or with parkinsonism; (3) to assess the severity of dysautonomia in disorders known to have a predilection to involve the ANS, such as diabetes mellitus or multiple system atrophy; (4) to evaluate for the possibility of a generalized autonomic disorder in a patient presenting with single-organ failure, such as erectile or sphincteric dysfunction, gastroparesis, or orthostasis; (5) to assess the risk and mechanism of syncope; and (6) to establish the mechanism of orthostatic symptoms (e.g., venomotor vs. arteriomotor failure vs. non-autonomic) and guide management.

Tests of Sudomotor Function

Quantitative Sudomotor Axon Reflex Test

The quantitative sudomotor axon reflex test (QSART) evaluates the postganglionic sudomotor (sympathetic

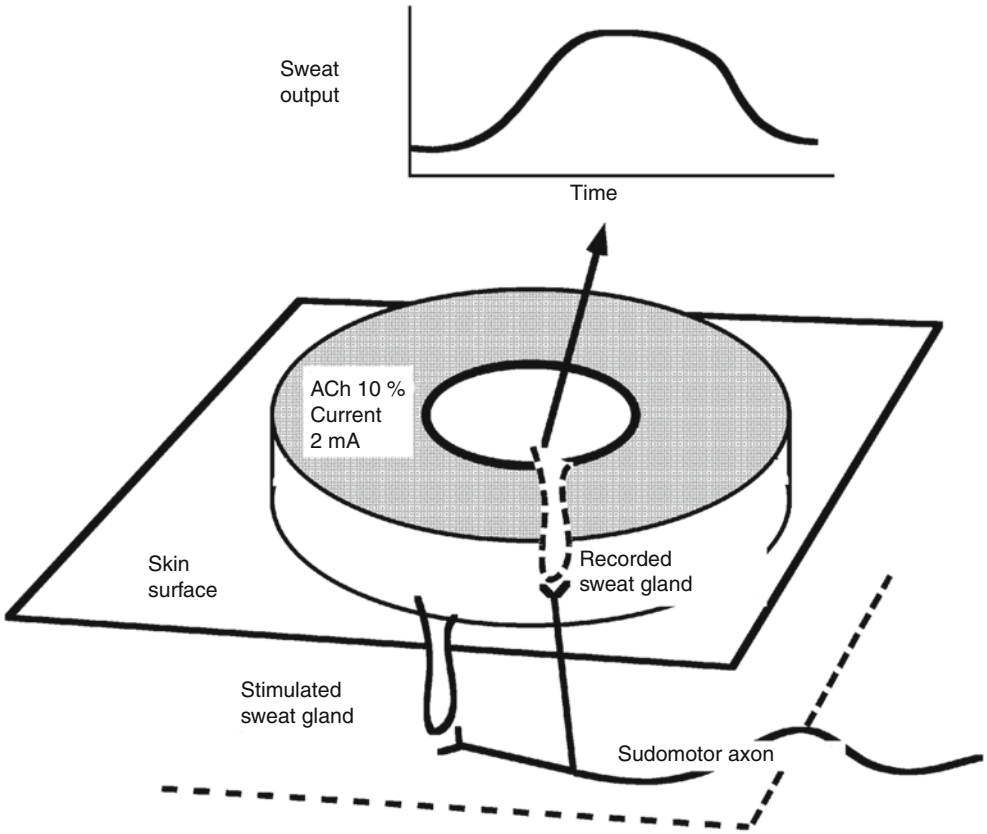

Fig. 10.3 Schematic view of axon reflex sweat test. Ten percent of acetylcholine is applied across the outer chamber of the capsule, stimulating a set of sweat glands, as shown. Sweat output is recorded from the central chamber

cholinergic) nerve fibers. As its name implies, it consists of stimulating the sudomotor nerve in one location and recording the sweat response at a distance. The principle of the test is that stimulating the nerve terminal (innervating a sweat gland) will produce a retrograde action potential along the axon until it reaches a collateral (branching) axon that innervates a different sweat gland. The action potential will then spread along this collateral and induce a release of acetylcholine at its terminal, which in turn will produce a sweat response that is recorded and quantitated (Fig. 10.3). An abnormal QSART can therefore be produced by an abnormality at any of the following five anatomical locations:

- Point 1: the stimulated presynaptic sudomotor nerve terminal
- Point 2: the postganglionic sudomotor nerve axon
- Point 3: the collateral axon
- Point 4: the collateral axon terminal or the synaptic cleft
- Point 5: the sweat gland from which the sweat response is recorded

QSART is widely employed as a sensitive marker of distal autonomic neuropathy, as the response depends on the integrity of the postganglionic segment of the sudomotor nerve. Because it is quantitative, distal-to-proximal gradients can also be detected, giving it good resolution for early disease, such as small-fiber neuropathy where the QSART is abnormal in 60–80 % of patients [33–35]. This test is abnormal in the following conditions:

- Small-fiber sensory neuropathy, such as with diabetes where it is quite sensitive [33]
- Complex regional pain syndrome (CRPS or reflex sympathetic dystrophy) where it may be exaggerated or reduced [32]
- Atopic dermatitis [36]
- Aging (only mildly decreased responses) [37]
- Generalized conditions affecting the ANS, such as generalized autonomic failure [38], postural orthostatic tachycardia syndrome (POTS) [39], parkinsonism-plus and cerebellar disorders with dysautonomia [40], multiple system atrophy (MSA), and pure autonomic failure (PAF) [41]
- Concomitant use of certain medications, particularly anticholinergic medications and tricyclic agents [42]

The test is gender-sensitive. Generally, women have lower sweat responses than men [43]. Table 10.4 lists the normative QSART values adjusted to age and site.

QSART is considered the most sensitive test for the detection of a postganglionic autonomic neuropathy. However, it is time-consuming and necessitates special equipment [45]. Practically, sweat is produced by the iontophoresis of acetylcholine through the skin, using a small-intensity electrical current. It is collected into a two-chambered cell (the sweat

Table 10.4 Normative data for quantitative sudomotor axon reflex test (QSART)

Age	20 years			40 years			60 years		
Site	Forearm			Forearm			Forearm		
Men	2.67	0.76	5.06	2.67	0.76	5.06	2.67	0.76	5.06
Women	1.15	0.20	2.78	1.15	0.20	2.78	1.15	0.76	2.78
Site	Calf			Calf			Calf		
Men	3.28	1.37	5.27	2.55	0.98	4.55	1.83	0.59	3.82
Women	1.83	0.61	2.85	1.26	0.39	2.28	0.68	0.18	1.70
Site	Foot			Foot			Foot		
Men	2.58	0.87	4.48	2.17	0.78	4.07	1.75	0.68	3.65
Women	1.27	0.23	3.07	1.05	0.18	2.85	0.84	0.12	2.64

Modified from Low [44]
Values are for mean, 5th, and 95th percentiles

cell) that is strapped to the skin [43]. The sweat response is quantitated by a sudorometer that detects the change in humidity of a nitrogen (or normal air) current flowing in and out of the capsule. The response overtime is a sweat curve, with a typical morphology (Fig. 10.4).

Resting Sweat Output

Measurement of baseline or resting sweat output (RSO) uses the same methodology as the QSART, except that there is no stimulation of sweat response. RSO is measured using larger sweat cells than those used for the QSART. Recording of sweat output is generally made over 5 min. It is important to measure RSO before proceeding with the QSART. The combination of both tests increases the specificity of autonomic testing for the diagnosis of CRPS type I [32]. Table 10.5 lists the normative values of RSO adjusted to sites.

Thermoregulatory Sweat Test

The thermoregulatory sweat test (TST) evaluates the integrity of the entire central and peripheral sudomotor pathway. The term "central" includes the hypothalamus, the bulbospinal pathways, the intermediolateral cell columns, and the preganglionic sympathetic fibers. The term "peripheral" encompasses the sympathetic chain and the postganglionic sudomotor fibers. TST is based on the following assumption: the maximal sweat response is directly proportional to the local skin temperature and the central temperature [46]. Therefore, the test consists of passively raising the body core temperature and the skin temperature in a sweat chamber, under constant conditions of ambient air temperature and humidity using infrared lamps, and visually evaluating the distribution of sweat production by the different regions of the body ("sweat pattern"). An indicator powder, usually Alizarin red mixed with cornstarch and sodium carbonate spread over the body, changes color when it becomes wet (Fig. 10.5) [46]. The powder that is orange when dry turns purple when wet.

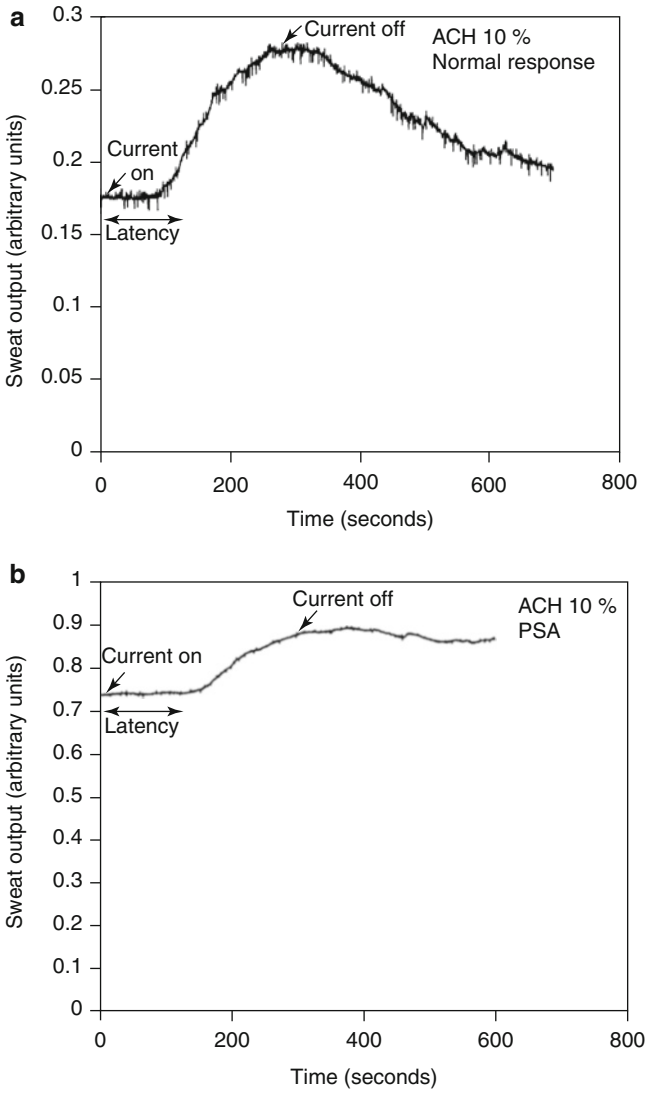

Fig. 10.4 Quantitative sudomotor axon reflex test (QSART). (**a**) Normal response. The tracing represents voltage output proportional to moisture level by an apparatus that senses humidity. Dry air is channeled through a capsule over the surface of the skin and returned to the apparatus for a moisture level assessment. After a baseline reading, current is turned on ("current on"), iontophoresing acetylcholine (10 %) across the skin all the way around the recording site. As a result sweat rate rises, after a 90 s latency. The sweat rate returns to baseline once current is turned off. Note the monophasic appearance of the normal response. (**b**) Abnormal response; "persistent sweat activity (PSA)". Two basic patterns of abnormality occur. The response may be reduced or absent, or (as in this figure) the response may persist excessively. Note the prolonged latency to onset, nearing 200 s, and the absence of clear drop in sweating after the current is turned off. Such a pattern may reflect early denervation and consequent supersensitivity

The TST is age- and sex-dependant [46]. Several sweat patterns are described in normal individuals and in different dysautonomias, and knowledge of these patterns is important for a correct diagnosis [46]. The most typical patterns are the *peripheral pattern*, indicating loss in a stocking-glove distribution, and its mirror image, the *central pattern*, with

Table 10.5 Normative data for resting sweat output (RSO)

Sites	Values		
Hypothenar	0.53	0.49	0.20–0.87
Forearm	0.08	0.10	0.06–0.12
Distal leg	0.12	0.12	0.09–0.72
Proximal foot	0.16	0.16	0.12–0.58

Modified from Low [44]
Values are for mean, 5th, and 95th percentile values

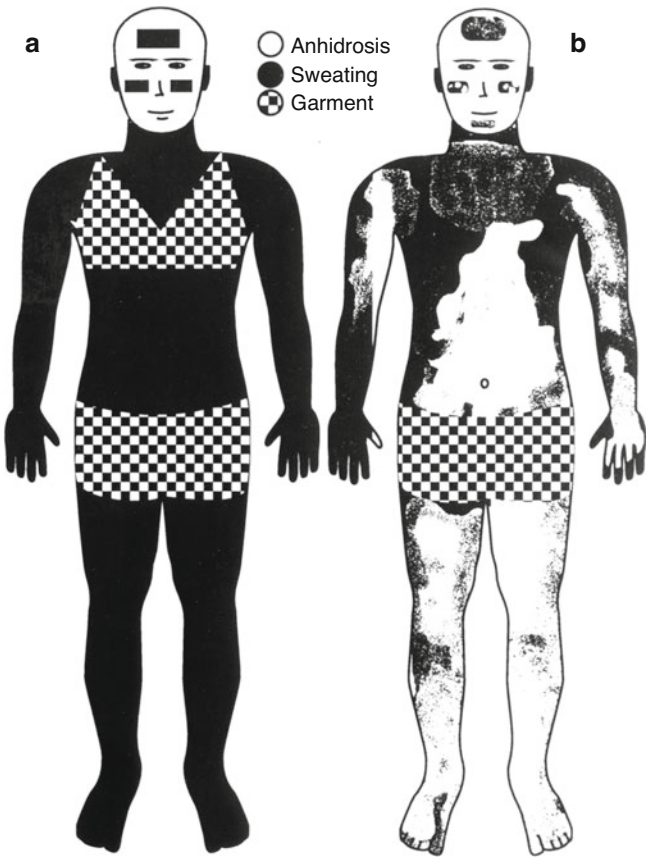

Fig. 10.5 Thermoregulatory sweat test. (**a**) Normal study. (**b**) Reduced sweating (60 % anhidrosis). Note the preservation of sweating along the lateral thigh, anterior leg, upper medial foot, and great toe, suggesting an L5 distribution. This finding would suggest a polyradiculopathy, rather than a peripheral neuropathy, in which one would expect a pure distal-to-proximal gradient of anhidrosis

preservation of sweating over the distal extremities. Other patterns include *radicular pattern*, with stripes of absent sweating marking particular dermatomes, particularly over the thorax, as seen in a ganglionitis or radiculitis, and a *patchy pattern*, with loss of sweating in patches as would occur in leprosy. A *myelopathic pattern* indicates loss of sweating clearly demarcated below a particular level.

Silastic Imprint Technique

The Silastic imprint technique consists of quantitating a local sweat response by iontophoresing pilocarpine into the skin and applying over the area a soft Silastic impression mold that shows the sweat droplets' imprint. The droplets are then counted using light microscopy or through computerized analysis of the molds, which allows automatic sweat gland counts and estimations of the secretion volume of each sweat gland [47]. This technique does not test any specific pathway of the sudomotor system. By directly stimulating the muscarinic receptors, it reflects the integrity of the sweat glands. Nonetheless, because the sweat gland undergoes denervation hyposensitivity (the denervated gland does not respond to pharmacologic stimulation), the Silastic imprint technique is sensitive for detection of sympathetic nerve involvement, even in asymptomatic patients. Its sensitivity and accuracy has been enhanced by the computerized analysis of the molds [47].

Sympathetic Skin Response

The sympathetic skin response (SSR) is of special interest to electromyographers, since it allows the assessment of the integrity of the peripheral sudomotor sympathetic nerve in the setting of an EMG laboratory, using standard EMG equipment and electrodes. The test is expected to be abnormal (reduced amplitude or absent) in diseases affecting the peripheral nerves such as peripheral neuropathies and distal small-fiber neuropathies and possibly (exaggerated) in diseases with sympathetically maintained pain (e.g., in CRPS) [48], but also in central autonomic disorders [49]. The physiologic principle of the test is based upon the observation that an electric potential recorded on the skin (termed "electrodermal activity") reflects the potential generated by sweat glands and the adjacent epidermis and dermis, in response to different stimuli [49, 50]. This potential can be evoked by microneurographically stimulating cutaneous nerve fascicles or postganglionic sympathetic efferent fibers [50] and be suppressed by sympathectomy [51], section of the peripheral nerve that innervates that portion of the skin [52], regional anesthesia of major nerve trunks, and administration of atropine [53]. SSR can be considered a test of sudomotor function, but it should be kept in mind that only a portion of the response (the early fast changes) is due to sweating, whereas the rest of the response (later changes) are due to skin potential changes which were present in patients with congenital absence of sweat glands [54]. SSR is simple to perform. The potential may be recorded by applying a recording (active) disc electrode (similar to the electrodes used in nerve conduction studies) on the palm of the hand or sole of the foot and a reference electrode (inactive) on the dorsum of these two body parts. The patient is stimulated electrically and strongly enough to cause a startle or induce pain. Stimulation is applied to a sensory nerve in the digit, ipsilateral or contralateral to the recording site. Other stimuli that produce a startle reaction can also be used (e.g., a loud noise). A cough or an inspiratory gasp is another acceptable stimulus.

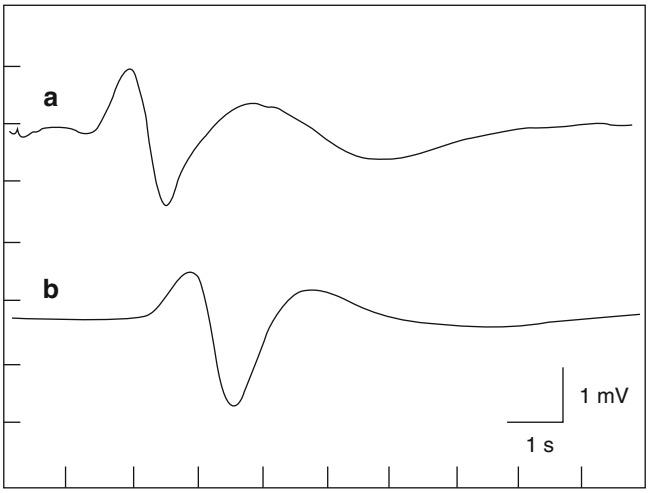

Fig. 10.6 Sympathetic skin response. A shock at the median nerve initiates the sweep. Recording occurs at the contralateral palmar (*A*) surface and contralateral sole (*B*). The response is assessed for latency, amplitude of the initial wave (peak to peak), and morphology. Evidence strongly suggests that this response reflects a wave of sweat secretion, with consequent alteration in surface potential

The amplitude of the SSR is generally variable (between 500 μV and 3 mV, peak to peak) due to the variable morphology of the potential (Fig. 10.6). Although controversy exists about the usefulness of this parameter, it is generally agreed that the latencies are not meaningful since they are produced by conduction along unmyelinated C fibers [48]. The amplifier low-frequency filter (high pass) should be set as low as possible (0.1–0.5 Hz). If it is higher, it attenuates the potential. High-frequency filter should be set between 500 and 1,000 Hz. The disadvantages of the method are that the response is only semiquantitative, can be difficult to elicit and habituates with repetition, and can therefore lead to false-positive results. Another drawback of this test is that it is not specific to the postganglionic portion of the sudomotor nerve and therefore cannot localize an abnormality.

Skin Biopsy

Even though this test is not technically part of the regular armamentarium of an autonomic laboratory, skin biopsy is a useful addition to the above-described sweat tests, as it allows direct visualization of autonomic sudomotor fibers surrounding sweat glands. As the only available quantitative test (as opposed to the above tests being qualitative tests), it can be considered a very useful complement to physiological testing of sudomotor function.

In the past decade, reports of the use of punch skin biopsy and the quantification of intraepidermal nerve fiber (IENF) density as a diagnostic tool in peripheral neuropathy started to flourish. This technique was first developed at the Karolinska Institute in Sweden [55] and then further developed and refined by the major centers that pioneered its use in clinical practice, mainly the University of Minnesota [56] and the Johns Hopkins University [57]. This technique allows the visualization of epidermal, dermal, and autonomic sudomotor nerve fibers surrounding sweat glands (see Chap. 13).

More recently, guidelines on the use of skin biopsy in peripheral neuropathy came out of a task force under the auspices of the European Federations of Neurological Societies (EFNS) [58]. We reproduce some of their major recommendations:

1. The EFNS task force recommends a 3 mm punch biopsy be performed. This biopsy is safe, causes minimal bleeding, and does not need stitches if proper care is taken. The recommended biopsy sites are the distal leg and the proximal thigh. These sites allow the assessment of a distal peripheral neuropathy and give information about a length-dependent process.
2. The recommended staining agent is the protein gene product (PGP) 9.5, a ubiquitin carboxyl-terminal hydrolase. It stains all types of axons. The biopsy specimen is immediately fixed in a cold fixative (2 % PLP) for up to 24 h at 4 °C, then kept in a cryoprotective solution for one night and serially cut with a freezing microtome or a cryostat. Each biopsy yields about 55 vertical 50 μm sections. The immunostaining methods commonly used are bright-field immunohistochemistry and indirect immunofluorescence with or without confocal microscopy. Quantification of IENF density is performed on images stacking 16 sections of consecutive 2 μm sections for a standard linear length of epidermis from 1 to 3 mm. IENF should be counted at high magnification (40×) in at least 3 sections per biopsy. Only fibers that cross the dermis-epidermis barrier should be counted, excluding secondary branching. This is controversial as some centers include free nerve fragments within the epidermis in the count, even if they do not cross the barrier. In order to calculate the IENF density, the number of counted fibers in a section is divided by the length of the section and expressed as #IENF/mm [59].
3. Diagnostic efficiency and predictive values of skin biopsy with linear quantification of IENF in the diagnosis of SFN are very high. Bright-field microscopy was used in order to determine cutoff values or epidermal densities, but immunofluorescence is an acceptable method for counting fibers. Normative data which is age, gender, ethic, and anatomical site-matched is available and should be used. Normal IENF density in the lower leg ranged in different studies between 17.4 ± 7.4 and 33.0 ± 7.9/mm.
4. Morphological changes of small fibers can also be assessed, such as axonal swellings, branching, and fragmentation. Axonal swellings in the lower limb are thought to have a predictive value to the progression of

the neuropathy. Whether or not one can diagnose a SFN based on swellings alone is not clear.

5. There is a correlation between skin biopsy and other neurophysiological tests, mainly sural nerve conduction studies, in large-fiber neuropathies, whereas IENF density is more sensitive than EMG in diagnosing SFN. A linear correlation between the medial plantar sensory nerve potential amplitude and IENF density has been reported [60]. IENF density inversely correlated more closely with warm and heat-pain threshold than with cooling threshold on quantitative sensory testing (QST) [61, 62]. A significant correlation was found between the decrease of IENF density and abnormal QSART [63], which is also our own experience.

The above recommendations and most of the experience gained in skin biopsy focused on the precise quantitation of somatic small nerve fibers. This is unfortunately not the case with sudomotor nerves. The complexity of their anatomical distribution around sweat glands has made it difficult to devise a simple generalizable technique for counting these nerve fibers, and as a result, normative data still do not exist. Most of determinations regarding the normality or abnormality of the test are based on a subjective impression of decreased or normal numbers of sudomotor fibers surrounding sweat glands. Therefore, caution is to be exerted in the interpretation of this test and it is important not to conclude hastily that an abnormality in IEFND necessarily reflects an abnormality in C-fiber autonomic function.

Cardiovascular Autonomic Tests

The heart is innervated by the PSNS and SNS. Similarly, the peripheral vasculature receives fibers from both arms of the ANS. However, sympathetic fibers have a predominant action at the level of the peripheral vasculature, whereas the parasympathetic has little influence. The responses of the heart and peripheral blood vessels to the autonomic tests described below are reflex compensatory responses. For example, a decrease in blood pressure (BP) leads to a reflex increase in heart rate (HR) and a reflex vasoconstriction, whereas the opposite is true with an increase in BP. Afferent fibers of this reflex pathway originate at the level of the baroreceptors of the carotid sinus, arterial walls, aortic arch, cardiac mechanoreceptors, and pulmonary stretch receptors. An increase in afferent activity leads to a decrease in sympathetic efferent activity, an increase of parasympathetic efferent activity, or both and vice versa [47]. *Photoplethysmographic blood pressure recordings*, also called the *Finapres* technique, is a noninvasive method of measuring BP with every heartbeat (BPBB). It consists of an infrared sensor that is applied to the finger within a finger cuff and records its blood volume. Through a computerized servo system, the blood pressure is recorded beat to beat and accurately reflects intra-arterial pressures [43]. This technique is useful in detecting sudden changes in hemodynamics as a result of the autonomic compensatory reflex. It is commonly used in the Valsalva maneuver, the deep breathing test, and the tilt test.

Heart Rate Response to Deep Breathing

Heart rate variability with deep breathing (HRDB) is one of the most commonly performed tests to evaluate the autonomic innervation of the heart. It is simple to perform and provides a sensitive, specific, and reproducible indirect measure of cardiovagal nerve function [64].

Basic Principles

The physiologic principle of the test is thought to be based on the following mechanisms that occur during the respiratory cycle (see Table 10.1):

- Inhibition of vagal efferent activity with inspiration [65].
- Baroreceptor reflex (carotid sinus reflex) (Fig. 10.7): changes in baroreflex sensitivity with respiratory phases and consequent variations in arterial BP [66, 67]. The variation in BP (mainly increases) also stimulates these receptors, which send impulses along the afferent limbs of the glossopharyngeal nerve (nerve of Hering) and vagus nerve to the nucleus tractus solitarius (NTS) in the medulla. The central-caudal area of the NTS also receives input from the hypothalamus. The response then decreases sympathetic activity, which, in turn, decreases HR [68].
- The Bainbridge reflex: responds to changes in the right atrium (RA) volume or central venous pressure via stretch receptors located within the RA wall and cavo-atrial junction. Increases in intravascular volumes or right-sided filling pressures stimulate these receptors, which also send their impulses through vagal afferents to inhibit PS activity and to increase HR [68].

The "time domain" measure of HR is a commonly used term that refers to statistical measures of HR variability with respiration. These measurements are derived from a regular strip of an electrocardiogram (EKG) performed while the patient is breathing deeply in the supine position. The most commonly used are maximum minus minimum HR difference and inspiratory/respiratory (I/E) ratio (i.e., the shortest RR interval during inspiration to the longest RR interval during expiration). We note that the duration of the RR interval is inversely proportional to the HR.

Practical Considerations

The patient is asked to take six deep breaths during 1 min (inspiratory and expiratory cycles of 5 s each). The procedure is repeated after 2 min of rest. An EKG recording is made during deep breathing and the previously described parameters are calculated by a computer (Fig. 10.8). Though

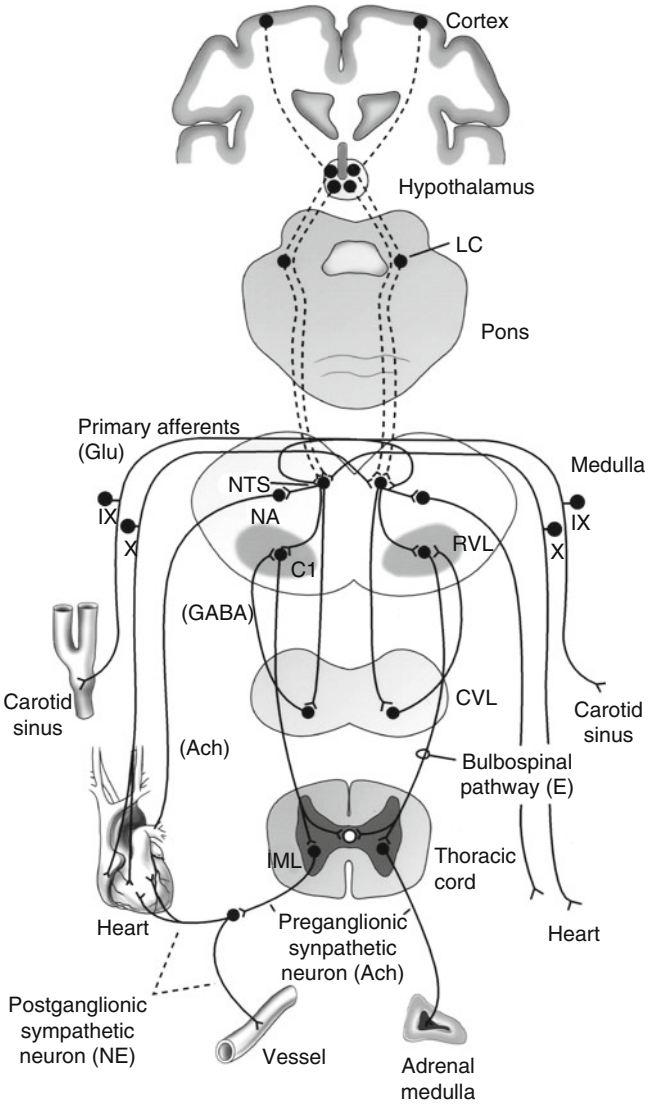

Fig. 10.7 Proposed pathways and neurotransmitters of the baroreceptor reflex. *NTS* nucleus tractus solitarius, *NA* nucleus ambiguus, *CVL* caudal ventrolateral medulla, *RVL* rostral ventrolateral medulla, *Cl* ventrolateral epinephrine cell area, *IML* intermediolateral cell column, *IX* glossopharyngeal nerve, *X* vagus nerve, *LC* locus ceruleus, *GABA* gamma-aminobutyric acid, *Glu* glutamic acid, *E* epinephrine, *Ach* acetylcholine, *NE* norepinephrine (Copyright Cleveland Clinic foundation 1999)

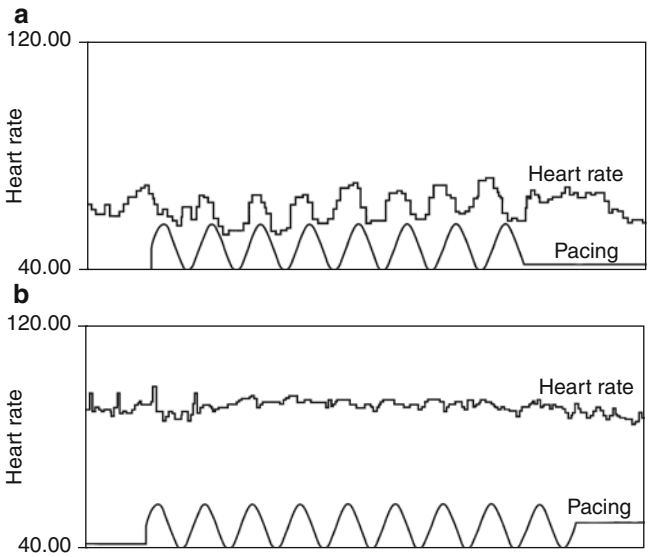

Fig. 10.8 Cardiac response to deep breathing. (**a**) Normal response. Breathing is paced at 6 breaths per minute (8 breaths are shown, *lower trace*). Heart rate is shown in the *upper trace* and increases with each inspiration. The difference in heart rate within each respiratory cycle is averaged for the five best responses. (**b**) Abnormal response. A patient with moderately severe autonomic failure demonstrates little to no heart rate variation with deep breathing. Note also that the baseline heart rate is higher than in **a**, a finding suggestive of cardiac denervation

Table 10.6 Variation in heart rate with deep breathing

Age (years)	Heart rate variation
20	13–43
40	9–36
60	7–29
80	7–29

Modified from Low [44]

other parameters are described [64], the HRDB test is the most commonly used and reproducible test of parasympathetic cardiac nerve function.

Pitfalls

Limitations of the HRDB involve the following factors:

1. *Age*: RR variation with respiration has been shown to vary with age in a linear fashion [37]. Therefore, normative data adjusted to age groups should be used in order to avoid false-positive or false-negative results (see Table 10.6).
2. *Time of testing*: there is a circadian variation of HRDB variability, this being largest at night and smallest in the morning [69].
3. *Medications*: Drugs, especially those with anticholinergic side effects, can alter the accuracy of the testing [42]. We recommend stopping them at least five half-lives prior to the test.
4. *Other factors*: body weight and body mass index [70], hypoxia [71], physical condition [72], and others [64] have an effect on HRDB variability.

The Valsalva Maneuver

Another commonly used test of parasympathetic cardiovascular autonomic function is the heart rate response to the Valsalva maneuver (VM). It consists of a precisely timed forced expiration against resistance, which leads to a series of hemodynamic changes.

Basic Principles

The hemodynamic changes induced by the VM are classically divided into four phases of which only phase II and IV

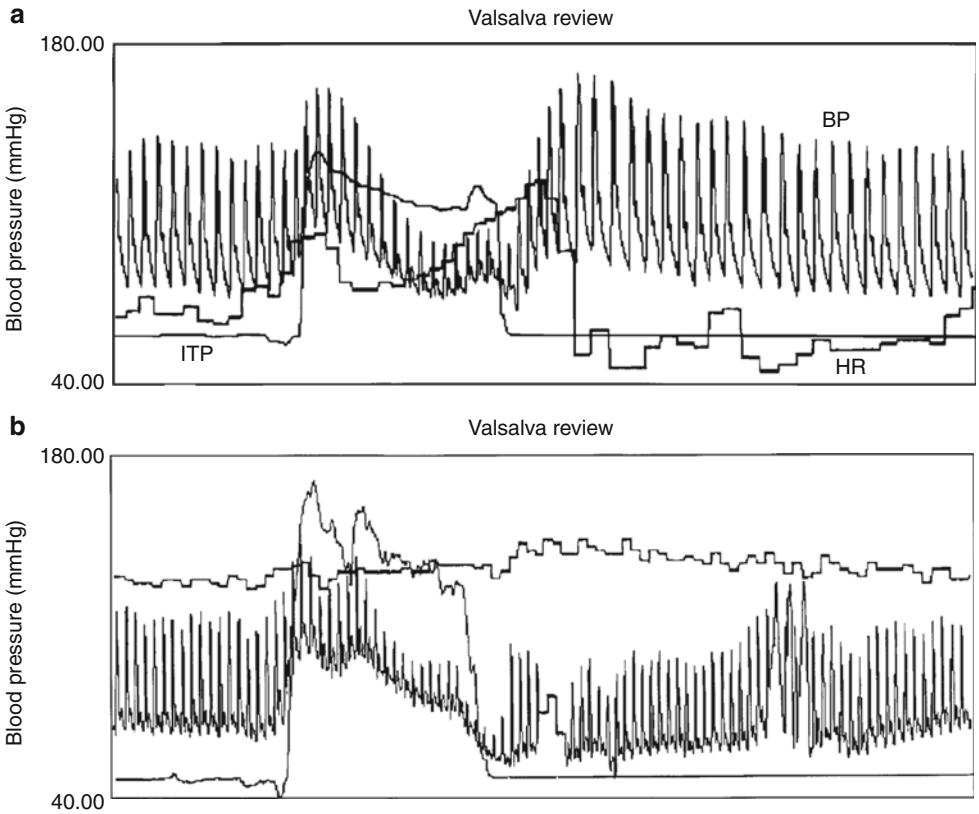

Fig. 10.9 Valsalva maneuver. (**a**) Normal response. The recording totals 60 s. The lowest trace shows oral/intrathoracic pressure maintained as recorded at the mouthpiece. The middle trace records heart rate, and the *upper trace* displays beat-to-beat blood pressure. About 12 s into the recording, the patient holds 40 mmHg and maintains pressure for 15 s. As a consequence of reduced venous return, blood pressure and pulse pressure drop, and heart rate rises in compensation. The Valsalva ratio is obtained by dividing the highest heart rate during pressure holding (phase II) by the lowest heart rate after release (phase IV). (**b**) Abnormal response. The heart rate is rapid at start and does not change, while the blood pressure drops without a plateau

are clinically significant (Fig. 10.9). Variation of BP during the test reflects the integrity of sympathetic adrenergic cardiovascular function [73]. Heart rate variation (Valsalva ratio) is a compound of heart rate acceleration in phase II (sympathetic) to heart rate deceleration in phase IV (parasympathetic). The ratio reflects the integrity of the parasympathetic cholinergic and the sympathetic adrenergic cardiovagal function. If the ratio is low, one then determines if the problem is in phase II or IV to conclude whether the SNS or PSNS is impaired (see Table 10.2).

Phase I: A transient increase in BP and drop in HR occurs at the start of the expiration. This phase is purely mechanical and not controlled by the ANS. It consists of a transient rise in BP and fall in HR due to the sudden increase in intrathoracic pressure, which leads to a transient compression of the aorta and propulsion of blood into the periphery.

Phase II: Early in phase II, there is a decrease in BP and increase in HR. The decrease in venous return caused by the increase in intrathoracic pressure leads to a decrease in cardiac output (drop in BP) with a compensatory increase in HR, through the activation of the low-pressure atrial receptors, and the integrator of this information is the nucleus tractus solitarius. Late in phase II, and with continued straining, there is a return of BP to normal and continued increase in HR. The BP normalizes due to peripheral vasoconstriction, which occurs secondary to activation of the muscular and vascular sympathetic systems. This normalization is sympathetic as it is blocked by the administration of phentolamine, an alpha-blocker. The early heart rate increase is vagally mediated, while the peak of phase II is sympathetic.

Phase III: There is a transient fall in BP and increase in HR, which corresponds to cessation of expiration. The release of the strain causes mechanical displacement of blood to the pulmonary vascular bed, which was under increased intrathoracic pressure, resulting in a transient drop in BP. Like phase I, this is mechanically induced and not mediated by the ANS.

Phase IV: There is a large increase in BP (overshoot) and fall in HR due to the return to normal of the venous return, leading to a return to normal of the cardiac output while peripheral vasoconstriction is still present. The accompanying bradycardia is a baroreflex-mediated response (see Fig. 10.7) [74]. The BP overshoot is sympathetically mediated through cardioacceleration as it is decreased by propranolol (a beta-blocker) and unaffected by phentolamine (an alpha-blocker) [73].

The analysis of VM is mainly based on the "Valsalva ratio" (VR). This is the ratio of the shortest RR interval (maximal tachycardia) in phase II to the longest RR interval (maximal bradycardia) during phase IV. This ratio is a sensitive, specific, and reproducible measure of autonomic, mainly cardiovagal, functions [64].

Practical Considerations

The patient is asked to blow into a bugle with an air leak (so that pressure really comes from the chest and the abdomen) for 15 s and maintain a pressure of 40 mmHg. BPBB and HR are recorded during the maneuver. The maneuver should be repeated until two responses of similar BPBB and HR are obtained. Typically, in cardiovascular dysautonomia, there is loss of the BP overshoot and the reflex bradycardia in phase IV. Table 10.7 lists normative data for the VR.

Pitfalls

Several factors can affect the accuracy of the Valsalva ratio. As with most tests of the ANS, gender and age are important considerations before interpreting the test. Medications, especially those with anticholinergic or anti-adrenergic effects, should be stopped five half-lives before the test. Patient position during the test and the duration and quality of the expiratory effort significantly affect test results. Another important pitfall was described in patients with isolated sympathetic vasomotor lesions but intact cardiovagal function [75]. In such patients, because of poor peripheral vasoconstriction in phase II, BP falls excessively and reflex tachycardia is also excessive, whereas BP overshoot is decreased in phase IV and consequently bradycardia does not occur. This situation yields a misleading normal VR.

Table 10.7 Valsalva ratio normal values

Age		20 years	40 years	60 years	80 years
Values	Men	1.50–2.97	1.36–2.60	1.21–2.23	1.21–2.23
	Women	1.41–2.97	1.47–2.88	1.36–2.65	1.36–2.65

Modified from Low [44]

Conclusion

The VM is a good indicator of both parasympathetic and sympathetic failure. The VR is thought to reflect the status of the cardiovagal system although this is controversial [76, 77]. The variation of BP during the maneuver, especially BP overshoot in phase IV, is indicative of the integrity of the sympathetic fibers to the heart and vessels.

Heart Rate Response to Standing

This simple test to perform is part of the routine autonomic screening of cardiovascular function. As in the VM, monitoring heart rate variation with standing reflects the integrity of parasympathetic cardiovagal function and sympathetic cardioadrenergic function, whereas BP variation reflects the state of sympathetic cardiovascular function.

Basic Principles

As in the VM, two major events occur during the test: an initial drop in BP and increase in HR, followed by a relative BP overshoot and bradycardia. The first event or phase 1 occurs within the first 15 s after standing up, and the second, or phase 2, at approximately 30 s after standing up (Fig. 10.10). The initial drop in BP is thought to be caused by

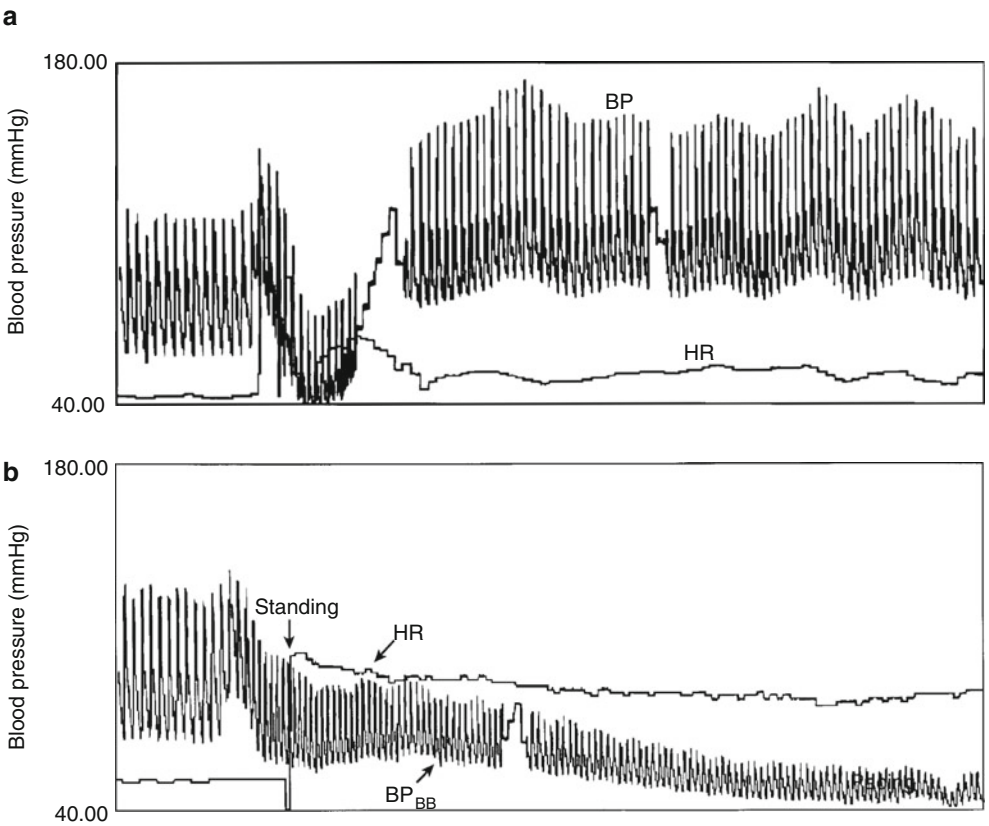

Fig. 10.10 Standing test. (**a**) Normal response. The *lower trace* shows heart rate, the *upper* beat-to-beat blood pressure. Total recording time is 1 min. At 10 s, the patient stands. Blood pressure drops and heart rate rises temporarily. Return to a new plateau occurs promptly, with a slightly higher heart rate and blood pressure. (**b**) Abnormal response. Heart rate rises and blood pressure drops as before, but return to near-baseline values does not occur. Blood pressure continues dropping, and the patient would have lost consciousness if the stand had continued

Table 10.8 Principal indications of head-up tilt test for evaluation of syncope

Tilt table testing is indicated
Recurrent syncope or single syncopal episode in a high-risk patient with or without structural cardiovascular disease, in which cardiac, cerebral, or cerebrovascular causes have been excluded
Further evaluation of patients with a structural cardiac cause of syncope (e.g., asystole, atrioventricular block), in whom the demonstration of a susceptibility to neurally mediated syncope would alter treatment
Evaluation of exercise-induced or exercise-associated syncope
Tilt table testing not indicated
Single syncopal episode with clear-cut vasovagal clinical features, without injury and not in a high-risk patient
Syncope in which an alternative specific cause has been established and in which additional demonstration of a neurally mediated susceptibility would not alter treatment
Relative indications
Differentiating convulsive syncope from seizures
Evaluating patients with recurrent unexplained falls
Assessing recurrent dizziness or presyncope
Evaluating unexplained syncope in the setting of peripheral neuropathies or dysautonomia
Follow-up evaluation to assess therapy of neurally mediated syncope

the orthostatic stress produced by standing up and a reflex release of vasoconstrictor tone. In one study, standing elicited a transient 25 % fall in mean blood pressure as a result of a 36 % fall in total peripheral resistance [78]. The initial increase in HR is thought to be due to 2 physiological events: (1) an "exercise reflex" triggered by standing up and caused by muscular contractions and (2) withdrawal of vagal tone. A more gradual increase in HR is caused by a reflex increase in sympathetic activity and further vagal inhibition. The later increase in HR occurs through a baroreflex-mediated mechanism in response to the transient hypotension. The second phase of the response occurs around 30 s after standing up and is characterized by a return to baseline of HR and BP followed by a BP overshoot and a reflex bradycardia.

Practical Considerations

The patient is kept at rest in the supine position for at least 20 min before standing. This is because shorter periods lead to different standing responses [79]. Continuous EKG and BP recordings are made during rest and for 1–3 min after standing up. The EKG allows calculation of the 30:15 ratio. This test allows determination of orthostatic hypotension (OH). Its hallmark in autonomic failure is the absence of compensatory tachycardia [47]. This diagnosis should only be made after ruling out all other possible medical causes of OH.

The principal measurement from the standing test is the 30:15 ratio. This is made by dividing the longest RR interval that occurs at or around 30 cardiac beats after standing (reflects the minimum HR) by the shortest RR interval that occurs at or around 15 s (reflects the maximum HR). With a lesion of the parasympathetic cardiovagal fibers, phase 2 bradycardia does not occur, hence decreasing the ratio. This ratio provides a measure of cardiovagal function.

Pitfalls

Caution should be taken in interpreting the standing test as its results can vary according to the technique used. For example, it is important to specify the starting point for measuring HR after standing: onset of standing or a complete erect position. Age and medications are other factors to be considered before the interpretation of the test. Finally, as with the VM, patients with an isolated sympathetic vasomotor lesion with intact cardiovagal function can display a decreased 30:15 ratio due to failure of the BP to increase during phase 2 of the response, leading to an absence of the reflex bradycardia. Therefore, this ratio should not be interpreted as a cardiovagal failure. For this reason, it is always important to assess HR variation in relationship to BPBB during the interpretation of the test [53].

Head-Up Tilting

Basic Principles

Head-up tilting represents a passive form of standing, and therefore, the initial hemodynamic events differ from the standing test. The initial drop in BP is less marked or absent. Instead, there is a slow increase in BP, mainly the diastolic. Similarly, HR increases gradually and the initial increase seen during active standing is not observed. This difference is probably due to the absence of "exercise reflex" produced by the orthostatic stress and activation of the muscle pump, during passive tilting [80]. Because the above-mentioned event induces a series of neurally mediated changes, active standing is preferred over head-up tilting as a way to assess orthostatic neural control in the initial phase. However, during the later phases, head-up tilting and active standing induce similar hemodynamic adjustments. Head-up tilting remains a more advantageous technique in patients with severe OH since it provides the possibility of returning quickly to the supine position.

Practical Considerations

Despite controversies about the degree of tilting and the positive endpoints, this test constitutes the gold standard in assessing neurocardiogenic syncope (Table 10.8) [81, 82]. Most authors agree that the angle of tilt should be at least of 60°. Most laboratories use 70° or 90°, which produce similar hydrostatic effects. The speed of tilting has little or

no influence on the initial orthostatic response to upright tilting [81]. Reproducing syncope is the ultimate positive endpoint of the tilt test. Also, a cardioinhibitory response (bradycardia or asystole) and a vasodepressor response (hypotension without bradycardia) are equally positive endpoints.

Power Spectral Analysis of Beat-to-Beat Heart Rate Variability Signal (Valsalva and Tilt)

Basic Principles

A power spectrum graphically displays the prevalence of particular frequencies in a signal. For example, if a recording lasting 150 s comprises 100 s of 0.5 Hz signal (one occurrence every 2 s) and 50 s of a 0.1 Hz (one occurrence every 10 s), the power spectrum would show a peak over the *x*-axis at 0.1 and a larger peak over the *x*-axis at 0.5 (larger, because it occurred during a larger portion of the total signal). Heart rate naturally varies at two frequencies: a relatively higher frequency which matches breathing frequency and usually falls around 0.15 Hz and a lower frequency related to heart rate changes with activity, around 0.06 Hz. The higher frequencies are thought to represent parasympathetic cardiac influence, while the lower frequencies reflect sympathetic cardiac influence. Detailed reviews of this method are available [83–87].

Practical Considerations

The patient should be quiet and supine for 10 min of EKG recording. Respiratory rate should be monitored and recorded, as low-frequency respiration will cause the respiratory frequency to drop into the non-respiratory range. Data acquisition should proceed at a sampling rate of at least 250 Hz, and artifacts, such as extrasystoles and muscle "noise," are removed. Several functions then need to be applied to the data, including resampling for equidistant data presentation, with some filtering and smoothing, before computation of the Fourier power spectrum. Low frequency is defined as 0.04–0.15 Hz and high frequency as 0.15–0.4 Hz [85].

Pitfalls

The seeming simplicity of this method is deceptive. The power spectrum represents highly transformed data, and the method should not be used without clear and consistent evaluation of the raw data and great familiarity with the method. Absence of these safeguards results in, what the 1970s programmers call, "GIGO" (garbage in, garbage out) and has resulted in much retrospective criticism of the published literature. Two factors cause most of the misinterpretations: (1) inadequate control and recording of respiratory rate, with consequent inability to determine the expected high frequency, and (2) failure to adequately handle artifacts, such as extrasystoles and muscle, in addition to other factors.

Pupillometry

The use of pupillometry for testing the ANS is the object of renewed interest after the emergence of new-generation infrared dynamic pupillometers, which are reliable, relatively easy to use, and commercially available instruments [88–95].

Anatomy

The pupil is innervated by both the SNS and the PSNS. Preganglionic parasympathetic fibers travel along the third cranial nerve and synapse in the ciliary ganglion. Postganglionic fibers innervate the constrictor of the pupil through the short ciliary nerves. Activation of this smooth muscle produces constriction of the pupil. This is mediated by the release of acetylcholine at the synaptic junction and the interaction of the neurotransmitter with muscarinic ACh receptors.

Sympathetic innervation to the pupil is composed of three neurons designated first-, second-, and third-order neurons. The first two are preganglionic neurons, whereas the third-order neuron is postganglionic. Preganglionic first-order neurons emerge from the hypothalamus and their axons descend in the brainstem into the spinal cord where they synapse in the ciliospinal center of Budge, in the intermediolateral column, with the cell bodies of second-order neurons. Axons of second-order neurons exit the spinal cord through the ventral roots of the T1–T2 segments and enter the cervical sympathetic trunk at the level of the inferior cervical ganglion. They then take an upward course, traversing the inferior and middle cervical ganglions to the superior cervical ganglion where they synapse with the cell bodies of the third-order neurons. These postganglionic neurons project their axons along the course of the internal carotid artery and then join the ophthalmic branch of the trigeminal nerve to enter the orbit through the superior orbital fissure. These fibers finally enter the eye with the long ciliary nerves and innervate the dilator pupillae muscle by releasing norepinephrine that binds to mainly alpha-adrenoreceptors on this muscle.

Basic Principles

The principle of *dynamic infrared pupillometry* consists of quantifying the change of the pupil diameter during the course of a light reflex and dividing it into several kinetic parameters, which are analyzed separately (Table 10.9). These parameters reflect the activity of the two branches of the ANS in response to a light stimulus resulting in pupillary constriction and redilation phases (Fig. 10.11). The term "infrared" refers to illuminating the tested eye in a dark environment by an IR light that is reflected by the iris into the pupillometer, allowing this device to estimate the variation in pupil diameter.

Table 10.9 Some pupillometric parameters and their significance

Parameters	Initial diameter (ID)	Minimal diameter (MD)	Reflex amplitude (RA)	Constriction velocity (CV)	Redilation velocity (RV)	Latency
Definition and significance	Dark-adapted pupil diameter prior to light reflex. Reflects sympathetic-parasympathetic balance	Minimum diameter reached by pupil during light reflex. Reflects parasympathetic function?	ID – MD Depends on ID. Reflects parasympathetic function?	Reflects parasympathetic function	Reflects sympathetic function	Time between onset of flashlight and start of pupillary constriction. Unclear significance.[a] Reflects number of sphincter pupillae acetylcholine receptor? Parasympathetic function?

[a]Seems to be prolonged in myasthenia gravis (personal observation)

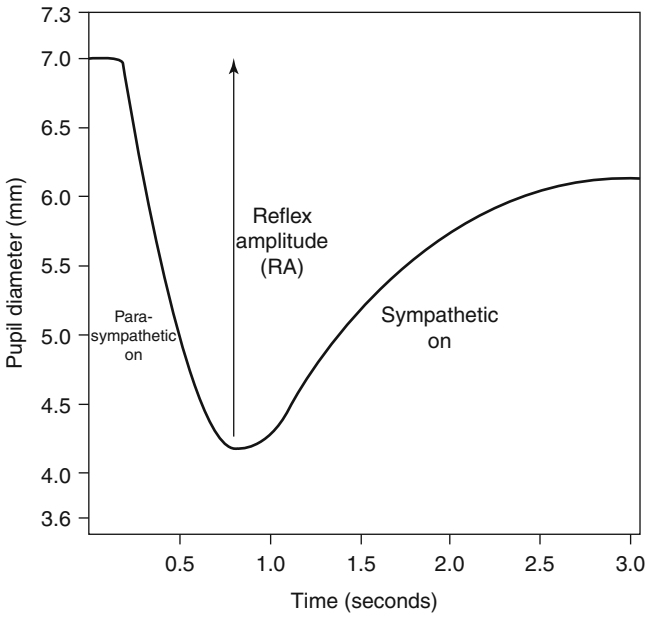

Fig. 10.11 Pupillometry. A 200 ms pulse of light shines into the eye at time 0. As a result, the pupil constricts and subsequently dilates (since the light turns off). This simple procedure yields the following information: (1) latency to onset of dilation, (2) slope of constrictive (parasympathetic) phase, (3) reflex amplitude, and (4) slope of redilation (sympathetic) phase

Pitfalls

Care should be taken in the interpretation of pupillometric data, taking into account multiple factors which could interfere with pupillary function. For example, patients with diabetes have abnormalities of pupillary reaction to light (near-light dissociation) and an increased incidence of cataracts which interfere with pupillary function.

Pupillary initial dark-adapted diameter and consequently reflex amplitude decrease with age, and the time to 75 % redilation increases with age [28]. Latency seems also to be affected by age and gender. Drugs, caffeine, nicotine, lack of sleep, and fatigue may also play a role in modifying pupillary kinetics (authors' unpublished observations). Normative data are lacking for most pupillometric parameters and studies of normal subjects and patients with dysautonomia are needed.

Table 10.10 Supine and standing norepinephrine levels by disease subtype

Position	Normal	Preganglionic lesion	Postganglionic lesion
Lying	X	X	0.25 X
Standing	X	1.25 X	0.5 X

In the normal state, the baseline value is assumed to be an arbitrary number (varies by laboratory) "X." This usually doubles after 10 min of standing. The disease states are assumed to have reduced the respective neuron population by 75 %. In a preganglionic disorder, baseline norepinephrine is unaffected because postganglionic release does not depend on central stimulation. In the upright position, since 75 % of the preganglionic neurons are gone, only 25 % of the postganglionic neurons receive a signal, and norepinephrine level rises by 25 % instead of 100 %. For a postganglionic disorder, only 25 % of terminals are left, reducing baseline norepinephrine by 75 %. However, those remaining have intact central connections, with normal doubling of value

Plasma Catecholamines

Supine plasma norepinephrine (noradrenaline) blood level is dependent on its release by unstimulated sympathetic postganglionic noradrenergic terminals. In contrast, the standing value reflects activation of these terminals by central command. Table 10.10 delineates the change in norepinephrine level after 10 min in each position. These levels are useful in large population studies, but the variation across individuals is such that the pre-/postganglionic distinction is often difficult to make. Levels can also be useful in the postural tachycardia syndrome in distinguishing the subset of patients who may have a norepinephrine transporter deficiency [96].

Skin Blood Flow

Skin blood flow has been vigorously explored by several groups as a measure of autonomic function. Several excellent laser devices range from the ability to measure a single point or an average of multiple points on the skin, to maintain skin at a steady predetermined temperature throughout the study, and to differentiate flow, volume, and velocity of red cells. Despite the constant improvement in the reliability and reproducibility of these measurements,

skin blood flow has not yet caught on as a clinical tool, except perhaps in assessing the diagnosis of complex regional pain syndrome. The main reason is probably that although these measurements are conceptually very attractive and simple, they are actually fraught with significant complexity. The skin vessels are highly localized, and enormous variability exists from point to point, even in a 250 μm distance, so that any physical disturbance of the laser probe will change the entire recording. Second, skin blood flow depends on more than just skin temperature. As with any autonomic measurement, one cannot interpret a random steady state recording, but rather one needs to measure the response to a specific stimulus, such as a change in skin temperature, ischemia, or iontophoresis of an agent. However, this is difficult to interpret without knowing the maximum and minimum physiologic blood flows at the point being measured, to provide a backdrop against which to compare the observed change. This adds one more step and is itself not easy to obtain. Finally, there are two types of vessels in the skin, nutritive vessels and arteriovenous shunts which help with dissipation of heat. It is difficult to determine which type of vessel is being recorded, and their responses to sympathetic stimulation differ considerably.

Anatomy

Like blood flow in most regions, skin flow is primarily controlled by the sympathetic nervous system through its influence on vasoconstriction. The contribution of sympathetic or parasympathetic cholinergic dilator fibers continues to be debated today. Constrictor fibers release norepinephrine or neuropeptide Y to activate the muscle cells in the vessel walls to produce constriction. In contrast, putative dilator fibers will release acetylcholine or vasoactive intestinal peptide (VIP) to activate the nitric oxide system and induce dilation. Dilation may also occur as a result of neuro-inflammatory activation of afferent C fibers releasing substance P or CGRP. An excellent review details factors influencing blood flow [97]. Sympathetic nerve fibers are controlled by postganglionic neurons, in turn under the influence of intermediolateral cell neurons, in turn controlled by hypothalamic activity and feedback from the various temperature centers in the brain, as well as emotional activity and local factors.

Basic Principles

Most devices are composed of two parts, a probe that is applied to the skin, usually composed of optic fibers that carry the laser signal to and from the skin surface, and a box of some type that generates laser light at a specific frequency and measures the frequency of returning light. Many devices also come with a probe housing that can maintain constant skin temperature during flow measurement, a vital aspect since skin temperature is one of the most important determinants of skin flow. As the name implies, laser Doppler technology uses the amplitude and change in frequency of reflected light from red blood cells coursing through vessels in the skin to determine blood volume and velocity, respectively. Flow is calculated by a formula that includes multiplication of these two parameters (flow = velocity × volume). Most devices provide only a flow display, but some will also provide primary velocity and volume measurements.

As with most other autonomic tests, a specific stimulus is usually applied to the skin and the resulting change in skin blood flow is determined. Examples include the iontophoresis of a dilating or constricting agent such as nitroprusside or phenylephrine [98], the application of a cooling or heating stimulus, or ischemia and reperfusion, depending on the approach. The inspiratory gasp is the best way to vasoconstrict the skin [99].

Pitfalls

In contrast to other tests of autonomic function, there are no absolute norms for skin blood flow, so it is difficult to know if a given measurement falls in or out of the range of normal. The laser probes cannot be moved since flow may be vastly different even a few microns away from any given location. Any protocol involving the application of a stimulus with comparison pre- and poststimulus cannot include moving the probe. Finally, the probes are mechanically quite delicate, and the optic fiber can break inside the plastic lining and still seem to be providing information when it is not.

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Quantitative Sensory Testing

11

Pariwat Thaisetthawatkul

Basic Principles in Sensory Physiology

The sensory system integrates and perceives sensory stimuli from the outside world. The sensory perception starts with a physical stimulus reacting on a sensory receptor. The receptor has an intrinsic mechanism to transform the physical stimulus into a nerve impulse. The nerve impulse reaches the central sensory system for integration and interpretation and becoming a perception. The modality of sensory perception is determined by the type of sensory stimuli and their specific receptors mediating nerve impulses along specific nerve fibers. There are five modalities of somatosensory system: vibration, touch, proprioception, pain, and temperature senses. These modalities are determined by specific receptors to mediate each type of sensory perception. There are three types of sensory receptors in the somatosensory system: mechanoreceptors, thermoreceptors, and nociceptors. The mechanoreceptors mediate vibration, touch, proprioception, and joint position senses. The nociceptors mediate pain, and the thermoreceptors mediate temperature senses. Each specific type of sense is mediated through a specific receptor. Most receptors are located in the skin with less or no hair (glabrous skin). The mechanoreceptors have two types of adaptation (decrease firing potentials with time even with constant stimuli): rapidly adapting (Pacinian and Meissner's corpuscles and most hair follicle receptors) and slowly adapting (Merkels discs and Ruffini end organs). Rapidly adapting mechanoreceptors responds best to rapidly changing stimuli such as swift movement (touch) or rapidly changing stimuli in sinusoidal wave forms (vibration). Slowly adapting mechanoreceptors respond better to continuous stimuli such as prolonged stretch or pressure [1]. Each of these receptors responds best to specific ranges of stimuli. For example, Pacinian corpuscles respond best to vibration stimuli with frequency range of 60–400 Hz, while Meissner's corpuscles are more sensitive to midrange stimuli of 20–50 Hz and Merkel discs to very low frequency of 5–15 Hz [2]. Because of these, humans are most sensitive to vibration at frequencies of 200–250 Hz, and vibration stimuli whose frequencies fall out of these ranges need higher intensity to be felt. Also, a sensory stimulus is felt best within the receptive field (the area where the density of the receptors is highest) of that particular modality. Proprioception sense is mediated through receptors outside the skin including muscle spindles, Golgi tendon organs, and receptors within the joint capsules. Thermoreceptors respond to changes in skin temperatures, resulting from the external temperature touching the skin, from baseline temperature, usually at 34 °C. Cool receptors respond most at 25 °C and stop responding at 5 °C, below which the cold nociceptors start responding. Warm receptors are most active at 45 °C, above which heat nociceptors start responding [2]. There are three types of nociceptors: mechanical, thermal, and polymodal. The mechanical nociceptors respond to painful tactile stimuli, often associated with tissue damage, and the thermal nociceptors respond to extreme changes in skin temperatures (<5 °C or >45 °C). Polymodal nociceptors respond to destructive mechanical, thermal, and chemical stimuli [2]. Not only the sensory modality depends on the sensory receptors, but also its nerve impulse is conducted via specific types of nerve fibers. Vibration, touch, and proprioception senses are conveyed through fast-conducting, large-diameter, myelinated (Aα or Aβ) nerve fibers while temperature and pain sensations are conveyed through slow-conducting, small-diameter, myelinated (Aδ) or unmyelinated (C) nerve fibers. The first group of the nerve fibers is often called "large fibers" and the latter "small fibers."

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Sensory Evaluation in Clinical Neurology

The examination of the sensory system is a very important part of clinical neurology. The results can confirm the presence, determine the localization, identify the cause, and grade the severity of the neurologic problem. Because the sensory system is organized by different modalities as mentioned above, the clinical exam is usually performed to check on each modality separately by utilizing different tools that can give different type of stimuli aimed to stimulate each type of sensory receptors. A tuning fork is commonly used to check on the *vibration sense*. The frequency of the tuning forks can vary from 64 to 165 Hz [3, 4]. However, the most commonly used frequency of a tuning fork is 128 Hz [5]. The method can be all-or-none response, where the subject reports whether he or she feels the vibration sense, or graded response, where the duration of the feeling of vibration is recorded, or comparative, where the sensation on one side is compared to the other corresponding side. Some type of tuning fork can be used quantitatively such as Rydel-Seiffer type [6]. The *touch sense* is checked on by swift touch on the skin by a cotton wool, tissue, or even a finger. Quantitative assessment of touch sense can be considered by using Semmes-Weinstein monofilaments [7]. This is noninvasive, rapid, and low-cost test that can be used in a clinical exam room. The filament is applied to the skin until it bends, and the patient will acknowledge each time he or she senses the monofilament. The touch threshold is determined by which filament can be sensed. The use of the filaments has been adopted widely. It is considered by some authors to be a good screening method to identify diabetic patients who are at risk of developing foot ulcers and having peripheral neuropathy [8, 9]. *Pain sensation* is tested most commonly by using a sharp object such as a safety pin, and *temperature sense* can be checked by using a warm or cold flask containing warm or cold water.

Even though routine sensory exams are used widely in clinical practice, the methods mentioned above are not usually quantifiable or, at most, semiquantitative. The intensity of stimuli and the methods of delivery of stimuli differ significantly between each test performance. In day-to-day experience, interobserver and intraobserver variability in routine sensory exam is frequently observed and makes the results of the exam not reproducible. Besides, different institutions may adopt a different approach for the assessment of the same sensory evaluation. A tuning fork has also been shown to overestimate vibration assessment compared to a more quantitative assessment [10]. Quantitative method of bedside sensory assessment such as the use of 64-Hz Rydel-Seiffer tuning fork may have a good correlation with sensory nerve action potential amplitudes on nerve conduction studies [3]. However, the use of Semmes-Weinstein monofilaments has been more controversial. It can be more or less specific for the diagnosis of peripheral neuropathy based on nerve conduction study [11, 12]. Moreover, if sensory assessment is used as an end point in a clinical trial, there will be a need for a more validated, gender- and age-control, quantifiable, and sensitive technique.

Method of Automated Quantitative Sensory Testing

An automated system to evaluate the sensory function has been designed. The concept of the system is to deliver each sensory stimulus, including touch-pressure, vibration, thermal, and heat-pain sensory stimuli, in a quantifiable and reproducible manner [13]. The system requires an apparatus that can deliver specific type of sensory stimuli in a method that is best time-efficient and accurate and employ the best method of presentation of stimuli to the subjects. At the same time, the method should be able to score the result by defining the threshold of each sensation and establishing normal values and validating them to a large number of normal subjects and adjusting them according to age, gender, and test site. In general, these methods will be categorized into the following: presentation of stimulus, subject's response, and method of threshold determination [14].

Presentation of Stimulus

There are two methods of the presentation of stimulus: method of limits and method of levels. In *method of limits*, the stimulus increases (such as in warm stimuli) or decreases (such as in cool stimuli) until the subject starts feeling the appearance or disappearance of stimuli, in which case, the subject will press a response key and that will stop the stimulation. This type of stimuli is also called dynamic stimuli [15]. The sensory threshold (appearance threshold) is the intensity of the stimulus at which the subject acknowledges the feeling. A good example of how dynamic stimuli work is to look at the Marstock method demonstrated by Verdugo and Ochoa [16]. This method delivers hot and cold stimuli by changing the direction and intensity of electrical currents applied to a thermostimulator. A thermostimulator creates changes in the temperature of a thermode attached to the skin. Incoming currents cause increase in the skin temperature and outgoing currents decrease in the temperature. Heat ramp is kept from 5 to 50 °C to prevent tissue damage and damage to the thermode itself, in which case, the direction of the currents is automatically reversed when those temperature limits are reached. Baseline skin temperature is kept at 32 °C. This method can evaluate warm and cool threshold (when the subjects start to feel the first change in skin temperature) and heat-pain and cold-pain threshold (when the

feeling of pain starts). Thresholds are expressed in the physical unit (temperature) at which the subjects acknowledge the change. An advantage of using dynamic stimuli is that this method is time-saving. However, the subject's response always includes reaction time which makes the subject overestimate the sensory threshold. To overcome issues on reaction time, trapezoid-shaped stimuli are recommended instead of the usual triangular-shaped stimuli [17]. Besides, the sensory threshold determined by this method can be affected by "learning effects" [18].

In the *method of levels*, the changes in the level of sensory stimuli happen in a stepwise manner. In each step, the stimulus is given with predetermined intensity and duration depending on the stimulus "step." The step is usually numbered from small to large with corresponding low and high level of stimulus, respectively. The duration and intensity of the stimulus at each step is quantified and reproducible. The intensity or duration of the stimulus at the next level depends on the response of the subject to the preceding stimulus. This method is reaction-time exclusive and, therefore, minimizes test response variability. However, it is more time-consuming. This type of the stimuli is called static stimuli [15]. The sensory threshold is the intensity level that is perceived by the subject 50 % of the time. Compared to static stimuli, using dynamic stimuli tends to overestimate sensory threshold, especially fast- and high-intensity stimuli, and also creates a sense of "expectation." These effects have been shown in vibration [19], temperature, and heat-pain testing [20]. To deliver static stimuli, a good example is to look at the use of Computerized Assessment of Sensory Examination (CASE IV®; WR Medical) QST equipment [21]. There are two methods or algorithms to deliver static stimuli: a *forced-choice* technique [19] and a *4-2-1 stepping algorithms* [22]. For either technique, a subject sits in front of a visual cuing device and will be let alert of a time period when the stimuli may be delivered (yellow light = get ready, green light = test in progress). In general, the time period when the stimuli may be delivered will be displayed in number 1 or 2. The stimuli are delivered randomly. Null stimuli are used only in 4-2-1 stepping algorithms. Null stimuli are delivered randomly in between to assure alertness and attentiveness of the subject. When and how many the null stimuli are delivered are unknown to the subject. The subject is, by that time, already attached to either vibration or thermal transducers depending on which modality of sensation is being tested. In a force-choice technique, the subject is forced to acknowledge at which time period (1 or 2) the stimuli are present after the last (2) period indicator appears in the visual cue. Even if the subject is not sure, he or she will still have to choose a "most likely" time period in which the stimuli might be. Null stimuli are not used in forced-choice method. The stimulus will never be delivered in both periods, only in period 1 or 2. Because the subject will have a 50 % chance of guessing where the stimulus is, a sensory threshold determined by a forced-choice method is set as the stimulus level at which a subject is correct 75 % of the time. In a 4-2-1 stepping algorithms, the subject acknowledges the presence of each stimulus at the time right when he or she feels it (in either 1 or 2 time period). The subject acknowledges the response by pressing a response key (yes = felt, no = not felt). The advantage of using a force-choice technique is that it eliminates the indecisiveness (slow reaction) from the subject and can help in discriminating "internal" sensation (if this sensation is there already) from external stimuli. The disadvantage of the force-choice technique is that it is more time-consuming and requires more understanding of the test and more attention from the subject. It is also easier for a subject to make mistakes in forced-choice methods. If done right, the thresholds estimated from 4-2-1 stepping algorithms are comparable to those from a forced-choice method [22].

In CASE IV, the magnitude of stimulus is measured not in physical units (displacement or temperature) but in a unit called *JND* (*just-noticeable difference*). One JND unit is the minimal difference of the intensity between two stimuli to make a subject feel different during the stimulation. The sensory perception is governed by psychophysical laws [23]. According to psychophysical laws, the relationship between the sensory perception and stimulus strength is not linear but exponential. Therefore, it is more accurate if the stimulus strength is expressed as JND, not physical units, when the numerical value of threshold is used for statistical calculation [4].

In delivering static stimuli (both vibration and thermal) with CASE IV, the magnitude of each step of stimuli has been discretely defined and set up as 25 JND steps(ranging from step 1 JND (smallest magnitude) to step 25 JND (largest magnitude)) [21]. For vibration testing, the stimulus is created from a stimulating probe, which is placed over the skin. This probe is part of a vibration stimulator set at precisely 125 Hz of vibration and has displacement between 0.1 and 576 μm [21]. In CASE IV, step 1 is defined as displacement of <1 μm and step 25 as 315 μm [4]. A 30-g preload weight is used to balance the movement so that there is no non-stimulus vibration. In vibration testing, the stimulus is shaped into sinusoidal curves wrapped in an exponential envelope. For thermal testing, a thermode is placed over the skin. This thermode provides a ramp of increasing (heat) or decreasing (cool) temperatures in a precise manner. The shape of the stimulus is either triangular or trapezoid. The lowest temperature is set at 10 °C and the highest 50 °C [4]. If more strength of stimulus is required for a higher or lower JND step after the highest or lowest temperature has been reached, the duration of the stimulus can be kept longer to increase the strength without causing tissue damage.

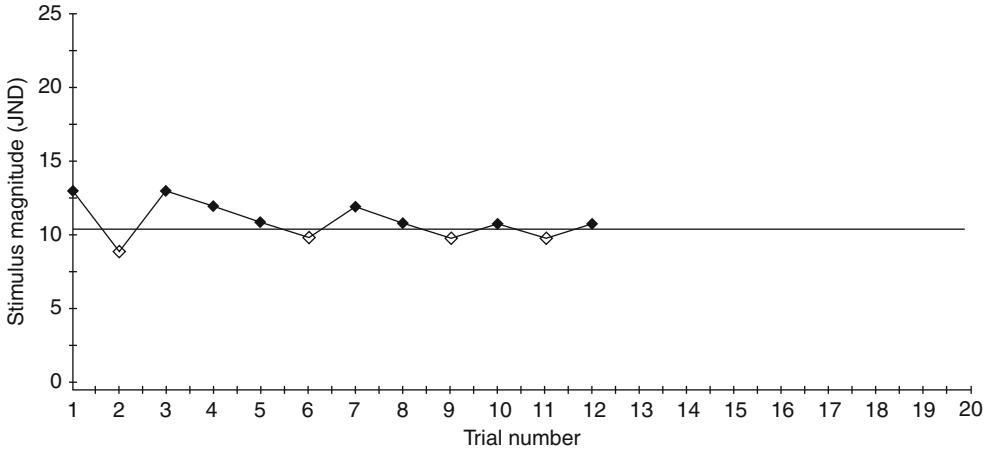

Fig. 11.1 Forced-choice algorithm. The diagram illustrates the sequence of a force-choice technique on vibration threshold testing performed on a subject using CASE IV device. The test was done at the fingertip of the left index finger. The test starts with JND 13. The ● represents success. The ○ represents failure. Success is defined as correct identification of a stimulus pair six of seven times or five of the first six times and seven times incorrect and the eighth and ninth time correct according to Dyck et al. [4]. Step 1(●, JND 13) = ssssss, step 2 (○, JND 9) = sfssf, step 3 (●, JND 13) = ssssss, step 4 (●, JND 11) = ssssss, step 5 (●, JND 10) = ssssss, step 6 (○, JND 9) = ff, step 7 (●, JND 12) = ssssss, step 8 (●, JND 11) = fssssss, step 9 (○, JND10) = ff, step 10 (●, JND11) = ssssfss, step 11 (○, JND10) = ff, step 12 (●, JND11) = sfssssss. The changes in stimulus level follow 4-2-1 rules. Null stimulus is not given in forced-choice algorithm. In this subject, the vibration detection threshold is 10.5 JND and 92nd percentile

Subject Response and Method of Threshold Determination

Either in forced-choice or 4-2-1 algorithms, the test usually starts with an intermediate JND step (step 13) delivered to the subject. The next level of JND delivered depends on the response from the subject. In general, the stimulus delivery follows the rule of up-down transformed rule described by Wetherill [24]. This rule dictates that every step of "felt" stimulus will be followed by the next stimulus of lesser strength until the subject no longer feels. Then, the next step will be of a stimulus of increasing strength (up-turnaround point). Similarly, every "not felt" stimulus will be followed by the next stimulus of greater strength until the subject starts to feel. Then, the next step will be of stimulus of lesser strength (down- turnaround point). In forced-choice algorithms, step 13 will be followed by larger or smaller steps depending on the response of the subject and the rule described by Dyck et al. [4]. At each stimulus level, the subject will be tested up to eight times before the next level of stimulus is given. If the subject answers correctly, the next stimulus level will be decreased. If the stimulus is identified incorrectly, the next stimulus level will be increased. The threshold is determined from the mean JND at the last six turnarounds. The sequence of testing results is shown in Fig. 11.1. In 4-2-1 stepping algorithms, the stimuli are similarly divided into 25 discrete JND steps. In this algorithm, null stimuli will be given randomly with the real stimuli. After the initial step (13), the next stimulus will depend on the subject's response and follow the rule above. The stimulus level will be changed by 4, 2, and then a sequence of 1 JND step change. Again, the threshold is determined by the mean JND at the last six turnarounds. The sequences of testing result are shown in Fig. 11.2. In 4-2-1 algorithms, if a subject gives affirmative responses to two or more of null stimuli, the test is not considered valid and needs to be retested, and if this happens again for two more subsequent occasions in the same subject, a forced-choice technique is recommended. If step 25 is not repeatedly felt (at least three times), the subject is considered "insensitive" (Fig. 11.3), and if step 1 is recurrently felt (at least three times), the subject is considered "hypersensitive." Some responses are not considered legitimate. For example, if the subject identified the same level of stimuli as "felt" one time and "not felt" another time, the subject may have not paid enough attention to the test. One possibility is that the subject fell asleep or his/her mind was occupied by other issues, not the test at hand (Fig. 11.4). In this case, the test needs to be repeated or switched to the force-choice technique.

Forced-choice and 4-2-1 stepping algorithms are not used in testing heat-pain threshold. These algorithms can produce overstimulation and cause tissue damage in this category of sensation test [25]. Instead, the method employs a series of non-repeating heat ramps of increasing level to stimulate pain sensation with null stimuli [25]. In CASE IV, the subject will be presented with a visual analog pain scale with pain level ranging from 1(least) to 10 (most), with 0 level indicating no discomfort or pain. At the level 0, the subject may feel only warm or hot feeling but still no pain feeling. When the subject starts feeling pain (minimal), the subject will choose level 1 and will report this to the operator. When the subject feels that he or she no longer wants the thermal stimulus to

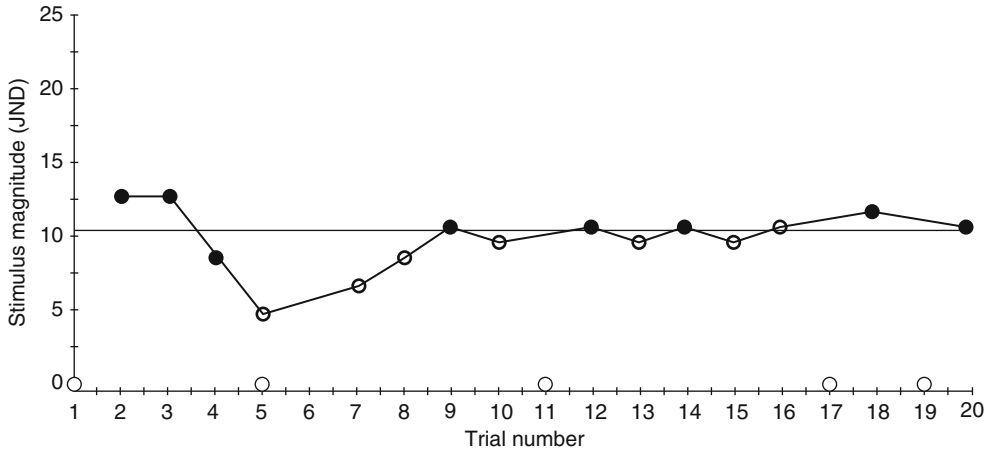

Fig. 11.2 4-2-1 stepping algorithm with null stimuli. The diagram illustrates the sequence of a 4-2-1 stepping algorithm on vibration threshold testing performed by the same subject as in Fig. 11.1 using CASE IV device. The test was done at the fingertip of the left index finger. The test starts with JND 13. The ● represents "felt." The ○ on the graph represents "not felt." The ○ on the trial number axis represents null stimuli. Please note that the changes in the stimulus level follow 4-2-1 stepping rule described in the text. In this subject, the vibration detection threshold is 9.8 JND and 89th percentile

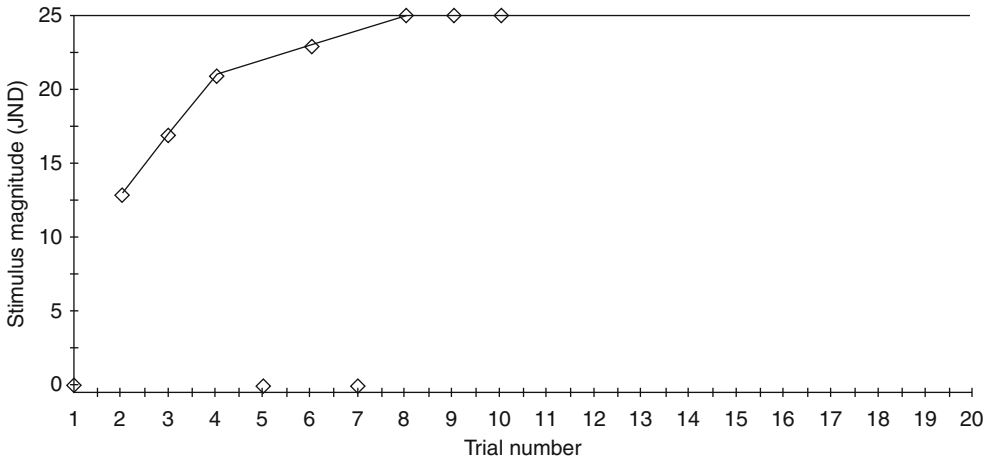

Fig. 11.3 Vibration insensitivity. The diagram illustrates the sequence of a 4-2-1 stepping algorithm on vibration threshold testing performed by another subject using CASE IV device. The ○ represents "not felt" as mentioned under Fig. 11.2. In this subject, the vibration sensate was not felt even though the stimulus level was raised to JND 25. When the subject did not feel JND 25 level for three consecutive times, the test was terminated and the subject was declared "vibration insensitive"

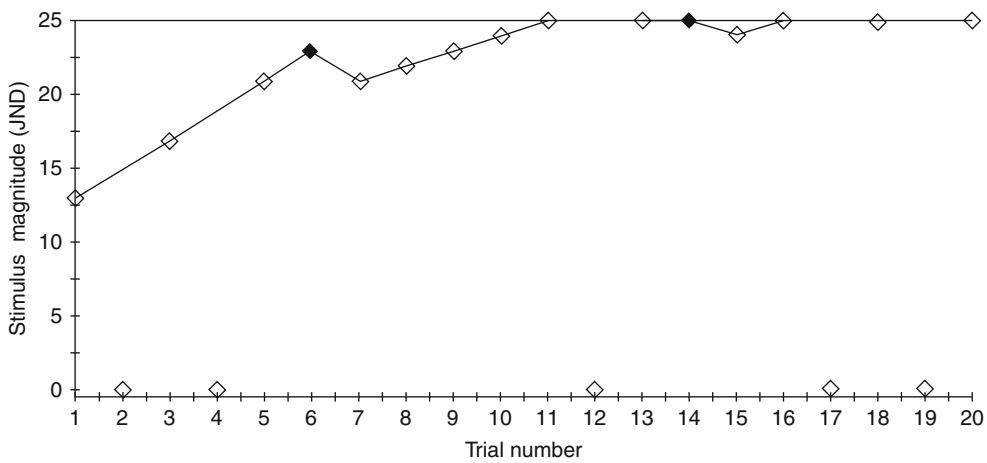

Fig. 11.4 Unacceptable result of testing. The diagram illustrates the sequence of a 4-2-1 stepping algorithm on vibration threshold testing performed by a subject using CASE IV device. In this subject, the step 6 (JND 23) was felt. However, subsequent steps with JND 23 or higher were not felt. With a pattern like this one, the threshold cannot be determined, and the test should be repeated. The ● represents "felt." The ○ represents "not felt"

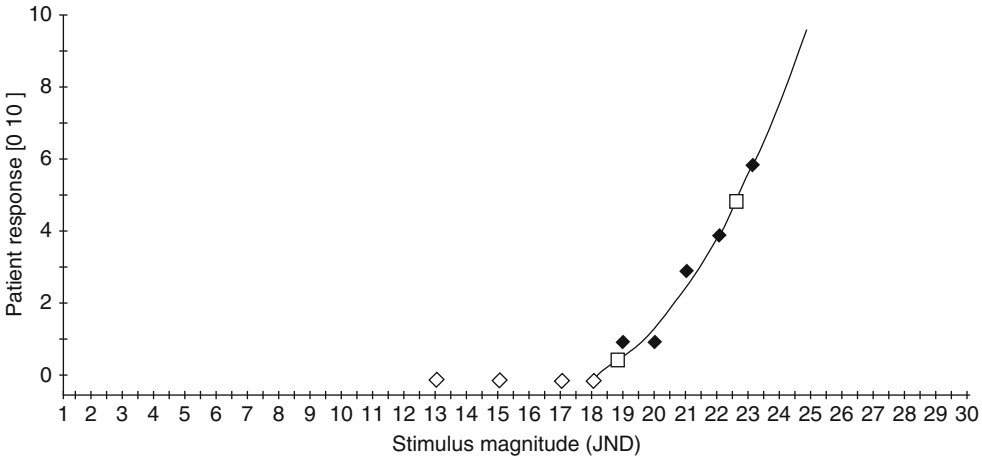

Fig. 11.5 Non-repeating heat-pain algorithm with null stimuli [4]. The diagram illustrates the sequence of steps to determine HP threshold by a subject using CASE IV device. The test starts with JND 13. The ● represents "pain feeling." The ○ represents "warm feeling only." The □ represents HP 0.5 and HP 5.0. The difference between HP 5.0 and HP 0.5 is HP 5.0-0.5. In this subject, HP 0.5 =18.8 JND (12th percentile), HP 5.0 = 22.5 JND (47th percentile), and HP 5.0-0.5 = 3.7 JND (88th percentile)

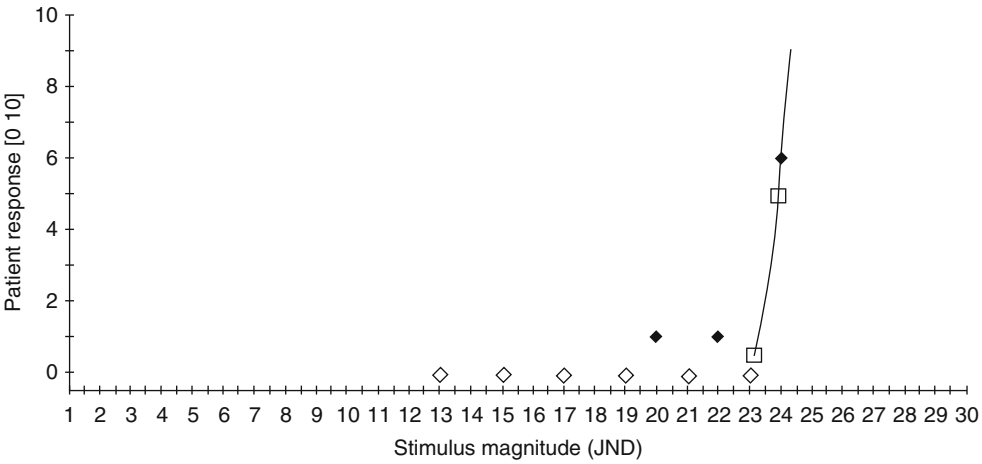

Fig. 11.6 Heat-pain hypersensitivity. The diagram illustrates the sequence of steps to determine HP threshold by a subject using CASE IV device. The test starts with JND 13. In this subject, HP 0.5 = 23.2 JND (97th percentile), HP 5.0 = 23.9 JND (75th percentile), and HP 5.0-0.5 = 0.7 JND (1st percentile). The ● represents "pain feeling." The ○ represents "warm feeling." The □ represents HP 0.5 and HP 5.0

increase, the subject will report level 10 (most discomfort). Because heat-pain threshold is the thermal level at which the subject feels pain 50 % of the time, the levels 0.5 (HP 0.5) and 5 (HP 5.0) are used for threshold description [25]. The sequence of test results is shown in Fig. 11.5. HP 0.5 is considered to be the heat-pain threshold, and HP 5.0 is the intermediate pain level. The difference between the threshold (HP 0.5) and the intermediate step (HP 5.0) is named HP 5.0-0.5. HP 5.0-0.5 indicates tolerability of a subject to increasing pain stimulus. In heat-pain testing, not only elevated thresholds (hypoalgesia) but also decreased thresholds (hyperalgesia) can be established (Fig. 11.6). Using this method, only erythema of the skin can happen, but tissue damage (burns) is not expected.

When performing automated quantitative sensory testing, vibration threshold estimation is usually done first, followed by thermal (cool and warm), then heat-pain threshold estimation the last. In all these tests, normal values controlled for age, gender, test sites, methods of tests, and stimulus presentation are available [4]. The threshold is usually reported in percentile value compared to the results obtained from normal populations. Elevated thresholds are considered when the thresholds obtained are >95th percentile compared to normal population. In evaluating heat-pain sensation, decreased thresholds or hypoalgesia is considered when the thresholds are <5th percentile. However, for more restricted criteria, especially for a research purpose, the cutoff points of >97.5th or >99th and <2.5th or <1st percentile may be considered [26]. Normal values for different type of equipment may not be applicable to CASE IV and have been established [27]. Normal values for children and adolescents are also available for a different type of equipment [28]. Cautions need to be taken on choosing normal values because this may change according to type of equipment, test methods chosen, and stimulus types.

Limitations of Quantitative Sensory Testing

Even though quantitative sensory testing (QST) is very helpful for the reasons mentioned above, the technique has some disadvantages or shortfalls. First of all, QST requires a special equipment and needs to be done in a quiet environment without distraction such as in a separate, quite room. The

subject needs to be alert, pay attention to the instructions, cooperative, and follows the testing protocol closely until the test ends. If the subject becomes drowsy, falls asleep, or is under influence of psychotropic drugs, the test results may deviate. However, a small dose of simple analgesics does not affect the test outcome [29]. Secondly, QST cannot differentiate between peripheral and central causes of sensory deficits. QST by itself has no anatomical-localizing value apart from telling which fiber types (large, small, or both) are involved. For example, QST is used to evaluate central pain syndrome after stroke [30]. Thirdly, the subject may deliberately alter the results, especially in a medicolegal case, so that they appear abnormal or more abnormal than what really is [31]. Fourthly, because it is a psychophysical testing, the response is always subjective.

Clinical Applications of QST

Because QST is a standardized, quantified, reproducible sensory testing with validated normal values, the use of QST has been adopted in many clinical situations [32]. QST can be used in establishing a diagnosis, quantifying severity, identifying fiber type involved, following up a patient after the use of medications or other treatment intervention, and following up the subjects participating in a research project if the research project uses QST as an end point [33]. In establishing the diagnosis of peripheral neuropathy, one has to keep in mind that an abnormal QST result is not by itself diagnostic of peripheral neuropathy but QST is a helpful tool when used in combination with another diagnostic test in defining the diagnosis of peripheral neuropathy.

The Role of QST in Generalized Peripheral Polyneuropathy

QST has been used mostly to evaluate generalized polyneuropathy. Diabetic distal sensorimotor polyneuropathy is the most common neuropathy that uses QST as a diagnostic and evaluating tool. QST assessing vibration and cooling threshold has been incorporated into diagnostic criteria to diagnose diabetic neuropathy in a large longitudinal study [34]. On long-term follow-up, it has been shown that vibration detection threshold was a good measure showing the worsening of diabetic neuropathy even though monotone worsening was better shown by the neuropathy impairment composite score of the lower limbs [35]. In diabetic patients without polyneuropathy, however, QST showed no monotone worsening toward the development of neuropathy, compared to a composite score from the nerve conduction study attributes [36]. The abnormalities in the patterns of QST, especially vibration (VDT), cooling (CDT), and heat-pain (HP 0.5 and HP 5.0) detection thresholds, correlate with the severity of diabetic polyneuropathy [37]. When using ≥97.5th percentiles as abnormal, patients with diabetic polyneuropathy who have abnormal VDT, CDT, HP 0.5, and HP 5.0 have more severe symptoms. HP 5.0-0.5, which indicates pain-stimulus response slope, if it is in the ≤2.5th percentile or suggests hyperalgeisa, was also correlated with the severity of diabetic polyneuropathy [37]. The use of QST has been accepted as a method of assessment of response to treatment in clinical trials on polyneuropathy [38]. In a clinical trial evaluating recombinant human nerve growth factor in patients with diabetic polyneuropathy, QST assessing CDT and HP 5.0 were used as a second end point to indicate the effect of the treatment and placebo on the studied subjects [39]. Likewise, QST was also used as a secondary end point in clinical trials assessing the use of antioxidant, alpha lipoic acid [40, 41], and aldose reductase inhibitor [42] in diabetic polyneuropathy. However, the centers participating in a clinical trial have to use the same QST device because different devices do not share the same normal values and the results may not be comparable [43]. When QST is used in that manner, the results are found to be reproducible [44].

The other common clinical application of QST is to assess and diagnose small fiber neuropathy (SFN). SFN is a very common sensory neuropathy seen in clinical practice. A patient is suspected to have SFN when one presents with positive sensory and pain symptoms but routine electrophysiologic studies are normal or minimally abnormal [45]. The diagnosis is based on demonstration of abnormal small fiber nerve functions and/or pathology [46]. Because QST can evaluate each modality of sensory function separately, QST has a role in diagnosis of SFN when abnormality is seen in cooling, warm, or heat-pain detection threshold while vibration detection threshold is normal [47]. The other diagnostic tools for SFN include skin biopsy to study intraepidermal nerve fiber density [48] and the assessment of sweat output by quantitative sudomotor axon reflex testing (QSART) or thermoregulatory sweat test [49]. In a large study on painful sensory neuropathy, the sensitivity of QST (abnormal cooling threshold) in diagnosing SFN was about 72 %, ranked between skin biopsy and QSART [50]. In the other study, the sensitivity of QST in SFN was up to 100 % [51]. In most cases, abnormal VDT can be allowed due to mild coexisting involvement of large fiber nerves [50]. QST abnormalities do not predict pain symptoms in sensory neuropathy [52, 53] suggesting that the mechanism of pain symptoms in sensory neuropathy, especially SFN, may have other associated mechanisms rather than small fiber dysfunction alone [54].

Assessment of sensory abnormalities by utilizing QST has been commonly used in cancer and chemotherapy researches to identify cancer subjects who have abnormal

sensation at baseline before, during, or after chemotherapy [55–59]. In some of these studies, QST alone was performed either to screen the patients before chemotherapy or to follow up on the patients after chemotherapy, especially when they developed neuropathic symptoms. However, without a gold standard of the nerve conduction studies, the validity of QST alone as a test to identify peripheral neuropathy is in doubt. Besides, the methods and devices of QST in these studies were different making comparison between studies impossible. In a study on subclinical peripheral neuropathy in colorectal cancer, touch detection was done by Semmes-Weinstein monofilament and BUMPS device while thermal detection was done by heat ramps with dynamic stimuli [59]. Another study on neurotoxicity of paclitaxel in patients with breast cancer used handheld biothesiometer to assess vibration threshold [58]. In a study on suramin-induced neuropathy after the use of the agent to treat prostate cancer, QST by CASE IV was incorporated into Total Neuropathy Score to categorize the patients along with standard electrophysiological studies and other clinical assessment [60]. In that study, QST showed good correlation with the presence of peripheral neuropathy after the treatment [60].

In diseases that have high prevalence of SFN, such as human immune deficiency (HIV)-associated sensory neuropathy and Fabry disease, QST has been widely used to assess and diagnose SFN. Heat-pain threshold (HP 0.5) and epidermal nerve swelling seen from skin biopsy were found to predict the development of HIV distal sensory neuropathy [61]. There was also a good correlation between the swelling of the intraepidermal nerves and HP 0.5 and HP 5.0 [62]. In a study with a longer follow-up, an abnormal CDT, HP 0.5, and leg intraepidermal nerve fiber density were found to predict transition to symptomatic HIV distal sensory neuropathy [62]. QST has been shown to add significantly to the research diagnosis of HIV-associated sensory neuropathy [63]. QST was included in a study on an antiretroviral medication, 2′,3′ dideoxycytidine (ddC), and its role in sensory neuropathy in HIV patients [64]. In this study, abnormal vibration detection threshold was found to precede the occurrence of clinical symptoms. Fabry disease is an X-linked metabolic disease caused by deficiency of alpha-galactosidase resulting in accumulation of galactosyl conjugates, especially globotriaosylceramide, in vascular endothelial cells in various organs. QST has an important role in identifying SFN related to this disorder [65]. QST was one of the outcome measures in a clinical trial assessing enzyme replacement therapy in Fabry disease, showing significant reduction in warm and cooling detection threshold after 3 years of treatment [66].

QST has also been used in the assessment of abnormal sensibility in many other disorders that cause predominantly sensory neuropathy or SFN such as uremia [67], leprosy [68], familial dysautonomia [69], and hypothyroidism [70].

The Role of QST in Focal Peripheral Neuropathy (Such as Carpal Tunnel Syndrome)

Because of its noninvasiveness, QST has been tried to identify cases of entrapment neuropathy, especially carpal tunnel syndrome. If QST is going to be helpful in carpal tunnel syndrome, the sensory threshold at the tip of the second digit should be higher than the fifth digit, and the sensitivity of abnormal QST should be at least equal to or, better, higher than the nerve conduction study that is already the gold standard diagnostic test for carpal tunnel syndrome. However, many studies that were done to look at these particular issues failed to support the use of QST as a diagnostic test for carpal tunnel syndrome. One study looked at vibration threshold at the second and fifth finger tips on 28 affected limbs in 17 patients with carpal tunnel syndrome [71]. The VDT was compared to the standard nerve conduction studies. Even though there was a good correlation between elevated VDT at the second digit and abnormal nerve conduction study indicating a median mononeuropathy across the wrist, concomitant elevation of vibration threshold was found in 36 % of the patients [71]. Another study looked at thermal (hot and cold) threshold using automated force-choice procedure at the second and fifth finger tips on 24 patients with carpal tunnel syndrome and 25 controls [72]. Again, the thermal threshold detection was compared to the standard nerve conduction studies. Abnormal thermal (both hot and cold) threshold was found to correlate well with the nerve conduction studies. However, abnormal thermal threshold, especially cold threshold, was found frequently on the fifth digit [72]. The sensitivity of abnormal vibration and thermal threshold in carpal tunnel syndrome was unacceptably low [73], especially when compared to the nerve conduction studies [74]. Similar findings were found in a large study using vibrometry and electrophysiologic testing in 130 factory workers for carpal tunnel syndrome [75]. In a large study using vibrometry with different frequency to screen for carpal tunnel syndrome compared to the nerve conduction study in 169 industrial workers, vibration threshold was found to correlate poorly with the nerve conduction studies when the carpal tunnel syndrome was mild or early thus precluding a vibrometer as a good screening method [76].

The Role of QST in Central Nervous System Disease

The role of QST in diseases of the central nervous system is limited. Neuroimaging studies such as magnetic resonance imaging study or computerized tomography scan and electrophysiologic studies such as somatosensory evoked potential study already are efficient in demonstrating a lesion within or detecting objective physiologic changes in the

central nervous system, respectively. QST is not usually used to diagnose central nervous system diseases. However, QST has an advantage of detecting functional abnormalities in spinothalamic- or posterior column-specific modality of sensory system separately. So, its use has been limited to study sensory abnormality in the central nervous system pertaining to specific modality of sensory function. QST has been used to study sensorimotor dysfunction in patients with multiple sclerosis correlated with magnetization transfer imaging of the spinal cord [77]. QST was also used in the study of the mechanism of central pain in patients with syringomyelia [78] and stroke [79]. The other use of QST in central nervous system diseases can be demonstrated by the use of QST in studying sexual dysfunction in female patients with multiple sclerosis [80] and the use of QST in studying recovery of sensory symptoms in acute stroke [81].

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Nerve and Muscle Biopsies

12

J. Douglas Miles and Mark L. Cohen

Peripheral Nerve Biopsy

Several texts, small monographs, and reviews give comprehensive accounts on the surgical techniques of nerve biopsy, the specialized procedures required to process the biopsy, and the pathology of peripheral nerve disease [1–13]. As is the case with neuropathology in general and neuromuscular pathology in particular, the interpretation of histopathologic and molecular biologic findings derived from examination of the nerve and muscle biopsies always requires detailed correlation with information on the patients' clinical status. This brief account will give an overview of the topic; for in-depth information, the reader is referred to the references noted above.

The distal sural nerve on the lateral aspect of the ankle, posterior and just superior to the lateral malleolus, is the most common site of nerve biopsy. There are several reasons that the sural nerve is a favorite site: surgical sampling is easily accomplished with a superficial skin incision, the clinical deficit is limited to a small patch of sensory loss on the skin of the foot, and there is extensive morphometric data at this site. Since the sural nerve is a sensory nerve, the information derived from the study of the biopsy must be extrapolated to apply to any type of peripheral nerve. As sensorimotor neuropathies are so common, compared to pure motor neuropathies, this expediency is justified.

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General Remarks

Peripheral neuropathy is a very common disorder in clinical practice and its causative factors numerous. On the other hand, the need for nerve biopsy in the diagnosis of peripheral neuropathy is uncommon. History, physical exam, electrodiagnostic testing, and laboratory workup are sufficient in the majority of cases to reach a diagnosis. But there remain cases when nerve biopsy is essential, and in those cases, it is imperative for the physician reading the nerve biopsy to be cognizant of all the available clinical, laboratory, and neurophysiologic information. Dialogue between the neuropathologist and the neurologist will bring out essential clinical data such as the time of onset of the patient's peripheral neuropathy, the duration and rate of progression of the illness, and the anatomic distribution of the involved nerves.

As described fully in other portions of this text, *acute neuropathy* is characterized by an abrupt onset over the course of several days; at times, the patient may point a single day when the symptoms began. *Subacutely evolving neuropathy* occurs more slowly, becoming manifest over an interval of several weeks. *Chronic neuropathies* develop insidiously over months or years and may either have a slow, relentlessly progressive evolution or follow a relapsing course, with episodes of partial improvement followed by variable, gradual deterioration. The distribution of symptoms and signs may take on a symmetric or asymmetric pattern, affect the most peripheral portions of the limbs ("stocking–glove" distribution), or involve a single or multiple nerves or roots. *Mononeuropathy* refers to involvement of a single nerve, *radiculopathy* to injury affecting one or multiple spinal roots, *plexopathy* to damage to a nerve plexus, and *multiple polyneuropathy* or "*mononeuropathy multiplex*" to disease of multiple individual nerves [14, 15].

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Processing Peripheral Nerve Biopsies

Optimal processing of a peripheral nerve requires that the biopsy be as free as possible from artifactual distortion. This goal is difficult to attain because peripheral nerve is particularly susceptible to damage from handling at the time of biopsy; such iatrogenic injury may render the biopsy findings uninterpretable. Surgical access to the sural nerve is gained through a superficial skin incision just posterior to the lateral malleolus. The surgeon must take special care to avoid applying traction or pressure on the nerve and not to infiltrate the nerve itself with local anesthetic. A segment of nerve, about 4 cm long, is carefully dissected out and then removed in continuity. It is recommended to use intraoperative frozen sections to make certain it is the sural nerve itself which has been obtained rather than a neighboring sclerotic vein. This practice is especially valuable in children where the smallness of the nerve within fibroadipose connective tissue renders dissection difficult or in elderly patients with disease states which may cause the nerve to be embedded in dense aggregates of connective or inflamed tissue. The pathologist should be notified from the operating room to be prepared to receive the biopsy promptly after surgery. Transport of the specimen to the laboratory can be carried out by wrapping the nerve in a saline-moistened gauze; some prefer to bring a tray with necessary materials to the operating room so that the tissue can be processed immediately after biopsy. An effective technique is to place the length of nerve onto a strip of dental wax and then with a very sharp blade, divide the specimen into four roughly equal segments. The specimens from both ends (i.e., those that might have been clamped by the surgeon at the time of removal) are frozen, and those from the middle are fixed. Specimens designated for fixation are pinned (or clamped) at both ends to ensure that the nerve remains stretched during fixation. One of these linear mid-specimens is placed in a container filled with formalin: this specimen will be embedded in paraffin, and transverse and longitudinal sections can be stained with H&E, Masson trichrome (connective tissue), stains for myelin and axons, immunohistochemistry, and other special stains as needed. The other stretched midportion of the specimens is quickly flooded with cold glutaraldehyde and later cut in smaller fragments to be embedded in plastic (resin) for semi-thin sections and subsequently, electron microscopic examination according to standard protocols. If nerve teasing studies are anticipated, a 1-cm segment of formalin- or glutaraldehyde-fixed tissue should be set aside for this purpose. Tissue segments designated for freezing can be embedded on a chuck for frozen section, thereby permitting immunofluorescence studies and special stains for metachromasia, or can be quick-frozen in liquid nitrogen for biochemical and genetic studies [16, 17].

The disposition of the biopsy does, of course, vary from case to case depending on clinical considerations. When the amount of tissue is limited, such as when dealing with a nerve biopsy in an infant, the procedure of choice may be resin embedding rather than paraffin embedding. Paraffin embedding with routine H&E staining is the most efficient method to evaluate tumors of peripheral nerve or to identify interstitial lesions such as vasculitis, granulomas, and amyloid. When the reason for the biopsy is to address the possibility of vasculitis, it can be argued that it is best to process all of the tissue for paraffin embedding with step sections, as this approach is the most sensitive way to detect focal lesions [18, 19]. On the other hand, paraffin embedding has limited utility in assessing properties of individual axons, whereas plastic embedding is indispensable to determine the extent of axonal loss, the specific populations of damaged axons, or abnormalities of the axon or myelin sheath. Teased-fiber analysis is performed on glutaraldehyde-fixed segments of peripheral nerve after osmication. Teased-fiber preparation is most helpful in the identification of demyelinating neuropathies, which typically have slowed nerve conduction velocity. Examples include suspected cases of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) or hereditary neuropathy with liability to pressure palsies. Assessment of the status of unmyelinated fibers or evaluation of peripheral nerve in hereditary metabolic disease ordinarily requires ultrastructural study.

Normal Nerve Histology

In the central nervous system, axons are enveloped by myelin derived from oligodendroglia. In the peripheral nervous system, myelin is derived from Schwann cells. The Redlich–Obersteiner zone or central-peripheral transitional zone is that boundary between the central and peripheral nervous systems where the one form of myelin transitions to the other. In spinal sensory and motor nerve roots, this is about 2 mm distal to the cord root entry/exit point. The site of the transitional zone in cranial nerve roots varies considerably: in the eighth cranial nerve, it is at the level of the internal auditory meatus (i.e., 8–10 mm from the nerve's point of entrance in the brainstem); in the fifth cranial nerve rootlets, it is well out into the subarachnoid space; in the lower cranial nerves, it is just a few millimeters off the brainstem [8, 20, 21].

Peripheral nerves are organized as multiple fascicles within connective tissue sheaths (Fig. 12.1) [22]. The *epineurium* is the outer sheath of connective tissue that defines the macroscopic structure of the entire nerve. It contains the large blood vessels which supply the nerve, variably dense connective tissue, and adipose tissue. The *perineurium* is composed of skeins of concentrically arranged layers of specialized perineurial cells which enclose the nerve fibers of each fascicle. In addition to this role serving as the

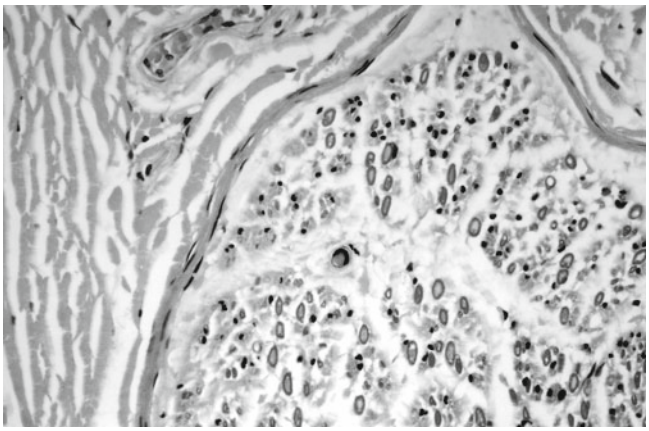


Fig. 12.1 Normal nerve. The fascicles are surrounded by perineurial layers. The epineurium is the condensation of connective tissue external to the perineurial layers, and the endoneurium is composed of axons and Schwann cells within each fascicle

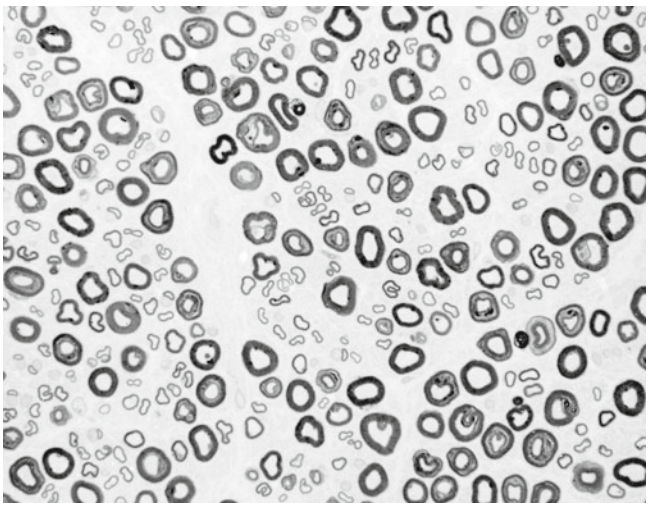


Fig. 12.2 Normal nerve. The endoneurial compartment is populated by myelinated fibers with a bimodal distribution of fiber diameter

structure responsible for the anatomic compartmentalization of fascicles, the perineurium also functions as a physiological barrier that regulates the microenvironment of the endoneurial space. The number of perineurial layers is directly related to the diameter of the fascicle. The *endoneurium* is the supporting tissue that surrounds individual axons and their Schwann cells, forming the interstitial connective of each fascicle.

Nerve fibers are the principal components of the endoneurial compartment. Nerve fibers can be demonstrated histologically in paraffin-embedded sections, resin-embedded semi-thin sections, electron microscopy, and by teased nerve fiber preparations. The latter three are by far the best methods to carefully analyze them, although general information can be gleaned also from the study of paraffin-embedded sections.

Plastic-Embedded Semi-Thin (1–2-μm-Thick) Sections

Transverse sections of plastic-embedded nerve are the best method of evaluating peripheral nerve fibers (Fig. 12.2); longitudinal sections can also be prepared to yield additional information. The sections are ordinarily stained with toluidine blue, though other suitable dyes also can be applied. This method beautifully demonstrates the orderly array of small myelinated and large myelinated fibers as well as, to a lesser extent, the unmyelinated fibers. The myelinated axon fiber diameters range from 2 to 12 μm. There is a bimodal distribution of small and large fiber diameters; small myelinated fibers are about two to four times as numerous as large myelinated fibers (Fig. 12.3). Small-caliber myelinated axons range from 2 to 6 μm; large-caliber myelinated axons range from 6 to 12 μm in diameter. The relationship between axonal diameter and myelin thickness is relatively constant; accordingly, large myelinated fibers have a thicker myelin

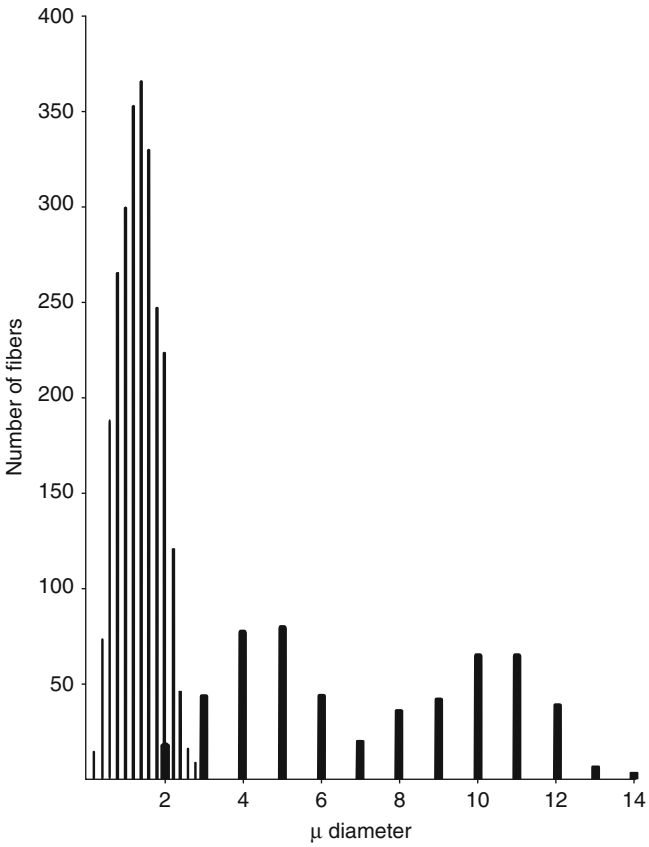


Fig. 12.3 Morphometric analysis of the normal human sural nerve. In addition to the bimodal population of myelinated fibers (*thick bars*), there is a unimodal population of unmyelinated fibers (*thin bars*) (Reproduced with permission from Ochoa and Mair [23])

sheath in comparison to that of small myelinated fibers. The *G ratio* (axonal diameter/fiber diameter) is 0.5–0.7 over a large range of axonal diameters. Plastic-embedded sections

also beautifully demonstrate the connective tissue sheaths of peripheral nerve and all of the cellular components of the endoneurial compartment.

Electron Microscopy

Electron microscopy may be an integral part of the evaluation of a sural nerve biopsy, especially in children. Detailed information on the fine structure of the myelin, axon, and supporting cells is obtainable with this technique (Fig. 12.4). Axons have a lucent cytoplasm that contains microtubules and neurofilaments. Neurofilaments, unlike intermediate filaments in other cell types, are oriented along the long axis of the axon and are evenly spaced throughout the axoplasm with perpendicular side arms. In myelinated fibers, the outer surface of the axonal plasma membrane is immediately adjacent to the innermost membrane layer of Schwann cells, with multiple concentric layers forming myelin membranes. Small portions of Schwann-cell cytoplasm, known as Schmidt–Lanterman incisures, are sequestered between the layers of myelin. The cytoplasm of Schwann cells contains intermediate filaments, microtubules, mitochondria, and occasional cytoplasmic multilayered membranous structures (known as pi, or Greek letter π, granules). The entire external surface of the Schwann cell is surrounded by a condensation of extracellular matrix, the external lamina.

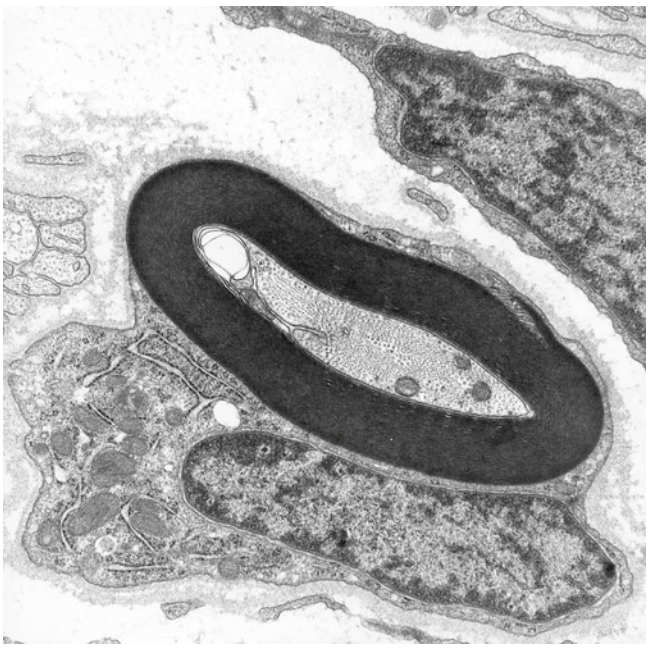


Fig. 12.4 Electron micrograph of a normal myelinated axon. The Schwann-cell nucleus is visible just below the axon

Teased-Fiber Preparations

Precise longitudinal sections of peripheral nerve are very difficult to prepare since the plane of section is usually not perfectly parallel to the long axis of the axons. To circumvent this problem, single fibers need to be teased apart from their connective tissue sheaths within the fascicles. This is accomplished as follows: after fixation with aldehydes, osmication, and treatment with glycerin (or cedar oil), large-caliber axons are teased apart with fine needles under direct visualization with a dissecting microscope; they are then lined up in parallel for detailed examination and measurement under the light microscope (Fig. 12.5). Under the light microscope, the teased fibers appear as stretches of darkly stained myelin internodes interrupted by short gaps (nodes of Ranvier) wherein course pale, barely discernible axons. The external contour of the myelin sheath is usually smooth or slightly corrugated. The nodes of Ranvier are short discontinuities of the myelin sheath where "naked" axons can be seen to course through the fiber. The length of a myelin internode varies in proportion with cross-sectional diameter of the fiber. In large-caliber fibers (around 10 μm thick), they are approximately 1 mm in length. In the peripheral nervous system, a given myelin internode corresponds to a segment of the axon that is myelinated by a single Schwann cell. In general, the internodal length and myelin thickness within the internode is constant along the length of any one fiber.

Morphometry

Transverse, plastic-embedded sections through nerve fascicles clearly demonstrate the array of seemingly randomly distributed myelinated nerve fibers of varying sizes. Morphometric methods can provide precise quantitative data concerning the density of axons within fascicles. Histograms of the human sural nerve reveal a bimodal distribution of myelinated fibers, with an overall density of 7,000–20,000 myelinated axons/mm^2. Of these, small myelinated fibers outnumber large myelinated fibers two to fourfold (see Fig. 12.4). Several excellent accounts are available on the topic of normal sural nerve morphometry in adults and children including analyses of both unmyelinated and myelinated fiber populations at different ages [6, 23–32].

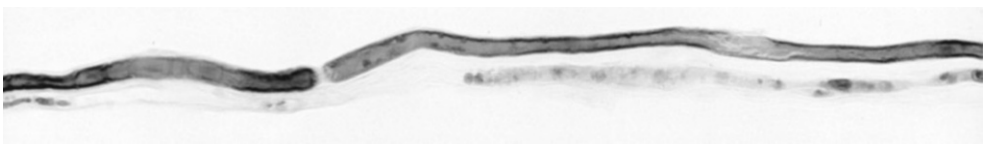


Fig. 12.5 Teased-fiber preparation of a normal nerve. The node of Ranvier is visible as the gap between internodes in the upper fiber. The lower fiber is undergoing axonal degeneration

Artifacts and Structures of Uncertain Pathologic Significance

Several artifacts may be introduced during the handling of nerve biopsies, the most common being compression, or crush artifact. With the low resolution afforded by H&E sections, the problem is less apparent; however, on resin-embedded sections and teased-fiber analysis, crush artifacts may hamper the interpretation. The large-caliber fibers show coiled myelin layers and distorted axoplasm, findings which may be confused with axonal degeneration. However, the distortion is often limited to one region of the cross section or to one region of the individual teased fibers, an important point for its recognition. Fixation of nerve biopsies without pinning down the specimen is another common problem. It may be impossible to obtain cross sections if the specimen is coiled, and the resulting resin-embedded sections show axons cut tangentially with elliptical profiles aligned parallel to each other. The effect of coiling on teased-fiber preparations may be even more dramatic. Extensive coiling precludes any effort to untangle individual fibers and eliminates the option of teased-fiber analysis. In less extensively coiled specimens, the individual fibers can be identified and separated, but the fibers have a saw-toothed appearance. Nodes of Ranvier may be identifiable, but the analysis is often hampered by frequent breaks of the fiber within the saw-toothed regions. Hypo-osmolar solutions may cause axons to swell and yield a uniformly rounded population of axons. These biopsies may be interpretable, but morphometry and other measurements may not be accurate since the axonal caliber has been altered. In addition, Schmidt–Lanterman incisures may be prominent, appearing as concentric rings within the myelin layer on cross sections and as periodic, symmetric clefts along the lengths of fibers on longitudinal sections or teased-fiber preparations.

Renaut bodies are subperineurial, loosely textured, fibrous whorled structures; they are believed by some investigators to develop in response to mechanical pressure on the nerve [33]. *Polyglucosan bodies* (*Lafora bodies*) are round or oval concentrically laminated acellular structures, ranging between 2 and 20 μm in diameter, and are located within axons and in others cells within the endoneurial compartment. They are composed largely of glucose aminoglycans. They are especially common in older individuals but are seen as well in some hereditary metabolic diseases which affect the central and peripheral nervous systems [34].

Basic Peripheral Nerve Pathology

The general pathologic processes involving peripheral nerve fibers may be subdivided into two broad categories: those primarily affecting the axon (*axonal neuropathies*) and those primarily affecting the Schwann cell or its myelin sheath (*demyelinating neuropathies*) (Fig. 12.6). It is worth noting that even when the primary pathology is demyelinating, subsequent axonal loss may sometimes occur. The neuropathologic findings of axonal loss may be further subdivided into those characteristic of the acute phases of the illness (*Wallerian degeneration*) and those that are observed in long-standing disease (*chronic axonal degeneration*).

General tissue reactions of peripheral nerve may also be viewed from the perspective of processes which cause peripheral neuropathy secondary to damage to the connective tissue elements of peripheral nerves (e.g., vasculitic neuropathies, compression neuropathies).

Acute Axonal Degeneration (Wallerian Degeneration)

When a peripheral axon is cut (or damaged in such a way as to interrupt its continuity), the portion distal to the cut undergoes a series of changes that are collectively designated as Wallerian degeneration after the original descriptions of experiments by Augustus Waller in 1850 [36]. The distal axon remains morphologically intact for a period of 3–5 days, depending on the length of the severed part (distal stump) of the axon (longer in long distal stumps than in short ones). The first discernible changes in the distal stump require electron microscopy for visualization; these consist of disintegration of cytoskeletal structures (neurofilaments and microtubules), with accumulation of granular debris in the axoplasm. Soon, the cell membrane disappears, and the axon undergoes fragmentation, whereas the myelin remains intact for a while, enclosing the remnants of the axon. The myelin then rapidly disintegrates, forming strings of round or oval fragments (ovoids, ellipsoids) (Fig. 12.7a, b). Accompanying the breakdown of axons and myelin, there are changes in the Schwann cells of the distal stumps. Within the first and second weeks, the Schwann-cell processes increase in number and fill with intermediate filaments. In addition, the Schwann cells proliferate actively, dividing longitudinally within the tubes formed by the intact basal laminae. Ultimately, these proliferated Schwann cells within the encirclement of the original basal laminae form long cellular chains known as the bands of Büngner [37]. Meanwhile, macrophages become increasingly evident at the site of fiber degeneration and are the principal cell responsible for myelin removal [38]. Although there normally are a few macrophages in the walls of the endoneurial blood vessels, most of those participating in the reaction to nerve injury are derived from the blood stream. Their numbers increase greatly, and then they pass through the intact Schwann-cell basal lamina and actively phagocytose the remains of the myelin and the axons.

The morphologic findings can be summarized as follows:

In the first days following transection of a peripheral nerve, there is (1) initially swelling of axon with disintegration

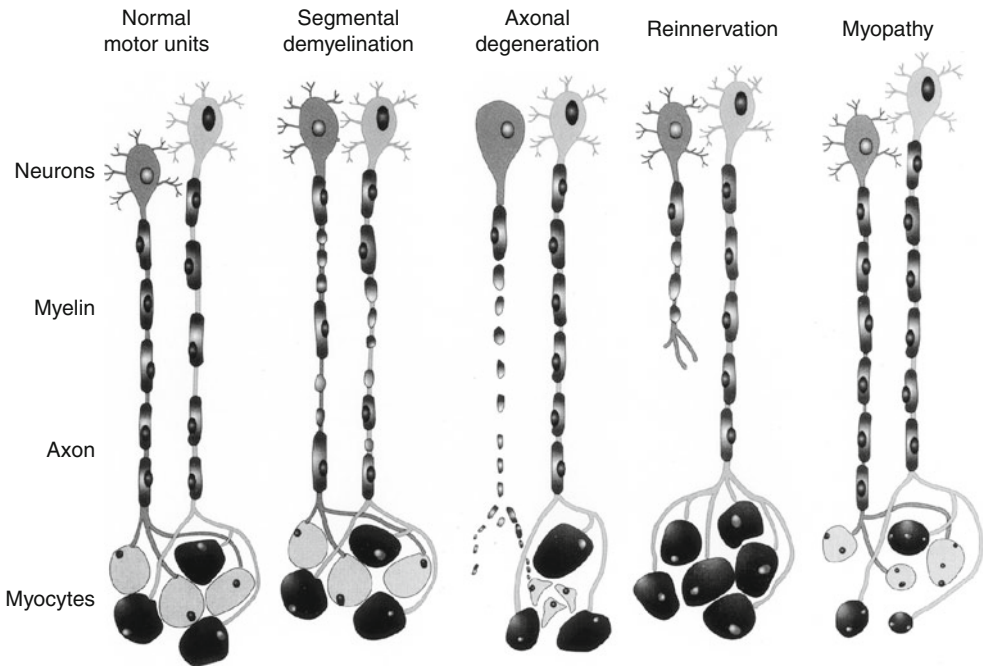


Fig. 12.6 Diagram of normal and abnormal motor units. The normal motor units show myocytes whose fiber type is determined by the axon which innervates them. Segmental demyelination results in the loss of myelin, followed by remyelination over distinct segments of the axon. Axonal degeneration, the process of the anterograde degeneration of an axon from a single point, is followed by atrophy of the myocytes within that motor unit. Reinnervation results from both sprouting of axonal termini, with grouping of muscle fibers of a single fiber type (type grouping), and from sprouting and elongation of the distal stump of the degenerate axons. In contrast, myopathies are characterized by retention of the fiber-type distribution with atrophy of scattered individual myocytes (With permission from De Girolami et al. [35])

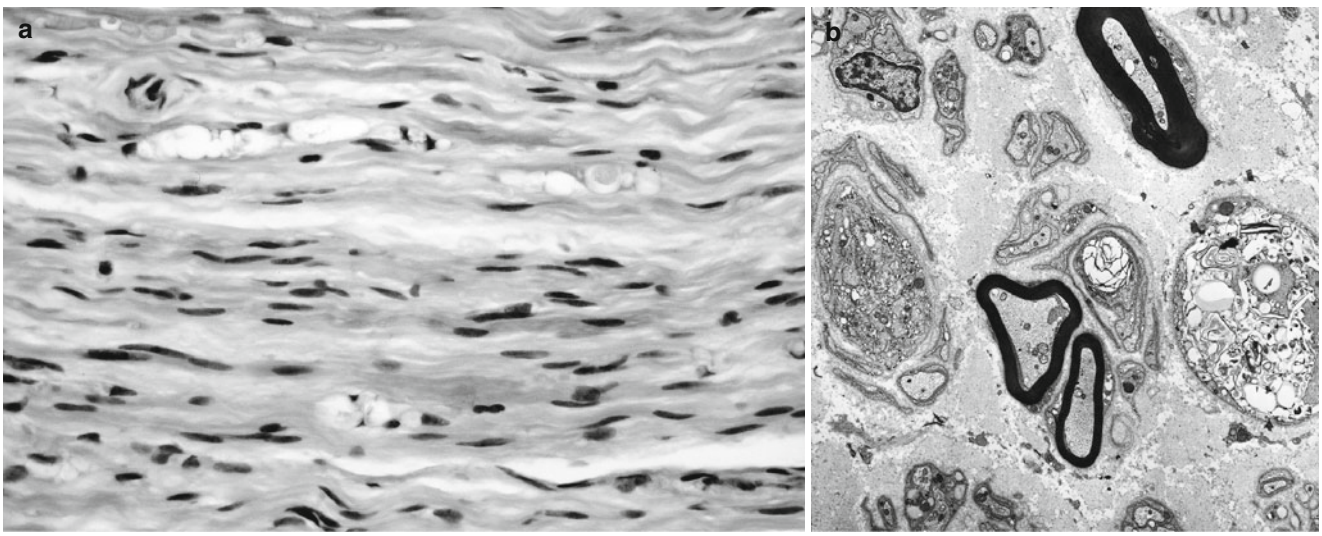


Fig. 12.7 Wallerian degeneration. (**a**) Light microscopic appearance of degenerating axons, with ovoid vacuoles arranged in a row. (**b**) Electron micrograph showing several normal myelinated axons and two degenerating axons

of tubules and filaments in the distal segments, (2) retraction and disintegration of myelin at nodes of Ranvier, (3) accumulation of vesicles and degenerating mitochondria at the proximal stump, and (4) progressive disintegration of both the axon and myelin at all points distal to the site of transection. Subsequently, but within the first weeks following transection of a peripheral nerve, there is (5) phagocytosis of axon and myelin debris by macrophages, (6) regeneration, consisting of thinly myelinated axonal sprouts, and (7) proliferation of Schwann cells along the course of the disintegrated axon.

Chronic Axonal Degeneration

Unlike Wallerian degeneration, which is the result of an abrupt interruption of the continuity of a nerve, chronic axonal degeneration characteristically proceeds slowly, with

little interstitial cellular response. Loss of the axon leads to breakdown of the myelin sheath, which undergoes fragmentation, and is ultimately removed by phagocytosis. Examination of tissue preparations of nerves in a chronic axonal neuropathy often shows no evidence of active breakdown of any component of the nerve. This is because the damage occurs in widely scattered individual fibers and therefore may not be contained in a particular tissue sample. The presence of axonal degeneration is established by the finding of decreased numbers of myelinated or unmyelinated axons in a cross section of nerve and an increased amount of endoneurial connective tissue.

Comparative counts of the numbers of fibers in the distal and proximal parts of a nerve have suggested that in some instances of axonal neuropathy, the degeneration appears to begin distally and to progress centrally. It has been postulated that under these circumstances, the primary site of the disease is in the neuronal cell bodies, which become unable to maintain the great length of the axon in the periphery—resulting in a "dying back" of the axon from its termination toward the parent neuron, but this formulation still remains hypothetical.

Axonal degeneration is described in a wide variety of chronic slowly progressive and symmetric toxic and metabolic polyneuropathies. The gradual evolution of the pathologic process to involve progressively more proximal portions of the peripheral nervous system appears to be the basis for the clinical manifestations. The pathogenesis is not certain, but dysfunction of the metabolism of the neuron rendering it incapable of supporting the axon and a direct effect on axoplasmic flow within the axon are common hypotheses.

In summary, the neuropathologic features of chronic axonal degeneration include (Fig. 12.8) (1) involvement of the most distal portions of the longest nerves, (2) initial increase in neurofilaments followed by (3) decrease of axonal organelles, (4) retraction of the axon from the myelin sheath, (5) disintegration of the axon and myelin sheath, and (6) Schwann-cell proliferation in distal portions of axons.

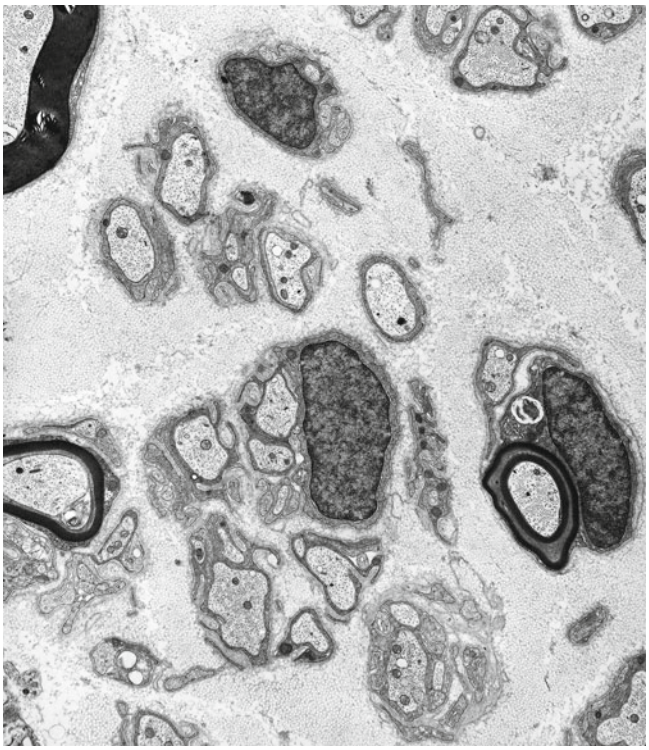


Fig. 12.8 Chronic axonal loss. Electron micrograph showing diminished population of myelinated fibers and increased endoneurial collagen

Axonal Regeneration ("Sprouting")

Axonal regeneration is observed in both acute and chronic axonal neuropathies. Following Wallerian degeneration, the central stumps of the severed nerve, still in continuity with the cell bodies of motor, sensory, and autonomic neurons, are the site of regeneration of the axons. From the severed ends of the axons, regenerative sprouts (as visualized by electron microscopy in experiments on dorsal roots in rats) begin to appear within 20 h of the transection. These characteristically are multiple—a single axon can give rise to as many as 25 sprouts. What happens to these axonal sprouts depends on the proximity to the distal stump of the nerve and the extent to which collagenous scar tissue has developed at the site of transection. If the sprouts are closely approximated with little intervening scar, many of the regenerating axons traverse the gap and enter the bands of Büngner, by which they are guided to the periphery. Other sprouts, meeting obstructions, form tangled skeins and aberrant structures that achieve no useful purpose. With wider separation of the cut ends or denser accumulations of scar tissue, the regenerating axons are prevented from reaching the distal stump and thus turn back and form tangled masses, forming neuromas.

If the original ensheathments of the axons and myelin sheaths remain in continuity, as occurs with injuries such as crushing, compression, or ischemia, the pathway for regeneration of axons is relatively intact. Regeneration under these circumstances can be more effective, with more complete functional recovery, than can be achieved following total transection.

As regeneration continues, multiple axonal sprouts enter each of the Büngner bands forming clusters of axons that are surrounded by the basal lamina of the parent Schwann cell. The presence of these clusters gives, in fact, unmistakable evidence that regeneration is occurring. Gradually thereafter, some of the axons enlarge, and a few may nearly reach the diameter of the parent axon. Meanwhile, the Schwann cells in the Büngner bands undergo rearrangement, such that a one-to-one relationship becomes established between Schwann cells and axons. These Schwann cells then remyelinate the axons that have attained a certain critical size. The new myelin sheaths, however, remain disproportionately thin for the size of the axon, and the internodes

remain disproportionately short. In chronic axonal neuropathies, it is common for cross sections of nerve biopsies to show evidence of axon loss (reduced number of myelinated fibers), axon degeneration (profiles of axonal degeneration), and axonal regeneration (axonal clusters). The groups or clusters of thinly myelinated fibers appear to arise as the proximal axonal stump sprouts multiple small neuritic processes, all of which are surrounded within the Schwann tube of the original axon. Such formations are referred to *as regeneration clusters* and are common in cross sections of nerve biopsies taken from patients with toxic or metabolic neuropathies. Soon after nerve crush or transection (24 h in experimental animals), regeneration commences in the axons proximal to the site of injury.

The typical morphologic characteristics of axonal regeneration are (Fig. 12.9) (1) scattered thinly myelinated axons or axons with undetectable myelin in a cluster, (2) clustered axons with similar diameter sizes and myelin thickness, (3) collagen fibrils interspersed among the myelinated and unmyelinated axons, and (4) a basal lamina tube that had previously enclosed a healthy axon, surrounding the complex of clustered axons.

On teased-fiber preparations, the internodal lengths of regenerated axons appear uniformly shorter than normal. (Normal internodal lengths depend on fiber diameter. A typical 10-μm-diameter fiber has an intermodal length of 0.7–0.8 mm).

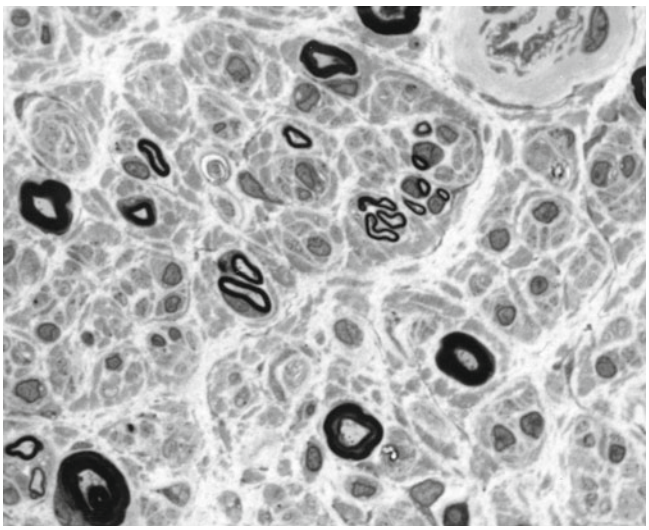


Fig. 12.9 Axonal "sprouting." In addition to axonal loss, there is axonal "sprouting" (*center*), recognized as the presence of small regenerating axons within a cluster

Segmental Demyelination and Remyelination

Demyelination refers to degeneration of the myelin sheath with preservation of the axon. In the peripheral nervous system, this results from an insult that is directed toward the Schwann-cell body or its cytoplasmic process, namely, the myelin sheath. Peripheral nerve segmental demyelination was first described by Gombault in 1880 [39] in experimental lead neuropathy and soon after in human diphtheritic neuropathy by Meyer [40].

The usual tissue preparations that are made from frozen or paraffin-embedded sections of nerve do not satisfactorily demonstrate segmental demyelination. Plastic-embedded semi-thin (1 μm) sections are more useful in showing both axons and myelin sheaths in the same section, and these may at times demonstrate demyelinated axons (in cross section) or a segmental distribution of demyelination (in longitudinal sections). Demyelinated axons can also be clearly shown in electron micrographs, but the fields disclosed by this are ordinarily too small to tell if the demyelination involves individual segments. The best visualization of segmental demyelination is with teased-fiber preparations. With this method, in the acute stages of the process, individual internodes or multiple internodes along the length of a single fiber can be shown to be devoid of myelin thereby leaving a stretch of "naked" axon between two nodes of Ranvier. Almost immediately following demyelination in the peripheral nervous system, remyelination ensues. Some Schwann-cell proliferation occurs, and these Schwann cells produce new myelin sheaths around the denuded axons. The new myelin segments, however, are shorter and thinner than those originally present. These altered myelin segments also are best shown by teased-fiber preparations.

Under some circumstances—both in naturally occurring states of disease and under experimental conditions—repeated episodes of demyelination and remyelination occur. When this happens, increasing numbers of replicating Schwann cells form concentric encirclements around the axon (or sometimes around bundles of collagenous fibers); these events are accompanied by production of large numbers of collagen fibers that become interdigitated among the Schwann cells. Under light and electron microscopy, these intermixed aggregates of Schwann-cell cytoplasm and collagen fibers present the appearance of concentrically laminated structures that resemble the cross section of an onion and thus are regularly referred to as "*onion bulbs*"[41]. Because the reparative process of remyelination begins soon after demyelination, most cases of demyelinating peripheral neuropathies include active remyelination along with demyelination. Segmental demyelination is seen typically in the Guillain–Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), some hereditary demyelinating neuropathies, experimental allergic neuritis, and certain toxic neuropathies (such as lead and diphtheria).

In summary, the histologic features characteristic of segmental demyelination and remyelination are (Figs. 12.10a, b and 12.11a, b) as follows:

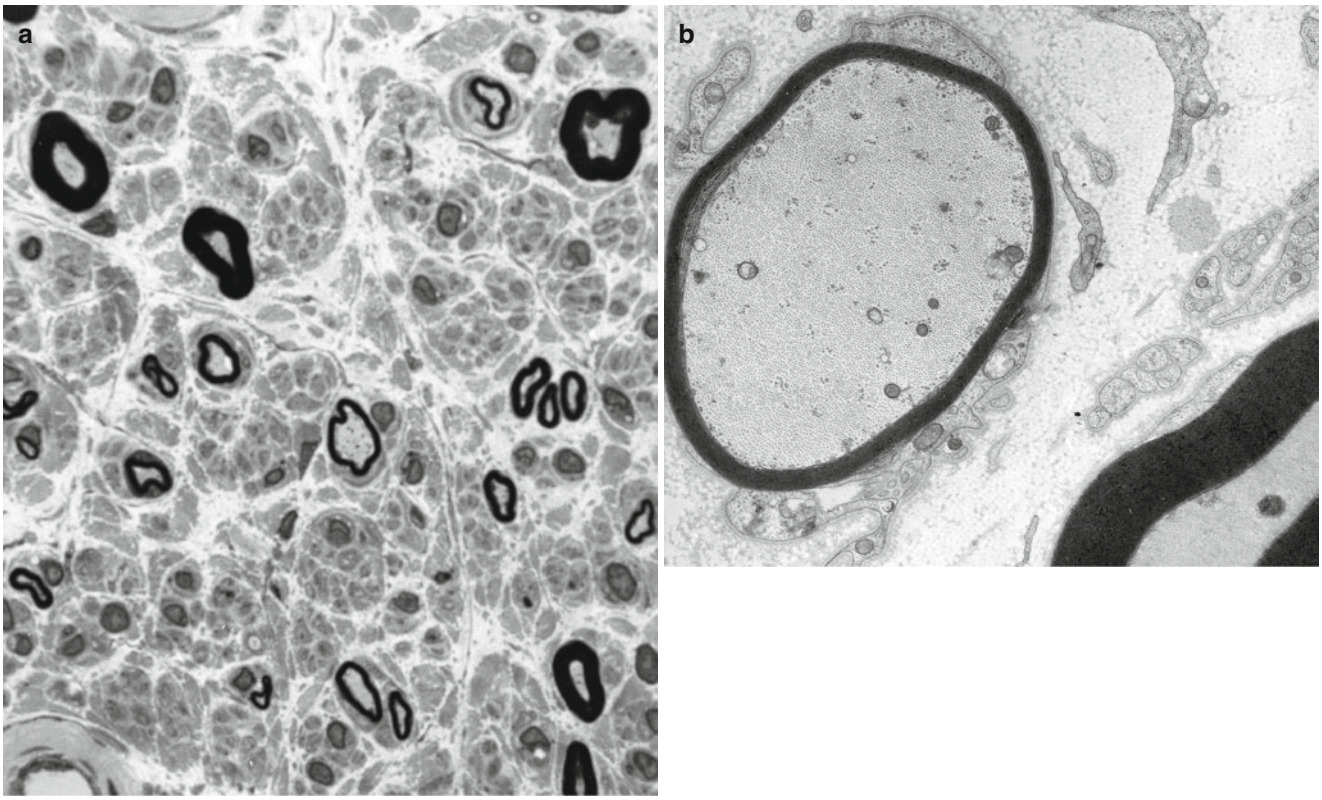


Fig. 12.10 Segmental demyelination and remyelination. (**a**) Demyelination with remyelination is seen as thinly myelinated fibers (Note normal thick myelin sheath of adjacent axons of similar diameter). (**b**) Electron micrograph of thinly myelinated axon

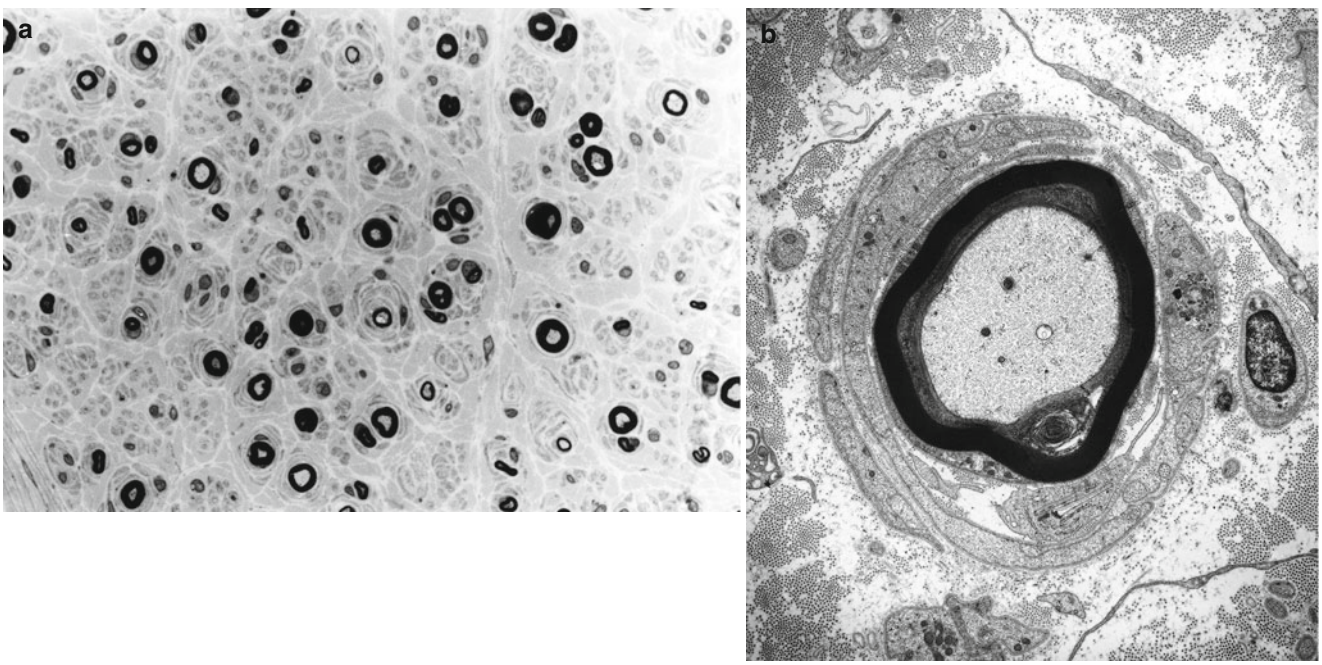


Fig. 12.11 Onion bulbs. (**a**) Light micrograph of onion bulbs, showing axons with prominent concentric layers of Schwann cells. (**b**) Electron micrograph of onion bulb, showing excess Schwann-cell layers around the myelinated axon

Demyelination

1. Early changes in myelin sheaths detected at nodes of Ranvier (paranodal retraction)
2. Insertion of macrophage cell processes between myelin sheath and axon may occur
3. Disintegration of myelin with preservation of the axon

Remyelination

1. Proliferation of Schwann cells at sites of demyelination
2. Remyelination of demyelinated segments, with shorter internodes and thinner myelin sheaths
3. Schwann-cell hyperplasia (redundant Schwann-cell processes around individual axons) as a result of repeated episodes of demyelination and remyelination
4. Progressive onion-bulb formation with multiple concentrically arranged Schwann-cell processes surrounding a thinly myelinated axon

Molecular Basis of Genetically Determined Peripheral Neuropathies

Many peripheral polyneuropathies are hereditary. Due to recent advances in understanding the molecular basis of many of these diseases, most of these diseases are now diagnosed based on genetic testing using blood samples. However, these tests are expensive, and often many genotypes need to be tested. History, family history, physical examination, and electrodiagnostic testing are essential prerequisites to narrowing the differential diagnosis. Despite advances in genetic testing, nerve biopsy may still be necessary if the family history does not suggest a hereditary pattern, genetic testing does not provide a diagnosis, or for other reasons. We will discuss two of the most common categories of hereditary neuropathies: Charcot–Marie–Tooth disease (CMT) and the familial amyloid polyneuropathies (FAPs).

To classify and diagnose CMT (formerly known as hereditary motor and sensory neuropathy or HMSN), which has a broad range of phenotypes and genotypes, an understanding of the classification system is essential. Unfortunately, the classification system is continuously evolving, and different classifications may be found in different references [42–44]. For the purposes of the diagnostician and pathologist, the ultimate goal is to try to determine the genetic cause. We suggest the following rules of thumb for classification.

CMT is categorized based on the inheritance pattern, on whether the disease is primarily axonal or demyelinating, and ultimately by the genotype. Demyelinating polyneuropathies are referred to as CMT1, unless they have an autosomal recessive inheritance pattern, in which case they may be referred to as CMT4. CMT2 refers to axonal polyneuropathies. CMTX refers to X-linked polyneuropathies. The term CMT3 or Dejerine–Sottas disease is less specific and refers to inherited polyneuropathies with an early age of onset. As the ability to classify CMT genetically has developed, these diseases are now often regarded as severe phenotypes of mutations that are better classified in another category. Letters added to the name of each disease to designate the gene identified as the etiology. For example, CMT1B refers to a demyelinating polyneuropathy with autosomal dominant inheritance associated with a mutation in the MPZ gene. A more complete description of these diseases and their classification can be found in Chap. 26. Descriptions of specific pathological findings are not available for all of the varied subtypes of CMT. Below, we describe findings that can be seen in the more common and well-documented subtypes.

CMT1 is the most common hereditary peripheral polyneuropathy. CMT1A results from duplications or point mutations of the PMP22 gene. Nerve section reveals numerous onion-bulb formations characteristic of a demyelinating polyneuropathy. Hypomyelinated axons may be seen. The nerve may be hypertrophic. In severe cases, density of myelinated fibers may be reduced. Using fluorescent in situ hybridization techniques, it is possible to utilize genetic probes to detect PMP22 duplication in CMT1A. A closely related disorder, hereditary neuropathy with liability to pressure palsies (HNPP), is also associated with PMP22, either with different point mutations or with a haploinsufficiency of the gene. Focal hypertrophies of myelin, called tomaculae, can be seen at multiple sites along an axon. This may be best appreciated on teased-fiber analysis. Fluorescent in situ hybridization can also identify HNPP.

CMT1B is associated with a mutation in myelin protein zero (MPZ), an integral membrane protein of Schwann-cell myelin that appears to mediate apposition of membrane layers in compact myelin. On nerve section, hypomyelinated axons are seen, as are onion-bulb formations. Ultrastructurally, abnormal myelin compaction may be seen, with abnormally wide spaces between the dense lines of myelin.

The most common X-linked form of CMT is associated with the gene GJB1 (CMT1X), but other subtypes have been associated with other identified genes. GJB1 encodes the protein connexin 32 (Cx32), a gap junction subunit. Nerve sections of CMT1X may show thinly myelinated nerve fibers in clusters, representing regenerating fibers. Onion bulbs may also be seen.

CMT2A2 represents about 20 % of all axonal CMT cases. It results from a mutation in the gene MFN2, which encodes mitofusin 2, a protein in membranes of mitochondria. Consequently, mitochondrial abnormalities can be visualized on electron microscopy. On light microscopy, nerve fiber density is reduced, and in some cases, onion bulbs may be seen.

The familial amyloid polyneuropathies (FAPs) are a group of autosomal dominant genetic diseases characterized by the deposition of amyloid fibrils in various tissues, including peripheral nerve and muscle. Clinically, this manifests as a

multisystem disease which includes a length-dependent polyneuropathy. Pain, temperature, and autonomic tracts tend to be affected before other modalities [45].

There are three main types of FAP, defined by the protein whose gene carries the causative mutation. They differ clinically and are managed differently. Most forms of FAP are the result of specific mutations of transthyretin (TTR, also known as prealbumin). Over 100 different TTR point mutations have been described, the most common being the Val30Met mutation. FAP may also result from mutations of the gene for apolipoprotein A-I (apoA-I), a protein mediating binding and transport of lipids in serum, or the gene encoding gelsolin (GSN).

In TTR amyloidosis, nerve biopsy may show extracellular amyloid in the endoneurium and around blood vessels. Nerve fiber density may be reduced, and unmyelinated fibers are lost first. Nerve sections stained with Congo red and visualized under polarized light will demonstrate apple-green birefringence of amyloid deposits, if they are present. Electron microscopy may reveal unbranched amyloid fibrils 7–10 nm in diameter. Immunohistochemistry with antibodies against the specific protein (i.e., TTR, apoA-I, or GSN) can determine the specific form of FAP, since in each instance the presence of amyloid is due to the specific protein. Amyloid depositions are multifocal, and the sample biopsied may not contain any amyloid deposits; thus, absence of amyloid on biopsy does not exclude the diagnosis but is thought to have a sensitivity of about 85 %.

Muscle Biopsy

Comprehensive monographs and websites are available on the subject of muscle biopsy techniques and interpretation of findings [46–50]. This overview gives a brief introduction to muscle biopsy techniques and histopathologic interpretation.

General Remarks

The proper evaluation of a muscle biopsy requires joint assessment of the patient's medical history, physical examination, laboratory values, nerve conduction studies (NCS), and needle electromyogram (EMG), together with the morphologic and biochemical data derived from study of the muscle tissue itself. Often, the clinician who decides on a muscle biopsy is not the person who performs the surgical procedure, so communication is essential to ensure that the optimal biopsy site is selected based on clinical assessment, electrodiagnostic results, and radiologic data. Prior notification of the pathology laboratory is also needed so that preparations for the proper handling of the biopsy specimen can be made. The muscle chosen for biopsy is often guided by an EMG. If not done, then the muscle sampled in rapidly evolving muscular disorders should be weak. In chronic muscular disorders, the biopsied muscle should be one that is moderately affected, as clinically uninvolved muscles are less likely to show pathologic changes and severely affected muscle may only demonstrate end-stage disease. Perhaps because most primary myopathies preferentially affect proximal muscles, biopsies of more distal muscles (biceps rather than deltoid, gastrocnemius rather than vastus lateralis) have been associated with slightly lower probabilities of obtaining definitive diagnoses [51]. Sites of previous biopsy, EMG needle implantation, intramuscular injection, or prior trauma should be avoided by the surgeon since the inflammatory and reactive changes that attend these procedures interfere with biopsy interpretation. Collagenous connective tissue, variable cross-sectional diameter of fibers, and internalized nuclei characteristic of muscle tissue at tendinous insertions may also be misinterpreted as pathologic change, so the biopsy should be taken from the belly of the muscle by a surgeon experienced in the muscle biopsy procedure.

Processing Skeletal Muscle Biopsies

Although some questions may be answered with needle biopsy specimens, an open biopsy of muscle is preferred by most laboratories because it affords sufficient tissue for complete study and is more likely to be free of artifact than a needle biopsy. For open biopsies, the individual performing the biopsy should obtain *two* separate specimens: a clamped and an unclamped sample of skeletal muscle. The first specimen (a thin linear segment) is removed in situ on a muscle biopsy clamp to avoid contraction artifacts and is the one destined for light and electron microscopy. Slivers of the surface portions of the muscle are carefully dissected out and immersed in cold glutaraldehyde, preferably within minutes of retrieval; these are later minced, osmicated, and embedded in plastic for light and possibly electron microscopic study. For plastic-embedded specimens, cross and longitudinal sections are first prepared (semi-thin sections 1–2 μm thick), stained with toluidine blue, and examined with the light microscope, and then selected regions are processed for electron microscopic study, if needed. The remainder is washed in buffer, post-fixed in formalin, embedded in paraffin, processed for cross and longitudinal sections, and stained with H&E at several levels to look for interstitial pathology (inflammation, vasculitis, etc.). This portion of the muscle biopsy specimen may also be used for immunohistochemical staining for the presence of specific subtypes of lymphocytes or other immunohistochemical markers. Although many laboratories still use ATPase histochemistry to reveal fiber types, myosin heavy-chain immunostains of

formalin-fixed paraffin-embedded tissue are increasingly being utilized for this purpose.

The second specimen, the unclamped muscle, is retained unfixed and placed in foil or wrapped in saline-moistened gauze (but NOT flooded with saline). One portion of this specimen is snap frozen in isopentane (2-methylbutane) thoroughly precooled by liquid nitrogen (the isopentane should be given time to become partially frozen) and mounted in a suitable embedding medium on a chuck that will allow for cryostat sections. The relatively high specific heat of isopentane compared with liquid nitrogen drops the temperature of the muscle specimen from room temperature to below freezing quickly enough to avoid formation of ice crystals that disrupt the integrity of the fibers and may render the specimen uninterpretable. Frozen sections are then stained with hematoxylin and eosin and may be used for a variety of histochemical reactions and other special stains. The histochemical reactions and stains routinely employed vary somewhat from one laboratory to another. Most investigators run at least an H&E, a modified Gomori trichrome stain, and an oxidative histochemical stain such as nicotinamide adenine dinucleotide-tetrazolium reductase (NADH-TR), succinate dehydrogenase (SDH), or cytochrome oxidase (COx). Many labs also routinely do periodic acid–Schiff (PAS) with and without diastase; oil red O; adenosine triphosphatase (ATPase) performed at pH 4.3, 4.6, and 9.4; and sometimes acid phosphatase and/or amyloid stains. In selected instances, frozen sections can also be stained with antibodies to demonstrate loss of sarcolemmal proteins or other molecular abnormalities [52]. A second portion of the unclamped, unfixed specimen is frozen directly in liquid nitrogen for potential biochemical and molecular studies. Frozen tissues may be stored at −80 °C for extended periods of time and may yield important information as new molecular genetic methods become available.

Normal Muscle Histology

The earliest cell recognized as committed to develop into skeletal muscle is the myoblast, a proliferating cell containing intracytoplasmic myosin and actin filaments [53]. Myoblasts fuse with one another to primary myotubes, multinucleate cells with a roughly cylindrical configuration. As sarcomere structure develops peripherally, the nuclei are initially arranged internally about a myofibril-free zone. By the time the myotube is ready for innervation, the sarcolemma contains abundant, diffuse receptor protein for the neurotransmitter acetylcholine (ACh). When the tip of the nerve fiber comes in contact with the muscle fiber, establishing a motor end plate, the receptor proteins become concentrated at the neuromuscular junction and disappear from the surface of the fiber elsewhere. Once innervated, the nuclei move to the periphery and the interior becomes packed with regular arrays of myofibrils as the myotube becomes a mature myofiber.

It appears that the full complement of muscle fibers is attained by mid-fetal life. At the mid-fetal period, muscle fibers are thin (4–5 μm), their nuclei fill nearly the entire transverse diameter of the fiber, and only a few coarse, striated myofibrils are visible beneath the sarcolemma. Fiber types differentiate in late fetal life, and by the time of birth, the fibers have grown to a width of 8–10 μm.

The functional unit of the neuromuscular system is the *motor unit*. Each motor unit consists of (1) a neuron located in the anterior horn of the spinal cord, or motor nucleus in the brainstem; (2) the axon of that neuron leaving the cord or brainstem, traversing the subarachnoid space, continuing on as the peripheral portion of the spinal or cranial nerve, terminating at the motor end plate; and (3) the muscle fibers being innervated. The number of muscle fibers within a motor unit (those innervated by the axon of a single motor neuron) varies from a few to several hundred. Muscles responsible for highly refined movements, like the extrinsic muscles of the eye, have a high innervation ratio (neuron-to-muscle-fiber ratio, 1:10) while those with relatively coarse movement requirements, like the calf muscles, have a much lower ratio (1:2,000). With increasing voluntary effort, more autonomous units can be called upon to work together.

Light Microscopy

Muscle fibers are arranged in fascicles supported by several connective tissue sheaths. The *epimysium* envelops large groups of muscle fibers. Variable numbers of muscle fibers are grouped in primary and secondary bundles or fasciculi enveloped by *perimysium*, which is contiguous with the epimysium. The *endomysium* consists of a delicate network of connective tissue fibers, blood vessels, lymphatic tissue, and nerves, which surrounds individual muscle fibers (Fig. 12.12a).

Muscle fibers vary considerably in diameter, depending on the function of the muscle and the degree of exercise to which the muscle has been subjected. Cross-sectional muscle diameter is inversely proportional to their degree of involvement in activities demanding precision (e.g., extrinsic eye muscles, 17–20 μm in diameter; gluteus, about 90 μm in diameter). Fiber size is also regulated to some extent by testosterone; males tend to have larger fibers than females. Within each muscle, there may also be some variability in the size of its fibers, closely conforming to a narrow bell-shaped curve in most muscles. In embryos, infants, and children, there is a distinctive bimodal distribution of fibers. Standardized histograms of muscle fiber diameter based on site, age, sex, and preparative techniques are available for many muscles and may be

useful in the analysis of muscle biopsies taken from infants and young children. Myofiber size remains relatively constant in adulthood and then tends to decline with old age ("sarcopenia"). The cross-sectional shape of infant fibers tends to be round, while adult muscle fibers are normally polygonal (Fig. 12.12b). In longitudinal sections, the adult muscle cell (or muscle fiber) is bounded by a plasma membrane (sarcolemma) and basement membrane. Nuclei are positioned at the periphery of the fiber, just beneath the sarcolemma, and are spaced about 10–50 μm apart, depending on the muscle (Fig. 12.12c). The nucleoplasm is fine and evenly distributed, and nucleoli are ordinarily inconspicuous. Nuclei located toward the center of the fiber ("internalized" nuclei) are normally seen in about 3 % of normal adult muscle fibers. The familiar striations of the muscle fiber are imparted by repeating units called *sarcomeres*, composed of interlaced, longitudinally directed thin (actin) filaments anchored to perpendicularly disposed Z disks and thick (myosin) filaments. Myofibrils are composed of serial arrays of sarcomeres that run the length (or at least much of the length) of the muscle fiber. The number of myofibrils in each muscle fiber varies from several hundred to several thousand, depending on the diameter of the fiber. At tendinous insertions, myocytes interdigitate with the basal lamina so that by light microscopy they appear to fuse with the connective tissue. In these areas, nuclei are normally internalized.

Muscle spindles are fusiform structures varying in length from 0.5 to 3.0 mm and oriented parallel to the muscle fibers and attached at the poles to the aponeuroses and connective tissue sheaths surrounding the muscle fasciculi. In cross section, the muscle spindle is a rounded structure with a diameter from 200 to 1,000 μm bounded by a fibrous capsule containing four to six intrafusal muscle fibers, nerve fibers, specialized nerve endings, and blood vessels (Fig. 12.12d). The function of spindles is to respond to muscle stretching and maintain muscle tone.

The junctional complex between nerve and muscle is called the motor end plate or neuromuscular junction (NMJ). In H&E-stained sections, the NMJ appears as an ill-defined aggregate of nuclei and nerve fibers on the surface of the muscle fiber. Special techniques (intravital dyes, metallic impregnation, immunoelectron microscopy) are required to adequately visualize this structure (Fig. 12.13a, b). At the NMJ, the muscle surface is adapted into a series of folds, and the motor axon, covered only by a connective tissue sheath, splays into an elaborate terminal arborization with terminal expansions which make synaptic contact with the muscle. These endings—the axon terminals—contain synaptic vesicles and mitochondria. The synaptic cleft is about 70 nm wide and is filled with fine granular material. Membrane specializations are found on both the axonal and muscular surfaces of the synapse.

Histochemistry

For diagnostic purposes, muscle fibers can be identified as either type I ("slow-twitch") or type II ("fast-twitch") myofibers (Fig. 12.14a). *Type I fibers* are concerned primarily with slow, sustained contractions and are relatively fatigue resistant. These fibers derive most of their energy from aerobic metabolism and breakdown of lipid and are, therefore, mitochondria- and oxidative enzyme-rich and glycogen- and glycolytic enzyme-poor. Human skeletal muscle contains two kinds of type II fibers. *Type IIx* (*formerly known*

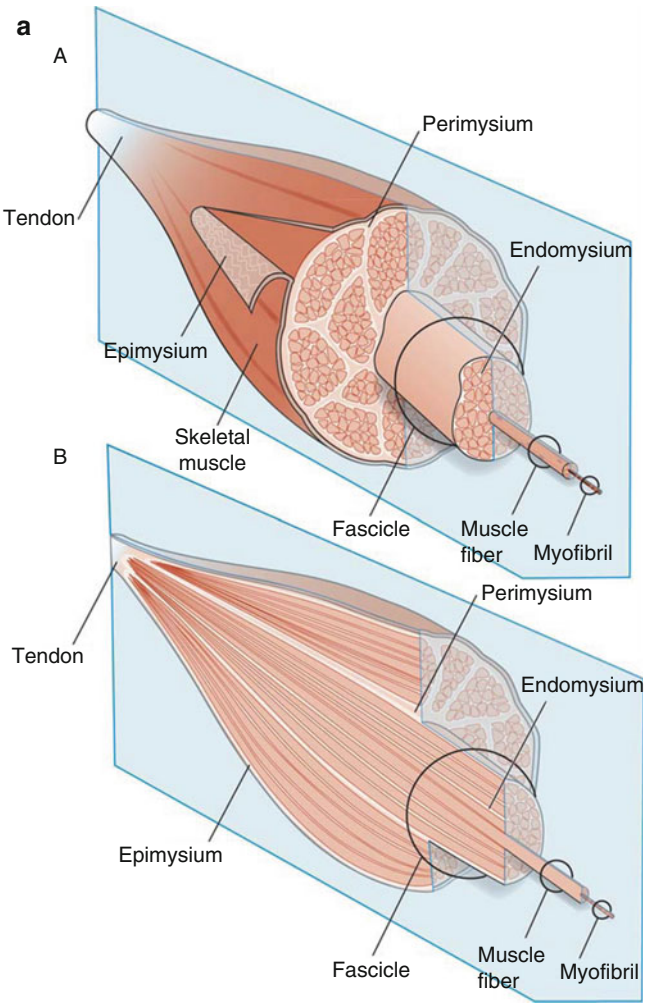
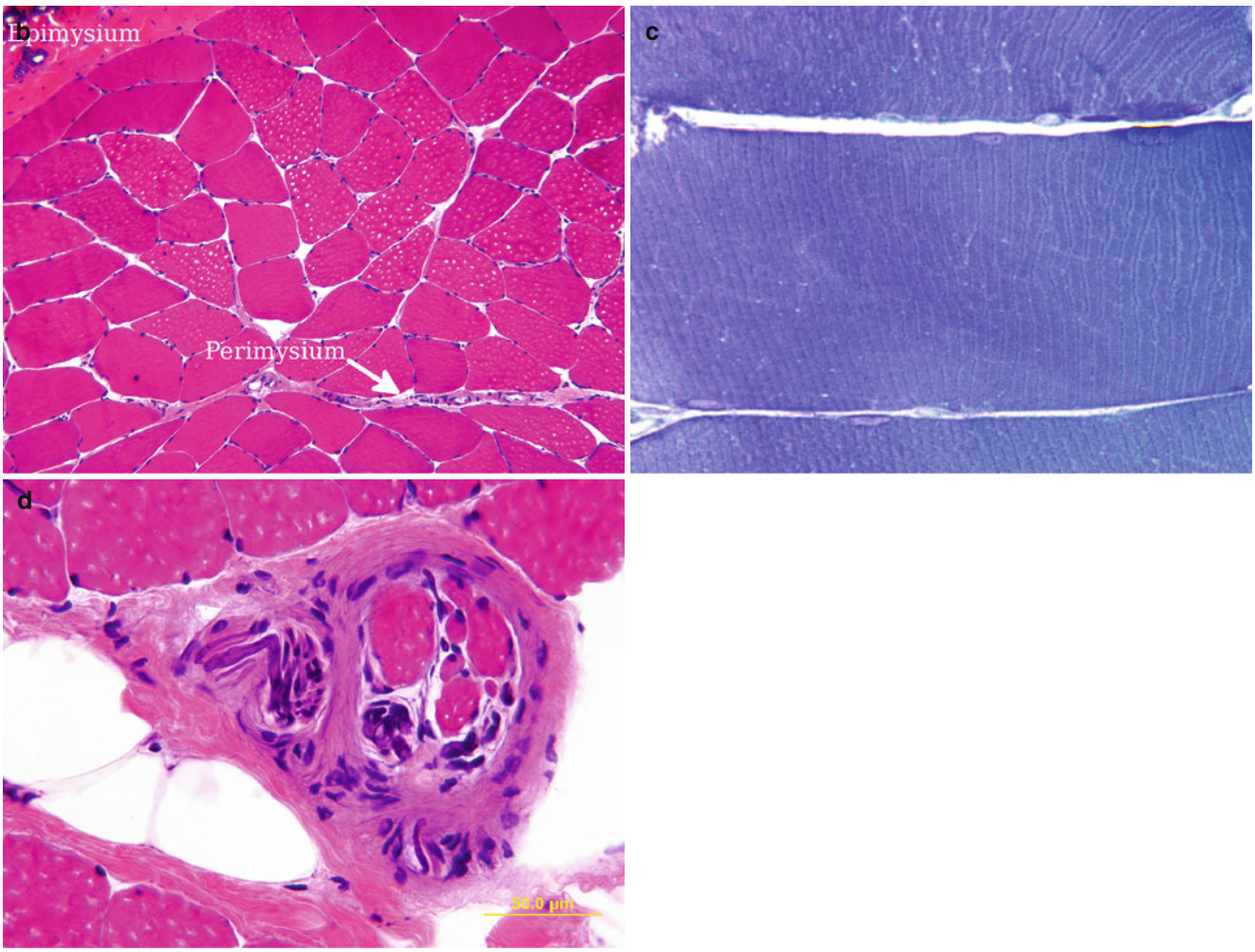


Fig. 12.12 Normal skeletal muscle. (**a**) Diagram A and B (cutaway version of A) showing the relationships between endomysium, perimysium, and epimysium. Awaiting permissions assessment. (**b**) In transverse section, the fibers have a normal polygonal shape, and the nuclei are located in their normal subsarcolemmal location. A small amount of ice crystal artifact is seen within the muscle fibers. The delicate perimysium demarcates individual muscle fascicles, while the thicker epimysium surrounds the entire muscle fiber. (**c**) This plastic-embedded, toluidine blue-stained longitudinal section of muscle fiber enables visualization of cross striations, resulting from the repeated pattern of overlapping thin and thick filaments comprising the muscle sarcomeres. (**d**) Muscle spindle in transverse section. Several irregularly sized muscle fibers are enclosed within the multilayered capsule and are innervated by a peripheral nerve twig



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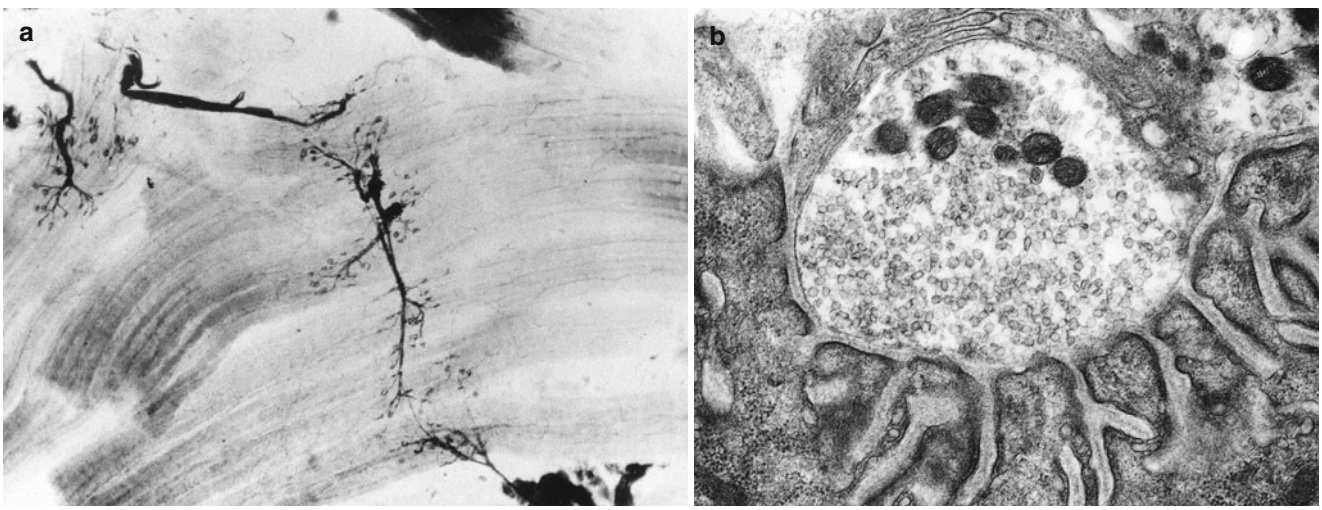

Fig. 12.13 Neuromuscular junction. (**a**) Cajal preparation showing terminal arborization of the axon of a motor unit (Courtesy of Dr. R. D. Adams). (**b**) Electron micrograph of neuromuscular junction showing axon terminal with synaptic vesicles and the sarcolemmal junctional folds (Courtesy of Dr. C. Cardasis)

a

MyHC type	Twitch duration	Shortening velocity	Cross–sectional area	Metabolism	Endurance	Energy efficiency
I	Slow	Slow	Small	Oxidative	High	High
IIa						
IIx						
IIb	Fast	Fast	Large	Glycolytic	Low	Low

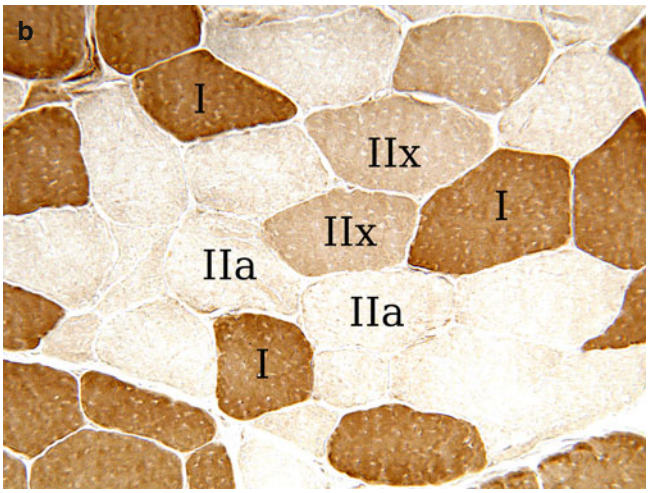

Fig. 12.14 ATPase histochemistry of skeletal muscle. (**a**) awaiting permissions resolution. (**b**) ATPase histochemical staining, performed after preincubation at pH 4.6, allows identification of all three fiber types normally encountered within human skeletal muscles

as type IIb) *fibers* are concerned mainly with quick, strong, short duration contractions, fatigue easily, derive most of their energy from anaerobic glycolysis, and are rich in glycolytic enzymes but poor in oxidative enzymes. *Type IIa fibers* share characteristics with both type I and type IIx fibers. These fast-twitch fibers are also somewhat fatigue resistant and are well endowed with both glycolytic and oxidative enzyme systems. *Type IIc fibers* are undifferentiated and are therefore usually encountered in fetal tissue. In most biopsied human muscles, both oxidative and glycolytic fibers are distributed in a mosaic pattern, with types I, IIa, and IIx fibers each comprising about a third of the total number of muscle fibers. The most widely used histochemical method for fiber typing is the ATPase reaction run at alkaline pH (9.4); in the "reverse ATPase" (r-ATPase) method, sections are preincubated in an acid medium, resulting in a reversal of the checkerboard pattern of dark and light fibers. If the preincubation is at pH 4.3, the reversal is complete, with the type I fibers staining dark and type II fibers light. At pH 4.6, the reversal is partial, allowing visualization of intermediate-staining type IIx fibers (Fig. 12.14b). In oxidative histochemical reactions, type I fibers tend to stain more darkly than type II fibers. Caution is indicated when attempting to assign fiber type on the basis of oxidative reactions, as fibers that are atrophic due to denervation are often excessively dark regardless of fiber type. The distribution of the different fiber types in normal human skeletal muscles varies considerably with anatomic region and age.

Immunohistochemistry

The availability of antibodies specific for myosin heavy-chain subunits has enabled many laboratories to switch to immunohistochemical recognition of fiber types. Advantages of immunohistochemical staining over traditional ATPase staining include (1) the ability to analyze fiber types on formalin-fixed sections, (2) the ability to distinguish markedly atrophic fibers from capillaries, and (3) the ability to automate double immunostaining for fast (MYH2) and slow (MYH7) myosin isoforms (which allows the simultaneous detection of type IIx and IIc fibers) [54]. The detection of acutely denervated and regenerating fibers may also be accomplished on routinely fixed tissues using antibodies to NCAM (CD56) and vimentin [55]. Finally, the detection of intracytoplasmic protein aggregates, critical to the diagnosis of inclusion body myositis and myofibrillar myopathies, may be accomplished using antibodies to CD56/NCAM, ubiquitin, p62/SQSTM1, or TDP-43 [56].

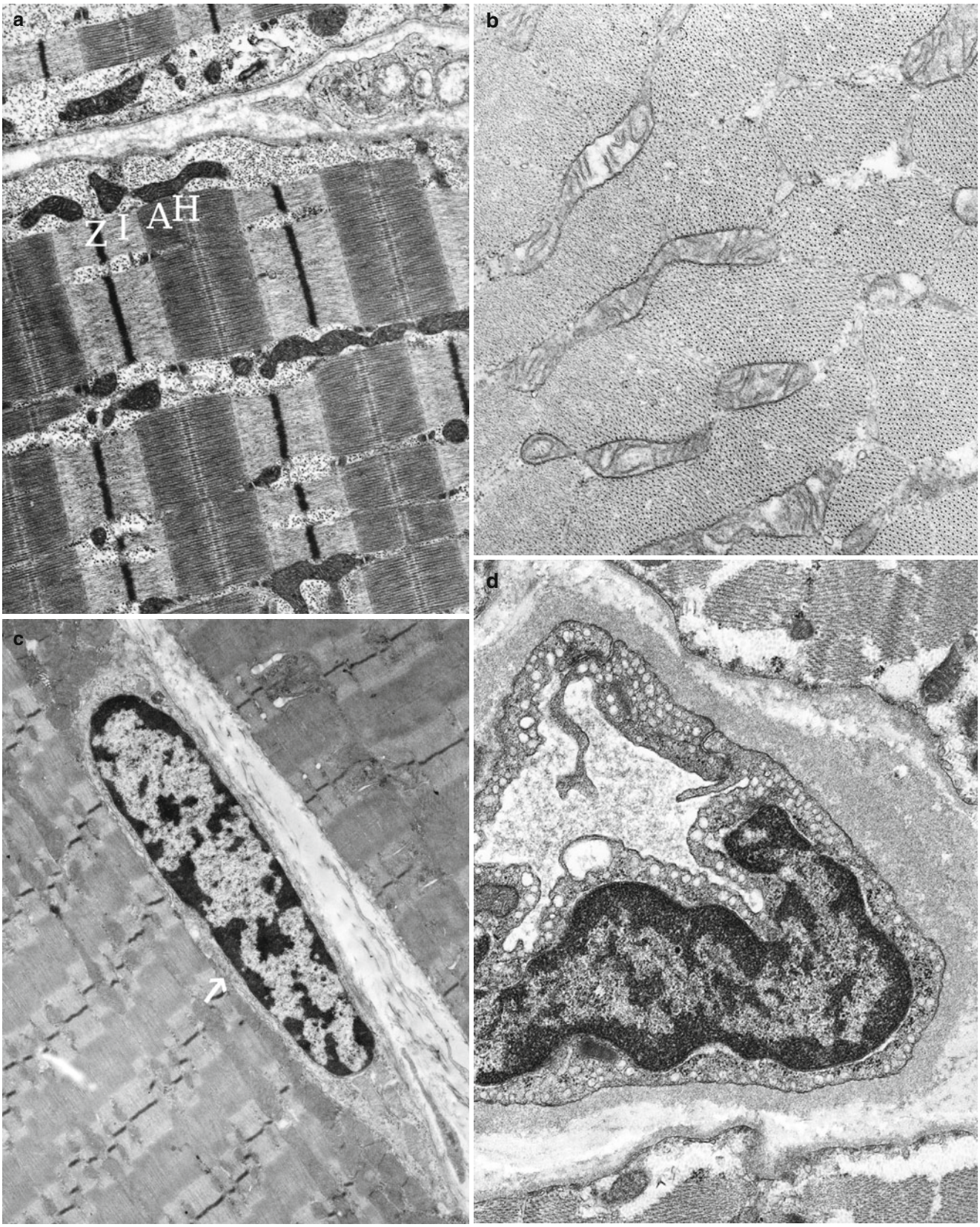

Fig. 12.15 Normal skeletal muscle ultrastructure. (**a**) Longitudinal section showing characteristic banding patterns of sarcomeres. A single sarcomere extends from one Z disk to the next and comprises a symmetric structure centered on the H band. The isotropic (I) band contains thin filaments only, while the anisotropic (A) band contains both thin and thick filaments. (**b**) High magnification of a cross section through several myofibrils showing interdigitation of thick and thin filaments. (**c**) Satellite cell. The interface between the plasma membrane of the satellite cell and the sarcolemma is best seen at the *white arrow*. (**d**) Endomysial capillary. The endothelial cell has prominent pinocytotic vesicles and is completely surrounding its basil lamina, distinct from the lamina of the adjacent myocytes

Electron Microscopy

Muscle fibers are bounded by a cell membrane (sarcolemma) and a basement membrane (basal lamina). The cell membrane is smooth and of even density (300–400 nm). Variability in sarcolemmal thickness, as well as redundancy or reduplication, is commonly seen both normally (e.g., contracted fibers) and in disease. The familiar striations of skeletal muscle are imparted by repeating units of interlaced, longitudinally directed, thin actin filaments and thick, dark myosin filaments (Fig. 12.15a, b). The dark regions are more electron-dense and are referred to as anisotropic, while the light regions are electron-lucent and are referred to as isotropic. The anisotropic region, or A band, is composed of myosin filaments alternating with actin filaments, while the isotropic region, or I band, contains only actin filaments. A narrow dark band, the Z line (or Z disk), bisects the I band. A narrow region of intermediate density, the H zone (composed of myosin filaments only), bisects the A band. A sarcomere is the contractile apparatus between two Z disks; a myofibril is a longitudinally oriented serial array of sarcomeres. Each myofibril is 0.5–1.0 μm thick and is separated from its neighbors by a loop of T tubule, smooth endoplasmic (sarcoplasmic) reticulum, mitochondria, fat globules, and intervening unstructured myoglobin-containing cytoplasm. The T tubular system is composed of invaginations of the sarcolemmal membrane into the interior of the cell and runs parallel to the Z disks. It is accompanied by two cisterns of endoplasmic sarcoplasmic reticulum on either side. The centrally placed T tubule flanked by two cisterns of sarcoplasmic reticulum is called a *triad*.

Satellite cells are located on the surface of the muscle fiber between the cell membrane (sarcolemma) and the basement membrane. They account for 1–2 % of muscle cells at rest but can increase to up to 10 % following muscle activity [57]. Satellite cells are composed of a single nucleus and scant cytoplasm containing many mitochondria and loosely strewn intermediate filaments. Satellite cells function as a reserve population of muscle cells called into action upon muscle injury (Fig. 12.15c). Elevated numbers of satellite nuclei may even represent a form of muscle memory, facilitating retraining [58]

The capillary network surrounding skeletal muscle is extensive. Ultrastructurally, the endothelium of muscle capillaries contains abundant pinocytotic vesicles and fenestrated intercellular junctions. The endothelial cells rest on a single layer of basement membrane; pericytes are visible outside this membrane (Fig. 12.15d).

Basic Skeletal Muscle Pathology

It would not be hyperbolic to call the past 10 years the decade of the skeletal muscle, and much of this newly acquired knowledge is now being applied to the diagnostic evaluation of muscle biopsies [58]. Muscle diseases formerly classified on the basis of morphology alone are increasingly diagnosed and treated based on advances in knowledge with regard to specific abnormalities involving the structure and function of skeletal muscle proteins [59]. For example, the two most prevalent "congenital myopathies" (central core disease and nemaline myopathy) are now known as manifestations of genetic disorders involving excitation–contraction coupling and sarcomeric function, respectively.

Disorders of Excitation–Contraction Coupling

Also referred to as the "muscle channelopathies," this group of disorders generally manifests as episodic or fixed abnormalities in muscle tone. Histopathologically, these disorders express a wide range of seemingly disparate structural abnormalities, most of which are secondary to chronic channel dysfunction. The most prevalent channelopathies affecting skeletal muscle are the myotonic disorders, particularly myotonic dystrophies type 1 and 2. The *myotonic dystrophies* are characterized by prominent central nuclear migration associated with muscle fiber atrophy. In classic myotonic dystrophy, type I muscle fibers are preferentially affected. Type II myotonic dystrophy demonstrates preferential histopathological abnormalities within type II muscle fibers, which are particularly well demonstrated using myosin heavy-chain-specific antibodies (Fig. 12.16a, b). The *periodic paralyses* also derive from mutations involving muscle ion channels. Although many cases demonstrate no specific myopathological alterations, occasional patients may manifest tubular aggregates and/or vacuolar degeneration (Fig. 12.16c). Core myopathies (formerly separated into central core disease and multi-minicore disease) demonstrate a well-known association with malignant hyperthermia. Approximately 50 % of core myopathies result from mutations involving ryanodine receptor 1 or selenoprotein N, leaving a large proportion of these myopathies currently genetically undefined [60].

Sarcomeric Diseases

This group of myopathies derives from mutations involving actin filaments, myosin filaments, Z disk proteins, and a variety of other proteins which are associated with maintaining the normal structure and function of the contractile apparatus. *Nemaline myopathy* has been associated with mutations in seven distinct genes, six of which encode proteins associated with the thin actin filaments [61]. The two most common are recessive mutations in nebulin and de novo dominant mutations in skeletal muscle alpha-actin. Nemaline myopathy derives its name from the Greek word for thread (nema), which describes the purplish red staining rodlike structures seen in Gomori trichrome-stained muscle fibers (Fig. 12.16d). Due to the wide range of muscle disease associated with these abnormal inclusions, it has recently been recommended that the diagnostic appellation "nemaline myopathy" be restricted to the classic presentation of early hypotonia and

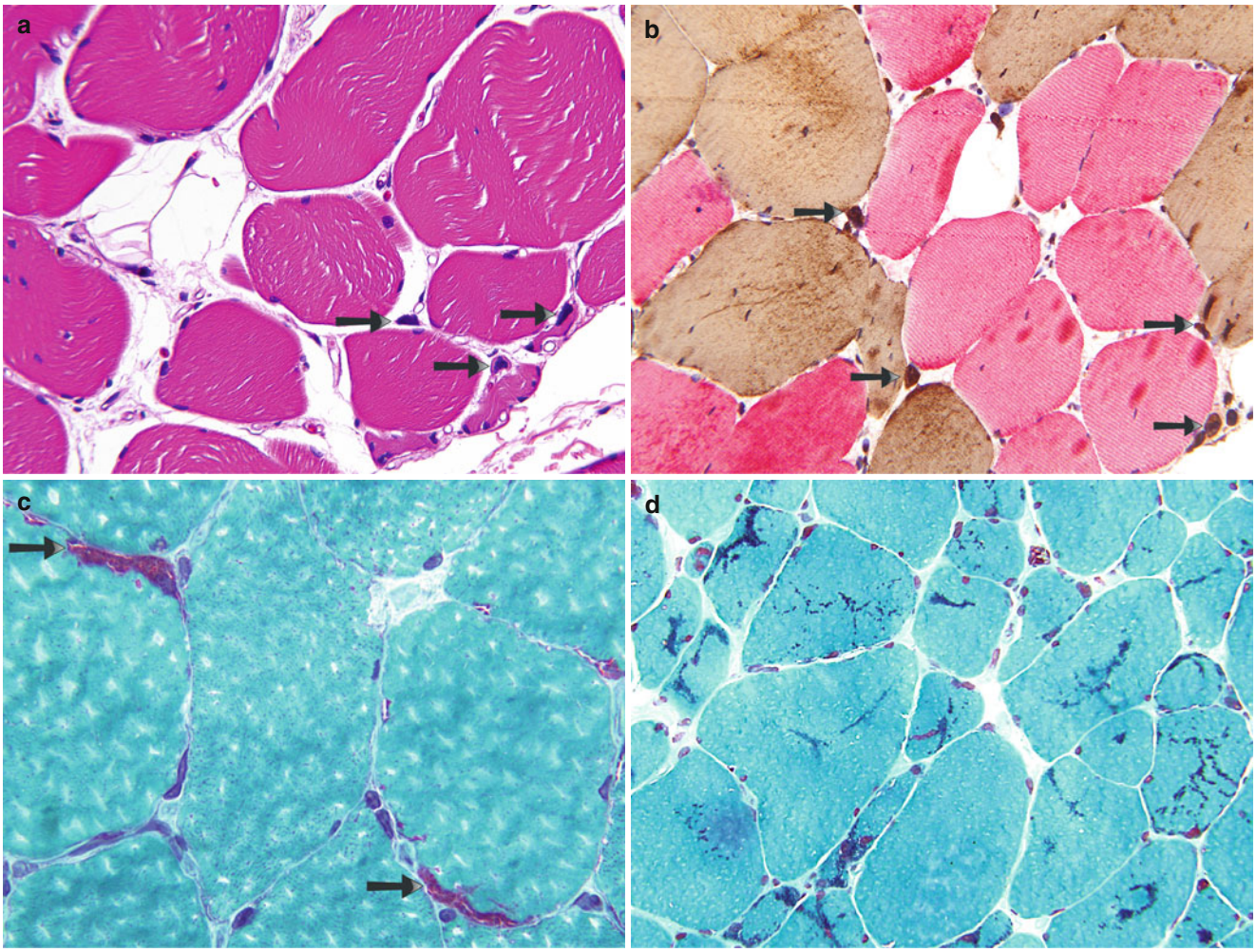

Fig. 12.16 Disorders of excitation–contraction coupling and sarcomeric structure (**a**) Myotonic dystrophy type 2 is characterized by scattered, extremely atrophic muscle fibers (*arrows*) and internalized nuclei within type II muscle fibers. (**b**) Immunohistochemical staining for type I (*red*) and type II (*brown*) myosin heavy-chain isoforms allows identification of both the severely atrophic fibers (*arrows*) and the non-atrophic fibers with internalized nuclei as being type II muscle fibers, characteristic of myotonic dystrophy type 2. (**c**) Tubular aggregates stain *bright red* on Gomori trichrome stain and typically are seen in a subsarcolemmal location (*arrows*). (**d**) As the name implies, nemaline myopathy is characterized by threadlike inclusions within muscle fibers, which are stained *purplish red* by Gomori trichrome

muscle weakness, with adult onset variants referred to more generically as "myopathies with rods." Although congenital myopathies caused by mutations in tropomyosin genes (including congenital fiber type disproportion and cap myopathy) have been described, by far, the most common clinical myopathy secondary to thick filament dysfunction is acquired acute quadriplegic myopathy in critically ill patients, often referred to as "*critical illness myopathy*." In these patients, a combination of circulating inflammatory cytokines, corticosteroids, and neuromuscular blockade eventuates in selective degradation of myosin filaments. Upon removal of the inciting stimuli, eventual reconstitution of sarcomeric structure and function generally supervenes. Finally, a large group of disparate myopathies apparently related only by the presence of myofibrillar degeneration on muscle biopsy have now been related to each other through involvement of muscle proteins responsible for maintaining the structural and functional integrity of the sarcomere [62]. Early-onset forms (often referred to as *desminopathies*) result from mutations either within the desmin gene or in desmin binding proteins, such as alpha beta crystallin. These patients' presentations are often dominated by cardiac dysfunction in addition to muscle weakness. Late-onset myofibrillar myopathies generally result from mutations within Z disk proteins. Late onset in these families is probably due to preservation of proteins with overlapping function, which enable normal sarcomeric function until late in life. As a group, these late-onset myofibrillar myopathies show distinct tendency to present with preferential distal muscle weakness [63].

Mechanical Transduction Disorders

For the muscular dystrophies, a group of genetically determined progressive myopathies, classification schemes are based on the mutated genes and their dysfunctional

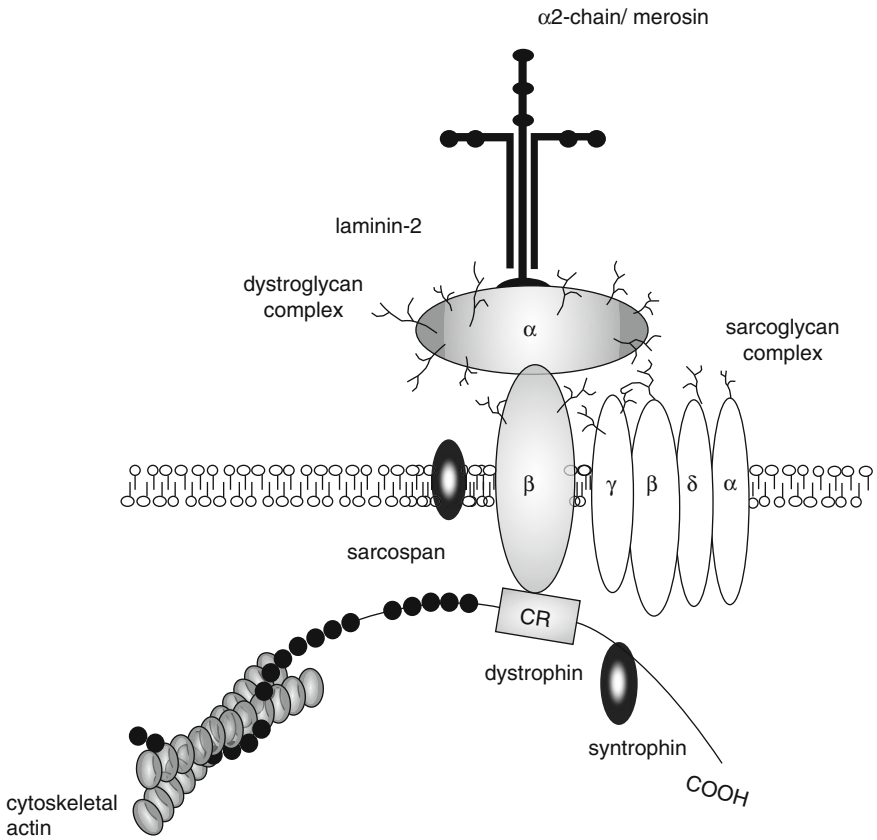

Fig. 12.17 Diagram of the interface between cytoskeletal proteins and the membrane proteins of the sarcolemma. Dystrophin interacts with cytoskeletal actin at its amino terminus and binds the beta subunit of the dystroglycan complex. Four subunits (*alpha, beta, gamma*, and *delta*) comprise the sarcoglycan complex within the cell membrane of the myocyte. The alpha subunit of the dystroglycan complex forms an interface with the laminin proteins of the extracellular matrix (Courtesy of Dr. H. G. W. Lidov)

proteins. Transmembrane protein complexes provide important links between the intracellular cytoskeleton and the extracellular matrix (Fig. 12.17). When various components of this f-actin/dystrophin–dystroglycan/sarcoglycan–laminin axis are absent, the muscle undergoes progressive degeneration with scarring, manifesting as Duchenne/Becker muscular dystrophy, limb girdle muscular dystrophies, or congenital muscular dystrophies [64].

The most common muscular dystrophy, Duchenne muscular dystrophy, is caused by frame-shifting mutations in the gene encoding dystrophin. Immunohistochemistry using commercially available antibodies to dystrophin domains permits the detection of dystrophin in normal muscle biopsies and may be used to demonstrate its absence in Duchenne muscular dystrophy. Becker muscular dystrophy is caused by in-frame mutations in the same gene. Protein epitopes are usually preserved, and western blotting is required to demonstrate a reduction in molecular weight of the dystrophin protein [65].

Limb girdle muscular dystrophies comprise a large heterogeneous group of non-X-linked, noncongenital muscular dystrophies [66]. Mechanistically, limb girdle muscular dystrophies include diseases involving the dystrophin–dystroglycan complex, sarcolemma, sarcomere, nuclear lamina, or cytosolic enzymes. Ninety percent of limb girdle muscular dystrophies (LGMDs) are autosomal recessive (designated LGMD2); 10 % are autosomal dominant (LGMD1). The most common mutations are those involving calpain 3 (LGMD 2A), dysferlin (LGMD 2B), γ-sarcoglycan (LGMD 2C), α-sarcoglycan (LGMD 2D), β-sarcoglycan (LGMD 2E), and δ-sarcoglycan (LGMD 2F). About one-third of limb girdle muscular dystrophy patients are still currently genetically unclassified. In general, western blot analysis of proteins extracted from skeletal muscle is considered to be the gold standard for diagnosis in this group of diseases. Occasionally, immunofluorescent or immunohistochemical assays may be sufficient. Importantly, limb girdle muscular dystrophies may be associated with either lymphocytic or eosinophilic inflammatory infiltrates (Fig. 12.18). Careful clinicopathologic correlation is critical to avoiding the misdiagnosis of primary inflammatory muscle disease in these patients.

The congenital muscular dystrophies (CMD) are a group of muscular dystrophies with onset at or around the time of birth frequently associated with central nervous system pathology [67]. Most result from mutations in a variety of proteins responsible for dystroglycan glycosylation. Although the dystroglycan protein itself is not mutated, these diseases are nevertheless referred to as *dystroglycanopathies*. The various syndromic presentations, including Walker–Warburg syndrome, muscle–eye–brain disease, and Fukuyama muscular dystrophy, are now subsumed under the moniker *muscular dystrophy–dystroglycanopathy* (*MDDG*) and then further subclassified according to the specific syndromic deficits identified.

Artifacts

It has often been said that the mark of an experienced pathologist is the ability to recognize artifacts, and this is nowhere more trenchant than in the interpretation of muscle biopsies. Living muscle fibers are highly irritable, and contraction bands are readily induced by excision (Fig. 12.19a, b). In longitudinal sections, these appear as fusiform widenings with shortening of the sarcomeres. In transverse sections, the contracted fibers are swollen, and the sarcoplasm has a vitreous appearance. Gaps may form in the sarcolemma, and Z lines may be smudged or have a streaming appearance. Sometimes, only the central parts of the fiber contract, giving rise to a central core of streaming Z bands. Extreme degrees of contraction result in irregular bands known as the *Nageotte banding artifact* after the French histologist who first described it [68].

In cryostat preparations, vacuolization may be caused by slow freezing (usually as a result of direct immersion in liquid nitrogen or inadequate precooling of the isopentane) resulting in formation of coarse ice crystals. A dull microtome knife produces cracks and rents.

As mentioned above, it is important to avoid mistaking the small diameters of fibers as they insert into their tendons as evidence of pathological fiber atrophy. Finally, as skeletal muscles are subject to the traumas of daily life, occasional atrophic, degenerating, or regenerating fibers are not at all unusual. In other words, it is generally a mistake to ascribe minor or focal fiber alterations to the presence of intrinsic muscle disease.

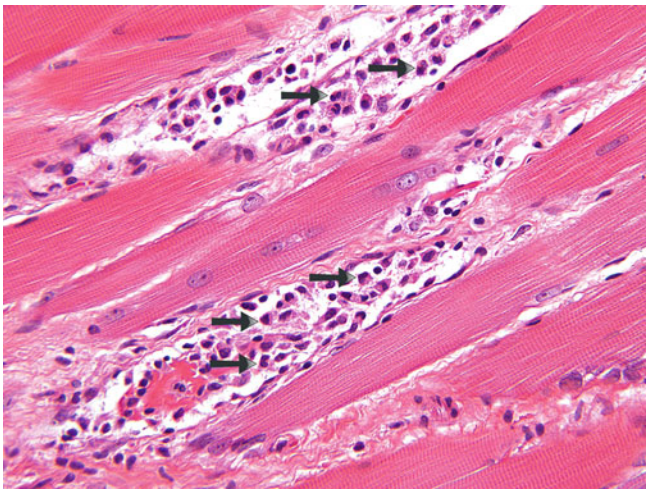

Fig. 12.18 Inflammation may be prominent within limb girdle muscular dystrophies. In this patient with limb girdle muscular dystrophy type 2A (calpainopathy), initial biopsies demonstrated histopathological features indistinguishable from eosinophilic myositis (*arrows*)

Fiber Size Alterations

The increase in the size of a muscle from birth to maturity and in exercise-induced hypertrophy is due to an increase in the number of sarcomeres (and therefore myofibrils) within muscle fibers, not to an increase in the number of muscle fibers. Repeated strong contractions (e.g., resistance training) may augment the girth of muscle fibers by as much as 25 %, and enforced inactivity may reduce it to a similar degree. These volumetric changes are referred to as work hypertrophy and disuse atrophy, respectively. Denny-Brown [69] proved that such alterations in size are a reflection of the number of myofibrils. The number of patent capillaries around the enlarged fibers also increases with exercise and decreases with inactivity. The accommodation of blood supply to fiber size appears to be an essential part of conditioning for increased muscle activity.

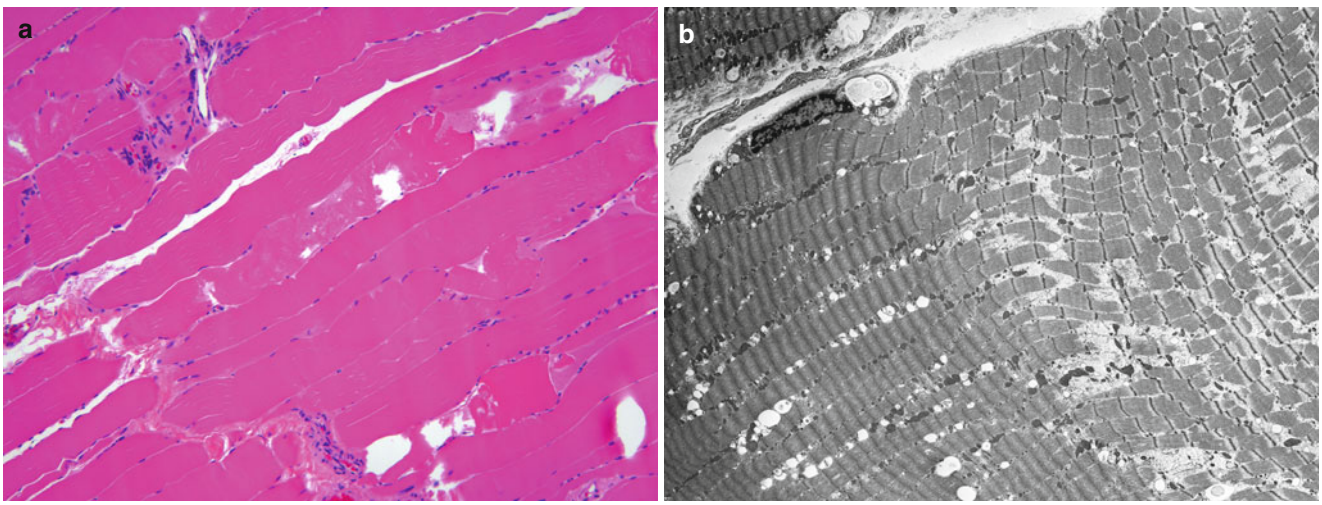

Fig. 12.19 (**a**) Hypercontraction bands may indicate acute muscle necrosis but are also commonly caused by handling of the muscle during processing. The absence of regenerating muscle fibers provides strong evidence in favor of processing artifact in this case. (**b**) Electron micrograph showing hypercontraction band (*left*) and normally contracted sarcomeres (*right*)

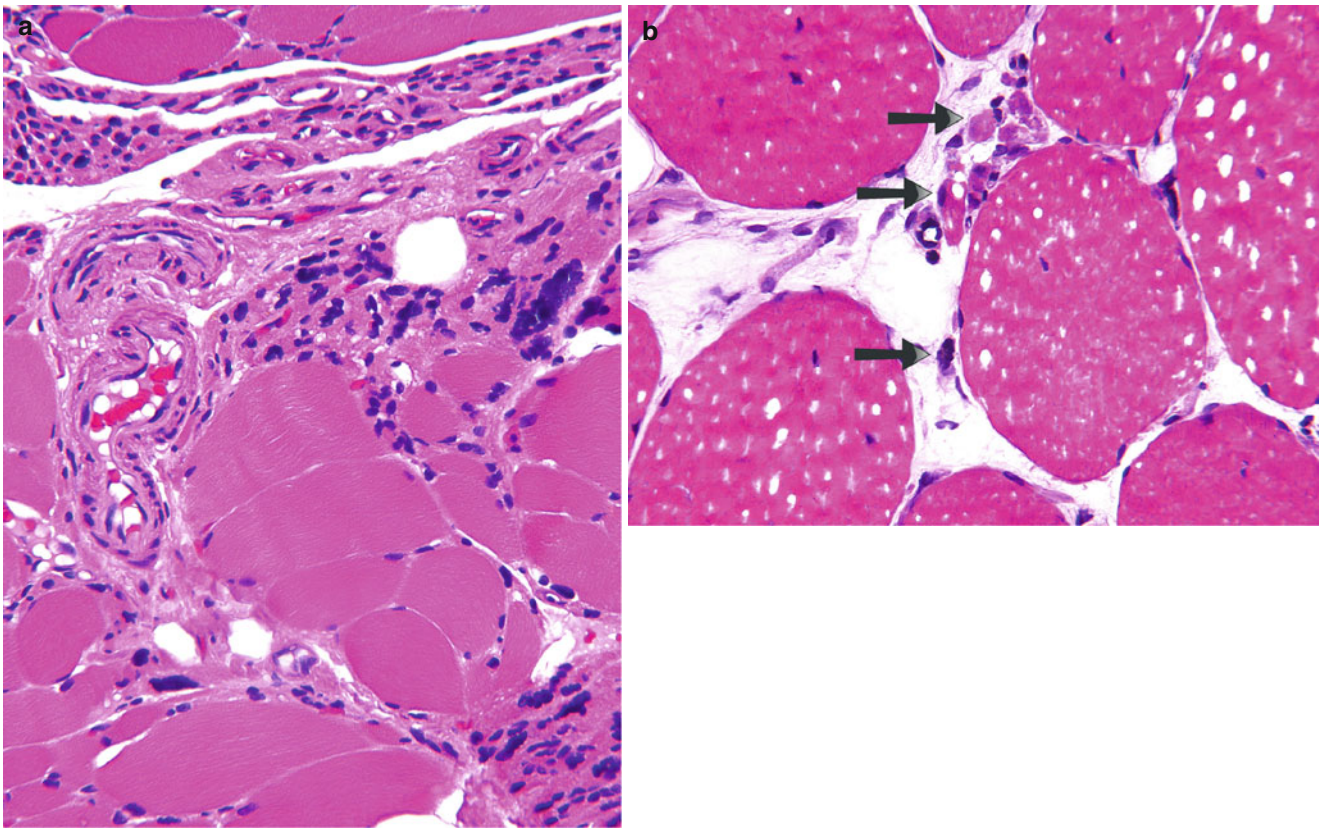

Fig. 12.20 (**a**) At first glance, extremely atrophic muscle fibers may resemble inflammatory infiltrates. (**b**) Careful examination at high power (*arrows*) discloses irregular remnants of eosinophilic cytoplasm, revealing their true myopathic derivation

The term "atrophy" as applied to a muscle fiber refers to a reduction in volume with preservation of sarcolemmal surface area. This may follow loss of innervation (termed neurogenic or denervation atrophy) or may be the consequence of a primary disease of the muscle fiber. Muscle fiber atrophy can also result from immobilization, malnutrition, compression, aging, or vascular insufficiency. Atrophic fibers are smaller than normal because the cytoplasmic contractile proteins are reduced, but the integrity of the cell membrane is preserved. As the cytoplasmic content is diminished, nuclei tend to pile up (transverse sections) or line up in a chain (longitudinal sections). End-stage atrophic fibers appear as "nuclear bags," which on casual inspection may be mistaken for lymphocytic infiltrates. Closer inspection, however, reveals minute amounts of eosinophilic cytoplasm in contradistinction to the discrete amphophilic cytoplasm of lymphocytes (Fig. 12.20a, b)

Due to their dependence on phasic stimulation, type II fibers atrophy more quickly than type I fibers and, therefore, tend to outnumber atrophic type I fibers in neurogenic atrophy. On transverse section, the fibers assume a roughly triangular ("angulated") shape, sometimes partially encircling neighboring normal fibers and conforming to their shape. The process of denervation and reinnervation is best demonstrated with immunocytochemical or histochemical stains that highlight fiber type (Fig. 12.21a–g). Under normal circumstances, type I and type II fibers are distributed so that they appear as alternating fibers, producing a mosaic pattern of staining with the ATPase reaction or myosin heavy-chain immunostaining. In the first phase of denervation, the atrophic fibers of an affected motor unit are distributed in groups throughout the biopsy (small group atrophy). Reinnervation by adjacent axons leads to a clustering of fibers of the same histochemical type in a group (fiber-type grouping). Instead of the usual checkerboard pattern of intermixed fiber types, there is a tendency for both type II fibers and type I fibers to be in large groups, with some fibers entirely surrounded by the same fiber type. Although fiber-type grouping has occasionally been reported in myopathies, it is much more strongly associated with chronic denervation atrophy of muscle, where it is responsible for the enlarged motor unit action potentials elicited on electrodiagnostic testing. Should there then be denervation of the previously reinnervating motor unit, there follows large group atrophy which is type-specific. Electron microscopic examination of atrophic fibers discloses a reduction in the number of myofibrils beginning at the periphery of the fiber. The nuclei of these atrophic fibers appear normal, and sarcotubular profiles and mitochondria increase

in density. The sarcolemma remains intact, but there is duplication and thickening of the basal lamina. In long-standing denervation atrophy, sarcomeric organization is eventually lost, and all that remains are aggregates of haphazardly oriented, poorly organized myofibrils comprising thickened Z lines from which filaments of variable thickness emanate. These, in turn, are interspersed with randomly scattered isolated myofilaments of variable thickness. Muscle fiber atrophy also occurs in myopathic injury secondary to either hereditary or acquired factors; under these circumstances, the atrophic fibers tend to retain either a polygonal or rounded contour (Fig. 12.22a, b).

After long-standing denervation (e.g., in Charcot–Marie–Tooth disease), myocyte cell death with ingrowth of fibroadipose tissue may ensue ("pseudomyopathic changes of chronic denervation"). In cases where the underlying neuropathic disorder has not been previously disclosed or diagnosed, this histological picture is referred to as

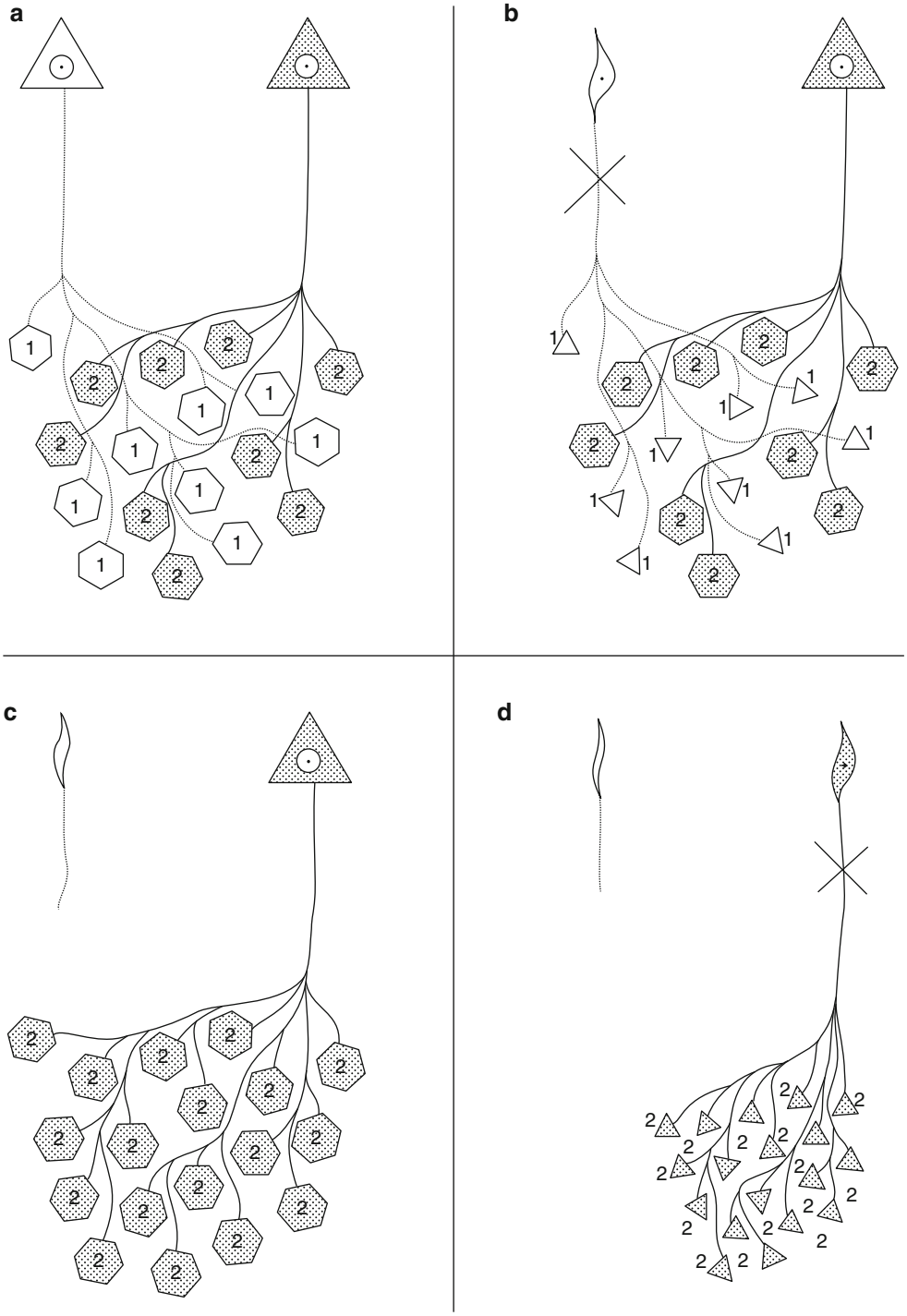

Fig. 12.21 Denervation and reinnervation of skeletal muscle. Diagram of denervation atrophy. (**a**) Normal checkerboard pattern of two motor units (*light* and *dark* anterior horn cells are depicted as triangles). (**b**) *Light* anterior horn cell is damaged, resulting in denervation of muscle fibers of that motor unit (indicated as type 1 fibers). (**c**) Reinnervation accomplished by sprouting of adjacent (*dark*) motor unit axons resulting in type grouping. (**d**) Damage to the axon of the *dark* motor unit results in group atrophy. (**e**) Transverse section showing clusters of angulated atrophic fibers (group atrophy). (**f**) Fiber-type grouping is only evident on the ATPase-stained serial section. (**g**) Electron micrograph showing myofibrillar disarray of an atrophic muscle fiber

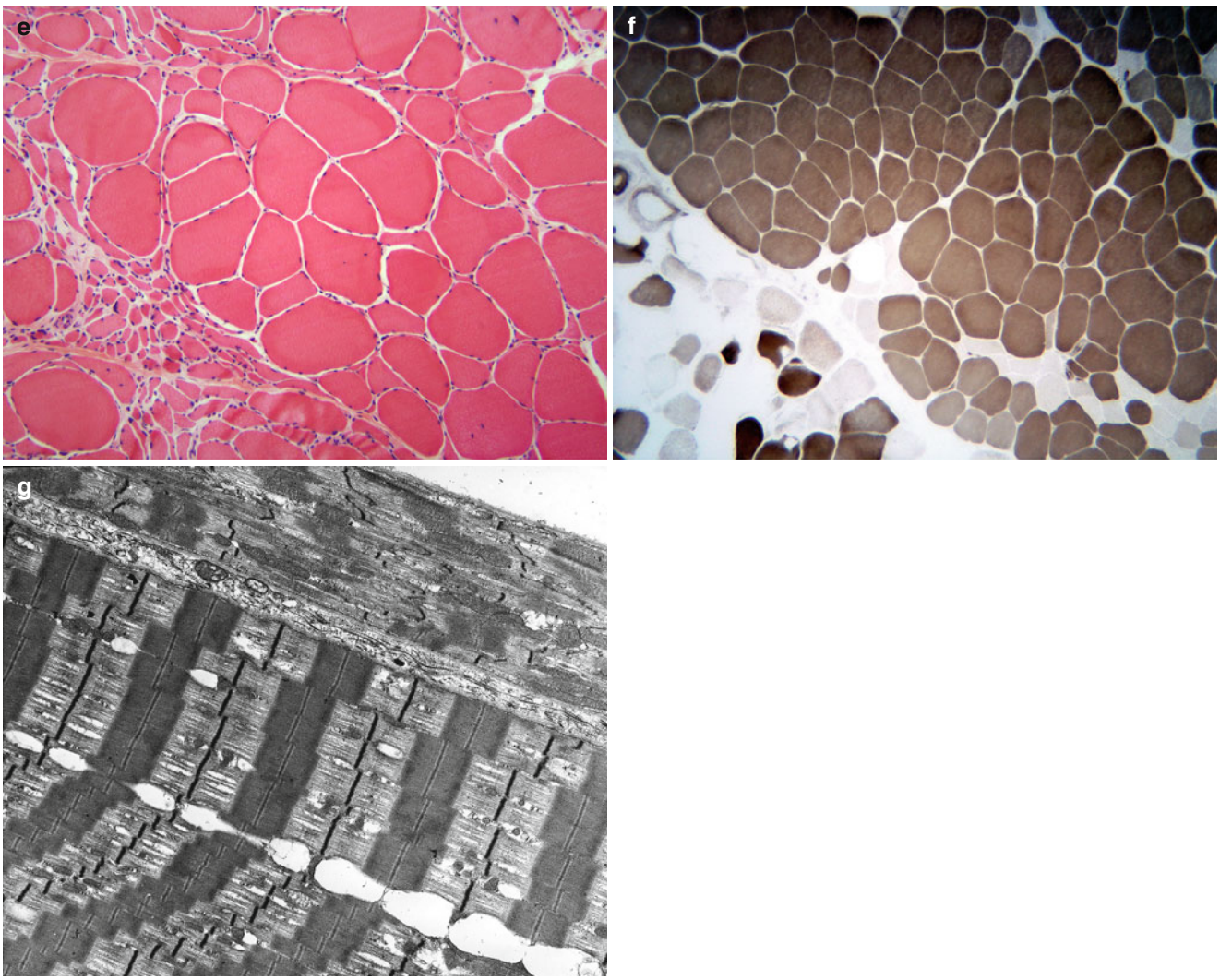

Fig. 12.21 (continued)

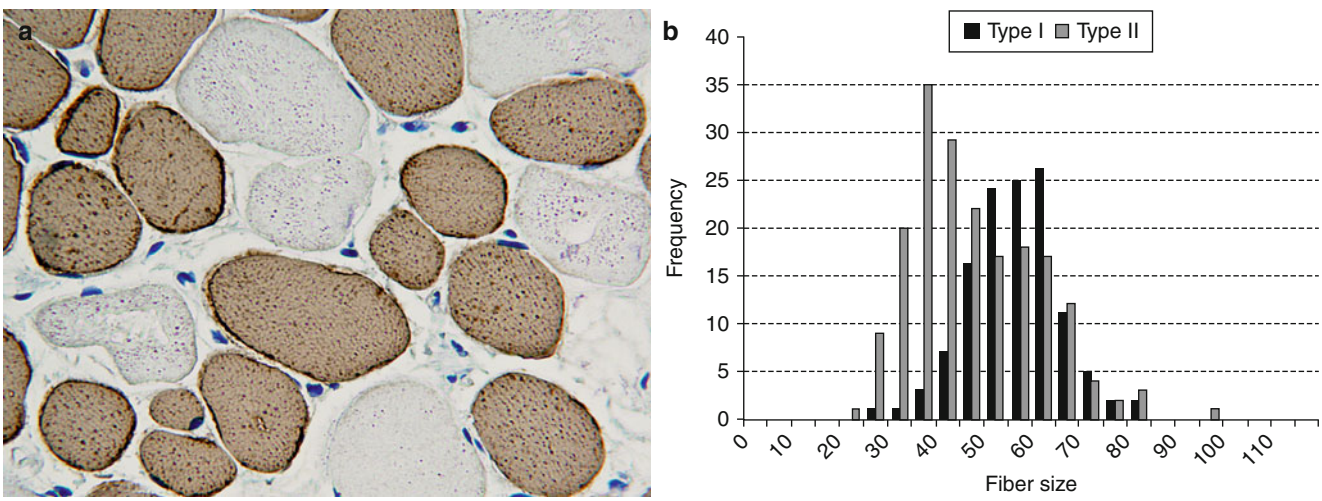

Fig. 12.22 Type 2 atrophy. (**a**) In this muscle biopsy specimen, immunohistochemical staining for fast myosin isoforms showed type II fibers (*stained brown*) to be slightly smaller on average than type I fibers (unstained). (**b**) Morphometric analysis of the muscle biopsy shows a different distribution of the sizes of myocytes of the two fiber types, with a smaller mean diameter of type II fibers

"end-stage" muscle injury, which marks the terminal phase of the muscle disease, be it of neurogenic or myopathic origin (Fig. 12.23).

Hypertrophic fibers are larger than normal, although well proportioned in terms of shape and constituent organelles. These may develop as a consequence of excessive work demands or, rarely, as a consequence of faulty neurogenic signaling. Work hypertrophy of muscle is the basis for increased muscle bulk in resistance training. Muscle fiber injury during training stimulates recruitment of satellite nuclei into injured fibers, eventuating in an increase in the number of myofibrils as the fiber heals.

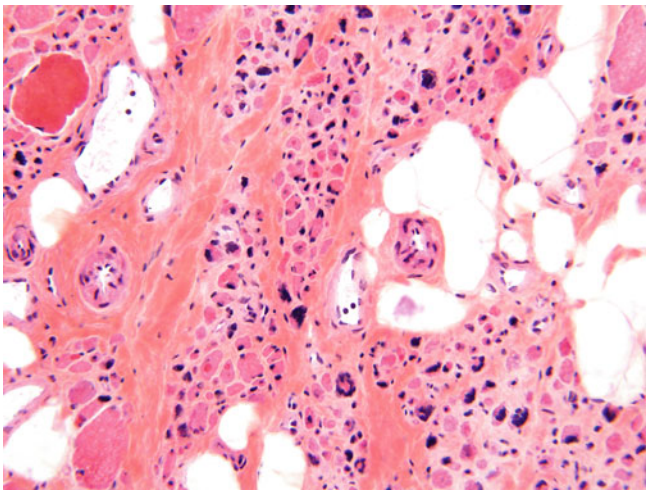

Fig. 12.23 "End-stage" skeletal muscle. Endomysial ingrowth of fibrofatty tissue surrounds clusters of extremely atrophic muscle fibers

Myofiber Degeneration and Regeneration

Segmental necrosis, the degeneration of a longitudinal segment of a muscle fiber, is seen in a large number of myopathies, including those due to vascular immunologic factors. The affected fiber shows focal loss of cross striations replaced by a smudge of hyalinized, somewhat darker-staining degenerated cytoplasm. There may be bulging of the cell at this site or irregular shrinkage of its diameter. The subsarcolemmal myofibrils are damaged preferentially, and the sarcolemma may rupture resulting in extrusion of portions of the sarcoplasm. At the same time, neighboring nuclei become pyknotic or disappear. Eventually, phagocytes are recruited to the necrotic segments, with phagocytic removal of necrotic debris. Simultaneously, satellite nuclei are stimulated and begin regenerating adjacent portions of the muscle fiber (Fig. 12.24a–d). As visualized on H&E, the cytoplasm is purplish blue, and the affected portion of the fiber is somewhat narrower than normal. The cross striations are not apparent, and there is an increase in the size and number of nuclei which also appear larger and vesiculated and contain one or more large nucleoli. Regeneration sometimes produces the appearance of multinucleated giant cells. Fusion between basophilic satellite fibers and the injured fibers is a critical part of the recovery process and may often be visualized during regeneration. Ultrastructurally, regenerating fibers/activated satellite cells can be recognized by the presence of large nuclei and nucleoli occupying an internal position within the fiber. The cell membrane and basal lamina are intact, and the number of organelles is not different from normal, except perhaps for an increased number of free ribosomes. The most striking cellular alterations in regeneration are found

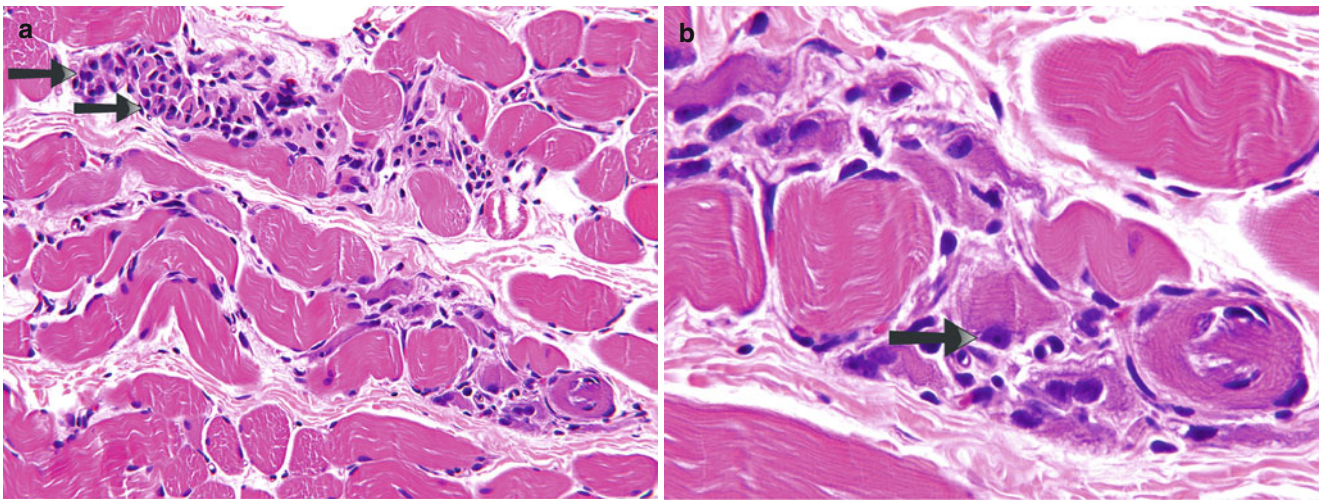

Fig. 12.24 Necrosis and regeneration of skeletal muscle. (**a**) Light microscopy showing a necrotic myocyte being ingested by macrophages (*arrows*), sometimes referred to as myophagocytosis. (**b**) Higher powered view of activated satellite cells characterized by amphophilic cytoplasm, and large nuclei, and prominent nucleoli (*arrow*). (**c**) Electron micrograph showing focal disintegration of a myocyte. (**d**) Electron micrograph showing the prominent nucleus of an activated satellite cells/regenerating myocyte

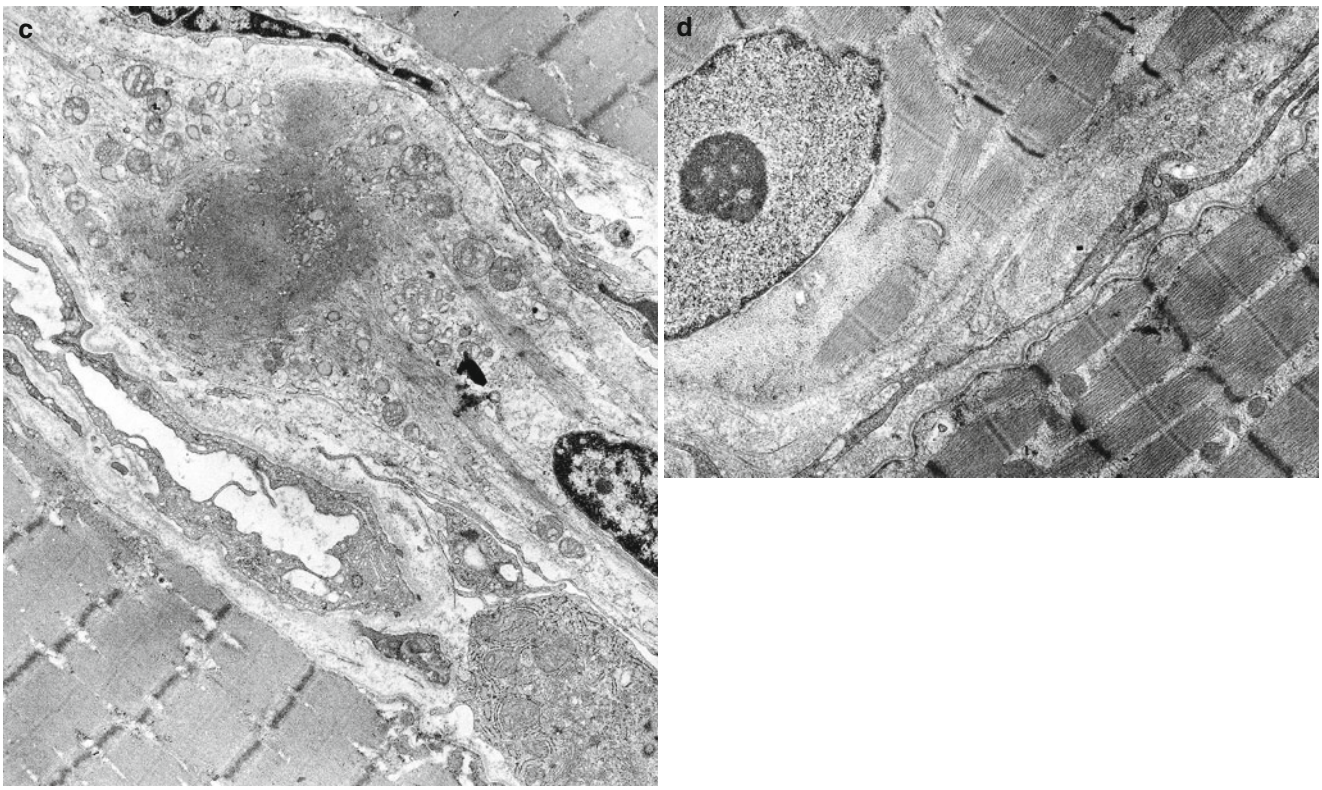

Fig. 12.24 (continued)

in the contractile system. There may be large areas of the fiber in which the filaments are poorly organized into myofibrils, although these may be oriented in parallel.

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Skin Biopsy

13

Lan Zhou

Introduction

Peripheral nerve fibers are classified according to size, which correlates with the degree of myelination. Small fibers are comprised of myelinated Aδ (delta) fibers and unmyelinated C fibers, which innervate skin (somatic fibers), cardiac muscle (autonomic fibers), and smooth muscles (autonomic fibers) lining gastrointestinal tract, genitourinary tract, blood vessels, glands, and others. They mediate pain and thermal sensation as well as autonomic functions.

Small fiber neuropathy (SFN) results from impairment of small myelinated Aδ (delta) and unmyelinated C fibers. When small somatic nerve fibers are affected, patients present with pain, burning, tingling, or numbness. Examination often shows allodynia, hyperalgesias, or reduced pinprick and thermal sensation in the affected area. Motor strength, proprioception, and tendon reflexes, however, are preserved because these modalities are the functions of large nerve fibers. When autonomic fibers are affected, patients may experience dry eyes, dry mouth, orthostatic dizziness, constipation, bladder incontinence, sexual dysfunction, trouble sweating, or red or white skin discoloration. Examination may show orthostatic hypotension and skin changes. The skin over the affected area may appear atrophic, dry, shiny, discolored, or mildly edematous due to sudomotor and vasomotor abnormalities [1, 2]. The symptoms and signs of SFN are typically length-dependent with a distal-to-proximal gradient. Rare cases of SFN may follow a non-length-dependent distribution in which symptoms and signs may be manifested predominantly in the arms, face, or trunk [3–5].

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SFN is a common peripheral nerve disorder. Electrodiagnostic testing – nerve conduction study (NCS) and needle electromyography (EMG) – which is widely used for evaluating peripheral nerve disorders with large fiber involvement, cannot be used to evaluate SFN as the conduction velocities of these small somatic fibers are too slow to allow their conduction responses to be captured during routine NCS. Hence, NCS and needle EMG are typically normal in patients with pure SFN. The lack of objective findings on NCS and EMG may lead many physicians to attribute the SFN symptoms to other disorders such as plantar fasciitis, vascular insufficiency, or degenerative lumbosacral spine disease [2].

Small somatic nerve fibers remained "invisible" until 1990s when the technique of skin biopsy with intraepidermal C fiber density evaluation was developed and utilized for clinical diagnosis of SFN [6–9]. This special test has greatly facilitated the diagnosis and management of SFN [10].

Processing Skin Biopsies

Performing Skin Biopsies

Two methods are used to biopsy skin for evaluating cutaneous innervation, the 3-mm punch biopsy [8] and the blister technique [11]. The blister technique only removes epidermis by placing a suction capsule over the skin without damaging dermal capillaries. Although it is less invasive, painless, and does not cause bleeding, it is not commonly used because it is time-consuming, does not allow evaluation of dermal innervation, and no normative reference value of intraepidermal nerve fiber density (IENFD) is established using this technique [12]. The 3-mm punch biopsy is the standard method for sampling skin. The current technique was initially developed at the Karolinska Institute [9] and later standardized at the University of Minnesota [7] and the Johns Hopkins University [8].

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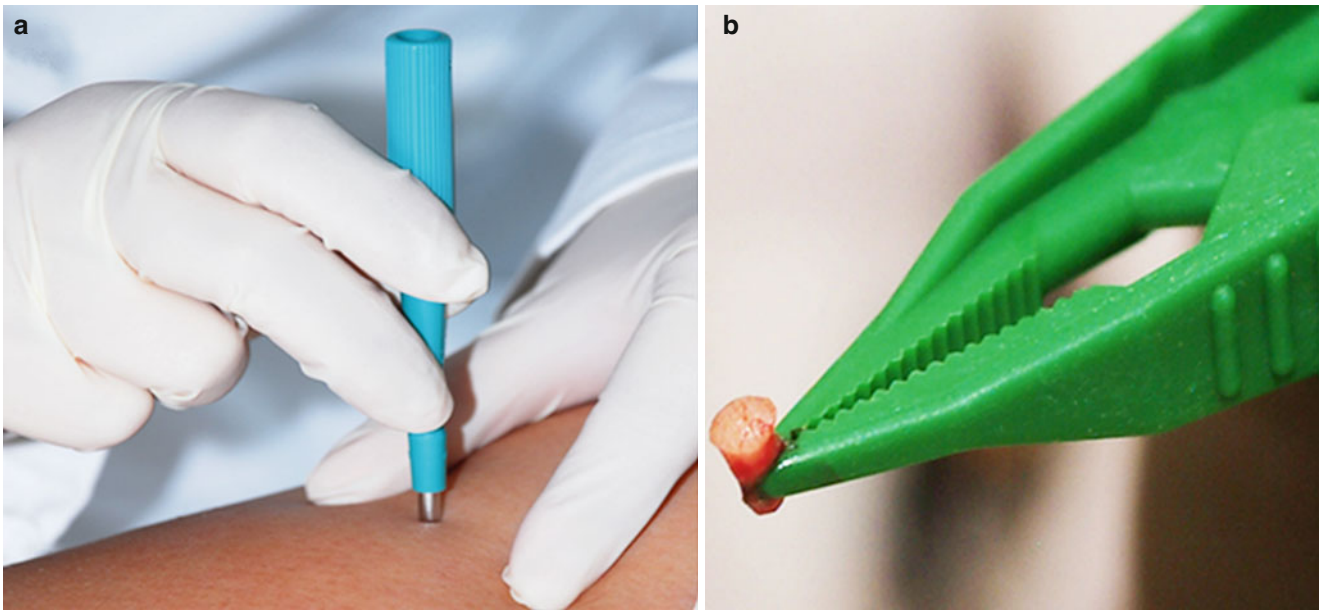

Fig. 13.1 3-mm punch skin biopsy for diagnosing SFN. (**a**) After cleaning the biopsy site, a 3-mm punch is placed on the site perpendicular to the skin surface and twisted down. (**b**). The skin biopsy should be picked up by forceps to pinch the subcutaneous layer but not the top epidermis

The 3-mm punch biopsy is routinely done in one lower limb. The biopsy is taken from distal leg, which is 10 cm above the lateral malleolus. Additional biopsies may be taken from lateral distal thigh (10 cm above the knee) and lateral proximal thigh (10 cm below the greater trochanter) for evaluating the severity and pattern of SFN, length-dependent vs. non-length-dependent [3–5]. Biopsies taken from other sites may be indicated if focal or unilateral small-caliber nerve fiber impairment is suspected [13–15].

The 3-mm punch biopsy is minimally invasive. It is done under local anesthesia using a sterile technique. After a biopsy site is identified, it is cleansed with alcohol swabs and injected with 1 % lidocaine. A 3-mm (diameter) disposable circular punch is then placed on the skin perpendicular to the skin surface and twisted down until the punch is 3–4 mm in. The biopsy is removed with the forceps and surgical blade technique. It is very important that the epidermis should not be pinched because intraepidermal nerve fibers will be evaluated (Fig. 13.1). Bleeding is usually minimum and easily controlled by applying firm pressure to the biopsy site. No sutures are needed, and the biopsy site is usually healed within 7–10 days by granulation which leaves a small scar that gradually resolves.

The 3-mm punch biopsy is well tolerated and is usually completed in about 10 min. The only time patient may feel pain is when lidocaine is injected to numb the biopsy site. It may not be necessary for patients to hold anticoagulants, antiplatelet agents, or nonsteroidal anti-inflammatory agents for the procedure. However, if patients are on these medications, 1 % lidocaine with epinephrine may be used for local anesthesia, because epinephrine has vasoconstrictive effect which can reduce bleeding. The biopsy site may need prolonged pressure, and an absorbable gelatin sponge (gelfoam) may also be applied for hemostasis.

The 3-mm punch biopsy is safe, and no serious adverse effects were reported. The estimated frequency of nonserious side effects, including mild infection and excessive bleeding, is 1.9:1,000 [12]. Mild infection at the biopsy site is usually controlled by topical antibiotics, such as Neosporin® (bacitracin, neomycin, and polymyxin B), and bleeding can usually be controlled by prolonged pressure to the biopsy site without sutures.

Neurologists may perform punch biopsies themselves but only after appropriate training to avoid damage to epidermis. They should send specimens to a cutaneous nerve laboratory, but not a routine reference laboratory, as a special technique, including unique fixative and immunostaining technique, is used to fix and process biopsy specimens. Therefore, it is very important to contact a specialized cutaneous nerve laboratory regarding fixative and processing before planning on a biopsy.

Processing Skin Biopsy Specimens

Immunohistochemical assays are used to detect an antigen expressed by nerve axons to visualize cutaneous nerve fibers to allow morphometric and morphological evaluation of cutaneous innervation. Two methods of immunostaining have been used, the bright-field immunohistochemistry [8] and the immunofluorescence with [7] or without [9] confocal microscopy. Since most diagnostic cutaneous nerve laboratories

use the bright-field immunohistochemistry and normative reference values have been established using this technique, this immunostaining method is briefly reviewed here.

After a skin biopsy is removed, it should be fixed immediately in a cold fixative for approximately 24 h. Two types of fixatives can be used, 2 % paraformaldehyde-lysine-periodate (2 % PLP) and Zamboni (2 % paraformaldehyde and picric acid) fixatives. Formalin, which is commonly used by routine histopathology laboratories, should be avoided because it may cause more fragmented appearance of nerve fibers [16]. The skin specimen is then cryoprotected for at least 6 h using 20 % glycerol in 0.1M Sorensen's phosphate buffer. After freezing, the specimen is sectioned at 50 um. About 45–55 sections can be obtained from each specimen. Four nonadjacent sections from each specimen are then chosen for immunostaining, which is done manually using free-floating skin sections under a dissecting microscope. The wavy nerve fibers can be better viewed in thick 50-um sections than in routine 5-um sections.

The primary antibody used for the immunostaining is the rabbit polyclonal antibody against protein gene product 9.5 (PGP9.5). PGP9.5 is an ubiquitin carboxyl-terminal hydrolase [17], which is a neuronal cytoplasmic marker. It is found in all types of efferent and afferent nerve axons [18, 19], so it is a useful pan-axonal marker to highlight all the nerve fibers. After primary antibody incubation, the sections are incubated with a biotin-conjugated secondary antibody which can bind the primary antibody. This is followed by incubation with avidin-conjugated horseradish peroxidase, and avidin can bind biotin. The immunostaining signal is then developed using the SG kit (blue chromogen/peroxidase substrate) that produces a blue-gray reaction product [8].

Counting IENF and Measuring IENFD

IENF are quantified using a light microscope with 40× objective. A counting rule has been established [20] and recommended to use by EFNS/PNS [12, 21]. Briefly, the nerve fibers that cross the dermal-epidermal junction into the epidermis are counted. The nerve fibers that do not cross the dermal-epidermal junction are not counted. If a nerve fiber branches within epidermis, count as one fiber. If a nerve fiber branches below or within the dermal-epidermal junction, count as two fibers. According to the European Federation of Neurological Societies (EFNS)/Peripheral Nerve Society (PNS) guideline, the nerve fragments within epidermis that do not cross the dermal-epidermal junction are not counted, due to the concern that these fragments may be the extension of adjacent fibers on the same skin section that are visualized to cross the dermal-epidermal junction and counted. Counting these fragments may result in overcounting. However, the original fibers crossing the dermal-epidermal junction may not be shown and counted on the same section due to the wavy nature of nerve fibers, excluding these fragments may thus result in undercounting. Some cutaneous nerve laboratories do count these individual fibers within the epidermis without crossing the dermal-epidermal junction [5, 8, 22–24].

To calculate the linear density of IENF (IENFD), the length of the epidermal surface is measured and a free software available at http://rsb.info.nih.gov/nih-image/index.html may be used [12]. The IENFD is expressed as the number of IENF per length of section (IENF/mm). An alternative "ocular" method has been described and used [25–27], in which special sections are chosen for immunostaining with the assumption that the length of the epidermal surface of these sections is close to 3 mm. So the IENFD is calculated simply by dividing the number of IENF by 3. It has been shown that the IENFD obtained by this method significantly correlated with the IENFD obtained from the conventional quantification by measuring the length of the epidermal surface [25]. However, the EFNS found that further studies are warranted to establish the reliability of the "ocular" method [21].

IENFD measurement is highly reproducible. Reproducibility is highest when four sections from each biopsy specimen are counted [23]. After reviewers are trained to use the same counting rule, the interobserver and intraobserver reliabilities are high [8, 22, 23, 28, 29]. There is no significant difference in IENFD for skin sections stained at different cutaneous laboratories as long as the identical methodology is used by these laboratories to process skin specimens and measure IENFD [23].

Normal Cutaneous Innervation

The skin consists of three layers firmly attached to one another: the outer epidermis, the deeper dermis, and the subcutaneous layer. The cutaneous innervation used to be considered to mainly consist of a plexus of nerve fibers in the reticular dermis and a more superficial plexus of nerve fibers in the papillary dermis parallel to the skin surface. Paul Langerhans first described the penetration of nerve fibers into the epidermis in 1868 by using the gold chloride method [30]. This insensitive staining method, however, made the intraepidermal fibers difficulty to visualize and led people to believe that the epidermal innervation was poor. The intraepidermal fibers were visualized by methylene blue and silver stains in 1950s and 1960s [31, 32]. By using electron microscopy and substance P staining, Kruger demonstrated the penetration of nerve fibers into the stratum spinosum layer of the epidermis in 1985 [33]. Rich innervation of human epidermis was subsequently demonstrated by immunostaining using PGP9.5 antibodies in late 1980s and early 1990s [6, 7, 9]. It was shown that PGP9.5 antibodies labeled more nerve fibers in human skin than

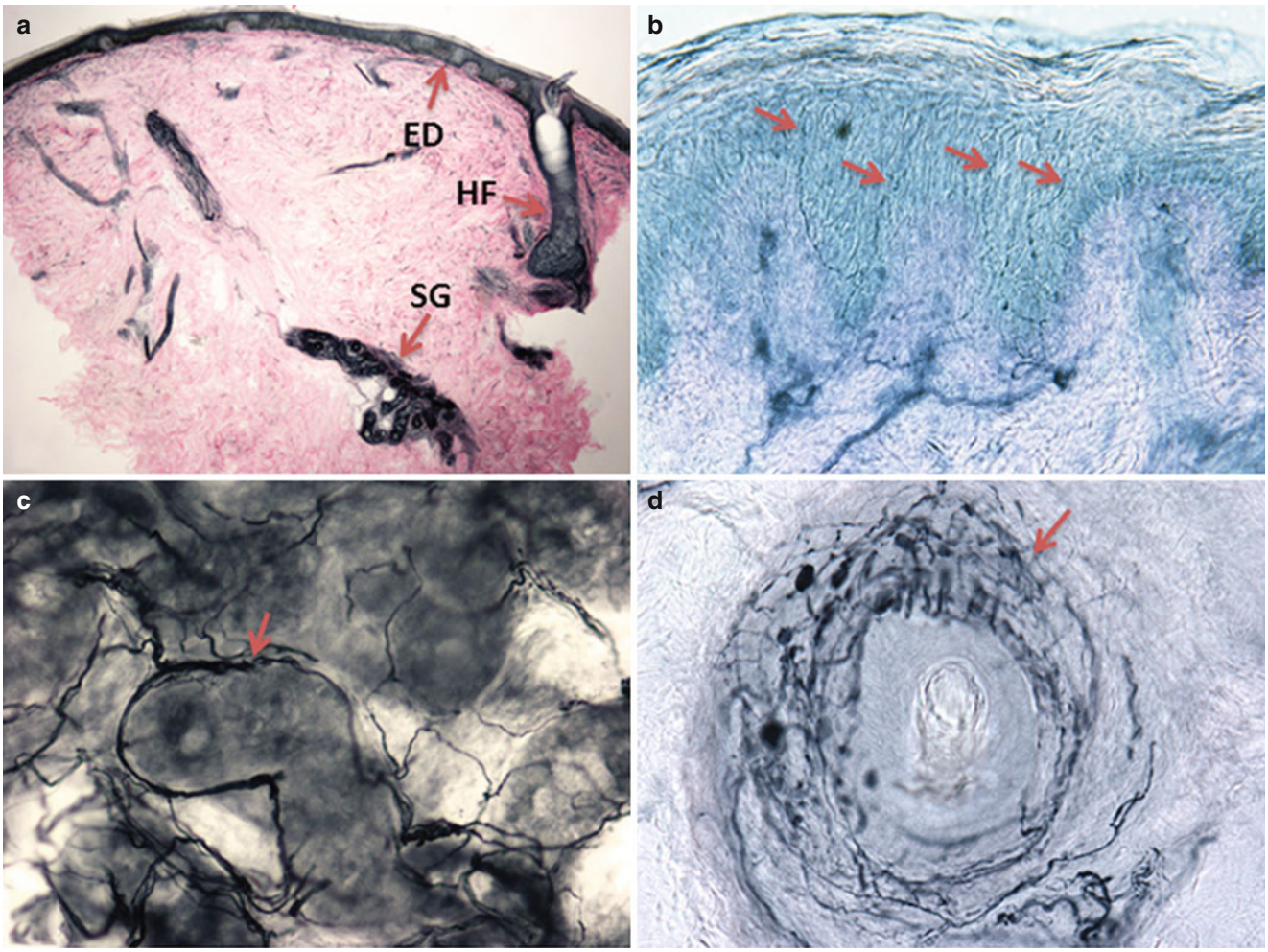

Fig. 13.2 Cutaneous innervation. (**a**) A skin section immunostained with PGP9.5 shows the *top* layer of epidermis (*ED*), hair follicle (*HF*), and sweat glands (*SG*) in the dermis. (**b**) Intraepidermal somatic fibers (*arrows*). (**c**) Dermal sudomotor autonomic fibers surrounding sweat glands (*arrow*). (**d**) Dermal vasomotor autonomic fibers innervating a blood vessel (*arrow*)

neuron-specific enolase, neurofilament, or other peptide marker [34].

The intraepidermal nerve fibers originate from sensory nerves as they express substance P and calcitonin gene-related peptide (CGRP) [35, 36]. In addition, these fibers arise entirely from dorsal root ganglion (DRG) as they disappear from skin after experimental dorsal root ganglionectomy, but not after dorsal rhizotomy, ventral rhizotomy, or sympathectomy [37]. The unmyelinated C fibers are arranged in Remak bundles which also consist of non-myelin-forming Schwann cells. The number of unmyelinated axons in a single Remak bundle varies from 1 to more than 10. Axons exchange among Remak bundles as they pass from DRG to skin [38]. The Remak bundles lose their Schwann cells and the S-100 staining of Schwann cells ends at the dermal-epidermal junction [8]. The unmyelinated axons then ascend vertically through the epidermis between adjacent keratinocytes as free nerve endings [39] (Fig. 13.2). The autonomic C fibers innervate sweat glands (sudomotor fibers), blood vessels (vasomotor fibers), and arrector pilorum muscles (pilomotor fibers) in the dermis.

The technique of 3-mm punch biopsy with intraepidermal nerve fiber density evaluation using PGP9.5 immunostaining was standardized and first utilized to evaluate patients with SFN by the University of Minnesota [7] and the Johns Hopkins University [8]. In 1995, the method of the bright-field PGP9.5 immunostaining and IENFD quantification was published [8]. The majority of diagnostic cutaneous nerve laboratories adopted this method. By using this method, they showed that IENFD at distal leg was lower in patients with HIV-seropositive and HIV-seronegative sensory neuropathy as compared with normal controls. Normative reference range was subsequently developed at distal leg and proximal thigh in 98 normal control subjects with age ranging from 13 to 82 years [22]. This showed no significant age effect except for a significantly higher IENFD in the youngest age decile (10–19 years) [16, 22]. By using the cutoff derived from the fifth percentile of the normative range at distal leg to evaluate 20 patients

with sensory neuropathy, the technique had a sensitivity of 45 %, a specificity of 97 %, a positive predictive value of 75 %, a negative predictive value of 90 %, and a diagnostic efficiency of 88 %. Using fifth percentile cutoff yielded a higher diagnostic efficiency than using tenth percentile cutoff. The high diagnostic efficiency of this technique was also demonstrated by other laboratories [40, 41]. By studying the cutaneous innervation at five sites – distal leg, proximal calf, distal thigh, proximal thigh, and trunk – in ten healthy controls (ages 23–75 years), a normal rostral-to-caudal gradient of IENFD, with a linear relationship to the distance from the spine, was also confirmed [16]. IENFD at a proximal site is higher than that at a distal site. IENFD at proximal thigh was higher than that at distal leg by about 60 % [22].

Several laboratories studied normative reference values at distal leg but did find a decline of IENFD with age [25, 27–29, 42–44]. Recently, a multicenter study was completed to assess the normative values of IENFD at distal leg by involving 550 healthy subjects from eight cutaneous nerve laboratories in Europe, USA, and Asia [45]. The study confirmed the age-related decline of IENFD and also showed no effect of height or weight. Women have higher IENFD than men before 70 years of age. The study developed age- and sex-stratified IENFD normative values for clinical use. However, the sensitivity, specificity, and diagnostic efficiency have not been determined, because no conclusive diagnostic criteria for SFN are available. However, most groups use a similar definition based on clinical symptoms and signs, normal NCS, and abnormal skin biopsy or QST findings [12].

A few reports described the reduction of cutaneous autonomic fiber densities in patients with idiopathic SFN [46] or SFN associated with diabetes [47], leprosy [48], familial dysautonomia [49], and Ross syndrome [50]. Several studies attempted to establish standard and reproducible methods to quantify dermal autonomic fiber densities [51–54] to facilitate clinical evaluation and research of autonomic dysfunction associated with SFN. Gibbons et al. developed and compared three methods of quantifying sudomotor fiber densities [52, 53]. The authors found that the semiquantitative method displayed poor inter- and intra-reviewer reliability and should not be used. The manual method is good but labor intensive. The automated method is superior because it is fast, strongly correlates with the unbiased stereologic technique, and correlates well with examination findings and IENFD. However, whether the sudomotor fiber density measured by this method correlates with the sudomotor function gauged by quantitative sudomotor axon reflex testing (QSART) needs to be determined. Nolano developed a method to quantify pilomotor nerve fiber density (PNFD), and by using this method, they found that the PNFD was significantly reduced in diabetic patients as compared with normal controls. However, PNFD did not correlate with IENF or total neuropathy score [54]. Further morphometric studies of dermal autonomic fiber densities are deemed warranted by EFNS/PNS [12].

Basic Reactions to Injury of Small Nerve Fibers

Small Fiber Degeneration

Small fibers undergo degeneration upon injury. Reduction of IENFD has been shown in neuropathies associated with various medical conditions, including diabetes and prediabetes [46–49], vasculitis [50, 55], systemic lupus erythematosus [56, 57], Sjögren syndrome [58], rheumatoid arthritis [59], HIV infection [8, 24, 60], celiac disease [61], restless leg syndrome [62], Fabry's diseases [63, 64], neurotoxic drug exposure [65], and paraneoplastic sensory ganglionopathy [66].

The diagnosis of SFN is made based on the reduction of IENFD (Fig. 13.3). The majority of SFN is length dependent, in which IENFD at distal leg is more severely reduced (or absent) than distal thigh and proximal thigh due to a "dying back" process affecting small sensory fibers. In some of these cases, IENFD are reduced at proximal sites despite no symptoms or signs developed at these sites [8, 22, 67]. The ability of detecting IENFD reduction in response to small fiber injury at asymptomatic sites demonstrates that skin biopsy with IENFD measurement is a sensitive tool for evaluating SFN. It has been shown that skin biopsy with IENFD analysis is more sensitive than quantitative sensory testing (QST) [40, 60] and more sensitive and less invasive than sural nerve biopsy [43, 68–70]. Patients who underwent both sural nerve biopsy and skin biopsy had reduced IENFD but normal unmyelinated fiber densities in their sural nerve biopsies [68]. Since IENF are more distal to the unmyelinated fibers in the sural nerve, these patients probably had terminal axonopathy with the "dying back" process affecting the terminal unmyelinated small fibers in the skin but not yet affecting the unmyelinated small fibers within the sural nerve trunk.

Non-length-dependent small fiber neuropathy (NLD-SFN) is not as common as length-dependent small fiber sensory neuropathy (LD-SFN). The primary defect in NLD-SFN is most likely at the level of dorsal root ganglia sensory neurons. In a study of 16 patients with sensory ganglionopathy diagnosed by their clinical presentations and NCS abnormalities, 11 had non-length-dependent reduction of IENFD with IENFD more reduced at the proximal thigh than the distal leg, which suggests disease involvement of both large and small dorsal root ganglia sensor neurons [66]. In contrast, all 16 patients with distal axonal neuropathy in the same study showed length-dependent loss of epidermal C fibers. Our recent study showed that in some patients with NLD-SFSN, although SFN symptoms were present in their

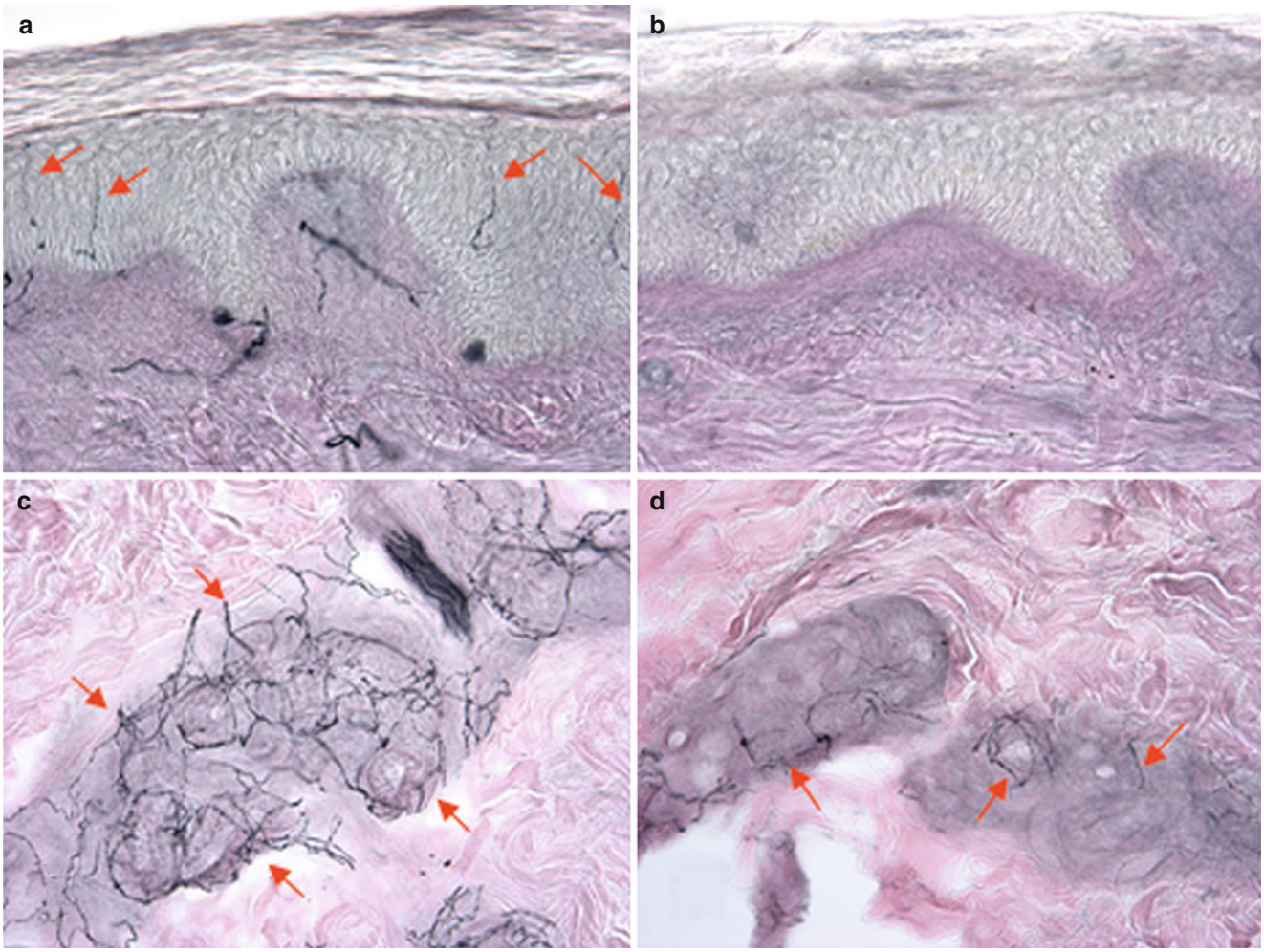

Fig. 13.3 Regional small fiber degeneration. In a patient with complex regional pain syndrome type I affecting the left lower extremity, intraepidermal C fibers were present (*arrows*) at the right foot (**a**) but absent at the left (**b**). Sudomotor autonomic C fibers (*arrows*) also appeared markedly reduced at the left foot (**d**) as compared to the right (**c**) (From Chemali and Zhou [13]. With permission)

face, trunk, and/or upper extremities, but not in their lower extremities, skin biopsies showed non-length-dependent reduction of IENFD in their lower extremities, which is diagnostic for NLD-SFSN [5]. These findings demonstrate that non-length-dependent small fiber degeneration does occur and can be evaluated by routine skin biopsy with IENFD evaluation. Skin biopsy is useful for determining the spatial pattern of SFN.

Small fiber impairment can also be focal, regional, or unilateral. Diabetic truncal neuropathy showed reduced IENFD in the affected dermatomes as compared with asymptomatic truncal areas [14]. We and others also demonstrated small fiber degeneration with reduction of both intraepidermal somatic C fibers and sudomotor autonomic C fibers in patients with complex regional pain syndrome type I [13, 15]. Evaluation of these conditions requires skin biopsy at unconventional sites with no normative values established. In this setting, the contralateral unaffected site should also be biopsied for comparison (Fig. 13.3).

Although skin biopsy with IENFD evaluation is a useful tool for diagnosing SFN, it is not that useful for identifying a specific etiology for SFN. Some cutaneous nerve laboratories perform additional stains on the skin biopsy sections to evaluate vasculitis and amyloidosis, but the diagnostic yield is unknown. Associated conditions have been identified in over 50 % patients with LD-SFN and 40–50 % patients with NLD-SFN, with diabetes/prediabetes being the most common [3–5, 71–73]. Our laboratory and others showed that NLD-SFSN is more commonly seen in women and presents at a younger age as compared with LD-SFSN [3–5]. Diabetes/prediabetes is less prevalent in NLD-SFN than in LD-SFN, while immune-mediated conditions are more commonly seen in NLD-SFN than in LD-SFN [5]. These findings are consistent with the notion that diabetes/prediabetes is more likely to affect distal nerve axons to generate a "dying back" process, while immune-mediated conditions are more likely to generate an immune response to randomly attack sensory neurons/axons.

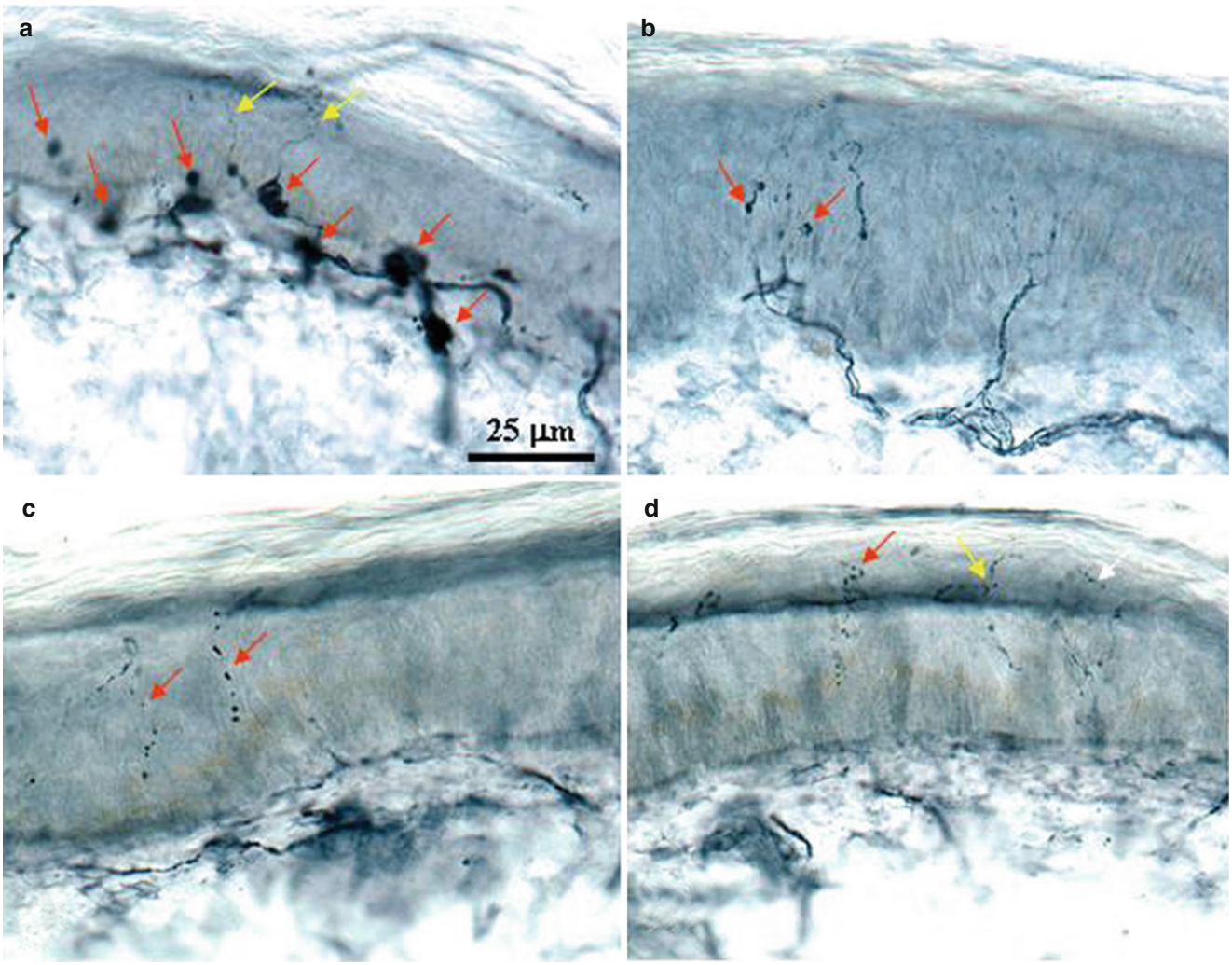

Fig. 13.4 Abnormal morphological changes of IENF. (**a**). Abundant nerve fiber swellings of varying size (*red arrows*) are noted in epidermis, papillary dermis, and dermal-epidermal junction. (**b**) Many small IENF swellings are seen (*red arrows*). (**c**) Intraepidermal fibers are fragmented (*red arrows*) as compared to continuous fibers in (**a**) (*yellow arrows*). (**d**) Tortuous (*red arrow*), branched (*yellow arrow*), and horizontal (*white arrow*) fibers are present (From Zhou et al. [24]. With permission)

Small Fiber Morphological Changes

IENFD can be normal at the early stage of SFN, but in this setting, skin biopsy often shows prominent small fiber morphological changes, including swellings, increased branching and fragmentation, and tortuous intraepidermal C fibers [16, 26, 48, 64, 68, 70, 74] (Fig. 13.4). In severe neuropathies, epidermal denervation was found at progressively more rostral levels, with prominent axonal swellings [70] and increased branching complexities [16] even at sites without neuropathic symptoms. Two studies investigated the diagnostic yield of IENF swellings in SFN [26, 70]. Both found a higher prevalence of swellings at the distal leg in neuropathies, including patients with normal ENFD and persisting painful symptoms in the feet, than in controls. Increased swellings at the distal leg correlated with impaired heat-pain threshold, development of symptomatic neuropathy, and progression of neuropathy. Large swellings of intraepidermal C fibers were found to be able to identify individuals who subsequently developed epidermal denervation, inferring that larger swelling increases the probability for nerve fiber degeneration [74]. Therefore, these abnormal morphological changes, especially large swellings, may represent small fiber pre-degeneration. If these changes are prominent but IENFD are still within normal limits, a follow-up biopsy in 6–12 months may be helpful to detect IENFD reduction and to reach a final diagnosis of SFN.

Small Fiber Regeneration

Small fibers may regenerate after degeneration in response to injury. Three models have been developed and used to study the cutaneous small fiber degeneration and regeneration in

human: (1) the intracutaneous axotomy models [75], (2) the skin blister mechanical denervation model [11], and (3) the capsaicin chemical denervation model [76–78]. The intraepidermal axotomy and skin blister models showed that intraepidermal fiber regeneration started from collateral sprouting from adjacent normal epidermal fibers followed by growing and extension of the transected axons. In the capsaicin model [76], intraepidermal fibers degenerated more rapidly than dermal autonomic fibers, correlating with more rapid decline of sensory function than autonomic function. However, autonomic fibers regenerated more rapidly than intraepidermal sensory fibers. These models demonstrated excellent regenerative capacity of cutaneous small fibers. These models are also useful for the study of molecular mechanisms underlying cutaneous small fiber degeneration and regeneration and for the study of disease-modifying therapies [75, 76].

Several studies showed that IENFD correlated with various clinical and diagnostic SFN severity measurements [24, 28, 47, 79, 80]. Small fiber regeneration correlated with neuropathy symptom improvement. Lauria et al. reported marked reduction of dermal and epidermal denervation in affected dermatomes in one patient with diabetic truncal neuropathy, whose follow-up biopsy 2 years later showed improved dermal and epidermal innervation along with symptom resolution [14]. A few studies [81–84] linked SFN to metabolic syndrome which consists of diabetes/prediabetes, hypertension, dyslipidemia, and central obesity. Smith et al. reported that lifestyle interventions in 32 subjects with prediabetes improved the parameters of metabolic syndrome, which were accompanied by significantly increased IENFD and decreased neuropathic pain [85]. Gibbons et al. also reported substantial improvement of IENFD in diabetic neuropathy patients after 18 months of glycemic control [86]. These findings demonstrate that IENF may regenerate well once the causes of neuropathy are under control. Identifying and treating underlying causes is thus critical to the management of SFN, and it may reverse SFN especially at the early stage of the disease when the damage is limited to the terminal cutaneous small fiber axons. The findings also suggest that serial skin biopsies with cutaneous small fiber density evaluation are potentially useful in future therapy trials to monitor small fiber regeneration and SFN treatment response.

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Molecular Diagnosis and Genetic Testing

14

Eric P. Hoffman, Lauren P. Hache, and Rose B. McGee

Introduction

The capability to assay for the status of individual genes or proteins in patient blood or tissues has grown exponentially over the last two decades. Molecular diagnostics has had a particularly important impact on the practice of neurology, both due to the keen interest of the practicing neurologist and the fact that many of the first identified disease genes have been for inherited neurological conditions. With the dramatically expanding knowledge of the primary biochemical defect for hundreds of disorders comes the anticipation that pathophysiological cascades can be slowed or halted, or primary biochemical deficiencies replaced. While this hope has yet to be realized, molecular human genetics has transformed the way in which the inherited and noninherited neurological diseases are researched, and experimental therapeutics are pursued. Finally, molecular diagnostics can provide a definitive diagnosis to a patient (both symptomatic and presymptomatic) while also permitting the genetic counseling of the patient's family.

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With the increased knowledge of the underlying genetic abnormality in a patient come ethical and legal hazards which are increasingly recognized by patients, health-care professionals, employers, and legislative oversight committees. These hazards are complicated by the fact that few, if any, molecular diagnostic tests have been approved by the Food and Drug Administration (FDA). The reluctance of most laboratory medicine divisions to provide large-scale molecular diagnostics services is a product of the advanced molecular expertise required for many assays, expensive and nonautomated equipment, and the relatively poor reimbursement from third-party payers. This same testing milieu results in a dispersion of specific genetic tests among hundreds of highly specialized laboratories, and navigating the maze of possible referral sites for each specific gene or protein test is often a daunting task. Fortunately, many Web-based resources are available that make finding an appropriate molecular testing laboratory relatively simple. Getting these tests paid for by Medicare, Medicaid, and private insurance remains more challenging, and this in turn may affect equal access to care.

In this chapter, we give several Web-based resources that assist in diagnosis as it pertains to molecular genetics. Next, we discuss the importance of genetic counseling for patients and families and protection and privacy of health information for molecular diagnostic testing. We provide an overview of molecular diagnostic methods most commonly used for neurological disorders and a review of emerging technologies which promise to greatly change the landscape of molecular diagnostic testing and referral.

Web-Based Resources

There are an estimated 480 neuromuscular disorders caused by a single gene [1], many of which have more than one testing type available with often complex genotype/phenotype correlations and differential clinically based diagnoses. As new information emerges on the variety and character of

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mutations and as new technology becomes available to test for them, the importance of determining which tests to order and when to order them is magnified. For instance, deletion/duplication testing is indicated first in some disorders, whereas initial gene sequencing is indicated in others. Reviewing testing strategies for each neuromuscular disorder is outside of the scope of this chapter. Fortunately, there are multiple Web-based databases that can facilitate this process, providing pertinent clinical, genetic, and testing information for these diseases.

The need for centralized reference sources for up-to-date information on genotype/phenotype correlations and available testing is well recognized, and a number of impressive efforts have generated Web-based resources that are openly available to the public. The most relevant are a pair of resources funded by the National Institutes of Health's (NIH) National Center for Biotechnology Information (NCBI), called GeneTests and GeneReviews (both available at http://www.ncbi.nlm.nih.gov/sites/GeneTests/). Institutionally sponsored by the University of Washington, the sites provide two types of resources. GeneTests includes a searchable database of clinics and molecular diagnostic tests offered in the USA and internationally, whereas GeneReviews contains reviews of diagnostic categories and specific diseases, with emphasis on genetic testing, genotype/phenotype correlations, and genetic counseling. Online Mendelian Inheritance in Man (OMIM) (http://www.omim.org) contains thousands of gene, protein, and inherited disorder descriptions, with extensive links to publications and databases further describing molecular features. Two such databases are NCBI's Gene (http://www.ncbi.nlm.nih.gov/gene/1756) and Université René Descartes' GenAtlas (http://genatlas.medecine.univ-paris5.fr/) which provide gene structure, function, phenotype, and reference citations for the molecular aspects of disorder-related genes. Europe-based Orphanet (http://www.orpha.net) contains descriptions of rare diseases as well as orphan drug information, diagnostic testing, and clinical sites in Europe. Lastly, there are several excellent websites focused specifically on neuromuscular disorders. Washington University in St. Louis maintains the Neuromuscular Disease Center (http://neuromuscular.wustl.edu/), a comprehensive, outline-format database devoted exclusively to neuromuscular disorders and syndromes. An online version of the annually updated neuromuscular disorders gene table, printed in the *Neuromuscular Disorders* journal, is available at http://www.musclegenetable.org/. The Leiden Muscular Dystrophy mutation database (http://www.dmd.nl/nmdb/) contains collections of DNA variants observed in the muscular dystrophies. In addition, there are Web-based resources devoted to policy, ethical, and confidentiality issues as they pertain to genetic testing. These resources are covered in the *Genetic Counseling and Genetic Confidentiality* section.

GeneTests is particularly useful for finding laboratories that offer specific molecular diagnostic tests. Information in the database is submitted on a voluntary basis by laboratories with a required annual review. This online database provides information on the nature of the testing offered (clinical or research-based), nature of the molecules tested (gene or protein) and types of methods used (e.g., sequencing, mutation detection). This site offers contact information for referring patient samples and links to the websites of the relevant reference laboratories. In addition, the site features a clinical directory with voluntarily submitted information on clinics offering genetic evaluation and counseling services and a section with educational materials for health-care providers. In early 2013, NCBI will begin the process of replacing the laboratory directory component of GeneTests with the Genetic Testing Registry (http://www.ncbi.nlm.nih.gov/gtr). This centralized resource will keep the features of GeneTests while expanding the range of genetic tests listed as well as providing more information and enhanced search capabilities on each test.

GeneReviews features disease-specific reviews that place molecular diagnostics in the context of diagnosis, management, and genetic counseling of inherited disorders. Each review is written by an expert in the field through invitation. Each contribution is then carefully screened for accuracy by two or more expert peer reviewers and substantially text edited by the database curators to ensure consistency and completeness of the contributions. A formal updating process for each review is undertaken every 2–3 years. A major advantage of this resource is that it provides significant guidance regarding the appropriate utilization of genetic and biochemical tests, even among a group of disorders with multiple molecular etiologies. For example, a chapter on congenital muscular dystrophy explains that *LAMA2* genetic testing alone (i.e., without a skin biopsy) can be performed in a patient with medical history and physical and neurological examinations strongly suggesting laminin alpha-2 deficiency. In the case of multiple causative genes, however, a suspected diagnosis of a dystroglycanopathy is better evaluated with an initial muscle biopsy to identify which protein deficiency is present prior to genetic testing. Each review also provides links to patient support organizations and PubMed for cited references. Unlike GeneTests, GeneReviews will not be replaced by the Genetic Testing Registry.

OMIM was the brainchild of Victor McKusick in the 1960s at Johns Hopkins University School of Medicine and was later developed for the Web by NCBI. This resource contains clinical reviews on each known inherited genetic disorder and associated research, with an overall emphasis on relationships between genotype and phenotype. OMIM is constantly updated through searches of the literature by experts at Johns Hopkins Medical School, with each entry organized as a running synopsis of the accumulated literature. As such, it is extensively referenced and usually quite up to date. The "running synopsis" format can sometimes be difficult to follow and they often quote directly from the

abstract or publication within the context of the entry. PubMed links are provided for each reference cited. Another invaluable feature of this site is the Clinical Synopsis search where a list of relevant disorders can be obtained by entering multiple phenotypic features in one search query. The results of this search can also be limited to a specific area (e.g., neurologic).

Orphanet is generated through a joint effort between 40 European countries and serves as an information portal on rare disease for professionals, patients, researchers, and industry. This resource defines a rare disease as occurring 1 in 2,000 or less; most of these are from genetic origin, but the site includes rare infectious and autoimmune diseases. The site offers an abundance of resources, including reference materials, an orphan drug inventory and directories of clinical services, diagnostic testing, and research investigations in Europe. A tool to aid in diagnosis (by entering clinical signs) and guidelines regarding emergency medical and anesthesia are also available.

The Neuromuscular Disease Center offers a comprehensive collection of bulleted lists containing essential clinical and pathological features, genotype/phenotype correlations, and laboratory findings (genetic and biochemical) for each disease. Within each list are links to references and other outlines to explain different concepts or principles. An extensive collection of pictures and illustrations demonstrating clinical, pathological, and even historical aspects of the diseases are included. A differential diagnosis page is also available. The site does not, however, give recommendations on testing strategies and, with the exception of several links, only offers information for their clinical laboratory antibody testing. The online version of the monogenic neuromuscular disorders gene table enables users to explore tables by disease group, name, gene, and gene product. Key references on gene discovery for a disease plus other diseases involving the same gene are included for each item in the table. The Leiden Muscle Dystrophy database features comprehensive collections of user-submitted pathogenic and nonpathogenic variations observed in muscular dystrophy-associated genes. Reference information for phenotypes associated with a variant is provided.

Use of Genetic Information and Genetic Counseling

Use of Genetic Information

Results of genetic testing are potentially volatile and ethically complex pieces of information. Unlike many medical tests, which give a clinical picture relevant to a point in time, genetic tests provide permanent information about the individual tested with implications for both the patient and relatives. Presymptomatic testing for individuals at risk for Huntington disease has been a paradigm for policy development and execution with regard to patient care, standard protocols, genetic counseling, test result confidentiality, and insurance issues, forged through joint efforts between professionals and patient advocacy groups. A core tenet in this paradigm is utilization of genetic counseling sessions prior to ordering the test and, if testing is pursued, after the results become available. From the perspective of the neurologist, such involvement of multiple clinical subdisciplines in what may be considered a relatively straightforward diagnostic test can seem like micromanagement of the neurologist-patient interaction. However, there are unusual aspects of the presymptomatic (and pediatric) patient with regard to genetic testing, with several highly visible media case reports demonstrating the complex issues involved. For example, a Quebec man with a family history of myotonic dystrophy obtained gene testing and was found to be an asymptomatic (preclinical) gene carrier [2]. The patient and his physician were well aware that many myotonic dystrophy patients lead perfectly normal lives due to the variable effects of this mutation. During the process of applying for life insurance, the man was asked if he had a preexisting condition to which he replied in the negative (as he showed no symptoms of the disease). He was subsequently in a car accident and died, but his wife was then denied collection on her husband's life insurance, as the insurance company learned of the myotonic dystrophy result and considered this gene test result evidence of a preexisting health condition. The Quebec Superior Court upheld the insurance company's claim and the wife was unable to collect on the insurance.

Government laws and policies (or lack thereof), as well as insurer and employer policies, regarding the use of genetic information can vary from country to country and state to state. One of the key issues, highlighted by the Quebec story, is whether health and life insurance companies or even employers can base individuals' insurance coverage or employment decisions on genetic information. In most of Europe, where universal health insurance is in place, the focus has been placed on life insurance. Basic life insurance is considered a societal right; therefore, genetic test results must be kept confidential and not be released to the insurance company. However, supplemental life insurance policies are considered differently and life insurance companies have the right to request genetic test results. In the USA, the Genetic Information Nondiscrimination Act (GINA) was passed in 2008 and became fully effective by the end of 2009 [3]. This landmark legislation protects individuals from the use of their genetic information in health insurance eligibility, coverage, premium rate, and underwriting decisions (Title I) and on employment hiring, firing, and promotion decisions (Title II). The law does not apply to life, disability, or long-term care insurances. Under this law, genetic information includes family medical history, genetic tests, and services used by individuals and their family members in

both the clinical and research settings. There are important limitations to recognize in the provisions of GINA. Once a genetic disease has manifested, an individuals' health information can be used in health insurance considerations. For example, a positive genetic test result for Huntington disease in an asymptomatic person cannot be used by health insurance companies as a preexisting condition or to raise premiums. Once the symptoms of the disease become apparent, however, the health information regarding the diagnosis can be used by the insurance company. In addition, a health insurance company can request genetic information (e.g., a documented family history of a genetic disease) if coverage of a service or test for an individual is appropriate only with a known genetic risk.

Patient Confidentiality

Outside of the insurance or employment framework, issues of confidentiality can surface in the context of genetic information within at-risk families. This is a particularly relevant issue in cancer genetic diagnosis, where routine clinical screening of a mutation-carrying presymptomatic patient is clearly able to save lives. In a relatively common scenario, a symptomatic cancer patient's family history reveals multiple members who died with the same cancer diagnosis. Subsequent genetic testing determines that the symptomatic patient is positive for a causative cancer gene mutation. About half of his immediate relatives are at risk for carrying this same mutation and thus are at risk for developing the same cancer. Routine screening could detect the cancer in these relatives at an early stage and lifesaving clinical intervention could be provided. While it might seem that the primary care physician of the original patient should contact the family members, explain the situation, and offer testing, the current practice is that contact initiated by the physician toward the patient's family members is not appropriate and represents a breach of patient confidentiality. Instead, the physician must work through patients, encouraging them to contact family members and ask the family members to contact the physician. In this manner, the testing is requested by the patient, and not the physician, and the breech of patient confidentiality is voluntarily done by the patient's own actions. Unfortunately, there are instances when the patient does not contact the family members, putting them at clear risk of harm. Is the physician then allowed to contact the family members, without the consent of the patient? Generally not, for in spite of the potential risk of disease to family members, the responsibility rests on the tested family member, who remains in charge of their own genetic information and whose family, if told by the proband, has the right to decide if they want testing or not. However, cases have been filed disputing this paradigm and some countries have passed legislation to the contrary, where the physician's obligation to the "general good" or duty-to-warn outweighs their obligation to the single patient. States and countries differ in their opinions and laws in such gray areas and one needs to consult specialists in genetic counseling or medical ethics when faced with such (usually rare) situations.

Consent Forms for Genetic Testing

Another set of issues in genetic testing regards consent forms. In addition to the above-described issues of confidentiality, there are also concerns regarding future commercialization of genetic findings (particularly in research samples), concerns of long-term storage of samples, issues concerning patient access to appropriate genetic counseling when receiving test results, and finally issues regarding future research-based tests which are often done on DNA samples. For all of these reasons, genetic testing requires the use of patient consent forms for diagnostic clinical testing, in addition to needing proper institutional review board (IRB) approvals for research-based testing. The physician's home institution should have an IRB passed for genetic testing of all patients referred to external molecular diagnostic laboratories, in addition to a patient-signed consent form from the testing laboratory. This can be cumbersome, particularly if different IRB protocols and consent forms must be developed for each genetic test available (e.g., carrier testing for Huntington disease and cystic fibrosis has completely different disease-specific issues to be dealt with). As a result, most genetic testing laboratories and referring institutions are content with the use of an external, laboratory-based IRB approval and consent form; however, this practice may be inappropriate. The extent to which the informed consent process is utilized by health-care providers and is covered in laboratory-provided consent forms in the arena of genetic testing varies, complicating matters. The goal of this necessary process is to ensure that the patient fully understands the test and its implications prior to undergoing testing; the responsibility of engaging in this process with the patient rests on the health-care provider offering testing [4]. Ideally, informed consent includes the benefits, risks, and limitations of testing; pretest considerations (e.g., testing of children, potential confidentiality consequences, impact to family members, and possible psychological impact from test results); and posttest considerations (e.g., career plans, reproductive planning, informing family members) [5]. Government standardization of informed consent requirements may simplify the process with universal consent forms in the future.

Clearly, it is imperative for both the physician and the patient to understand the implications of genetic test results on confidentiality, insurance, and lifestyle, before a test is requested. Given the maze of ethical dilemmas and

confidentiality issues that face the communication of gene test results to a patient, it behooves the neurologist to either become intimately familiar with all the issues and appropriate actions or to refer the genetic testing process to appropriate medical specialists such as a genetic counselor or medical geneticist who may be better informed to act appropriately. There is an important World Wide Web resource that provides easy access to genetic policies and regulations, both nationally and internationally. HumGen International (http://www.humgen.org/int/), maintained by McGill University's Centre of Genomics and Policy with support of foundations, pharmaceutical companies, and public funding, has a searchable database of laws, policy statements, and selected literature from governments and professional organizations on social, ethical, and legal aspects of genetics. Most search results link to the original Web source at the respective Web pages of each organization or government. In addition, the US National Human Genome Research Institute (NHGRI) sites feature a section called Issues in Genetics (http://www.genome.gov/issues) that includes resources on genetic testing, discrimination, health issues, and informed consent as well as a policy and legislation database. The US Centers for Disease Control and Prevention (CDC) Public Health Genomics site (http://www.cdc.gov/genomics) gives resources on public health genetic policy, research, and practice.

Basic Principles of Human Molecular Genetics

Molecular diagnostics is based on the principle that an underlying primary gene or protein change is responsible for a set of clinical symptoms and can be identified. It is important to point out that a primary genetic abnormality causes the initiating biochemical problem, either by the loss of a specific protein (recessive disease, "loss-of-function" biochemical defect) or by the production of a toxic protein (dominant disease, "gain/change-of-function" biochemical defect). The protein abnormality then often initiates many cascades of events leading to disease, which may manifest in patient symptoms immediately (e.g., hyperammonemia in ornithine transcarbamylase deficiency), or may not be seen for many years (e.g., toxic protein containing an excess of glutamine amino acids in Huntington disease). The downstream changes may themselves create a pattern of patient symptoms which reflects a specific biochemical problem and therefore becomes diagnostic (e.g., the facial features, myotonia, cataracts, conduction defects, and distal weakness indicative of myotonic dystrophy).

In the past 10 years, genetic tests for neuromuscular disorders have become more widespread and many are now available on a commercial basis. For some disorders, like Duchenne muscular dystrophy (DMD), the first line of testing [6] is genetic testing through deletion and duplication testing of the *dystrophin* gene. Muscle biopsy is not suggested in the flow chart for the diagnostic workup of a dystrophinopathy [6] until genetic testing has been completed and no mutations are identified through deletion/duplication testing and testing for point mutations. For many neuromuscular disorders, genetic testing is now a key component of the diagnosis. In some disorders, it may also have implications for disease prognosis as well as therapeutic approach interventions. Emerging technology such as whole genome or whole exome sequencing may also prove critical when nonspecific patient symptoms can reflect tens or hundreds of different underlying disorders (e.g., spastic paraplegia or epilepsy).

If we limit the initial discussion to the testing of a single molecule, defined here as molecular diagnosis, then either proteins or genes can be tested. Overall, a gene mutation is considered more specific than a protein abnormality. Protein defects (usually an abnormal amount of a single protein) can be primary or secondary to a specific genetic defect, and distinguishing between primary and secondary problems is often not trivial. Also, dominantly inherited disorders form the bulk of the disorders seen in the adult neurology or neurogenetic clinics, and dominantly inherited disorders are generally refractory to protein testing. This is because dominant disorders typically involve a gene mutation that results in a toxic protein, in which the toxicity is most often caused by a single amino acid change in the protein. Protein tests are generally not able to distinguish a normal protein from a toxic one with only one amino acid change. Sometimes the toxic protein can cause an obvious pathology (e.g., toxic glial fibrillary acid protein [GFAP] leading to the characteristic Rosenthal fibers in brain biopsies of Alexander's disease patients, or the amyloid due to beta-amyloid mutations in some cases of Alzheimer's). However, the specificity of such pathological findings is usually not good and in some cases requires difficult-to-obtain tissues for study.

Recessively inherited gene defects typically result in the loss of function of a single protein, and this loss of function is typically associated with the lack of detectable protein in patient tissues. In some instances, the protein deficiency is specific enough to be diagnostic, and in rarer instances, the detection of the protein deficiency can be more straightforward than detecting the gene defect. Of course, protein testing relies on having access to tissues in which the protein is normally expressed. One could test for GFAP protein in a brain biopsy from a patient with possible Alexander's disease, but this procedure is clearly more invasive than testing for specific gene mutations in the DNA in a small peripheral blood sample in the relatively small GFAP gene. As of 2012, 12 commercial laboratories in six different countries offer full sequencing of the GFAP gene.

Here, we will focus on methods and practice of mutation detection in a patient's genomic DNA sample (usually from a small peripheral blood sample). As genomic DNA contains all genes, it is not necessary for the gene to be expressed in order to detect the underlying gene mutation. Note that an exception to this is tumor samples, where typically only the tumor DNA contains the causative gene lesions, and the peripheral blood DNA does not.

Types of DNA Mutation and Their Detection

Cytogenetics

A relatively crude, yet often informative, means by which large genetic anomalies can be visualized is through direct visualization of the chromosomes. Nucleated cells in the body contain 46 chromosomes arranged in pairs with 22 autosomal pairs and six sex chromosomes. During the initial stages of mitosis and meiosis, chromosomes are highly condensed and may be visualized under basic light microscope. Several banding techniques exist which allow scientists to identify chromosomal alterations. Clear examples of cytogenetic abnormalities are seen in patients with aneuploidies (too many or too few chromosomes), such as Down syndrome. Aneuploidies involve many scores of genes, and as a result, the abnormal "dosage" of so many genes typically results in multisystemic syndromes, with neurological symptoms being only one of the manifestations of the disorder. The basic nomenclature for karyotype reporting involves the total number of chromosomes seen in the patient's cells, the sex chromosomes (XY or XX), and an indication of which chromosomes are missing, extra, or derived. Examples include 46,XX normal female; 46,XY normal male; 47,XY,+21 Down syndrome; and 45,X Turner syndrome.

Some nonaneuploid or euploid cytogenetic abnormalities can be visualized under the light microscope. For example, patients with cri du chat syndrome show the loss of the tip of chromosome 5 on one of their two number 5 chromosomes. They have the normal number of chromosomes but have a partial monosomy involving just part of one chromosome. Chromosomes with abnormalities visible by the light microscope are still very large in scale, with the resolution of detection limited to changes four to five million base pairs or larger. As the typical gene is about 30,000 bp in size, even a very small cytogenetic abnormality (four to five million base pairs) can contain a hundred or more of genes. Consistent with the polygenic nature of the change, large deletions are typically syndromes (called contiguous gene deletion syndromes), often including mental retardation, dysmorphic features, and cardiac defects as part of the clinical picture.

Another broadly used cytogenetic method called fluorescent in situ hybridization (FISH) can detect the presence or absence of specific DNA sequences. Pieces of cloned and purified human genomic DNA are labeled with biotin using molecular genetics techniques and then hybridized to a cytogenetic spread of patient chromosomes. The biotinylated probe DNA hybridizes to the complementary sequence of the region of interest on each chromosome in each cell. The biotin is then detected using streptavidin linked to a fluorophore and visualized using fluorescence microscopy. Alternatively, probes can be labeled with fluorescent nucleotides and directly visualized with the microscope, thereby reducing steps and giving clearer results. This method can detect deletions (one chromosome will fluoresce instead of two), duplications (one chromosome shows two areas of fluoresce), or rearrangements (incorrect chromosomes fluoresce) of chromosomes that are below the resolution of the light microscope (40 kilobases to 1 megabase, depending on the size of the probe used). For example Charcot-Marie-Tooth (CMT) 1A, which is caused by a duplication of the *PMP22* gene, can be detected using FISH. The one million base pair duplication is visualized by interphase FISH.

Comparative genomic hybridization (CGH) is a newer technology able to scan chromosome regions associated with loss or gain of genetic information. In CGH, DNA fragments are isolated from both a reference library (controls) and the patient's DNA. The DNA fragments are labeled and then pooled together as DNA probes in hybridization experiments. This method is relatively labor intensive and newer methodologies such as microarray-based CGH have been developed. Array-based CGH uses arrays that contain thousands of fragments of DNA adhered to a chip. The probes are labeled in the same fashion as CGH (green for the control or reference DNA and red for the patient's DNA), but the chip is then analyzed in an automated fashion.

Single Gene Defects and Inheritance Patterns

The large majority of monogenic disorders fall into two inheritance patterns: recessive and dominant.

Dominant Inheritance

Dominant disorders are vertically transmitted through a family, with an affected parent having a 50 % risk to pass the genetic mutation to each child. Major variables in dominant disorders are *penetrance* (chance that a family member with the abnormal gene will show any symptoms of the disorder) and *expressivity* (the severity of symptoms). An increasing number of disorders presenting as isolated cases are now recognized as new dominant mutations – that is, a de novo gene mutation in one copy of a gene causes the disease. Thus, although the disease is dominant at the gene and

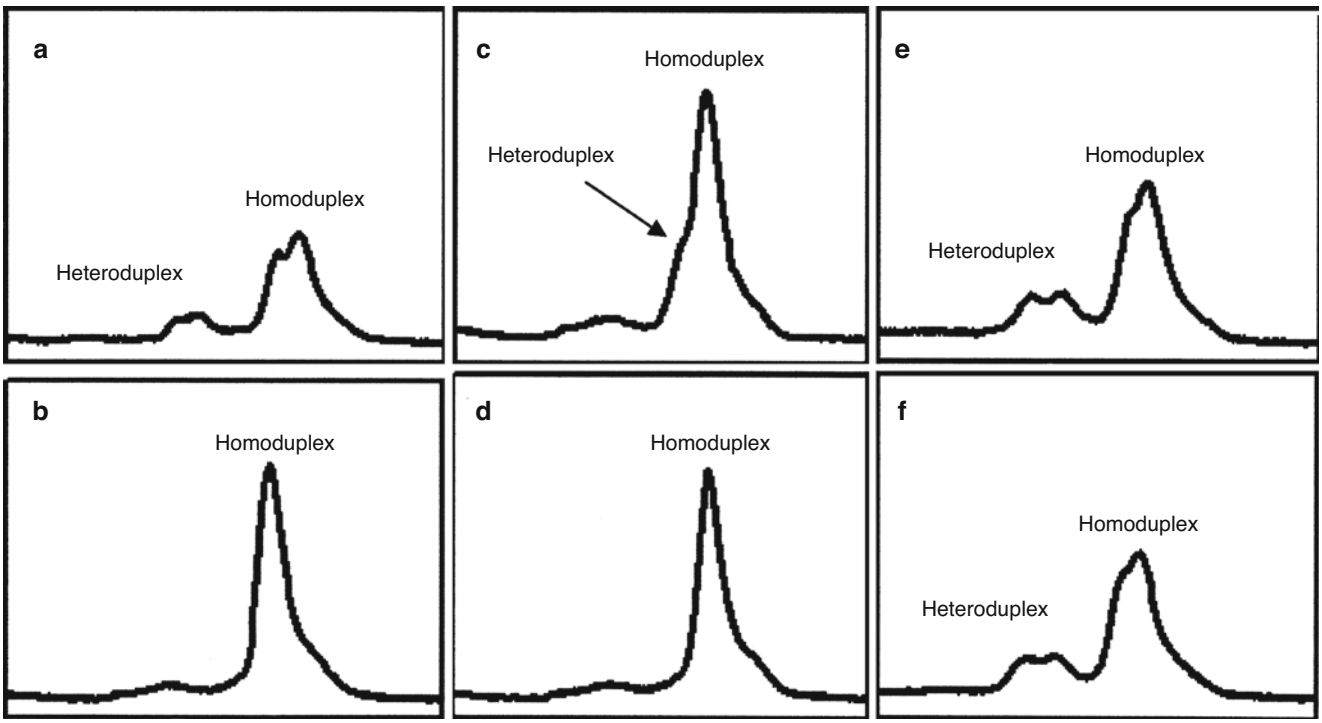

Fig. 14.1 Denaturing high-pressure liquid chromatography (DHPLC) for detection of genetic changes in Rett syndrome. Shown are a number of examples of DHPLC analysis of PCR products corresponding to the MeCP2 gene in Rett syndrome patients (Panels **a**, **c**, **e**, **f**) and controls (Panels **b**, **d**). The PCR product is loaded onto the paired-ion chromatography column and eluted at specific temperatures and denaturant concentrations. Heteroduplexes, which are double-stranded DNA containing both normal and mutant strands of DNA, come off the column at an earlier time, leading to extra leading peaks on the chromatogram. These heteroduplexes are then subjected to automated sequencing to identify the specific mutation (From Hoffbuhr et al. [8])

protein level, a multigenerational family history is not seen, although vertical transmission of the disease will occur if the patient is able to reproduce. Two neurological conditions that are almost always seen as isolated cases are Rett syndrome and Alexander's disease. In both cases, a new mutation of a sperm or egg leads to symptoms in the heterozygous child (a sporadic or isolated case). Rett syndrome patients have normal perinatal development, with a deceleration of head growth and ensuing repetitive hand wringing and apneic episodes. This disease is the result of new heterozygous mutations of the *MECP2* gene (methylated DNA-binding protein) (Fig. 14.1) [7]. The disease is X-linked dominant and could be transmitted to offspring if the women's phenotype is mild enough to permit reproduction. Variation in X-chromosome inactivation patterns protect some females from manifesting Rett symptoms [8]. Similarly, Alexander's disease, which is a severe progressive leukodystrophy showing specific Rosenthal fibers (astrocytic inclusions) on brain biopsy, is due to new dominant mutations of *GFAP* in the heterozygous state [9].

Most dominant disorders result from production of a *toxic protein* by the mutant gene (in contrast to loss of function or lack of protein in recessive inherited disorders, discussed next). The toxic protein is usually the result of a subtle change in the gene, which is compatible with production of the protein at relatively high levels. The most common type of mutation in dominant disorders is a missense mutation, where a single base pair change in the gene leads to a single amino acid change in the encoded protein. These toxic proteins can show altered solubility, with precipitation into aggregates that disrupt cell and tissue function over time (e.g., Parkin mutations in Parkinson's disease, beta-amyloid mutations in Alzheimer's disease). Alternatively, the toxic protein can change its function so that it now has a toxic effect on the physiology of the cell. A particularly illustrative example is with regard to voltage-sensitive sodium channels. The human sodium channel gene family plays a critical role in the central nervous system and peripheral nervous system [10].

Dominant missense mutations in three different tissue-specific sodium channels cause inherited disease. Missense mutations in the muscle sodium channel lead to hyperkalemic periodic paralysis (HYPP) and myotonias in humans and horses [11–13]. Missense mutations in the heart sodium channel lead to long QT syndrome [14], whereas missense mutations in a specific neuronal sodium channel lead to generalized epilepsy with febrile seizures [15]. In each case, the toxic missense mutations lead to failure of rapid inactivation of the respective sodium channel, with persistent inward sodium current in muscle, heart, or nerve leading to the phenotype. It is important to note that although half of the

sodium channels are abnormal (patients are heterozygous), the persistent inward sodium current has a dominant effect on the cell physiology. Such change- or gain-of-function proteins are characteristic of most dominantly inherited neurological disorders.

A second type of toxic protein change is termed *dominant-negative*, where the incorporation of a toxic protein into a chain of proteins destroys the function of the chain ("bad link in a chain" model). Many of these disorders are connective tissue diseases (osteogenesis imperfecta, Marfan's disease, others), which are not typically in the purview of the neurologist. However, some ion channels are multi-subunit and dominant-negative mutations can be observed (e.g., peripheral nerve hyperexcitability due to dominant-negative *KCNQ2* mutations in a multimeric potassium channel).

A third type of toxic protein change can result in poor solubility of the mutant protein often forming progressive aggregates in cells, or alterations in protein traffic through the cell, both of which will have a "dominant toxic" molecular pathophysiology. For example, dominant mutations in the P/Q-type calcium channel result in mutant proteins that alter traffic through the endoplasmic reticulum and a loss of this calcium channel at the cell surface resulting in episodic ataxia. The spinocerebellar ataxias and Huntington disease are caused by too many repeated glutamine residues in the relevant protein, and these cause aggregates that accumulate in specific neuronal subsets, leading to the disease.

Finally, a growing group of dominant disorders represents *haploinsufficiency*, in which "half is not enough." Patients with haploinsufficiency disorders are heterozygotes, with one normal gene and one inactive (loss-of-function) gene. This is functionally the same as the carrier state for autosomal recessive disorders (one normal, one inactive gene, and half the protein product produced). However, carriers of recessive disorders rarely show symptoms, whereas heterozygous patients with haploinsufficiency disorders are symptomatic. Many of the haploinsufficiency disorders involve proteins that play critical roles in pattern formation during development, where the developing organism is exquisitely sensitive to appropriate levels of the protein (e.g., growth factors, growth factor ligands, and transcription factors). As a result, many haploinsufficiency disorders result in dysmorphic features and multiorgan involvement. Examples of these include Waardenburg syndrome (heterozygous loss of function of transcription factor *PAX3*) and campomelic dysplasia (heterozygous loss of function of *SOX9*). Haploinsufficiency disorders tend to be some of the more clinically variable disorders, with the expression of the same gene mutation influenced by the environment, physiology, and genetic background of the individual patient. At a biochemical level, the clinical variability is somewhat intuitive, as biological systems so sensitive to protein levels ("half is not enough") are likely to be similarly sensitive to environmental perturbations of the system and to polymorphic variability between other gene products involved in the system.

Recessive Inheritance

Patients with autosomal recessive disorders typically have parents who are both asymptomatic carriers of the gene defect (heterozygous), whereas the patient is homozygous. With the small family size characteristic of developed countries, a typical autosomal recessive disease is often labeled as an isolated case as no other members of the family present with similar features. In the case of X-linked recessive disease, the mutation can occur during the development of the mother's ovaries, such that one or more eggs carry the mutations, and can then be inherited by a hemizygous male offspring (e.g., DMD). New germ-like mutations increase the recurrence risk for future offspring owing to the possibility that a population of germ cells have the mutation.

As all recessive and haploinsufficiency disorders are caused by a loss of function of the corresponding gene product, there are a plethora of types of gene mutations that can functionally inactivate the gene and encoded protein. Deletions of one or more exons, or the entire gene, are common (e.g., DMD). Single base deletions or insertions that shift the triplet codon reading frame for translation (frameshift mutations) are also seen. Single base pair changes that either introduce a new stop codon or change splicing patterns typically lead to a nonfunctional protein product. Finally, missense mutations are also possible in loss-of-function recessive disorders if the amino acid change interferes with the function of the protein (e.g., active site in an enzyme) or if the amino acid change interferes with the processing of the protein (e.g., failure to transport the protein to the cell surface for correct function).

Complex Genetic

Epigenetic is a term that has been used since the early 1940s. The more recent definition of the word refers to gene modifications that are no due to the DNA sequence itself. These modifications can include DNA methylation, histone modifications, imprinting, X-chromosome inactivation, and gene transcription regulation.

Hypomethylation of chromatin of the D4Z4 repeats are observed in patients with facioscapulohumeral muscular dystrophy (FSHD). Contraction of the D4Z4 repeats to between one and ten repeats is associated with DNA hypomethylation [16]. FSHD has a broad clinical spectrum from asymptomatic to wheelchair bound. There is additionally an infantile onset which is associated with a lower number of D4Z4 repeats and a more severe phenotype.

Imprinted regions of chromosomes show differential expression of genes depending on whether the region is

maternally or paternally inherited. The presence of imprinted regions of the genome was originally detected by cytogenetics and demonstrated the significance of the parental origin of some chromosomal regions. The prototypical examples are Angelman and Prader-Willi syndromes, both due to abnormalities of the same region of chromosome 15. Prader-Willi patients have small stature, hypotonia, small hands and feet, obesity, almond-shaped appearance of palpebral fissures, fair skin and hair, and IQs of 20–80. Angelman patients have ataxia, mental retardation, seizures, puppetlike gait, paroxysmic laughter, and a characteristic facies (microbrachycephaly, maxillary hypoplasia, tongue protrusion, and prognathia). While these disorders are readily distinguishable clinically, both involve the same region of chromosome 15 (15q11-13). Seventy percent to 80 % of Prader-Willi patients show a deletion of 15q11–13 by prometaphase banding cytogenetic studies, while 70 % of Angelman patients have deletions of the same region detectable by FISH. The molecular distinction between these patients is the parental origin of the chromosome upon which the deletion resides: If the chromosome 15 from the father carries the deletion, then Prader-Willi syndrome results; if the maternally derived chromosome carries the deletion, Angelman syndrome is seen.

Genetic testing for the more complex genetic principles such as hypomethylation, X-inactivation, and even imprinting are not as straightforward. These effects are not part of the standard testing on genomic DNA.

Mutation Detection Methods

The specific genetic testing methods utilized to directly detect mutations largely depend on whether or not most patients share one, or a few, specific mutations, or if most patients have their unique or "private" mutation. For example, essentially all patients with oculopharyngeal muscular dystrophy (OPMD) share the same specific mutation (Fig. 14.2). Thus, testing for mutations within the causative poly-A-binding protein 2 (*PABP2*) gene is limited to genotyping for that specific change (the remainder of the gene is not studied, as no patient will show mutations of these other gene regions). To the contrary, each Emery-Dreifuss dystrophy patient has their own gene mutation, so that testing for mutations must be done by screening the entire gene. Intermediate situations exist, where the majority of patients will show a handful of specific mutations, with the remainder showing a wide variety of rare or personal mutation types. For example, approximately 70 % of HYPP patients show one of two missense mutations (methionine to valine change at position 1592 [M1592V], or threonine to methionine [T704M]). So for HYPP patients, the first-tier testing is a targeted mutation analysis which includes these two mutations along with seven other more commonly observed point mutations. When selecting genetic tests, it is also important to note the test's sensitivity; for HYPP the targeted mutation analysis of the nine most common detected mutations is approximately 60 % of patients with symptoms of HYPP. Sequencing of the entire *SCN4A* gene should be considered if no mutations are identified through the targeted mutation analysis.

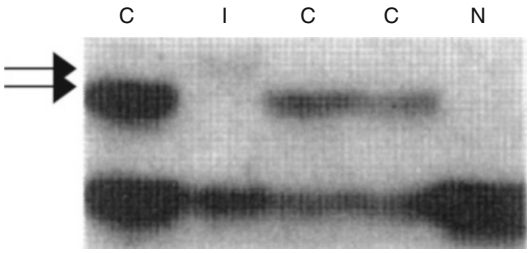

Fig. 14.2 Molecular diagnosis of an oculopharyngeal muscular dystrophy patient by detection of the characteristic small insertion mutation. Shown is detection of a small region of the PAB2 gene (poly-A-binding protein 2 gene) in genomic DNA from patients who may have oculopharyngeal muscular dystrophy (OPMD) based on clinical findings (ptosis, dystrophic biopsy, normal mitochondrial findings, possible dominant inheritance pattern). All OPMD patients studied to date show a small insertion of a few base pairs in the beginning of the PAB2 gene [18], and testing for this disorder is done by simply PCR – amplifying a small region of the PAB2 gene and determining whether the region is the correct size (lane "N"), or if the patients have one normal gene and one abnormally large gene (lanes *C* and *I*; heterozygotes). The patients being tested shows both normal and abnormal bands, indicating that they are affected with OPMD. The patient "I" has a slightly larger increase in the size of the band. Many of these patient's family members are at risk for the disease, due to the dominant inheritance pattern. Care must be taken when counseling presymptomatic family members, as some may wish to know whether they will be affected at a later age, and some may not wish to know. Initial contact with family members should always be done by the patient, as direct contact of family members by health-care workers is generally considered a breach of confidentiality (From Scacheri et al. [20]. with permission)

If many or most patients with a clinically discernible disorder are expected to share the exact same mutation of the exact same gene, then methods are used to detect only this specific mutation. This is termed *genotyping* of the patient, and the test result simply says whether that specific mutation was found or not. There are many dozens of highly sensitive and accurate neurogenetic tests that rely on genotyping for specific mutations. OPMD patients always show an insertion of guanine-cytosine-guanine (GCG) nucleotides in the *PABP2* gene (Fig. 14.2). This insertion mutation can be tested for by simply amplifying over the region of the gene containing this insertion and looking for normal-sized bands (normal) or patients with both normal and abnormally large bands (heterozygous OPMD patients). Similar tests are done for the trinucleotide repeat expansion disorders (e.g., Huntington disease, all spinocerebellar ataxia genes, fragile X, myotonic dystrophy, Friedrich ataxia), as all are caused by insertion of DNA sequence leading to an abnormally large mutant gene.

DNA Mutation Tests

The direct detection of a disease-causing mutation is generally the most specific and accurate form of genetic testing; however, the sensitivity depends on the particular gene under study.

Deletion Testing

Deletion testing is commonly used in the dystrophinopathies (Duchenne and Becker muscular dystrophies) and spinal muscular atrophies (SMA), where the presence or absence of exons in the gene is detected. Deletion testing can be done by polymerase chain reaction (PCR) analysis, or by Southern blotting. PCR testing is more rapid and less expensive; however, Southern blot analysis has a slightly higher sensitivity for deletions and significantly better sensitivity for duplication mutation. A newer approach is multiplex ligation-dependent probe amplification (MLPA®), a proprietary assay from MHC Holland. Primer probes that hybridize to exons of a gene are amplified (in contrast to amplification of DNA in conventional PCR). In one reaction, 40–50 DNA sequences can be detected by using probes unique to each sequence. Each probe has a pair of two oligonucleotides; each oligonucleotide contains a sequence (at the 3′ end of one oligonucleotide and the 5′ end of the other) that will hybridize next to each other on a targeted region of DNA. Each oligonucleotide also has a PCR primer sequence opposite the hybridizing end. When the two oligonucleotides in a probe set hybridize next to each other, a DNA ligase ligates them together and a PCR reaction will amplify the probe via the primer sequence ends. Products for each DNA sequence are distinguished by a stuffer sequence in each probe that gives it a unique size. Thus, the absence of amplified probe product(s) can indicate deletion(s) in a DNA sample. This technique is able to detect multiple and single exon deletions as well as point mutations. For example, an MLPA kit for SMA can detect the causative loss of both exon 7s in *SMN1* or the presence of multiple copies of *SMN2* and *SMN1*, which collectively account for most cases.

Array CGH (aCGH) enables an in-depth investigation for duplicated or deleted regions across the entire genome or in a targeted genomic area. In a targeted approach, a high-resolution aCGH has the benefit of each exon or intron being represented by multiple oligonucleotide probes. This is an advantage over PCR, Southern blot, and MLPA in that losses or gains are detected by more than one probe and therefore are less likely to represent false positives. A targeted aCGH is available for Duchenne and Becker muscular dystrophy that uses thousands of oligonucleotides to scan all 2.2 megabases (Mb) of the *DMD* gene (introns and exons) for deletions and duplications, which represent the cause for most cases of these diseases. In the event that no *DMD* alteration is found with aCGH, small and point mutation techniques may be appropriate since aCGH cannot detect these types of mutations.

Deletion testing is most frequently done in males who are thought to have specific X-linked disorders. This is due to the fact that males have only one X chromosome, so that testing for a deletion is not complicated by the presence of a normal gene on the second chromosome. Testing of female carriers for deletions is also done, although this requires a determination of "dosage" (e.g., whether a female has one or two copies of a specific exon). Large deletion mutations in autosomal conditions are less common, and there is a broad spectrum of mutations in autosomal recessive disease.

Small and Point Mutation Testing

Mutations affecting only one or a few base pairs of the gene are sometimes called *small mutations* or *point mutations* and are usually contained within the exons (coding sequence for the protein) or the exon-intron boundaries (RNA splice sites). If a common mutation exists, then this specific change can be tested for. For example, a single base change in the chloride channel gene (*CLCN1*) leading to the exchange of a glutamic acid (E) for a glycine residue (G) at position amino acid 230 in the protein (G230E mutation) causes about 15 % of cases of myotonia congenita. There are dozens of other mutations of the chloride channel gene that can also cause myotonia, but these are considerably less common. Thus, it is straightforward for the G230E mutation, but if the patient is negative for this change, full sequencing of the *CLCN1* gene should be considered. This can add time and increase costs to identify any other mutations. The interpretation of *CLCN1* sequencing is further complicated by certain mutations having been reported in both autosomal dominant and autosomal recessive myotonia congenital. In another example, about 70 % of cases of hyperkalemic periodic paralysis (HYPP) are caused by one of two missense mutations in the adult skeletal muscle sodium channel gene (either a threonine to methionine T704M or methionine to valine M1592V). If a patient is positive for one of these two changes, then the diagnosis of HYPP is confirmed. If the patient is negative, then they may have a different mutation of the same gene, a mutation of some as yet unidentified gene causing HYPP, or a completely different disorder.

Several methods used to detect point mutations or other small mutations rely on PCR amplification of the exon potentially containing the mutation, then detection of the change using several different techniques: either by detecting the change in restriction enzyme site (so-called *RFLP* [*restriction fragment length polymorphism*] (Fig. 14.3) or *ARMS* [*amplification-refractory mutation system*] (Fig. 14.4)), where primers are designed such that only the normal or mutant copy of the gene is PCR amplified. This assay includes internal controls for amplification efficiency of the sample (Fig. 14.4).

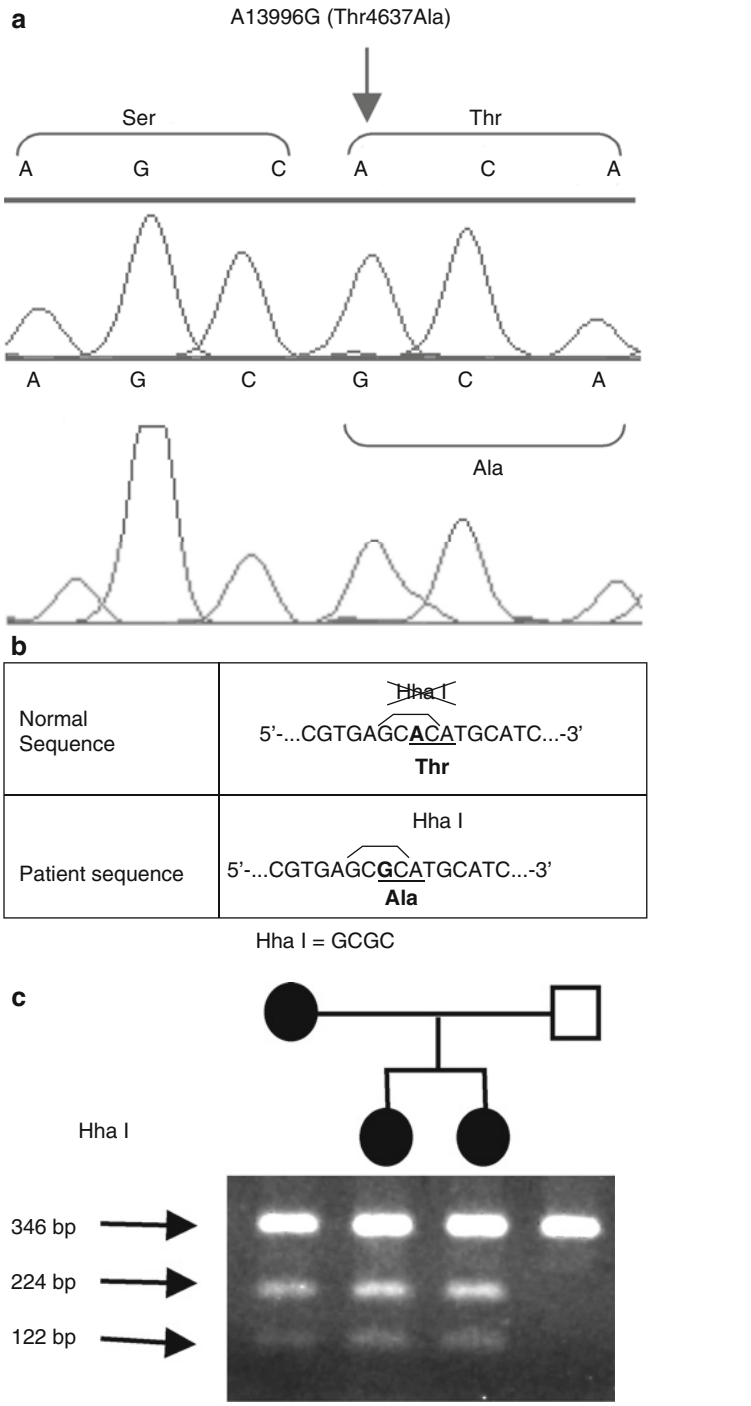

Fig. 14.3 Restriction fragment length polymorphism (RFLP) detection of known gene mutations. Restriction enzyme digestion can be used as a molecular diagnostic test for genetic mutations. In this example, we show the analyses of patients with the same heterozygous point mutation for an autosomal dominant neuromuscular disorder. As shown in the automated sequence data (Panel **a**), the substitution of a guanine (*G*) nucleotide for an adenine (*A*) nucleotide (A13996) changes a threonine amino acid residue to an alanine residue at amino acid position 4637 (*Thr4637Ala*). As shown in Panel **b**, the A→G point mutation creates a Hha I restriction enzyme site not present in normal sequence in unaffected individuals. Shown in Panel **c** is a PCR product from each of the pedigree members shown, digested with Hha I restriction enzyme. The unaffected father of the family shows a full-length PCR product with 346 bp which is *not* digested by Hha I; he has two normal copies of the gene (homozygous). His affected wife and two affected children show three bands after digestion with Hha I. They are each heterozygotes, with one normal gene and one abnormal. The normal gene shows the full-length undigested 346 bp PCR product, while the abnormal gene containing the Thr4637Ala change is cut into two bands by Hha I (224 bp, 122 bp)

Another assay, typically used in a nondiagnostic setting for localization of novel mutations, is *SSCP* analysis (*single-strand conformational polymorphism*) (Fig. 14.5). This assay begins with a double-stranded PCR product of the gene exon potentially containing a DNA mutation. This fragment is then denatured into its constituent single strands and then loaded on a non-denaturing gel (Fig. 14.5). The single-stranded state of a DNA molecule is thermodynamically unstable once it is in the non-denaturing environment of the gel. For this reason, the single molecule finds the lowest free energy of base pairing within the single molecule, forming a very specific "shape" based upon the sequence of the fragment. Any change in the DNA sequence can change the lowest free energy of base pairing within the fragment and hence the shape of the resulting molecule in the gel. Such a shape change, or *conformer*, simply indicates that a sequence change is present in the fragment. This fragment is then subjected to DNA sequencing to determine the precise change

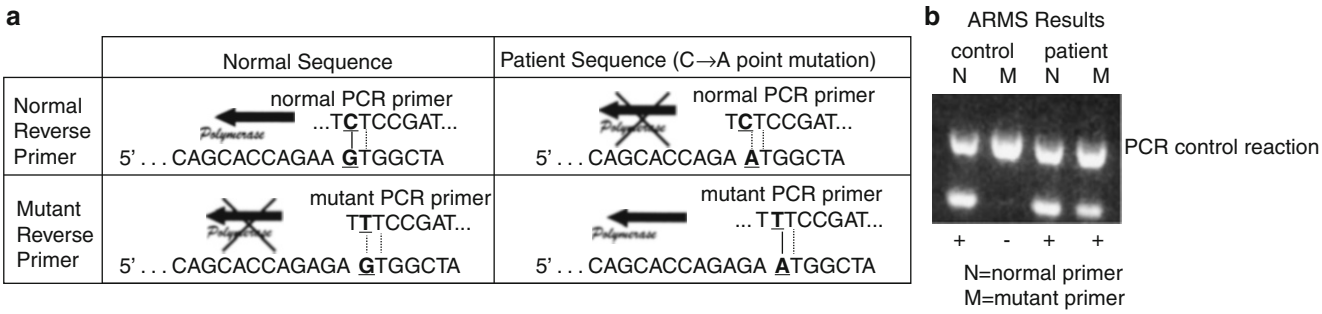

Fig. 14.4 ARMS (amplification-refractory mutation system) analysis of a mutation of the chloride channel gene. The ARMS technique is used to detect known single base changes and exploits the premise that PCR primers must be designed to very closely complement the sequence of interest; otherwise, they will fail to amplify the sequence under study. Two reactions must be run for each sample: one using a primer designed to amplify the normal sequence and one using a primer sequence designed to amplify the mutant sequence (Panel **a**). Intentional mismatches in the primer sequence determine which sequences will amplify with PCR, and a primer with more than one noncomplementary base to the DNA sample will not amplify that segment. Heterozygous positive controls must be run with each sample. An example of utilization of ARMS is shown for the G230E mutation in the CLCN1 chloride channel gene causing myotonia congenita (Panel **b**). The "control" has two normal chloride channel genes and thus amplifies only with the normal (*N*) primer set (in addition to an internal "PCR control reaction") and not with the mutation-specific primer set (*M*). The heterozygous myotonia congenita patient shows amplification with both normal (N) and mutant (M) primer sets, proving that they has the G230E change in the chloride channel. Failure to detect this particular point mutation does not rule out other mutations in this gene

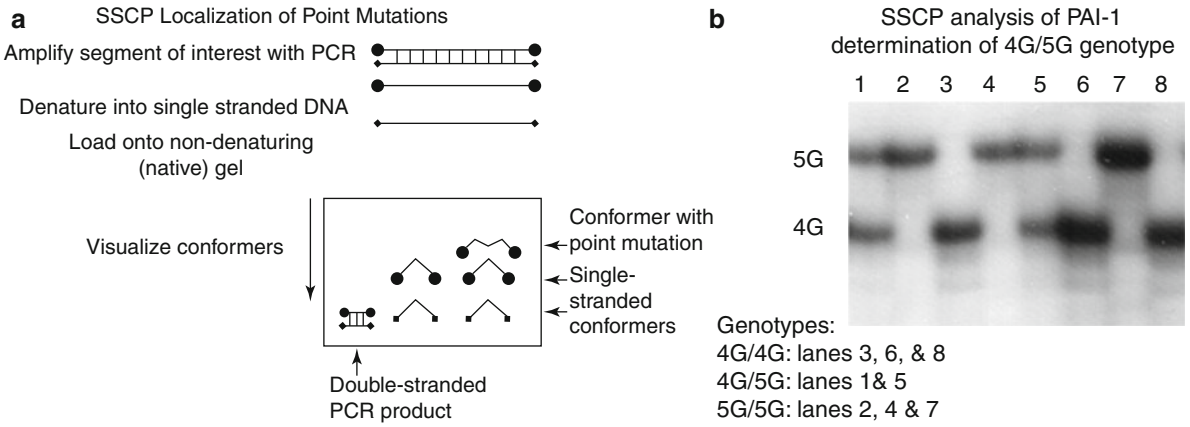

Fig. 14.5 Single-stranded conformational polymorphism (*SSCP*) identification of changes in a PCR product from a candidate gene. Single-stranded conformational polymorphism analysis requires amplification of the region of interest with the polymerase chain reaction (*PCR*). The double-stranded PCR product is heat denatured into single, separate strands which fold onto themselves in a specific conformation, or shape, determined by the DNA sequence (Panel **a**). Single-nucleotide changes affect the conformation of each single-stranded product, thereby altering the DNA migration on a native acrylamide gel (Panel **a**; "conformer with point mutation"). This technique is often used to detect single-nucleotide base changes and other small genetic mutations. Panel **b** shows an application of SSCP to detect changes in the plasminogen activator inhibitor (*PAI-1*). Here the change in the PAI-1 gene is used to test its association with increased risk for myocardial infarction. This example demonstrates the SSCP technique utilized to distinguish the usual DNA sequence in the PAI-1 gene – five consecutive guanine residues – from a polymorphism that predisposes individuals with protein S deficiencies to myocardial infarction. The polymorphism has only four consecutive guanines and is a deletion of one nucleotide

responsible for the mobility shift in the gel. SSCP analyses are not typically used for routine molecular diagnosis, because their sensitivity for detecting changes is only about 70 %, and specific mutations often do not give conformers which are consistent enough for precise molecular diagnostic applications. Nevertheless, this remains a popular technique for researchers attempting to identify novel mutations in cohorts of patients who are thought to possibly have a mutation of a candidate gene.

Highly Parallel Genome-Wide Technologies

The majority of DNA testing technologies described above relies on singling out a single gene or position in the genome (a "locus") and testing it. In such testing paradigms, the gene to be studied is suspected as a candidate due to clinical cues – e.g., a focused study of the dystrophin gene due to high CKs and proximal weakness in a young boy.

Advanced DNA technologies, and decreasing costs of applying these emerging technologies to patient DNA samples, have led to *genome-wide* studies of patient DNA, where the entire genome is put under scrutiny in a single experiment. There are two types of genome-wide approaches: array comparative genomic hybridization (aCGH) (mentioned briefly in the context of the dystrophin gene) and nextgen sequencing.

Array Comparative Genomic Hybridization (aCGH)

This method scans for changes in dosage across the entire genome on a single "chip." It is important to point out that array CGH is excellent for scanning for changes in the *dosage* (copy number) of the patient's DNA, but is not able to see changes in *sequence* (e.g., mutations). A microarray (chip) is utilized that has small oligonucleotides representative of all genes and/or regions of the genome, where each oligonucleotide is printed at a specific address (coordinates) on the microarray. One of the more commonly utilized microarray platforms, Affymetrix, has millions of individual oligonucleotides printed on a 1 cm^2 glass slide (called "features" on the array). The patient DNA is hybridized to the microarray, and the oligonucleotides then query the patient DNA for each region. Deletions are detected by unusually small amounts of the patient DNA hybridizing to a specific feature, and increases in copy number (duplications, amplified regions) are detected as an abnormally large amount of patient DNA binding to the feature.

aCGH is most extensively utilized in two clinical situations: cancer and syndromic (developmental delay, congenital abnormalities) patients. In cancer, the patient's tumor can have multiple chromosomal rearrangements with variable loss or gain of material, and the aCGH pattern across the tumor's genome can be diagnostic of specific cancer subtypes and is increasingly directing appropriate therapy. In intellectual disability, developmental delays, autism, or congenital anomalies, a molecular diagnosis can be provided to about 15–20 % of cases, with a detectable loss or gain of chromosomal material that causes the clinical phenotype observed (Fig. 14.6)[19].

The large majority of patients with single gene defects do not show copy number changes but instead have mutations of the DNA sequence that are not detected by aCGH. Recently, a method to sequence all genes simultaneously has emerged, known as nextgen or highly parallel DNA

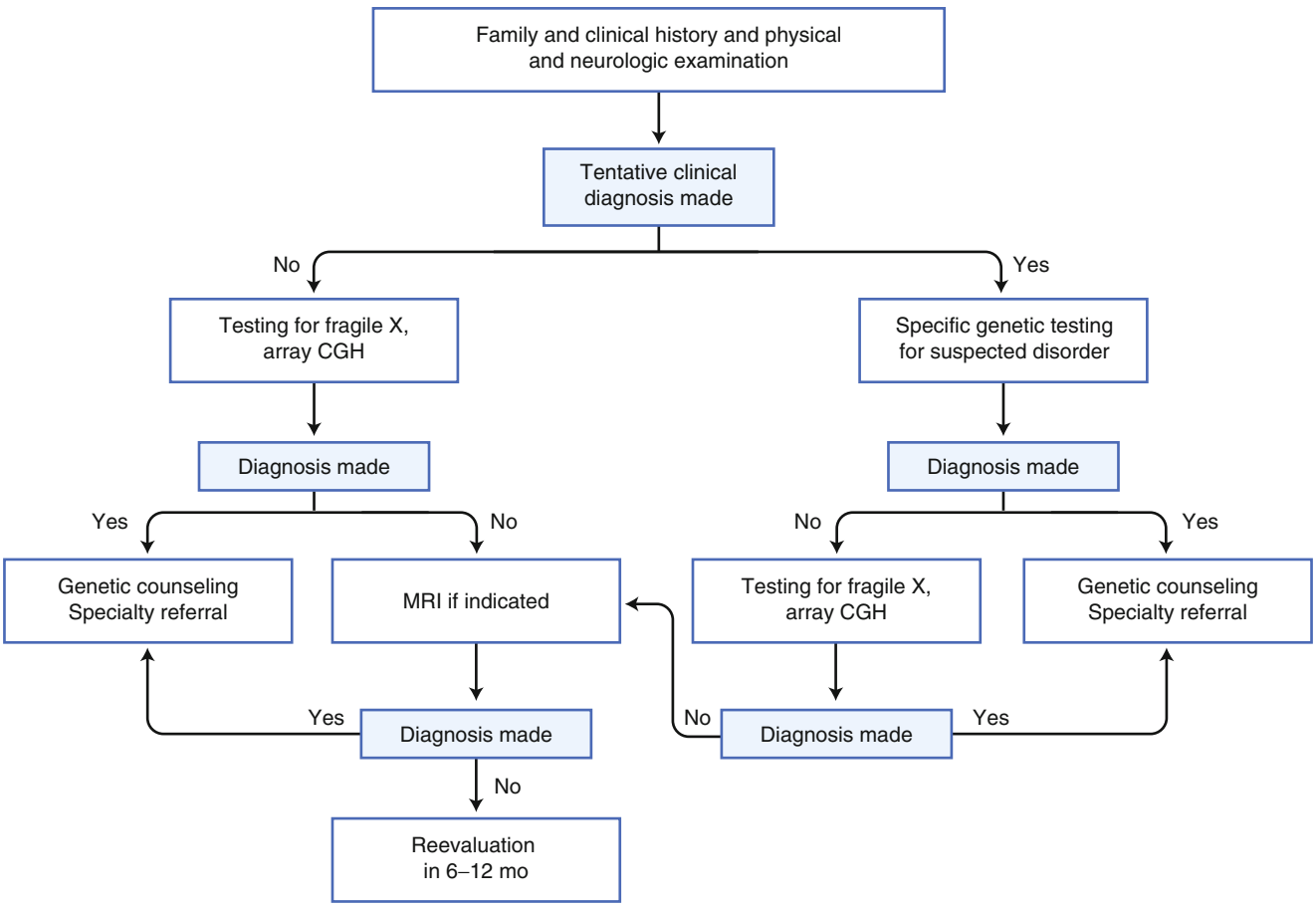

Fig. 14.6 Use of array comparative genomic hybridization (aCGH) in developmental and intellectual delay (From Mefford et al. [19])

sequencing. Nextgen sequencing involves taking patient DNA, fragmenting it into small pieces, then immobilizing individual fragments onto a solid support, where millions or billions of fragments are then sequenced simultaneously. The millions or billions of snippets of DNA sequence from the patient are then "assembled" into gene sequences and then searched for mutations.

A variant of whole genome sequencing (WGS) is exome sequencing. The amount of DNA sequenced in an exome is about 1 % of that sequenced in a whole genome. The difference is that the exome sequence focuses on coding sequences of genes (exons) and does not attempt to sequence all the introns and intervening sequences between genes. Carrying out nextgen sequencing on a patient exome assumes that most or all disease-causing mutations will occur in exons, and thus it is not necessary to sequence the 99 % of DNA that is non-exon. This is likely a generally good assumption, but exceptions almost certainly exist.

Every human contains about six billion bases of DNA: three billion from the mother and three billion from the father. In this three billion, there are about three million polymorphisms where one individual differs from another individual, and this creates the variation we see in the human race. Sequencing the entire genome or exome of a patient yields thousands of sequence differences, and singling out a specific DNA sequence change that is causative of the patient's disorder is not a trivial undertaking. However, as the costs of DNA sequencing continue to go down, speed and accuracy continue to increase, and bioinformatics tools become more powerful, WGS and exome sequencing is expected to become more and more commonplace in the clinical setting.

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Part III

Approach to Neuromuscular Diseases: Assessment and Treatment of Neurological Disorders

Outcome Measures and Clinical Assessment Instruments in Neuromuscular Disease

15

Jeffrey Rosenfeld and Carlayne E. Jackson

The number and complexity of clinical trials in neuromuscular disease have escalated steadily over the first part of this century. This increase in clinical trial activity has resulted from both advances in the basic science laboratory and the need for objective data to justify treatment decisions. Presentation of empiric data, without carefully designed and controlled studies, is not generally accepted or published. Managed care and insurance companies have embraced the long-held principles of the scientific process, providing consistent pressure on clinicians to generate justification for treatment decisions with "statistically significant" observations. Considering the large volume of neuromuscular clinical trials in the recent past, there have been relatively few studies which have yielded significant results, causing many treatment decisions being made by consensus rather than evidence. There have been an increasing number of opportunities for neuromuscular physicians to initiate "off-label" therapy and monitor progress by empiric observation. This dichotomy between the need for carefully designed clinical studies and pressures from daily clinical practice to initiate novel therapies has highlighted the importance of appropriate, valid, and reliable disease-specific outcome measures in neuromuscular disease.

Disability resulting from neuromuscular disease includes almost all functions ascribed to the nervous system. Sensation, strength, and coordination are primarily vulnerable depending upon the specific neuromuscular disease implicated. Measurement tools are, however, optimally developed for specific disease states as the implications of the same disability vary depending upon the underlying disease. Weakness resulting from myasthenia gravis, for example, may not have the same impact on a patient's level of function or quality of life compared with similar weakness caused by motor neuron disease. Sensory loss or dysesthesias resulting from neuropathy may require different measurement tools than those needed for measuring sensory pathology resulting from spinal cord or nerve root injury. Often, however, measurement scales are "borrowed" from one disease, for measurement in another. Validation of specific measurement tools is a critical process but is also dependent upon the standard against which a new measure is compared.

The emphasis on careful measurement of clinical efficacy for new neuromuscular therapies is well founded. Multiple reports of consistent and significant laboratory data in animal models have led to large and expensive clinical trials, which did not show the same significant clinical benefit. Examples of this abound in the testing of neurotrophic factors for motor neuron disease. Testing new therapies with great potential has highlighted the importance of selecting specific and sensitive measurement tools. Alternatively, selecting or designing a measure of disease progression that is either too sensitive or too specific can result in errors of data analysis (type I vs. type II) which may result in abandoning potentially beneficial therapy.

This chapter is designed to review issues which result from consideration of the optimal outcome measures, taking into account many of the concerns raised above. By its nature, the process of measurement requires reducing a dynamic process (the patient dealing with their disability) to a "2-dimensional snapshot" (the patient's score at one point in time) that will be used to reflect a patient's condition. Measurement is usually an imperfect process, especially when relatively small treatment effects are expected. Multiple examples of available treatment instruments will be reviewed with an emphasis on their benefits and limitations for future use.

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Importance of the Right Scale

The primary objective of any outcome measure is to assess a change specific to the disease under study. The concepts of validity, reliability, sensitivity, and specificity are essential to selection of a suitable outcome measure. Evaluating human disease is often confounded by the reality that disease progression does not usually occur in a single isolated modality suitable for study. Patients who experience pain may interpret it as weakness; patients with weakness may report subjective sensory changes; sensory complaints may be modified by objective weakness or concurrent depression. The primary goal of an ideal outcome measure in neuromuscular disease is to objectively evaluate the outcome relevant to the disease being studied while concurrently acknowledging, or ideally controlling for, the patient's overall disability.

Recently, *quality of life* scales have been recognized as valid and essential outcome measures in testing new treatments and drugs. Ideally, a therapeutic intervention would be desirable if it significantly improves quality of life even without showing similar benefit in more objective assessments of strength or function (gait, speech, breathing). Similarly, if a therapy were to have a significant benefit to strength or function – but failed to show any improvement in a patient's quality of life – it would diminish its value. Specific considerations and pitfalls in the available quality of life scales are considered below.

Selecting the *right outcome measure*, therefore, is the most important task of any researcher wishing to further our understanding and treatment of neuromuscular disease.

The ideal outcome measure should consider [1].

1. Whether it is *appropriate to the function* it is supposed to measure (*i.e.*, *does a test of motor function favor patients with greater preserved strength or will changes in weak patients be detected as well*).
2. Whether the *measure is valid* (*how does it compare with other measures designed to test the same function*).
3. Whether it is a *reliable and reproducible* test (*can the measure be repeated accurately*, *can it be reproduced by others*, *is it simple enough to be repeated without significant additional training*).
4. Whether it is *sensitive* to detect changes in the conditions under study, considering the variability arising from other aspects of the patient's disability.

World Health Organization: Defining Levels of Disease

Standardized classification and terminology has been developed by the World Health Organization for evaluating consequences of disease. The International Classification of Impairments, Disabilities, and Handicaps (ICIDH) was developed as a model for consistency in "reducing" any disease into four defined levels suitable for study:

- *Pathology* is defined as structural damage done to the body, organ, or organ system caused by the disease process.
- *Impairment* is the functional consequence of the underlying pathology (i.e., weakness, shortness of breath, spasticity).
- *Disability* is referred to as the inability to perform specific activities that are determined to be within the range of "normal" for human beings.
- *Handicap* reflects the consequence of an individual's disease on their community and in society. Societal consequences of disease might, by implication, include cultural biases, family attitudes, and economic impact (Table 15.1).

Table 15.1 An application of the ICIDH model to amyotrophic lateral sclerosis

Area of interest	Primary measurement	Available scale
Pathology	Motor neuron loss	Ubiquitin staining
		Abnormal neurofilament staining
		Estimates of motor neuron number by EMG
Impairment	Strength loss	Manual muscle Testing
		Maximal voluntary isometric contraction
		Hand-held dynamometry
	Breathing	Vital capacity (forced, slow)
		Tidal volume
		Maximal inspiratory pressure
		Maximal expiratory pressure
	Spasticity	Ashworth spasticity
	Fine coordination	Ashworth spasticity
Disability	Speech	Speech ALSFRS-R
	Swallowing	Swallowing ALSFRS-R
	Breathing	Breathing ALSFRS-R
	Arm function	Arm ALSFRS-R
		Timed pegboard
		Barthel Index
	Leg function	Leg ALSFRS-R
		Barthel Index
Handicap	Independence loss	Quality of life scales
	Work	Sickness impact profile
	Social integration	Sickness impact profile
	Self-care	Short form 36
	Death	Survival

Adapted from Brooks [2]

The ICIDH is a theoretical construct that is especially helpful in bringing to our awareness the multifactorial dimensions of human disease. It is not clear, and perhaps not appropriate, to ask whether an ideal clinical trial should take into account all aspects from each component of this model. Existing clinical outcome measures most readily assess *impairment*, while newer measures of quality of life and

function assess *disability* and *handicap* [3–6]. By contrast, most basic laboratory studies, which lead to these clinical trials, evaluate *pathology*. The implication from data gathered under a microscope in the laboratory is that preserved or improved anatomy/neurochemistry will directly relate to improvements in a patient's *impairment*, *disability*, *or handicap*; a humbling reality that has not been associated with an abundance of supportive data.

NINDS Outcomes Subgroup

Recently, the NINDS released a consensus statement pertaining to optimal common outcomes in neuromuscular disease trials (http://www.commondataelements.ninds.nih.gov/ALS.aspx#tab=Data_Standards). Domains of functional performance, pulmonary, muscle strength, and quality of life are defined for motor neuron diseases, myopathies, neuropathies, and neuromuscular junction disorders. Ideally, each domain of measurement is defined by a *core* measure central to the pathophysiology of the clinical manifestation. *Supplemental* measures are defined as clinically relevant and validated for use in the population. These measures can be focused on discrete clinical features and may not be as broad in scope as core measures. *Exploratory* measures are not validated, however may have a role in subsequent studies as supplemental or core measures if their use becomes more routine.

Validity

Despite major technologic advances in our ability to diagnose specific neuromuscular diseases, we are often unable to *directly* quantify pathology prior to postmortem study. Assessment techniques and published scales serve as surrogate markers of disease. Validation of these instruments by comparison with a "gold standard" reflecting the actual disease process, *in situ*, is not common. In motor neuron disease, this comparison has been attempted. Our current estimates on the extent of motor neuron loss required prior to the detection of weakness have followed. In other neuromuscular disorders such as neuropathy, myopathy, and disorders of the neuromuscular junction, similar morphometric analyses correlating pathology to loss of function have not been reported.

We are dependent upon the accepted or "validated" scales to use as a benchmark against which to compare newer measures. This process of validation, while necessary, introduces the caveat that a more sensitive or accurate measure might not yield the same results as an older, less sensitive, "validated" measure. This concern is best addressed through the use of multiple measurement tools which may overlap with respect to the measurement endpoints. For example, a newer measure of strength might be devised, and the data generated might correlate significantly with a measure of functional ability and a measure of quality of life. This newer measure might not, however, correlate with available manual or quantitative muscle testing. The newer measure might, therefore, be a better reflection of a patient's strength than the available strength measures against which it is compared.

These considerations are challenging in the process of evaluating and accepting new measures of neuromuscular disease progression. Lessons from the clinical trials summarized below suggest that we should not be complacent with only the accepted, available testing instruments. An ongoing comparison with newer, possibly more sensitive and specific measures should occur with each new clinical trial.

Sensitivity, Specificity, and Reproducibility

The choice of an appropriate measurement tool involves an ideal combination of sensitivity (the probability of detecting a result when it is present) and specificity (the probability of *not* detecting an effect that you do not want to measure). If, for example, a test had a high sensitivity, we would expect many abnormal values to be detected. If that same test had a high specificity index, we would expect that only instances reflecting the desired outcome measure would be detected rather than others that might be abnormal for another reason. When used in clinical trials, sensitivity and specificity have slightly different meanings as we are frequently measuring the *rate of change* in a clinical sign or symptom (i.e., strength, sensation, gait, and quality of life). A test that has a high sensitivity in a polyneuropathy trial, for example, would be a test whose results would change in most cases of polyneuropathy where there is progression or improvement. That same test with a high specificity would not be expected to change unless the improvement or progression was due to the polyneuropathy being tested [7]. Consequently, the related concept of reproducibility is essential, as measuring changes over time requires consistency so that change will not result from measurement error or variability in testing. Assessing the reproducibility of a test can therefore modify any interpretation of sensitivity or specificity.

Type I Versus Type 2 Errors

The most significant consequence in choosing an inappropriate or an insensitive measure when designing a clinical trial is the implication of making an ultimate error in interpreting the results. At the conclusion of a trial found to yield nonstatistically significant results, the possibility of inappropriately rejecting an effective treatment is referred to as *type 1 error*. Conversely, the scenario of wrongly concluding that there is a statistically significant benefit to a new treatment is

referred to as a *type 2 error*. The probability of committing a type 1 versus a type 2 error is dependent upon the outcome measure selected, the sample size, and the desired level of statistical significance or probability on which the analyses are based.

A detailed discussion of statistical considerations for minimizing the probability of a type 1 error, while not inappropriately increasing the possibility of a type 2 error, is beyond the scope of this chapter. Overall, however, minimizing the variability within a measurement (error variance) is the critical consideration. If, for example, a real difference existed between a control and treatment group, but the measurement variable was confounded by random error variance, the difference between groups would be lost in the analysis. Error variance increases with the number of treatment groups and with the complexity of the measurement. Generally, it is therefore ideal to keep the number and complexity of variables low while maximizing the number of observations or patients.

Ordinal Versus Continuous Measures: Parametric Versus Nonparametric Analyses

An appreciation of the difference between ordinal versus continuous data is a critical distinction. Available scales for the assessment of neuromuscular patients exist within both categories with significant implications to the type of data analysis appropriate to each category.

Ordinal data, as the name suggests, implies a rank order to the data, with one score being better or worse than another. An ordinal scale does not permit the user to determine how far apart the points on a scale are but only to hierarchically rank each point. Ordinal data is collected as discrete values. Also called categorical data, values collected are analyzed based upon predetermined categories. The most common ordinal scale in routine medical practice is the use of "severe, moderate, or mild" as a means of classifying the severity of disease. When using ordinal data, the different scores cannot be compared in an absolute way (i.e., a difference between a score of 2 and 3 is not assumed to be the same as a difference between a score of 9 and 10).

Ordinal scales must be analyzed using nonparametric statistics. The allowable statistical comparisons are usually less powerful than parametric statistics as only the relative relationship of one score to the other is taken into account. The magnitude of the differences between scores or the variability of scores is not considered [8]. Comparisons between groups of patients are made using tests such as Mann–Whitney, Wilcoxon, Kruskal-Wallis, or Sign test [9].

Continuous measures are characterized by having uniform tervals between scores. 50 % increment between scores at the low end of the measurement range implies the same relative change as a 50 % increment at the high end of the measurement scale. The use of continuous measures usually implies that the values will be normally distributed (bell shaped or Gaussian) around a mean value. Parametric statistics employ values such as the mean and median and, most importantly, variance to ascribe differences between groups. Analyses of variance and t-tests are examples of common parametric statistics (Table 15.2).

Generally, parametric statistics are more robust at detecting differences compared with nonparametric analyses. Nonparametric values are, however, often easier to gather and are much less prone to error variance.

Motor Scales

Assessment of motor function has been the primary outcome measure for the majority of neuromuscular clinical trials, yet there are relatively few assessment scales available. Most

Table 15.2 Applications of continuous verses ordinal data

	Continuous data	Ordinal data
Sample measurements available	Height, weight, blood pressure, quantitative muscle testing	Manual muscle testing
	Forced vital capacity	ALSFRS-R, Appel ALS Score
	Tidal volume	Quantitative sensory testing
	Maximal inspiratory/expiratory pressure, visual analogue scales	Ashworth spasticity scale
		Quality of life scales
		Neuropathy Disability Scale
		Quantitative Myasthenia Gravis Score
Appropriate statistics	*Parametric* analyses: mean, median, mode, variance, analysis of variance (ANOVA), correlation, regression, T-tests	*Nonparametric* analyses: Spearman rank-order analysis, Mann–Whitney, Wilcoxon, binomial testing, Kruskal-Wallis analysis of variance
Power	More powerful	Less powerful
Advantages	More sensitive to detect a difference	Easier to administer
	Measured differences can be proportional to changes in disease severity	

Table 15.3 Manual muscle testing

Grade	Description
5	Normal strength
4+	Ability to resist against strong pressure throughout range of motion
4	Ability to resist against moderate pressure throughout range of motion
4–	Ability to resist against minimal pressure throughout range of motion
3+	Ability to move through full range of motion against gravity and to resist against minimal pressure through partial range of motion, the contraction breaks abruptly
3	Ability to move through full range of motion against gravity but unable to take any resistance
3–	Ability to move through partial range of motion against gravity
2	Ability to move through full range of motion with gravity eliminated
1	A flicker of movement is seen or felt in the muscle
0	No contraction palpable

typically, manual muscle testing and/or quantitative dynamometry are used to access strength. As noted below, manual testing is simple and widely used as part of the routine neurologic examination. It involves the examiner's subjective determination of the patient's strength using accepted scoring guidelines relative to the patient's ability to resist force (gravity or applied). Quantitative motor assessment is more objective yet may introduce additional sources of variability in measurement. Focal strength determination using dynamometry (grip, pinch, or isokinetic) has also been used in an effort to limit the measurement variability introduced with measurement of multiple muscles. Other composite scales, summarized below, assess a combination of patient's strength and function, usually specific for a disease process.

Manual Muscle Testing

Manual muscle testing (MMT) is the most common method of assessing strength in routine clinical evaluation. Originally developed to assess strength in polio patients [10], the scale is composed of a rating of 0–5 assigned to each muscle group tested [11] (Table 15.3). The scale has been modified and formalized to account for more grades of muscle weakness using a plus or minus designation [12]. A primary distinction in the grading scale is made based on the patient's ability to move against gravity and then against the resistance of the examiner [13].

Advantages: MMT is a quick, simple measure of muscle strength. It requires no specialized equipment and is cost-efficient. The testing can result in highly reproducible data when the protocol is standardized and examiners trained [14, 15].

Disadvantages: MMT data is ordinal and intervals between the various ranks are not equal. There can be significant variation in the force generated by a muscle group graded by the same MMT rank [16]. A decrease in as much as 40 % of a muscle's capacity for contraction could be graded with the same MMT score [13].

Quantitative Dynamometry

Quantitative measurement of force requires a maximal isometric voluntary contraction (MVIC) and the use of a transducer to measure the force. MVIC testing yields continuous data, eliminating the difficulties with MMT due to the limitations of ordinal data collection. When compared with MMT, MVIC has been shown to be more sensitive to early changes in muscle strength, highlighting the relative insensitivity of an ordinal grading of manual muscle strength [17, 18]. A method for standardizing MVIC scores as a deviation from a standard reference from a population of ALS patients (z-score) has been suggested [19]. Z-scores can be averaged in individual muscle groups to yield a "megascore," reflecting strength in a specific extremity [20, 21]. Applications of quantitative dynamometry testing include grip/pinch testing, hand-held dynamometry, and fixed dynamometry.

Advantages: With proper testing conditions, test-retest reliability and sensitivity is better than the alternative, more subjective, measures of muscle strength [22]. Data can be analyzed using more powerful parametric statistics. MVIC testing is more sensitive than MMT and the Appel Score which is dependent upon MMT. Specifically, as noted above, MVIC may be a more sensitive measure for detecting subtle changes in muscle strength, critical for early disease detection and diagnosis.

Disadvantages: Testing requires specialized training and equipment. Reliable data is dependent upon consistent testing conditions including accurate positioning of the patient in the testing apparatus. Comparison of data between different test sites and different examiners must be continually reviewed, due to the many inherent variables affecting the consistency of the testing. While normative data exists from several sources, MVIC testing for clinical trials has been validated primarily in the ALS population [19, 23]. The potential benefit of MVIC in a more slowly progressive neuromuscular disease remains to be established.

Functional Scores

One of the most common methods of assessing outcome of care or treatment in a broader sense is in terms of a patient's ability to perform tasks of daily living. Measurements of function are usually more meaningful to people's lives than objective measures such as grip strength or timed walking.

One of the major problems with a functional scale is that people may react differently to similar levels of impairment depending on their support networks, goals, priorities, and expectations. Functional disability may relate not only to physical factors but also to cognitive, social, economic, or environmental factors. For example, the level of dependency may be a function of the existence of either aids or the availability of assistance from a caregiver. In addition, most disability scales focus narrowly on a range of mobility and self-care tasks and do not always provide assessments of mental functioning, social interactions, or pain.

Measurements of functional status implicate a combination of strength and the consequence(s) of impaired strength or ability (walking, eating, dressing, standing, etc.). There may also be a measure reflecting quality of life within a functional score measure. Such composite functional measures have been most widely used in neuromuscular disease research due to the multisystem impact of that disease. Functional measures can be divided into general (global) measures, applicable to multiple disease states, and disease-specific measures, validated in a specific disease population.

Global Measures of Functional Impairment

Barthel Index

The Barthel Index was initially developed in 1965 to assess the mobility and functional status of musculoskeletal and neuromuscular patients in Maryland's chronic disease hospitals [24]. The Barthel Index assesses the degree of independence a patient demonstrates in various activities of daily living (ADLs) including bowel and bladder function, grooming, toilet use, feeding, transfers, mobility, dressing, climbing stairs, and bathing (Table 15.4). Two versions of the original Barthel Index have been commonly used. Wade and Collin's version [25, 26] contains 10 ADL functions, and the total score ranges from 0 (total dependence) to 20 (total independence) in 1-point increments. Granger's version [27] includes 15 ADL functions, and the total score ranges from 0 (total dependence) to 100 (total independence) in 5-point increments. A score of 60 is the point between independence and some dependence. A score of 20–40 indicates severe dependence, and a score below 20 suggests total dependence in self-care and mobility. In practice, a difference of 4/20 points or more will usually reflect a real difference; smaller differences might arise from errors. The Barthel Index can be self-administered, administered face to face, or over the telephone. In addition, it can be given to a caregiver, nurse, or therapist depending on who can give the most accurate information regarding the patient's actual level of function. Direct observation is not required but may improve the reliability of the index. The Wade and Collin's instrument takes approximately 2–3 min to complete.

Advantages: The Barthel Index has demonstrated high test-retest reliability ($r=0.89$) and inter-rater reliability ($r>0.95$) [27]. It is one of the best known and commonly used ADL instruments [28]. It is best suited for assessing and following patients with paralysis and/or patients with

Table 15.4 The Barthel ADL Index

Bowels
0 = Incontinent (or need to be given enema)
1 = Occasional accident (once/week)
2 = Continent
Bladder
0 = Incontinent
1 = Occasional accident (max. once per 24 h)
2 = Continent (for over 7 days)
Grooming
0 = Needs help with personal care
1 = Independent face/hair/teeth/shaving (implements provided)
Toilet use
0 = Dependent
1 = Needs some help, but can do something alone
2 = Independent
Feeding
0 = Unable
1 = Needs help cutting, spreading butter, etc.
2 = Independent (food provided in reach)
Transfer
0 = Unable – no sitting balance
1 = Major help (one or two people), physical, can sit
2 = Minor help (verbal or physical)
3 = Independent
Mobility
0 = Immobile
1 = Wheelchair independent including corners, >50 yards
2 = Walks with help of one person (verbal or physical)
3 = Independent (but may use any aid, e.g., stick)
Dressing
0 = Dependent
1 = Needs help, but can do about half unaided
2 = Independent (including buttons, zips, laces)
Stairs
0 = Unable
1 = Needs help verbal, physical, carrying aid)
2 = Independent up and down
Bathing
0 = Dependent
1 = Independent (or in shower)
Total = (0–20)

Table 15.5 Rankin scale

Grade	Description
0	No symptoms at all
1	No significant disability, despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability, requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention

continence or mobility problems. It is simple to administer and score, and the score is easily communicated.

Disadvantages: The Barthel Index is an ordinal scale; therefore, changes in points in one function do not reflect equivalent changes in ADL function across different activities. Another criticism is that the maximum range of activities measured does not include the full range of behavioral changes that might occur resulting in a floor and ceiling effect [29]. Some changes may occur outside the range measured and would not be detected by this instrument. Although it is relatively sensitive in detecting functional change over time, small differences may be missed.

It is not recommended for assessing general health status, psychosocial status, or communication skills [27], since it only assesses physical activities and does not include measurement of psychological well-being. It omits tasks of daily living such as shopping and cooking and other tasks essential for living within a community. Therefore, it is mostly suitable for institutionalized patients (for whom it was originally designed) with moderate to severe disability.

Rankin Scale

The Rankin scale was initially developed as the stroke research equivalent of the Glasgow Outcome Scale [30]. The Rankin scale is another ordinal scale of functional outcome which assigns a grade from 0 (no symptoms at all) to 5 (severe disability; bedridden, incontinent, and requiring constant nursing care and attention) (Table 15.5). Most studies divide patients into two groups (0–3, 4–5) or three groups (0, 1–3, 4–5) for the purpose of quantitating the outcome measures.

Advantages: The Rankin scale has been shown to be reliable and simple to administer, making it ideal for use in large multicenter clinical trials [31]. Although it was initially designed to evaluate outcome in stroke patients, it has been used in several neuromuscular trials.

Disadvantages: The Rankin scale has been criticized due to its inherent insensitivity. It mixes objective and subjective items as well as assessments of impairment and disability. In a sense, is not a true measure of handicap since it relies so strongly on mobility.

Purdue Pegboard

The Purdue Pegboard is used to evaluate fine coordination and hand dexterity.

Five subtests comprise the test: right hand (RH), left hand (LH), both hands (BH), RH + LH + BH, and assembly [32]. The test board consists of a board with four cups across the top and two vertical rows of 25 small holes down the center. The two outside cups contain 25 pins each; the cup to the immediate left of center contains 40 washers, and the cup immediate to the right of center contains 20 collars. Performance of the RH and LH subtests requires participants to first use their right hand then left hand to place as many pins as possible down the respective row within 30 s. The score for each of these subtests is the total number of pins placed by each hand in the time allowed. The BH subtest is a bimanual test where the participants use their right and left hand simultaneously to place as many pins as possible down both rows in 30 s. The RH + LH + BH subtest is a mathematical computation of the scores for the RH, LH, and BH subtest. The assembly subtest requires that both hands work simultaneously while performing different tasks for 60 s. The score for this subtest is the total number of pins, washers, and collars placed in 60 s. Each stage of the test is administered three times.

Advantages: Purdue pegboard is one of the best methods that evaluate fine dexterity and coordination of the hand. In the test, memory and learning are important. Remembering the steps of the subtest immediately influences the scores, especially in the assembly subtest.

Disadvantages: It takes 15 min to complete.

Timed Up and Go

The timed "Get-Up and Go" test was initially developed as a clinical measure of balance in elderly people [33, 34]. The test must be performed with the patient wearing regular footwear, using usual walking aid if needed, and sitting back in a chair with arm rest.

On the word "Go," the patient is asked to do the following:

1. Stand up from the arm chair.
2. Walk 3 m (in a line).
3. Turn.
4. Walk back to chair.
5. Sit down.

Observation of the patient for postural stability, steppage, stride length, and sway is recommended in addition to the total time. Normal: completes task in <10 s. Abnormal: completes task in >20 s.

Advantages: Administration time is 5 min or less. The test requires no special equipment or training and is easily included as part of the routine medical examination. Studies

have shown that the time score is reliable, correlates well with log-transformed scores on the Berg Balance Scale, gait speed, and Barthel Index of ADL. It also appears to predict the patient's ability to go outside alone safely.

Disadvantages: This test cannot be used in non-ambulatory patients.

Timed Walk

The 6-min walk test (6MWT) measures the distance an individual is able to walk over a total of 6 min on a hard, flat surface [35–38]. The goal is for the individual to walk as far as possible in 6 min. The individual is allowed to self-pace and rest as needed as they traverse back and forth along a marked walkway. The primary outcome is the distance covered in meters or converted measure (such as feet) over 6 min.

The 10-m walk test assesses walking speed in meters per second over a short duration (10 m). It has been used in various patient populations including stroke, Parkinson's disease, general neurologic movement disorders, and spinal cord injury. The time (seconds) is reported and can also calculate a walking speed m/s. It is performed using a "flying start": the patient walks 14 m and the time is measured for the intermediate 10 m. The individual walks at their preferred walking speed. Individuals can use an assistive device and must wear shoes. Testing can be completed in less than 5 min.

Advantages: The timed walk tests provide a functionally meaningful assessment of walking ability and do not require any specialized equipment or training.

Disadvantages: The assessment cannot be used in non-ambulatory patients. Studies have shown that longer walks (12 min) are more discriminating and highly reproducible, but are more time consuming for the investigator and exhausting for the patient.

Trunk Control Test

The trunk control test was initially developed to assess motor improvement after stroke. It is a simple test of motor function examining only four movements: rolling to a weak side, rolling to a strong side, sitting from a lying position, and balance in the sitting position (Table 15.6) [39, 40]. Tasks are graded on a three-point ordinal scale that has been validated in stroke patients.

Advantages: The simplicity of this test makes it easy to use for routine clinical evaluations. The test appears to be as sensitive and reliable as the more complex Rivermead motor assessment and is much simpler.

Disadvantages: This test of motor function has not, however, been utilized in neuromuscular clinical trials to date. Two of the four tests are defined based upon the identification of a "weak and strong side" which may not be applicable to the majority of neuromuscular disease patients.

Table 15.6 Trunk control test

Tests (*on bed*)	
1.	Rolling to weak side
2.	Rolling to strong side
3.	Sitting up from lying down
4.	Balance in sitting position (on side of bed)
Scoring	
0	Unable to do on own
12	Able to do, but only with non-muscular help – for example, pulling on bed clothes, using arms to steady self when sitting, pulling up on rope or monkey pole
25	Able to complete normally
Trunk score = score (1) + (2) + (3) + (4)	
Trunk control test (guidelines)	
Four movements/functions are tested, with the patient lying on the bed.	
Rolling to weak side	
From lying on back, rolling on to weak side, may push/pull on bed with good arm	
Unable to perform without assistance	0
Requiring assistance	12
Able to perform normally	25
Rolling to strong side	
From lying on back, bringing weak limbs over	
Unable to perform without assistance	0
Requiring assistance	12
Able to perform normally	25
Sitting up from lying down	
From lying on back – may use arm(s) to push or pull	
Unable to perform without assistance	0
Requiring assistance (pulls on pole, rope, sheets, etc.)	12
Able to perform normally	25
Sitting balance	
Sitting on edge of bed, feet off ground – balance for 30 s.	
Unable to perform without assistance	0
Requiring assistance	12
Able to perform normally	25

Motor Club Assessment

The motor club assessment is a specialized test that has been used to measure both impairment and disability following stroke [41–43] and in multiple sclerosis patients [44]. The assessment is easy to administer and grade using fixed categories referring to how easy the various tasks are to complete (Table 15.7). The motor section of the test (measuring impairment) is similar to the grading of manual muscle testing; however, the number of possible categories is more limited (no movement, some movement, normal movement). The functional movement section evaluates motor function common to many activities of daily living (i.e., lying down, sitting up, transferring, kneeling, walking, and climbing stairs).

Advantages: The scale is simple to administer, reducing inter- and intra-observer variability. The nature of the tasks performed has obvious relevance to a patient's ability or level of function.

Table 15.7 Motor club assessment

Motor section	
Scale	
0 = No movement	
1 = Limited range of movement (add-or + for further detail)	
2 = Completed range of movement (compared with other side). Coordination neednot be normal, but range should be full	
Measure of motor impairment	
Positions	
A = Good side lying	
B = Lying	
C = Sitting	
D = Standing	
Movements – arm	**Position/score**
Shoulder shrugging	
Elevation of the shoulder girdle	A___
	B___
	C___
Arm thrusting	
Forward extension of the arm from the flexed position	A___
	B___
	C___
	D___
Arm lifting	
Upward extension of the arm from the flexed position	A___
	B___
	C___
	D___
Forearm supinating	
Supination of the forearm from the prone position (Elbow at right angles in front of the body)	C___
Wrist cocking, forearm supported	
Extended wrists from mid-position	C___
Wrist cocking, with arm raised straight in front	
Extend wrist from mid-position	
Straight arm raised in front	C___
Pinch grip, forearm supported	
Pick up 1 cm marble between index finger and thumb (pass = 2, fail = 0)	C___
Pinch grip, with arm raised straight in front	
Pick up 1 cm marble between index finger and thumb (Pass = 2, fail = 0)	C___
Movements – leg	
Hip and knee bending	
Bend (flex) hip and knee from straight position; combined movement	A___
	B___
	D___
Knee Flexion	
Isolated knee flexion, thigh immobilized	A___
	B___
	D___
Ankle dorsiflexion; leg straight	
Dorsiflex from the mid-position	B___
	D___
Ankle dorsiflexion; hip and knee bent	
Dorsiflex from the mid-position	C___

Table 15.7 (continued)

Motor club assessment: functional movement activities		
Scoring		
0 = Impossible (no cooperation, help from two or more people)		
1 = Assistance (patient cooperates; help of only one person required)		
2 = Independent with use of aid		
3 = Independent		
X = Not tested (state why)		
Grade	**Activity**	**Notes**
___	Supine to left side sitting	Pulling on edge of bed = aid
___	Supine to right side sitting	Pulling on edge of bed = aid
___	Bridging	Using unaffected leg to help affected/bad leg straighten = aid
___	Sitting balance (60 s)	Use of hands for support = aid
___	Sitting, touch floor and return	Use of hands for support going down or up = aid
___	Sitting to standing	Use of hands to push down on chair for standing = aid
Grade	**Activity**	**Notes**
___	Standing balance (30 s)	Must have both feet on the floor. Use of chair, stick, etc. = aid
___	Standing on left leg (5 s)	Use of chair, stick, etc. = aid
___	Standing on right leg (5 s)	Use of chair, stick, etc. = aid
___	Standing, get down on floor	Use of chair, stick, etc. = aid
___	Kneel standing balance (10 s)	Use of stool, etc. = aid
___	Kneel standing, left (5 s)	Use of stool, etc. = aid
___	Kneel standing, right (5 s)	Use of stool, etc. = aid
___	Get up from floor to standing	Use of stool, etc. = aid
___	Transfer sitting on chair to lying on bed	Use of tripod/stick = aid Support on bed/chair = 1
___	Transfer lying on bed to sitting on chair	Use of tripod/stick = aid Support on bed/chair = 1
___	Walking (15 m)	Also record time and aid used
___	Stairs (up and down 10 steps)	Also record time and aid used
___	Total	

Disadvantages: There have been no formal validity studies, and the scale has not been used frequently. The data are ordinal and the assessment would not likely be sensitive to small changes in muscle strength.

Disease-Specific Functional Assessments

Motor Neuron Disease

Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R)

The ALSFRS-R is perhaps the most widely utilized functional rating scale in the motor neuron disease population to date. It was designed to assess the ability of ALS patients to perform activities of daily living in order to determine if there is any functional improvement or decline during a study period [3] (Table 15.8). The ALSFRS-R assesses three bulbar functions, two upper extremity functions (cutting

Table 15.8 ALSFRS-R

1.	*Speech*	
	4	Normal speech processes
	3	Detectable speech disturbance
	2	Intelligible with repeating
	1	Speech combined with nonvocal communication
	0	Loss of useful speech
2.	*Salivation*	
	4	Normal
	3	Slight but definite excess of saliva in mouth; may have nighttime drooling
	2	Moderately excessive saliva; may have minimal drooling
	1	Marked excess of saliva with some drooling
	0	Marked drooling; requires constant tissue or handkerchief
3.	*Swallowing*	
	4	Normal eating habits
	3	Early eating problems – occasional choking
	2	Dietary consistency changes
	1	Needs supplemental tube feeding
	0	NPO (exclusively parenteral or enteral feeding)
4.	*Handwriting*	
	4	Normal
	3	Slow or sloppy: all words are legible
	2	Not all words are legible
	1	Able to grip pen but unable to write
	0	Unable to grip pen
5a.	*Cutting food and handling utensils* (*patients without gastrostomy*)	
	4	Normal
	3	Somewhat slow and clumsy, but no help needed
	2	Can cut most foods, although clumsy and slow; some help needed
	1	Food must be cut by someone, but can still feed slowly
	0	Needs to be fed
5b.	*Cutting food and handling utensils* (*alternate scale for patients with gastrostomy*)	
	4	Normal
	3	Clumsy but able to perform all manipulations independently
	2	Some help needed with closures and fasteners
	1	Provides minimal assistance to caregiver
	D	Unable to perform any aspect of task
6.	*Dressing and hygiene*	
	4	Normal function
	3	Independent and complete self-care with effort or decreased efficiency
	2	Intermittent assistance or substitute methods
	1	Needs attendant for self-care
	0	Total dependence
7.	*Turning in bed and adjusting bed clothes*	
	4	Normal
	3	Somewhat slow and clumsy, but no help needed
	2	Can turn alone or adjust sheets, but with great difficulty
	1	Can initiate, but not turn or adjust sheets alone
	0	Helpless
8.	*Walking*	
	4	Normal.
	3	Early ambulation difficulties.
	2	Walks with assistance.
	1	Non-ambulatory functional movement only.
	0	No purposeful leg movement.
9.	*Climbing stairs*	
	4	Normal
	3	Slow
	2	Mild unsteadiness or fatigue
	1	Needs assistance
	0	Cannot do
10.	*Dyspnea*	
	4	None
	3	Occurs when walking
	2	Occurs with one or more of the following: eating, bathing, dressing (ADL)
	1	Occurs at rest, difficulty breathing when either sitting or lying
	0	Significant difficulty, considering using mechanical respiratory support
11.	*Orthopnea*	
	4	None
	3	Some difficulty sleeping due to shortness of breath, does not routinely use >2 pillows
	2	Needs extra pillows to sleep (>2)
	1	Can only sleep sitting up
	0	Unable to sleep
12.	*Respiratory insufficiency*	
	4	None
	3	Intermittent use of BIPAP
	2	Continuous use of BIPAP at night
	1	Continuous use of BIPAP day and night
	0	Invasive mechanical ventilation by intubation/trach

food and dressing), two lower extremity functions (walking and climbing), two other functions (dressing-hygiene and turning in bed), and three respiratory functions. The score ranges from 48 (normal function) to 0 (unable to attempt the task). The instrument can be administered by a physician, nurse, physical therapist, or trained assistant. The patient's response to how they perform each activity is recorded to the closest approximation from a list of five choices, scored from 0 to 4.

Advantages: The ALSFRS-R is simple, easy to administer, and takes approximately 10 min to complete. It is a sensitive, accurate, and reproducible measure of the clinical course of ALS patients. It has been used extensively in ALS clinical trials and correlates well with quantitative strength testing results. As a result of its widespread use, a large volume of control data are available from prior trials. The expected rate of decline in large populations of motor neuron disease patients adds utility for this measure as a comparison to historical controls.

Table 15.9 Appel ALS scale

Appel ALS Scale

Bulbar Sub-score			6-30
Swallowing Grade	3-15		
Speech Grade	3-15		
Respiratory Sub-score			6-30
Vital Capacity Grade	6-30		
Muscle Strength Sub-score			6-36
Upper Extremity Muscle Strength Grade	2-14		
Lower Extremity Muscle Strength Grade	2-14		
Hand Grip Grade	1-4		
Lateral Pinch Grade	1-4		
Lower Extremity Muscle Function Sub-score			6-35
Stand from Chair Grade	1-5		
Stand from Lying Grade	1-6		
Walk 20 feet	1-5		
Need for Assistive Devices Grade	1-5		
Climb & Descend Four Standard Steps Grade	1-6		
Hips and Legs Grade	1-8		
Upper Extremity Muscle Function Sub-score			6-33
Dress and Feed Self Grade	1-5		
Propel Wheelchair 20 Feet Grade	1-6		TOTAL APPEL ALS SCALE SCORE
Arms and Shoulders Grade	1-6		
Cut Theraplast Grade	1-6		
Pegboard Grade	1-5		
Block Coordination Grade	1-5		30-164

Disadvantages: The ALSFRS-R is an ordinal scale and is likely insensitive to small differences. The scale cannot give information regarding the reason for a decline or disability (i.e., weakness, spasticity, rigidity, etc.).

Appel ALS Scale

The Appel scale was developed as a quantitative estimate of clinical status and disease progression in amyotrophic lateral sclerosis (ALS) patients [45, 46]. The total Appel scale score consists of five domain subscores: bulbar, respiratory, muscle strength, lower extremity function, and upper extremity function (Table 15.9). The scale consists of 16 tests (one pulmonary and 15 extremity tests) and three subjective evaluations. The muscle strength subscore consists of manual muscle testing according to the Medical Research Council grading system [11]. The evaluation yields a total Appel ALS score (starting from 30 for healthy subjects and 164 for maximum impairment) and a subscore for each group of the functions

tested. A retrospective analysis of 1,200 patients, using the Appel scale, has identified important risk factors for disease progression as well as validation with clinical progression on examination [45].

Advantages: The Appel ALS scale has been one of the most widely used composite indices of disease progression among ALS patients, surpassed by the ALSFRS-R score noted above. There is a large volume of data using this scale, reflecting the natural progression of disease, and this can be useful for comparison with smaller samples of patients. The scale is very well suited to a multidisciplinary evaluation of the ALS patient with individual subscales being derived by specialized therapists (occupational, physical, speech, etc.).

Disadvantages: The scale is more time and labor intensive than other composite scores of progressive motor impairment. There is some specialized equipment required, and the evaluations are not all "standard" components of a routine neurologic evaluation in centers not using this measure. Individual subscales have not been validated separately although the tendency to interpret these component subscales as similar markers of linear disease progression can be misleading.

Norris ALS Scale

The Norris scale was also designed as a measure of disease progression in ALS patients [47]. The scale uses a four-point categorical grading of both impairments and disabilities in all levels of the neuraxis (Table 15.10). Motor functions, reflecting both signs and symptoms, are graded as either normal, impaired, minimally present (trace), or not present. Deep tendon reflexes, jaw jerk reflex, Hoffman's sign, and the extent of atrophy with fasciculations are all evaluated in this composite score.

Advantages: The Norris scale is fairly easy to administer, not requiring specialized equipment. It has been used most extensively in evaluating motor neuron disease. Much of the evaluation is done routinely as part of a standard follow-up evaluation for patients with progressive weakness.

Disadvantages: The scale is primarily oriented to patients with progressive motor neuron disease and may not be as appropriate or sensitive to more indolent changes in other disease states. This is an ordinal scale, and the implications of relative changes at both the low and high end of the range cannot be made. The scale includes both measures of functional disability *and* elements of the neurologic examination. This combination assumes a good correlation between disability and clinical pathology, which may not be true. If, for example, hyperreflexia does not correlate with a greater functional disability, the combination of both elements in the same scale may lessen the sensitivity to detecting small changes in either.

Table 15.10 The NORRIS ALS scale [48]

	3 (normal)	2 (impaired)	1 (trace)	0 (no use)
1. Hold up head (test)				
2. Chewing (history)				
3. Swallowing (test)				
4. Speech (test)				
5. Roll over (test)				
6. Sit up (test)				
7. Bowel/bladder pressure (history)				
8. Breathing (test)				
9. Cough (test)				
10. Write (test)				
11. Buttons, zippers (test)				
12. Feeding (history)				
13. Grip/lift self (test)				
14. Grip/lift book, tray (test)				
15. Grip/lift fork, pencil (test)				
16. Change arm position (test)				
17. Climb stairs (test)				
18. Walk (test)				
19. Walk one room (test 15 ft)				
20. Walk assisted (test only if assist required above)				
21. Stand (test)				
22. Change leg position (test)				
23. Biceps, brachioradialis, triceps muscle stretch reflexes (test)				
24. Quadriceps, Achilles, internal hamstring muscle stretch reflexes (test)				
25. Jaw jerk (test)				
26. Plantar response – right (test)				
27. Plantar response – left (test)				
28. Fasciculation (test)				
29. Atrophy – face (test)				
30. Atrophy – arms, shoulders (test)				
31. Atrophy – legs, hips (test)				
32. Labile emotions (history and observation)				
33. Fatigability (test): requiring only two grades: 2 (normal) or 0 (present)				
34. Leg rigidity (test): requiring only two grades: 2 (normal) or 0 (present)				

Point scores range from 0 (maximum impairment) to 100 (healthy)

Table 15.11 CNS-LS

CNS-LS

	Applies never	Applies rarely	Applies occasionally	Applies frequently	Applies most of the time	
	1	2	3	4	5	
Assessment questions						**Answers**
There are times when I feel fine one minute, and then I'll become tearful the next over something small or for no reason at all.						
Others have told me that I seem to become amused very easily, or that I seem to become amused about things that really aren't funny.						
I find myself crying very easily.						
I find that even when I try to control my laughter, I am often unable to do so.						
There are times when I won't be thinking of anything happy or funny at all, but then I'll suddenly be overcome by funny or happy thoughts.						
I find that even when I try to control my crying, I am often unable to do so.						
I find that I am easily overcome by laughter.						

CNS Lability Scale

The Central Nervous System Lability Scale (CNS-LS) is a 7-question validated scale that provides a score which assesses the frequency and severity of episodes of inappropriate laughter and crying (Table 15.11) [49, 50]. A score greater than 11 is considered abnormal and should prompt discussion with the patient regarding possible treatments. The CNS-LS was a secondary endpoint leading to the approval of dextromethorphan/quinidine as the first and only FDA-approved treatment for pseudobulbar affect.

Advantages: The CNS-LS is the only scale which has been validated to measure the severity of pseudobulbar affect in patients with ALS and multiple sclerosis. The scale takes less than a minute to complete.

Disadvantages: The total score may not actually reflect the burden of the PBA symptoms to the patient and caregiver. Patients with scores >11 may not perceive a need for treatment.

SMAFRS

The Spinal Muscular Atrophy Functional Rating Scale (SMAFRS) was adapted from the ALSFRS to assess function in patients with SMA [51, 52]. Patients (or caregivers) are asked to compare how they are today versus how they were before the start of the disease. Patients are graded from 0 to 5 with 5 being no restrictions or normal and 0 being unable to perform. Categories covered are (1) eating, (2) dressing upper body, (3) dressing lower body, (4) bathing, (5) toileting, (6) grooming and oral hygiene, (7) turning in bed and adjusting bed clothes, (8) transfers, (9) walking, and (10) climbing stairs.

Advantages: The SMAFRS is simple, easy to administer, and takes less than 10 min to complete. The instrument was used as a secondary outcome measure in a trial of gabapentin.

Disadvantages: The SMAFRS is insensitive to small differences.

ACTS

The Amyotrophic Lateral Sclerosis Ciliary Neurotrophic Factor Treatment Study ALS Evaluation is a composite measure adapted from multiple independent measurement scales developed earlier [21, 23, 53]. This scale was developed specifically for comprehensive evaluation of ALS patients receiving experimental ciliary neurotrophic factor (CNTF), taking into account impairments *and* disabilities as outlined in the ICIDH guidelines. Impairments are measured by:

- Quantitatively evaluating the rate of speech generated
- Pulmonary function tests

- Purdue pegboard testing
- Timing a 15-ft walk
- Isometric muscle testing in ten muscle groups using computerized dynamometry
- Ordinal scale grading of spasticity, fasciculations, atrophy, and cramping

Standardized scores matching for age and gender are available for comparison [54, 55]. Disability is measured by the ALSFRS scale, described below.

Advantages: The ACTS index has been validated in a large cohort of ALS patients [3]. Consequently, a large volume of data (from patients and normal controls) is available, enhancing the reliability of the test and providing empiric estimates of variability critical to sample size determination. The multidimensional aspect of the test yields a composite index of both functional impairments and physical disabilities important when evaluating a disease with multisystem involvement.

Disadvantages: Specialized equipment and training are required for reliable testing. The testing procedure has been developed for and tested only in ALS patients. The composite ACTS score may be insensitive to heterogeneous changes in muscle strength or functional capability. Differences in strength between proximal (stronger) muscles and distal (weaker) muscles are lost when the overall "percent predicted" value of muscle strength is derived by combining values from the two muscle groups. Similarly, if muscle groups, stronger at the start of a trial, became weaker at a slower rate than those which were weaker at the outset, then this difference could not be detected.

Myopathy

IBMFRS

The Inclusion Body Myositis Functional Rating Scale (IBMFRS) was adapted from the ALSFRS to assess function in patients with IBM [56]. The areas addressed in the questionnaire include swallowing, handwriting, cutting food and handling utensils, fine motor tasks, dressing, hygiene, turning in bed and adjusting covers, sitting to standing, walking, and climbing stairs. Answers to each item are graded on a 0–4 scale, with 4 being normal and 0 being unable to perform. The best possible score is 40.

Advantages: The IBMFRS is the first functional scale developed exclusively for IBM clinical trials. It can be administered in less than 10 min and does not require any expensive, specialized equipment, or personnel training to administer. The IBMFRS was utilized as a secondary outcome measure in a multicenter pilot trial of the clinical safety and tolerability of high-dose beta-interferon-1a. It appeared to correlate well with traditional measures of efficacy (MMT and MVIC) and was the measure most sensitive to change over time.

Disadvantages: Further studies are needed to determine whether the IBMFRS can also be self-administered or given over the phone.

Myositis Intention to Treat Activities Index (MITAX)

The MITAX assesses specific manifestations in seven organs/systems, including constitutional, cutaneous, skeletal, gastrointestinal, pulmonary, cardiac, and muscular [57, 58]. Each question is answered as 0 = not present, 1 = improving, 2 = the same, 3 = worse, or 4 = new. This score is then converted by a scoring schema to a final score ranging from A to E for each system, where A indicates very active disease requiring treatment with high-dose daily corticosteroids or a significant immunosuppressive therapy, B indicates a need for modest doses of corticosteroids and/or ongoing immunosuppression, C indicates a need for low-dose steroids or symptomatic drugs only, D indicates the system is no longer active, and E indicates that the system was never active. Each organ system receives only a single A–E score (which can be numerically converted to A = 9, B = 3, C = 1, and D/E = 0 to obtain a global score) based on the score of the most severe item in that organ system. The organ system scores are summed to obtain a total MITAX score with a range of 0–63 or 0–54 when the muscular system is excluded.

Advantages: The MITAX is accepted by the Pediatric Rheumatology International Trials Organization as a core set measure to assess the core set domain of global disease activity tool. The MITAX has excellent content validity, good inter-rater reliability, and excellent responsiveness. The criterion validity of the MITAX score supports use in the clinical setting. The time to administer the tool would not be much greater than a routine clinical assessment.

Disadvantages: For a patient with a complex condition, it can take up to 15–20 min to complete.

Myositis Disease Activity Assessment (MYOACT)

The MYOACT is a tool that assesses disease activity of extramuscular organ systems and muscle to assess patients with adult and juvenile dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM) (57, Rider, 2011 #6792). The MYOACT is a series of physician's assessment of disease activity in various organ systems based on history and examination, using a VAS to assess the severity of activity. Each organ system is scored from 0 to 10 cm, and the 6 extramuscular organ systems can be summed to obtain an extramuscular score of 0–60 cm or a total score that includes the muscle system that ranges from 0 to 70 cm.

Advantages: The MYOACT is accepted by the Pediatric Rheumatology International Trials Organization as a core set measure to assess the core set domain of global disease activity tool. The MYOACT has excellent content validity, with a large amount of input in their development from myositis researchers. It has good inter-rater reliability, moderate construct validity, and excellent responsiveness in adult and

Table 15.12 Quantitative Myasthenia Gravis Scale

Test items weakness	None	Mild	Moderate	Severe	Score
Grade	0	1	2	3	
Double vision (lateral gaze) sec.	60	11–59	1–10	Spontaneous	
Ptosis (upward gaze) sec.	60	11–59	1–10	Spontaneous	
Facial muscles	Normal lid closure	Complete, weak, some resistance	Complete, without resistance	Incomplete	
Swallowing 4 oz. water (1/2 cup)	Normal	Minimal coughing or throat clearing	Severe coughing, choking, or nasal regurgitation	Cannot swallow (test not attempted)	
Speech following counting aloud from 1 to 50 (onset of dysarthria)	None at #50	Dysarthria at #30–49	Dysarthria at #10–29	Dysarthria at #9	
Right arm outstretched (90°, sitting) sec.	240	90–239	10–89	0–9	
Left arm outstretched (90°, sitting) sec.	240	90–239	10–89	0–9	
Forced vital capacity	>80 %	65–79 %	50–64 %	<50 %	
Rt handgrip: male	>45	15–44	5–14	0–4	
(Kg): female	>30	10–29	5–9	0–4	
Left handgrip: male	>35	15–34	5–14	0–4	
(Kg): female	>25	10–24	5–9	0–4	
Head, lifted (45 %, supine) sec.	120	30–119	1–29	0	
Right leg outstretched (45–50 %, supine) sec.	100	31–99	1–30	0	
Left leg outstretched (45–50 %, supine) sec.	100	31–99	1–30	0	

juvenile PM/DM patients. To assess a patient in remission or close to remission takes less than 5 min.

Disadvantages: For a patient with a complex condition, it can take up to 15–20 min to complete. The VAS may be subjective and somewhat dependent on the experience of the rater.

Myasthenia Gravis

Quantitative Myasthenia Gravis (MG) (QMG) Score

The QMG was initially developed by Besinger and Toyka in 1981 and later modified by Tindall et al. [4] and Barohn et al. [5]. The QMG consists of 13 independent assessments including:

- The time to develop diplopia with prolonged lateral gaze
- The time to develop ptosis with prolonged upgaze
- Facial strength
- Ability to swallow 1/2 cup of water
- Speech following counting aloud from 1 to 50
- The time the patient can outstretch either arm
- Vital capacity
- Right and left grip strength
- The time the patient can lift head 45° in a supine position
- The time the patient can outstretch either leg

Each item is graded from 0 (normal) to 3 (severe weakness) with a total score ranging from 0 to 39 (Table 15.12).

This measure has been widely used in many MG trials and has been recommended as a primary outcome measure. It is frequently compared with the MG Composite score (see below) by the MG task force. This easy to use scale has been validated and has high reliability in accessing relevant clinical changes. There is also a measurement of fatigability within the measure, and this has been especially relevant to measurement of outcome in MG [4, 5, 59, 60].

Advantages: Inter-examiner reliability has been demonstrated for the QMG, and it has been used in several MG therapeutic trials (mycophenolate, IVIG) as an outcome measure.

Disadvantages: A patient can have an improved total score but be incapacitated by poor strength in one or two areas; therefore, it does not necessarily reflect the patient's functional status. In addition, for similar reasons, it cannot be used to compare severity between patients. Completion of the QMG is time consuming, and some investigators have proposed only testing one arm and leg.

MG Composite Score

This score assesses a quantitative evaluation of signs and symptoms in ten functional domains. It is validated and reliable, and currently, the 2011–2012 MG task force is recommending this as the preferred primary outcome measure for clinical trials in MG (Table 15.13). It can be completed more quickly than the Quantitative MG Score [59, 61, 62].

Advantages: This scale is currently recommended by the MGFA task force as the preferred measure for subsequent trials in myasthenia gravis. It has been shown to be validated and reliable. A 3-point change in the scale is thought to be clinically meaningful and correlates with a myasthenia gravis quality of life scale.

Disadvantages: The scale involves reporting from both physician and patient. Ceiling and floor effects have not been addressed as possible confounds.

Table 15.13 MG composite scale

Ptosis, upward gaze (physician examination)	>45 s = 0	11–45 s = 1	1–10 s = 2	Immediate = 3
Double vision on lateral gaze, left or right (physician examination)	>45 s = 0	11–45 s = 1	1–10 s = 3	Immediate = 4
Eye closure (physician examination)	Normal = 0	Mild weakness (Can be forced open with effort) = 0	Moderate weakness (Can be forced open easily) = 1	Severe weakness (Unable to keep eyes closed) = 2
Talking (patient history)	Normal = 0	Intermittent slurring or nasal speech = 2	Constant slurring or nasal but can be understood = 4	Difficult to understand speech = 6
Chewing (patient history)	Normal = 0	Fatigue with solid food = 2	Fatigue with soft food = 4	Gastric tube = 6
Swallowing (patient history)	Normal = 0	Rare episode of choking or trouble swallowing = 2	Frequent trouble swallowing, for example, necessitating changes in diet = 5	Gastric tube = 6
Breathing (thought to be caused by MG)	Normal = 0	Shortness of breath with exertion = 2	Shortness of breath at rest = 4	Ventilator dependence = 9
Neck flexion or extension (weakest) (physician examination)	Normal = 0	Mild weakness = 1	Moderate weakness (i.e., ~50 % weak, ± 15 %) = 3	Severe weakness = 4
Shoulder abduction (physician examination)	Normal = 0	Mild weakness = 2	Moderate weakness (i.e., ~50 % weak, ± 15 %) = 4	Severe weakness = 5
Hip flexion (physician examination)	Normal = 0	Mild weakness = 2	Moderate weakness (i.e., ~50 % weak, ± 15 %) = 4	Severe weakness = 5

Myasthenic Muscular Score (MMS)

The MMS consists of nine assessments ranging from timed tasks (maintaining upper limbs horizontally and maintaining lower limbs above bed plane while supine) in which patients are assigned points based upon how long they can perform the test to functional activities (raising head above gravity, sitting up from a lying position, ocular muscle function, eyelid occlusion, chewing, swallowing, and speech) (Table 15.14). The timed tasks are scored from 0 to 15, and the functional assessments are scored from 0 to 10. The total score can range from 0 (most severely affected) to 100 (complete remission).

Advantages: The MMS has been used in two multicenter randomized trials. It can be administered in 5–10 min and does require any specialized training.

Disadvantages: The reproducibility of the MMS has not been assessed. In both trials in which this score was used as a primary endpoint, no difference was identified between the treatment groups (intravenous gamma globulin versus plasma exchange and prednisone versus azathioprine), suggesting that the instrument may not be sensitive in detecting small changes in clinical outcome.

Myasthenia Gravis Severity Scale (MSS)

The MSS was developed for use in a trial comparing intravenous gamma globulin and plasma exchange in the treatment of myasthenic crisis [63]. The scale rates ability to cough, ocular function, bulbar function, and extremity strength on a scale from 1 (most severely affected) to 3 (normal) and rates dyspnea on a scale from 1 (intubated) to 4 (asymptomatic). The total score, therefore, ranges from 5 to 16 (Table 15.15).

Table 15.14 Myasthenic Muscular Score

Maintain upper limbs horizontally outstretched	
1 point per 10 s	Maximum 15
	Minimum 0
Maintain lower limbs above bed plane, while lying on back	
1 point per 5 s	Maximum 15
	Minimum 0
Raise head above bed plane, while lying on back	
Against resistance	10
Without resistance	5
Impossible	0
Sit up from lying position	
Without help of hands	10
Impossible	0
Extrinsic ocular musculature	
Normal	10
Ptosis	5
Double vision	0
Eyelid occlusion	
Complete	10
Incomplete with corneal covering	5
Incomplete without corneal covering	0
Chewing	
Normal	10
Weak	5
Impossible	0
Swallowing	
Normal	10
Impaired without aspiration	5
Impaired with aspiration	0
Speech	
Normal	10
Nasal	5
Slurred	0

Advantages: The MSS was designed to functionally evaluate critically ill myasthenia gravis patients and, therefore, is heavily weighted to the assessment of respiratory function. It can be administered easily and quickly.

Disadvantages: The MSS is an insensitive measure in myasthenia gravis patients with mild to moderate disease.

Myasthenic Functional Score (MFS)

The MFS was used along with the Myasthenic Muscular Score in a trial comparing azathioprine to prednisone [64]. It is a five-grade functional scale, defined as 1: complete remission; 2: minor symptoms allowing normal activity, except for exertional activity; 3: moderate symptoms allowing occupational or partial daily activity; 4: major disability requiring discontinuation of occupational activity or major reduction of daily activity; and 5: major disability requiring continuous help by others or mechanical ventilation.

Advantages: The MFS can be performed quickly with no specialized training required.

Disadvantages: The MFS is a very crude assessment of function and is insensitive in detecting small changes in function.

Table 15.15 Myasthenia gravis severity scale

Dyspnea
1 = Intubated
2 = Dyspnea at rest
3 = Dyspnea on exertion
4 = None
Cough
1 = Intubated
2 = Weak
3 = Normal
Ocular
1 = Weakness at rest
2 = Weakness on fatigue
3 = None
Bulbar
1 = Weakness at rest
2 = Weakness on fatigue
3 = None
Extremities
1 = Worst affected muscle 3/5 or less
2 = Worst affected muscle 4/5 motor strength or weakness on fatigue
3 = No detectable weakness

Myasthenia Gravis Activities of Daily Living Score (MG ADL Score)

The MG ADL Score is an example of a disease-specific functional status measurement score. It consists of eight functional tasks which are scored on a scale from 0 (normal) to 3 (severe impairment): talking, chewing, swallowing, breathing, impairment of ability to brush teeth or comb hair, impairment of ability to arise from a chair or toilet, double vision, and eyelid droop (Table 15.16). The total score ranges between 0 and 24.

Advantages: The MG ADL Score is a disease-specific functional scale for MG which has been adopted in several MG clinical trials. It is simple and economical to administer and does not require an extensive amount of time to complete.

Disadvantages: The responses are largely subjective and based upon the patient's response rather than objective assessment of function.

Peripheral Neuropathy

Neuropathy Disability Scale

This functional scale was initially developed for use in a controlled trial of prednisone in acute polyneuropathy [65]. Patient function is ranked as: 0 (healthy), 1 (minor symptoms

Table 15.16 MG activities of daily living (ADL) scale

Grade	0	1	2	3	Score
Talking	Normal	Intermittent Slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
Impairment of ability to arise from a chair or toilet	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, require assistance	
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	
			Total MG ADL Score ___		

Table 15.17 INCAT disability scale

Arm disability
0 = No upper limb problems
1 = Symptoms, in one or both arms, not affecting the ability to perform any of the following functions: doing all zips *and* buttons, washing *or* brushing hair, using a knife and fork together, and handling small coins
2 = Symptoms, in one arm or both arms, affecting but not preventing any of the above-mentioned functions
3 = Symptoms, in one arm or both arms, preventing one or two of the above-mentioned functions
4 = Symptoms, in one arm or both arms, preventing three or all of the functions listed, but some purposeful movements still possible
5 = Inability to use either arm for any purposeful movement
Leg disability
0 = Walking not affected
1 = Walking affected, but walks independently outdoors
2 = Usually uses unilateral support (stick, single crutch, one arm) to walk outdoors
3 = Usually uses bilateral support (sticks, crutches, frame, two arms) to walk outdoors
4 = Usually uses wheelchair to travel outdoors, but able to stand and walk a few steps with help
5 = Restricted to wheelchair, unable to stand and walk a few steps with help
Overall disability = Sum of arm and leg disability

or signs, able to run), 2 (able to walk >5 m without assistance but unable to run), 3 (able to walk >5 m with assistance), 4 (bed or chair bound), 5 (requiring assisted ventilation for at least part of the day), and 6 (dead). This scale can be self-administered, administered face to face, or administered over the telephone.

Advantages: The Neuropathy Disability Scale is simple, reliable, and can be administered quickly.

Disadvantages: The Neuropathy Disability Scale is unable to distinguish between the potentially wide ranges of functional disability within particular grades and has not been systematically validated. The difference between grade 2 and grade 1 is at times difficult to determine, particularly in older individuals who are not in the habit of running [66]. It has also not been compared to other universally accepted functional outcome scales.

INCAT Disability Scale

The INCAT Disability Scale was initially used as the primary outcome measurement in a trial comparing intravenous immunoglobulin versus oral prednisone in chronic inflammatory demyelinating polyneuropathy (CIDP) (Table 15.17) [67]. It was subsequently used in a randomized, response-conditional crossover trial of immunoglobulin versus placebo. Participants whose INCAT score did not improve by > 1 point received alternate treatment in a 24-week crossover period.

Advantages: The scale is simple to perform and has been established as the primary endpoint in two pivotal trials in CIDP. A very similar scale has been validated as reproducible and responsive to change [68]

Disadvantages: The scale may not be sensitive to small changes in strength or function and does not assess the function of sensory nerves.

CMT Neuropathy Scale

The CMT Neuropathy Score (CMTNS) was modified from the earlier total neuropathy score, a composite measure of disability in length-dependent axonal neuropathies (Table 15.18). The CMTNS provides a single measure of function and disability in patients with Charcot-Marie-Tooth Disease [69].

Advantages: The CMTNS is validated measure of length-dependent axonal and demyelinating CMT disability and has been used as an end point for longitudinal studies and clinical trials of CMT. The test is short and can usually be administered in several minutes. The CMTNS has also can be used for demyelinating and/or axonal length-dependent neuropathies.

Disadvantages: Within the CMTNS, some measurements (such as the sensory nerve amplitude, vibration) may be expected to decrease with the patient's age and therefore could artificially affect the score. The authors of the test emphasize the importance of age-matched controls. There have also been concerns for both floor and ceiling effects with the use of the CMTNS.

Overall Neuropathy Limitations Scale (ONLS)

The ONLS is a measure of disability in patients with peripheral neuropathies (Table 15.19). The scale focuses on common activities of daily living. It is composed of one section with measurements relative to the lower limb and mobility and another for the upper limb [70].

There are 14 total items and 2 domains (arm scale, 7 items; leg scale, 7 items) with a final score between 0 and 12. Higher scores indicate greater limitations.

ONLS can be administered as an interview or as an observation in patients with communication or cognitive difficulties.

Advantages: This is a short, easily administered, validated test in patients with peripheral neuropathy. The scale surveys both functional limitations (turning a key, use of utensils, etc.) as well as an objective/subjective grade of motor strength and disability. It can be used in patients with communication or cognitive impairment.

Disadvantages: Due to the broad spectrum of disability that can be associated with neuropathy, the ONLS may not be especially sensitive to more selective or focal deficits as seen in sensory predominant neuropathy, multifocal neuropathy, or mononeuropathy.

This may be of use to people with communication or cognitive difficulties. If it is to be based upon an observed score, the following equipment is required: a key and lock, hair brush, knife and fork (or other eating implements, e.g., chopsticks), and a shirt with buttons and zips.

Table 15.18 CMT Neuropathy Score

	Score				
Parameter	0	1	2	3	4
Sensory symptoms	None	Limited to toes	Extend up to and may include ankle	Extend up to and may include knee	Extends above knees
Motor symptoms					
Legs	None	Trips, catches toes, slaps feet	AFO on at least 1 leg or ankle support	Cane, walker, ankle surgery	Wheelchair most of the time
Arms	None	Difficulty with buttons/ zippers	Unable to do buttons or zippers but can write	Cannot write or use keyboard	Proximal arms
Pin sensibility	Normal	Reduced in fingers/toes	Reduced up to and may include wrist/ankle	Reduced up to and may include elbow/knee	Reduced above elbow/knee
Vibration	Normal	Reduced at fingers/toes	Reduced at wrist/ankle	Reduced at elbow/knee	Reduced above elbow/knee
Strength					
Legs	Normal	4+, 4, or 4– on foot dorsiflexion	≤3 ft dorsiflexion	≤3 dorsiflexion and plantar flexion	Proximal weakness
Arms	Normal	4+, 4, or 4– on intrinsics or finger extensors	≤3 intrinsics or finger extensors	<5 wrist extensors	Weak above elbow
Ulnar CMAP (median)	>6 mV (>4 mV)	4.0–5.9 mV (2.8–3.9)	2.0–3.9 mV (1.2–2.7)	0.1–1.9 mV (0.1–1.1)	Absent (absent)
Ulnar SNAP (median)	>9 μV (>22 μV)	6.0–8.9 μV (14.0–21.9)	3.0–5.9 μV (7.0–13.9)	0.1–2.9 μV (0.1–6.9)	Absent (absent)
Total (max. 36)					

AFO ankle-foot orthosis, *CMAP* compound muscle potential, *SNAP* sensory nerve action potential

Sensory Scales

Perceptions of sensory stimuli are among the most challenging to quantitate. By definition, sensation is dependent upon the patient's perception and report of the testing stimuli. Consequently, a patient's prior experience and current emotional state confound clinical detection of sensory pathology by physical examination.

Quantitative sensory testing (QST) is based on methods that define not only the stimulus (type, characteristics, quantity, presentation, testing format, and environment) but also the response (form and analysis) [71]. Using available computer technology, it is possible to deliver precisely defined stimuli, which can be quantified and graded over a broad range of intensities. Graded intensities of pressure, temperature, vibration, and light touch can be consistently delivered via a commercially available apparatus.

The main application for QST is in quantifying modality-specific detection thresholds [72]. These methods can standardize an important, but historically, variable aspect of the neurologic examination.

Computer Aided Sensory Evaluator System IV (CASE IV)

The CASE IV system has been utilized in several clinical trials evaluating peripheral neuropathy patients [73–75]. This automated, commercially available device allows for reliable assessment of several sensory modalities including temperature, pain, vibration, and pressure. These stimuli directly activate sensory receptors. Computerized sensory testing allows the stimulus intensity to be varied in a fixed pattern. Patients are asked to report which changes in intensity are detectable.

Available software for QST allows for a *forced-choice algorithm* where subjects are told that a stimulus will be delivered in one of two intervals. Subjects are forced to choose in which interval the stimulus was delivered. If the correct interval is chosen, the intensity is reduced in the next presentation. The interval in which the stimulus is presented is randomly varied. Through repeat testing and varying the stimulus intensity, the threshold below which the subject has a predetermined chance (50 or 75 %) of guessing correctly can be determined. Approximately 10–15 min may be required to administer a single forced-choice QST. If multiple modalities are tested in multiple nerves, several hours may be required to complete an entire testing session.

An alternative algorithm, referred to as the *4-2-1 stepping algorithm*, is more time efficient. Using a single stimulus interval, a mid-intensity stimulus is delivered. If it is perceived, intensity is reduced by 4 threshold differences (referred to as just-noticeable differences, which are standardized) until the stimuli are no longer detectable. The intensity is then increased by 2 *just-noticeable differences* until it is again perceived. This protocol requires only 3 min per modality and, therefore, is considerably more time efficient [76].

Advantages: Ideally, this level of stimulus control results in a testing procedure which yields more unified sensory responses to selected stimuli. Data from QST can also be correlated with the amplitude of a sensory nerve action potential and eventually with the number and sizes of nerve fibers. In detecting patterns of sensory abnormality, QST can

Table 15.19 The overall neuropathy limitations scale [70]

ARM SCALE

Does the patient have any symptoms in their hands or arms, eg tingling, numbness or weakness?
Yes ☐ **No** ☐ (if "no", please go to "legs" section)

Is the patient affected in their ability to:	Not affected	Affected, but not prevented	Prevented
Wash and brush their hair	☐	☐	☐
Turn a key in a lock	☐	☐	☐
Use a knife and fork together (or spoon, if knife and fork not used)	☐	☐	☐
Do or undo button or zips	☐	☐	☐
Dress the upper part of their body excluding buttons or zips	☐	☐	☐

If all these functions are prevented can the patient make purposeful movements with their bands or arms? Yes ☐ No ☐ Not applicable ☐

Arm Grade
0 = Normal
1 = Minor symptoms in one or both arms but not affecting any of the functions listed **SCORE = ____**
2 = Disability in one or both arms affecting but not preventing any of the functions listed
3 = Disability in one or both arms preventing at least one but not all functions listed
4 = Disability in both arms preventing all functions listed but purposeful movement still possible
5 = Disability in both arms preventing all purposeful movements

LEG SCALE

	Yes	No	Not applicable
Does the patient have difficulty running or climbing stairs?	☐	☐	☐
Does the patient have difficulty with walking?	☐	☐	☐
Does their gait look abnormal?	☐	☐	☐
How do they mobilize for about 10 meters (i.e. 33 feet)?			
Without aid	☐	☐	☐
With one stick or crutch or holding someone's arm	☐	☐	☐
With two sticks or crutches or one stick or crutch holding onto someone's arm or frame	☐	☐	☐
With a wheelchair	☐	☐	☐
If they use a wheelchair, can they stand and walk 1 meter with the help of one person?	☐	☐	☐
If they cannot walk as above are they able to make some purposeful movements of their legs, eg reposition legs in bed?	☐	☐	☐

Does the patient use **ankle foot orthoses/braces?** (please circle) ☐ ☐ **If yes:** (please circle) **right/left**

Leg Grade
0 = Walking/climbing stairs/running not affected
1 = Walking/climbing stairs/running is affected, but gait does not look abnormal SCORE = ____
2 = Walks independently but gait looks abnormal
3 = Requires unilateral support to walk 10 meters (stick, single crutch, one arm)
4 = Requires bilateral support to walk 10 meters (sticks, crutches, crutch and arm, frame)
5= Requires wheelchair to travel 10 meters but able to stand and walk 1 meter with the help of one person
6 = Restricted to wheelchair, unable to stand and walk 1 meter with the help of one person, but able to make some purposeful leg movements
7 = Restricted to wheelchair or bed most of the day, unable to make any purposeful movements of the legs

Overall Neuropathy Limitation Scale = arm scale (range 0 to 5) + leg scale (range 0 to 7):
|range 0 (no disability) to 12 (maximum disability)| TOTAL SCORE: ____

Is there any disorder, other than peripheral neuropathy, which affects the above functions? **Yes** ☐ **No** ☐
If **yes**, please describe:

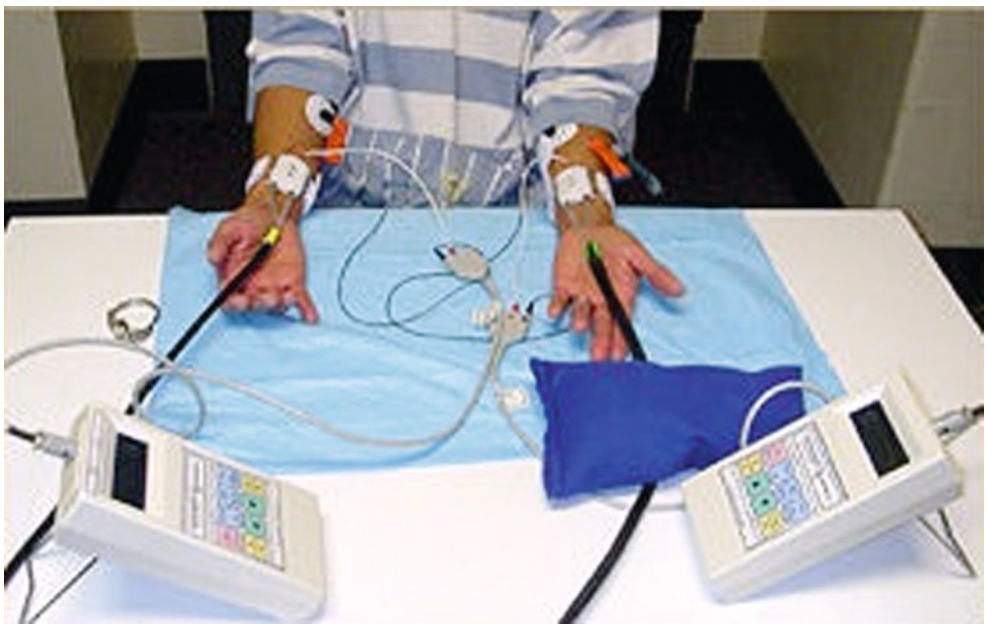

Fig. 15.1 Arrangement to perform the quantitative sudomotor axon reflex test

also suggest the presence of specific diseases and be used to follow the course of the sensory loss [71].

Quantifying and monitoring sensory pathology can involve the use of summated or averaged sensory nerve action potential amplitudes. These data can be correlated with vibratory detection thresholds which are sensitive, specific, and highly reproducible for the assessment of large myelinated sensory fibers. Quantitative evaluation of cooling and warming detection thresholds yields an estimate of pathology in small myelinated sensory fibers. Although less well validated for longitudinal trials, a visual analogue scale scoring of heat pain provides an additional assessment of unmyelinated sensory fibers. Heart rate variation to deep breathing, Valsalva, or standing is useful to assess cardiac autonomic function [7].

Disadvantages: Despite the consistency of the stimuli presented, accurate testing still requires significant patient cooperation and attention. The data are not entirely objective; as with any sensory testing, the patient's subjective perception is the primary endpoint. Equipment is commercially available but expensive. The time involved in testing sessions can be long, further increasing the expense of acquiring these data.

QSART

The quantitative sudomotor axon reflex test (QSART) is designed to look at small nerve fibers which innervate sweat glands [77, 78].

The test includes measures of resting skin temperature, resting sweat output, and stimulated sweat output. Upper and lower extremities are sampled. A plastic collection cup is placed on the skin. Temperature and sweat production under the skin can be measured. Sweat production is stimulated via iontophoretic application of acetylcholine delivered through the skin.

Advantages: Evaluation of sudomotor function is a technical and logistic challenge. The QSART is a commercially available apparatus that can standardize sudomotor function within the context of a clinical trial or laboratory.

Disadvantages: Specialized equipment must be purchased along with the availability of a trained technician. The test usually takes approximately 45 min to complete and may invoke mild burning discomfort to the patient (Fig. 15.1 [79]).

Nerve Conduction Studies

Nerve conduction studies have been used as markers of disease progression in clinical trials of polyneuropathy [72]. A decrease in conduction velocity is a fairly specific index for loss of large myelinated axons [80, 81]. If sensory conduction is unchanged, a reduction in the amplitude of the motor response is very specific for a loss of motor axons at the level of the motor root or anterior horn cell, by contrast to the generalized changes expected in a polyneuropathy [7]. Late responses (F-wave and H-reflex) can also be useful in measuring conduction over long segments, avoiding the errors incurred in distance measurements. In trials which include patients with severe polyneuropathy (significant loss of fibers), concurrent study of less affected upper extremities is important to insure that normal responses are detectable. In trials targeting more mild neuropathy, nerve conduction studies limited to the lower extremities may be sufficient due to the length-dependent pathology [7]. Careful consideration must be given to studying the *rate of change* rather than the actual value of amplitude or velocity in trials using nerve conduction data. Physiologic variability contributed by a patient's age, limb temperature, and body habitus can confound electrophysiologic data collection.

Advantages: Techniques for testing sensory nerve conduction are standardized. Electrophysiologic equipment is readily available and used in routine practice.

Table 15.20 Modified Ashworth scale for grading spasticity

Grade	Description
0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension
2	More marked increase in muscle tone through most of ROM, but affected part(s) easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

Disadvantages: Nerve conduction studies are generally insensitive to small fiber loss which is common in many neuropathies. Variables such as temperature, measurement, and the patient's age and height can add significant sources of measurement error.

Spasticity Scales

Validation of spasticity scales as an outcome measure in neuromuscular disease and especially ALS clinical trials is limited. Whether increased muscle tone correlates with impairment and, therefore, whether or not it is a valid indicator of clinical improvement or deterioration will ultimately require further study.

Modified Ashworth Scale

The Ashworth scale was originally developed for use in a trial of carisoprodol in multiple sclerosis patients to assess spasticity in the upper and lower extremities [82]. It is the only clinical measurement of abnormal muscle tone which has been formally evaluated [83]. The modified Ashworth scale consists of an ordinal scale which grades spasticity on a scale from 0 (no increase in tone) to 4 (Table 15.20). The grading was modified to be opposite to that which was originally reported by Ashworth where normal tone was given a grade of 4. Spasticity is assessed by passive range of motion on flexion and extension of the forearm at the elbow and on flexion and extension movement about the knee.

Advantages: The Ashworth scale has been shown to be a valid measurement of spasticity, and reliability has been proven at the elbow. It is a simple scale which can be taught with minimal training. The scale has been used in several ALS multicenter clinical trials.

Disadvantages: Although this scale is felt to be valid, the importance of disturbance in muscle tone as a specific impairment requires further study. Studies suggest that disability is more closely related to weakness than to spasticity [83].

Respiratory Scales

Progressive respiratory impairment is the primary cause of death in many neuromuscular diseases. Measurements of respiratory muscle strength, therefore, are being used more commonly as secondary outcome measures in clinical trials. The use of pulmonary function studies to assess the efficacy of a particular treatment or clinical intervention is best reserved for those disorders associated with more rapid and predictable declines in respiratory function such as ALS.

Forced Vital Capacity

The forced vital capacity (FVC) is the maximal amount of air that can be forcibly exhaled after a maximal inspiration. FVC is often reported as a percentage of a predicted vital capacity based on the patient's gender, height, and age. The FVC measurement should be performed with a nose clip with the patient in either a seated or supine position. The maneuver involves two steps: a full inspiration to total lung capacity, followed by a rapid, forceful maximal expiration (to residual volume) into a spirometer. Some authors have suggested that supine FVC may be a more sensitive measurement of diaphragmatic weakness [84]. In patients who have difficulty obtaining a tight lip seal on the mouth tube, it may be necessary to use a mouthpiece or mask. Three trials of the FVC are commonly compared, and variability is acceptable when less than 5 %.

Advantages: The deterioration in FVC has been used as a surrogate measure for survival in patients with motor neuron disease [85]. Schiffman et al. [86] reported that a reduction in FVC% was the factor most related to a patient's respiratory symptoms. This is a standard measure of pulmonary function which all respiratory therapists are trained to perform. In addition, measurement of FVC assesses the strength of both inspiratory and expiratory muscles in a single test.

Disadvantages: The accuracy of FVC measurements decreases with progressive bulbar spasticity and lower facial weakness [87]. In addition, the administration of noninvasive ventilation (NIV) can alter the results of this test over time since NIV has been shown to slow down the rate of FVC deterioration [88]. A decline in FVC may also be influenced by factors such as emphysema, congestive heart failure, and asthma as well as by muscular weakness. As a primary measure of respiratory impairment, FVC may not be sensitive to early or small changes in underlying motor neuron loss or muscle weakness. Due to compensatory mechanisms ensuring adequate respiratory function, a significant number of

motor neurons are likely to be lost prior to the onset of decline in FVC.

Slow Vital Capacity

The slow vital capacity (SVC) is the maximal volume of air that can be exhaled over a period of at least 30 s [89]. The values generated for SVC and FVC, in the same patient, should be quantitatively similar unless airway obstruction is present. SVC, however, may be an easier and more reliable measure to obtain, requiring less coordinated effort.

Advantages: This study attempts to accommodate patients who have significant spasticity and difficulty forcibly exhaling with a single coordinated effort. With a proper spirometer, SVC may be less variable as it is not confounded by an inconsistent (spastic) expiratory effort.

Disadvantages: Experience with using SVC as a primary or secondary endpoint in neuromuscular trials is limited. Computerized spirometers require specialized programming to accommodate the measure. Measurement via manual spirometry (Wright's spirometer) requires specialized training and awareness by the examiner.

Tidal Volume

Measurement of tidal volume requires patients to breathe normally without further instruction or demand. The volume of each individual breath is recorded and averaged over 1 min.

Advantages: Measurement of TV is less dependent on patient cooperation, coordination, and lower facial strength. In patients with lower facial weakness, tidal volume appears to be a better, more accurate predictor of respiratory function compared with FVC [87].

Disadvantages: TV measurements have not been used in any major clinical trial, although preliminary data suggests that it significantly correlates with changes in FVC in ALS patients ($r = 0.625$) [87].

Maximal Inspiratory/Expiratory Pressures

Measurement of maximal static respiratory pressures is particularly important in evaluating respiratory muscle weakness in patients with neuromuscular disease, and it has been performed as an outcome measure in several clinical trials [90–92]. In order to determine maximal expiratory pressure, the patient is urged to inspire fully to total lung capacity and then to exhale as forcefully as possible into a pressure gauge. The highest pressure attained and held for at least 1 s is the maximal expiratory pressure (MEP). The lower limit of normal for males is 71 cm H_2O and for females is 39 cm H_2O [93]. The maximal inspiratory pressure (MIP) is determined by having the patient inspire maximally from the pressure gauge after having expired completely to residual volume. The value recorded is the lowest pressure attained and held for at least 1 s. The lower limit of normal for males is 111 cm H_2O and for females is 88 cm H_2O [93]. Low peak inspiratory or expiratory pressures may be the result of any of a number of factors including suboptimal effort, fatigue, weakness of the respiratory muscles, deformity of the chest wall, or intrinsic diseases of the lungs or chest wall. Although the first three factors characteristically reduce both the MIP and MEP, disease of the lungs or chest wall often reduces, selectively, either the MIP or MEP. For example, diseases that reduce lung volume, such as interstitial fibrosis, shorten the length of the expiratory muscles at the end – inspiratory position and generally reduce the MEP. Alternatively, diseases such as obstructive airway disease that increase lung volume by decreasing the inspiratory muscle length at end-expiration, generally reduce the MIP.

Advantages: Patients with no respiratory symptoms may demonstrate significant reductions in MIP and MEP and still have normal spirometry [94] since maximal pressures are not required to achieve maximal expiratory flow rates. This suggests, therefore, that measurements of MIP and MEP are probably more sensitive in detecting early respiratory insufficiency in comparison to FVC measurements [95]. Determination of the MIP and MEP may also be helpful in suggesting the mechanism of reduced airflow during spirometry. Poorly reproducible peak flows that are consistently subnormal raise the question of poor patient effort. Conversely, consistently low values that occur despite maximal effort may signal an underlying neuromuscular disease.

Disadvantages: Experience with using maximal respiratory pressures as an outcome measure is limited.

Quality of Life Scales

Quality of life (QOL) is an extremely important issue particularly to patients who suffer from chronic, debilitating, and, many times, terminal diseases. A medication or intervention that merely prolongs life without improving quality of life may not be considered an effective therapy. For this reason, quality of life assessment is currently incorporated into most clinical trials as a secondary outcome measure. Unfortunately, the most commonly used instruments are actually a measure of health status (an objective description of a person's ability to perform certain roles) rather than of health-related quality of life (the personal valuation of these different disabilities). In addition, the majority of QOL instruments are heavily weighted to physical function. As a result, they show a decline with disease progression even if the patient's perception of QOL does not necessarily worsen. Psychological, existential, and spiritual factors presumably play an essential role in perceived QOL, and yet these areas are poorly evaluated using standardized scales. QOL may change at different stages of a disease

despite the intervention or medication being tested. While one instrument may be adequate early in disease, it may not be suitable to assess palliative care. Traditional questionnaires impose an external value system in which weighting of the component parts is standardized and is usually derived from grouped data. These measures may be reliable, but may not be relevant to an individual's present life situation. Similar impairments and functional disabilities do not have the same relevance or importance for all individuals. Furthermore, the importance of particular functions does not necessarily remain the same for a given individual over the course of a chronic illness.

Individualized Neuromuscular Quality of Life Questionnaire (INQoL)

The Individualized Neuromuscular Quality of Life Questionnaire is a neuromuscular disease-specific quality of life measure for adults [96, 97].

There are 12 domains: daily activities, leisure, employment, relationship with partner, relationships with family, relationships with friends, general social interaction, psychological impact on emotions, perception of the future, identity/self-image, independence, and coping strategies. For each domain, patients are asked the extent to which their neuromuscular disease affected this domain (on a five-point Likert scale from "not at all" affected to "very much" affected) and the importance that they attached to this impact (on a five-point Likert scale, ranging from "not at all important" to "extremely important").

Advantages: INQOL is one of few QOL measurements that were specifically designed for patients with neuromuscular disease.

Disadvantages: The INQOL takes approximately 20 min to complete. It has only been used in a single trial of dermatomyositis.

Short Form-36 (SF-36)

The 36-item short form (SF-36) is a multidimensional health questionnaire which was designed to survey the health status of the general population in the Medical Outcomes Study (Table 15.21) [98, 99]. The Medical Outcomes Study is an observational study examining practice styles and outcome measures in different clinical disease states [100]. The SF-36 measures both functional status and emotional well-being by utilizing eight health subscales: (1) physical functioning, (2) social functioning, (3) role limitations because of physical health problems, (4) role limitations because of emotional problems, (5) mental health status (psychological distress and psychological well-being), (6) bodily pain, (7) vitality (energy/fatigue), and (8) general health perceptions. The SF-36 contains 36 questions, 35 of which pertain to the 8 subscales and one item which relates to the perceived change in health over the past year. For each subscale, items are coded, totaled, and transformed to a 0–100 scale, with 100 indicating the best health state and 0 representing the worst health state. Each subscale employs its own response format which varies from "yes/no" responses to a six-point scale of "none" to "very severe." Two versions are available varying in the time of recall to current health status questions; respondents are asked about their health over the past 4 weeks (the most commonly used form) or over the past 1 week (used in evaluating acute conditions).

Advantages: The SF-36 can be reliably completed either over the phone or face to face and can also be self-administered in approximately 10 min. It is a comprehensive assessment and is applicable across many demographic and social groups. Test-retest reliability has been shown to range from $r=0.60$ (social functioning) to $r=0.81$ (physical functioning) [101].

Disadvantages: The SF-36 appears to be less comprehensive and not as suitable to an elderly population in comparison to the Sickness Impact Profile (SIP) [102]. This is due to the fact that the items pertaining to vigorous activities and work are not generally applicable to an elderly population. In addition, areas such as sleep disturbance, pain, emotional well-being, and mobility are not comprehensively addressed. On the other hand, when studying a more active population, the SF-36 appears to be a more sensitive mobility measure than the SIP [103]. The SF-36 also tends to have a floor or ceiling effect due to the limited range of responses [28]. In addition, the SF-36 is not able to assess change in health status over a short period of time due to the time frame in which questions are asked [104]. Finally, the SF-36 is a generic questionnaire, and although it is sensitive enough to detect changes in health state in a general population, this instrument should probably be combined with a disease-specific questionnaire when assessing a specific population of patients.

Short Form-12 (SF-12)

In an attempt to shorten the SF-36, a SF-12 version has also been used and validated in several clinical trials [99]. The 12 items are all contained in each version of the SF-36 (Table 15.22). The 12 items include self-assessment of health, physical functioning, physical role limitation, mental role limitation, social functioning, mental health items, and pain. Both 4-week and 1-week recall versions are available. The 12 items in this instrument yield the same eight scale profiles of the SF-36.

Advantages: The main advantage of the SF-12 in comparison to the SF-36 is its simplicity and ease of administra-

Table 15.21 SF-36 health survey (standard)

SF-36 HEALTH SURVEY (STANDARD)

INSTRUCTIONS: This questionnaire asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Please answer every question by marking one box. If you are unsure about how to answer, please give the best answer that you can.

1. *In general, would you say your health is:*

☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor

2. Compared to one year ago, how would you rate your health in general now? (Check one box)

☐ Much better now than one year ago
☐ Somewhat better now than one year ago
☐ About the same as one year ago
☐ Somewhat worse now than one year ago
☐ Much worse now than one year ago

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

		Yes, Limited A lot	Yes, Limited A Little	No, Not Limited At All
3.	**Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	☐	☐	☐
3.1	**Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	☐	☐	☐
3.2	Lifting or carrying groceries	☐	☐	☐
3.3	Climbing several flights of stairs	☐	☐	☐
3.4	Climbing one flight of stairs	☐	☐	☐
3.5	Bending, kneeling, or stooping	☐	☐	☐
3.6	Walking more than a kilometre or 2/3 of a mile	☐	☐	☐
3.7	Walking several blocks	☐	☐	☐
3.8	Walking one block	☐	☐	☐
3.9	Bathing or dressing yourself	☐	☐	☐

4. During the past 4weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

		YES	NO
4.1	Cut down on the **amount of time** you spent on work or other activities	☐	☐
4.2	**Accomplished less** than you would like	☐	☐
4.3	Were limited in the **kind** of work or other activities	☐	☐
4.4	Had difficulty performing the work or other activities (for example, it took extra effort)	☐	☐

Table 15.21 (continued)

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

		YES	NO
5.1	Cut down the **amount of time** you spend on work or other activities	☐	☐
5.2	**Accomplished less** than you would like	☐	☐
5.3	Didn't do work or other activities as carefully as usual	☐	☐

6. During the 4 past weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups? (Check the box which applies)

☐ Not at all
☐ Slightly
☐ Moderately
☐ Quite a bit
☐ Extremely

7. How much bodily pain have you had during the past 4 weeks (check the box which applies)

☐ None
☐ Very mild
☐ Mild
☐ Moderate
☐ Severe
☐ Very severe

8. During the past 4weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Check the box which applies)

☐ Not at all
☐ Very mild
☐ Mild
☐ Quite a bit
☐ Extremely

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks.

		All of the Time	Most of the Time	A good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
9.1	Did you feel full of pep?	☐	☐	☐	☐	☐	☐
9.2	Have you been a very nervous person?	☐	☐	☐	☐	☐	☐
9.3	Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐
9.4	Have you felt calm and peaceful	☐	☐	☐	☐	☐	☐
9.5	Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
9.6	Have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐
9.7	Did you feel worn out?	☐	☐	☐	☐	☐	☐
9.8	Have you been a happy person?	☐	☐	☐	☐	☐	☐
9.9	Did you feel tired?	☐	☐	☐	☐	☐	☐

Table 15.21 (continued)

9.5	Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
9.6	Have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐
9.7	Did you feel worn out?	☐	☐	☐	☐	☐	☐
9.8	Have you been a happy person?	☐	☐	☐	☐	☐	☐
9.9	Did you feel tired?	☐	☐	☐	☐	☐	☐

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the Time	Most of the Time	Some of the Time	A little of the Time	None of the Time
☐	☐	☐	☐	☐

11. How TRUE or FALSE is each of the following statements for you? (Check the box which applies on each line)

		Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
11.1	I seem to get sick a little easier than other people	☐	☐	☐	☐	☐
11.2	I am as healthy as anybody I know	☐	☐	☐	☐	☐
11.3	I expect my health to get worse	☐	☐	☐	☐	☐
11.4	My health is excellent	☐	☐	☐	☐	☐

Table 15.22 SF-12 health survey (standard)

INSTRUCTIONS: This questionnaire asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Please answer every question by marking one box. If you are unsure about how to answer, please give the best answer that you can.

1. *In general, would you say your health is:*

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

		Yes, Limited A lot	Yes, Limited A Little	No, Not At All
2.	**Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	☐	☐	☐

Table 15.22 (continued)

3. Climbing several flights of stairs ☐ ☐ ☐

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	YES	NO
4. **Accomplished less** than you would like	☐	☐
5. Were limited in the **kind** of work or other activities	☐	☐

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	YES	NO
6. **Accomplished less** than you would like	☐	☐
7. Didn't do work or other activities as carefully as usual	☐	☐

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Check the box which applies)

☐ Not at all ☐ Quite a bit
☐ Very mild ☐ Extremely ☐ Mild

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks.

	All of the Time	Most of the Time	A good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
9. Have you felt calm and peaceful	☐	☐	☐	☐	☐	☐
10. Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
11. Have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐

12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

☐	☐	☐	☐	☐
All of the Time	Most of the Time	Some of the Time	A little of the Time	None of the time

tion. Ware et al. [105] reported that the 12 selected items were able to reproduce at least 90 % of the variance in the physical and mental subscales of the SF-36 and therefore suggested that the population norms for the SF-36 can also be used as norms for the SF-12.

Disadvantages: The eight scale profiles provided by the SF-12 have fewer levels and provide less precise scores than the SF-36 since some subscales have just one or two items.

Sickness Impact Profile (SIP)

The SIP is a popular generic health status questionnaire that was initially developed in 1976 as a measure of perceived health [106]. The SIP contains 136 behavioral items covering 12 areas of behavior or performance: work, recreation, emotion, affect, home life, sleep, rest, eating, ambulation, mobility, communication, and social interaction. The questionnaire asks respondents to mark the statements that relate

to them on the day of administration. The wording of items and instructions focuses on performance rather than capacity. The SIP can be self-administered and requires 20–30 min to complete. The total score on the SIP ranges from 100 (poor health) to 0 (better health). The SIP can be scored by item, by broad domains (psychosocial health or physical), or by the 12 subscales [107]. A normal, healthy population will typically score a 2 or 3 on this instrument, whereas a stroke patient or terminally ill cancer patient may score in the mid-30s [108]. The developers of the SIP have designated a change of 5 % points as clinically meaningful. In a study of ALS patients [109], the patients gained between 7 and 8 % points on the SIP per year.

Advantages: The SIP has demonstrated high test-retest reliability ($r = 0.88–0.92$) [106]. The SIP can be applied to a large number of different patient populations since it is a comprehensive, global measure of health status. It has been widely used in the United States as an outcome measure. Since the questions have to be answered yes or no, it can be administered even to severely speech-impaired patients. It has been shown to correlate strongly with muscle strength measurements [109].

Disadvantages: The major disadvantage of the SIP is the time required for its completion. This is particularly relevant when the SIP is being used as a supplement to a more detailed disease-specific measure. The SIP19 ("mini-SIP") has also been validated and was used in the National ALS Care Database. It contains 19 of the 33 items within the Body Care and Movement and Home Management categories. These items were shown to correlate as well as with the MVIC megascore as the entire SIP score [110].

Another criticism of the SIP is its failure to detect changes over time in the same individuals [111]. This limitation is especially critical when considering use of this instrument in clinical trials in which quality of life is a secondary endpoint in evaluating the efficacy of a specific intervention or medication. Patients are continuously reminded of all the activities they can no longer perform, which can result in depressive symptoms and reluctance to complete subsequent SIP questionnaires. Most of the questionnaire examines what the patient can or cannot do, while only a very small portion actually assesses the patient's subjective state of well-being. Finally, when analyzing the responses, there is no way of knowing whether the columns left blank represent "no" replies or whether the respondent/interviewer omitted them deliberately or in error.

Short Form Individual Quality of Life Measure (SEIQoL)

The SEIQoL was developed to assess quality of life from the individual's perspective [112]. It is an interview-based instrument derived from a technique known as judgment analysis. An abbreviated form of the measure, the SEIQoL-direct weighting (SEIQoL-DW) [113], replaces the more cumbersome and time-consuming judgment analysis technique with a procedure for measuring the relative importance or weight to the respondent of selected life areas. The direct weighting apparatus consists of five interlocking, colored circular laminated disks that can be rotated around a central point to form a type of pie chart. The laminated disks are mounted on a larger disk, which displays a scale from 0 to 100, and from which the size of each colored segment can be read. Each colored segment is labeled with a life area selected by the respondent as being important to his or her quality of life. The respondent adjusts the disks until the size of each colored segment corresponds to the relative importance of the life area represented by that segment.

As with the full measure, the SEIQoL-DW is administered in a standardized semi-structured interview and takes 5–10 min to administer. Individuals are initially asked to name the five areas of life (cues) which are most important to the overall quality of their life. The respondent then rates their current status against a vertical visual analogue scale from "as good as could possibly be" to "as bad as could possibly be." The possible score range for each cue level is 0–100. The final step involves quantifying the relative contribution of each cue to the judgment of overall quality of life using the direct weighting instrument described above. The total value of all five weights sums to 100.

For making group comparisons, a global quality of life score can be calculated by multiplying the individual's current self-rating on each cue by the corresponding cue weight and summing the products across the five cues. The global quality of life score can range from 0 to 100. The score is a continuous measure which can be subjected to parametric statistical analyses.

Advantages: Administration of the SEIQoL-DW is relatively simple and requires minimal training [113]. The SEIQoL-DW was developed and validated against the full version of the SEIQoL and found to be a valid and reliable measure of explicit weighting policies for quality of life domains. Studies in healthy subjects have indicated that the measure is reproducible and has high criterion validity. This instrument has the capacity to evaluate an individual's quality of life on the basis of the areas of life that he or she considers to be important, quantifies current functioning in each of these personally nominated life areas, and weights their relative importance for that individual at that particular time in the course of their illness.

Disadvantages: While the weights derived from the direct weighting and the full judgment analysis are similar, some differences exist suggesting that the SEIQoL-DW may be measuring explicit weights about which the respon-

dent is consciously aware, whereas the full measure may include elements of judgment about which the respondent is unaware but which may have a bearing on their actual quality of life [113].

McGill Quality of Life Scale (MQoL)

The MQoL is a 20-item scale developed to measure quality of life in patients with severe, life-threatening illness. It has had specific applicability in patients at the end of life. The scale has been revised in several versions [114, 115].

The scale measures quality of life in four domains: physical, psychological, outlook on life, and meaningful existence. Of all the available subscores, meaningful existence (existential life) has been suggested as most valid due to the correlation with previously validated Spitzer Quality of Life Index.

Advantages: This is a simple, accepted, and reliable measure of quality of life, measured in a palliative care setting. Some cross-cultural validity has also been reported.

Disadvantages: The measure was validated in patients identified in palliative or "terminal" care settings. Evaluation of quality of life in chronically ill patients receiving aggressive symptomatic or adjunctive therapy may identify different issues than those captured in the population identified as receiving "end-of-life care."

Prior Clinical Applications in Neuromuscular Disease

The use of outcome measures in neuromuscular disease has varied widely. There has been significant variability in the use of available outcome measures, even within the confines of clinical trials testing patients with the same disease (Tables 15.23, 15.24, 15.25, and 15.26). Most clinical trials, testing potentially therapeutic agents in neuromuscular disease, have yielded negative results, despite laboratory data suggesting significant beneficial effects in animal models. The continued use of different outcome measures, in new combinations, for new trials, may be justified considering the lack of a "gold standard" against which significant clinical efficacy has been determined. We regularly validate new scales with established scales that appear to be sensitive to changes in a disease process, often despite the absence of data showing efficacy when those scales were originally established.

There is a clear need for newer, more sensitive outcome measures to detect small changes in disease progression. This has been highlighted by the importance of early diagnosis as a therapeutic advantage as well as the modest benefit of currently available therapeutic agents. In neuromuscular diseases such as ALS, the heterogeneity of disease presentation and progression also confounds the ability to select optimal outcome measures and favors new trials which are stratified based on more selective clinical criteria.

Table 15.23 Selected trials in amyotrophic lateral sclerosis

Name	Duration	Motor scale	Functional scale	Other
Creatine monohydrate in ALS: effects on strength, fatigue, respiratory status and ALSFRS [116]	9 months	MVIC fatigue	ALSFRS	Survival FVC SEI
Efficacy of minocycline in patients with amyotrophic lateral sclerosis: a phase III randomised trial [117]	4 month lead-in 9 month treatment	MMT	ALSFRS	FVC QoL Survival
A randomized, placebo-controlled trial of topiramate in amyotrophic lateral sclerosis [118]	12 months	MVIC	ALSFRS	FVC Grip strength Survival
Trial of celecoxib in amyotrophic lateral sclerosis [119]	12 months	MVIC	ALSFRS	Survival FVC CSF prostaglandin
Recombinant-methionyl human brain-derived neurotrophic factor (BDNF) given by intrathecal infusion to subjects with amyotrophic lateral sclerosis (phase III) [120]	Randomized 18 months	MMT	ALSFRS	Survival SIP Profile of mood states (POMS-Bi) Health resource utilization questionnaire
A controlled trial of recombinant methionyl human BDNF in ALS: the BDNF study group (phase III) [121]	Randomized 12 months		ALSFRS Schwab and England scale	Survival SF-36
Efficacy and safety of xaliproden in amyotrophic lateral sclerosis: results of two phase III trials [122]	Randomized 18 months Stratified	MMT	ALSFRS	Survival SIP Slow VC Ashworth spasticity scale Clinical global impression scale Symptom visual analog scales
Intracerebroventricular recombinant methionyl human glial cell line derived neurotrophic factor (r-metHuGDNF) for the treatment of patients with amyotrophic lateral sclerosis (unpublished)	Randomized 9 months Safety study	MVIC	ALSFRS 15′ walk PATA repetition	Survival FVC Ashworth spasticity scale
A controlled trial of recombinant-methionyl human BDNF (r-met HuBDNF) in ALS: Phase III [120]	Randomized trial 9 months		ALSFRS Walking speed PATA repetition	FVC Survival SIP
Placebo-controlled trial of gabapentin in patients with amyotrophic lateral sclerosis [123]	Randomized trial 9 months	MVIC (slope of arm megascore)	ALSFRS Walking speed	FVC SF-12 Ashworth Spasticity Scale
Effect of recombinant human insulin-like growth factor I (rhIGF-1) on progression of amyotrophic lateral sclerosis: a placebo-controlled study [124]	Randomized trial 9 months	Appel ALS rating scale (slope)		SIP FVC

(continued)

Table 15.23 (continued)

Name	Duration	Motor scale	Functional scale	Other
Insulin-like growth factor I in the treatment of amyotrophic lateral sclerosis: results of the European multicenter, double-blind, placebo-controlled trial [125]	Randomized trial 9 months	Appel ALS rating scale (change in score)		SIP FVC Clinical global impression scale
A placebo-controlled trial of recombinant human ciliary neurotrophic factor in amyotrophic lateral sclerosis [126]	Randomized trial 6 months	MVIC (combination megascore, arm and leg megascores)		SIP FVC
A double-blind placebo-controlled clinical trial of subcutaneous recombinant human ciliary neurotrophic factor (rhCNTF) in amyotrophic lateral sclerosis [90]	Randomized trial 9 months	MVIC	ALSFRS Schwab and England scale	FVC NIF Ashworth spasticity scale
Randomized, double-blind controlled trial of acetylcysteine in amyotrophic lateral sclerosis [127]	Randomized trial 12 months	MMT	Barthel Index	FVC Survival
Dose-ranging study of riluzole in amyotrophic lateral sclerosis [128]	Randomized trial 18 months	MMT Norris ALS scale		Survival FVC Clinical global impression scale
A controlled trial of riluzole in amyotrophic lateral sclerosis [129]	Randomized trial 573 days (median duration of placebo-controlled period)	MMT	"Functional status"	Survival FVC Clinical global impression scale
Selegiline is ineffective in a collaborative, double-blind, placebo-controlled trial for treatment of amyotrophic lateral sclerosis [130]	Randomized trial 6 months	Appel ALS rating scale (rate of change)		Survival
A clinical trial of verapamil in amyotrophic lateral sclerosis [131]	Randomized trial 9 months	MVIC (arm and leg megascores)		FVC (pulmonary megascore)
Controlled trial of nimodipine in amyotrophic lateral sclerosis [132]	Randomized trial 7 months	MVIC	"Timed upper and lower extremity functions"	FVC
Intravenous thyrotropin-releasing hormone in patients with ALS dose response and randomized concurrent placebo-controlled pilot studies [133]	Randomized 4 weeks	MVIC	Timed rise from seat Timed step onto footstool Timed walk	FVC MVV Exercise capacity tests Oxygen consumption at maximal exercise
Levamisole is ineffective in the treatment of ALS [134]	Crossover trial 12 months	Norris ALS Scale		
A double-blind controlled trial of bovine brain gangliosides in ALS [135]	Randomized trial 6 months	MVIC	Timed syllable repetition Timed swallow Arm and leg ADL scale Timed motor activities	FVC MVV Forced cough EMG NCS

Trial of immunosuppression in amyotrophic lateral sclerosis using total lymphoid irradiation [136]	Randomized trial 2 years	MVIC MMT	Timed swallow Timed gait Timed rise from seat Modified Kurtzke disability scale	FVC Survival
Branched-chain amino acids and amyotrophic lateral sclerosis [137]	Randomized 12 months	Appel ALS rating scale MMT Norris ALS scale		
Comparative efficacy and safety of intravenous and oral administration of a TRH analogue (Rx 77368) in motor neuron disease [138]	3–5 weeks	MMT Norris scale	Timed tongue protrusion Timed jaw movements Timed word repetition Timed swallowing	FVC MIP/MEP

Table 15.24 Selected trials in myopathy

Name	Duration	Motor scale	Functional scale	Other	Comments
Deflazacort in Duchenne dystrophy: study of long-term effect [139]	24 months	MMT	Timed gower Timed chair Timed stairs Timed gait		
Randomized, double-blind 6-month trial of prednisone in Duchenne's muscular dystrophy [91]	6 months	MMT	Timed stand from lying position Timed walk 30 ft Time to climb 4 stairs	MEP FVC MVV Lifting weights	Disability precluded determination of measurements
Pilot trial of albuterol in facioscapulohumeral muscular dystrophy [140]	3 months	MMT MVIC			MVIC detected difference;
Treatment of inclusion body myositis with IVIG [141]	6 months	MMT MVIC		Swallowing function	
Inclusion body myositis: treatment with intravenous immunoglobulin [142]	4 months	MMT	"Disability Score" based upon ability to ambulate	Creatine kinase	
The treatment of inclusion body myositis: a retrospective review and a randomized, prospective trial of immunosuppressive therapy [143]	6 months	MMT	ADL scale (adapted from Convery Assessment scale)	Creatine kinase	
Azathioprine with prednisone for polymyositis [144]	3 months	MMT		Creatine kinase Muscle biopsy (inflammatory score)	
A clinical trial of the safety and activity of recombinant human insulin-like growth factor 1/ recombinant human insulin-like growth factor binding protein 2 in myotonic dystrophy type 1 [145]	24 weeks	MMT MVIC Handgrip	Timed walk 30 ft Purdue pegboard 6-min walk	FVC) DEXA (lean body mass SIP	
a randomized, pilot trial of etanercept in dermatomyositis [146]	24 weeks	MMT MVIC	MITAX MYOACT	VAS (patient self-assessment and pruritus) SF-36 INQoL PFTs DEXA	

Table 15.25 Selected trials in neuropathy

Name	Duration	Motor scale	Functional scale	Other
Treatment of chronic inflammatory demyelinating polyneuropathy with intravenous immunoglobulin [147]	Retrospective review of 15 patients	MMT		Nerve conduction studies
Treatment of chronic inflammatory demyelinating polyneuropathy with interferon - 2a [148]	Open-label prospective study 6 weeks	MMT Grip dynamometry	Rankin disability	Nerve conduction studies Sensory score
A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barre syndrome [149]	Randomized trail 6 months	MMT	Neuropathy disability scale	
Randomized trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barre syndrome [150]	Randomized trial 48 weeks		Neuropathy Disability Scale Arm grade	FVC
Plasma exchange in polyneuropathy associated with monoclonal gammopathy of undetermined significance [151]	Randomized trial		Neuropathy disability scale	Nerve conduction studies Vibratory detection threshold
The Rochester diabetic neuropathy study [152]	Cross-sectional survey		Neuropathy Disability Score	Neuropathy symptom score Neuropathy symptom profile Nerve conduction studies Quantitative sensory exam Quantitative autonomic exam
Plasma exchange in chronic inflammatory demyelinating polyradiculoneuropathy [92]	6 weeks	Handgrip dynamometry Maximal finger pinch		Neurologic disability score MIP MEP Touch and vibratory thresholds Nerve conduction studies
Chronic inflammatory demyelinating polyneuropathy: clinical features and response to treatment in 67 consecutive patients with and without a monoclonal gammopathy [153]	Retrospective review of 67 patients	MMT	Rankin disability scale	Nerve conduction studies Sensory exam
Cyclosporin A in resistant chronic inflammatory demyelinating/ polyradiculoneuropathy [154]	Retrospective review of 17 patients		Disability scale (similar to Rankin)	Nerve conduction studies
Intravenous immune globulin (10 % caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomized placebo-controlled trial [155]	Randomized, double-blind, response-conditional crossover trial of 117 patients 48 weeks		INCAT disability score Rotterdam handicap scale	SF-36

Table 15.26 Selected trials in myasthenia gravis

Name	Duration	Motor scale	Functional scale	Other
Clinical trial of plasma exchange and high-dose intravenous immunoglobulin myasthenia gravis [64]	Randomized trial 15 days		Myasthenic Muscular Score	Acetylcholine receptor antibody titer
A randomized clinical trial comparing prednisone and azathioprine in myasthenia gravis. Results of the second interim analysis [156]	Randomized trial 60 months		Myasthenic Muscular Score Myasthenic Functional Score	
A clinical therapeutic trial of cyclosporine in myasthenia gravis [60]	Randomized, placebo-controlled		Quantitative Myasthenia Gravis Score	Acetylcholine receptor antibody titer Dosage of medications
Plasma exchange versus intravenous immunoglobulin treatment in myasthenic crisis [63]	Retrospective chart review		Myasthenia Gravis Severity Scale Functional Outcome	Ventilatory status
Randomized, controlled trial of intravenous immunoglobulin in myasthenia gravis [157]	Randomized, placebo-controlled double-blind trial 42 days		Myasthenia Gravis activity of daily living scale Quantitative Myasthenia Gravis Score	Repetitive stimulation Single fiber electromyography Acetylcholine receptor antibody titer Dosage of medications
A trial of mycophenolate mofetil with prednisone as initial immunotherapy in myasthenia gravis [158]	Randomized, placebo-controlled double-blind 12 weeks	MMT	Quantitative Myasthenia Gravis Score MG ADL Score	SF-36 Acetylcholine receptor antibody titer FVC
Comparison of IVIG and PLEX in patients with myasthenia gravis [159]	Randomized trial for 60 days		Quantitative Myasthenia Gravis Score	VAS (patient assessment of benefit) MGFA classification MG quality of life SFEMG Jitter %Decrement on RNS Acetylcholine receptor antibody titer

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Physical Management of Patients with Neuromuscular Diseases

16

John R. Bach and Priya Bolikal

Interventions to Optimize Habilitation

Prevention of Joint Contractures

The physical/orthopedic treatment goals for neuromuscular diseases (NMD) are to maintain the balance of strength at each joint, prevent contractures, prolong the ability to walk safely with minimal or no bracing, and maximize arm function. There is often an imbalance of strength at major joints. When this imbalance is severe, shortening of skin, muscle, tendon, and ligament occurs which, over time, results in joint contractures.

Lower Extremities

Stretching

Loss of the ability to walk results from muscle weakness and from loss of articular range-of-motion (ROM). ROM is largely lost due to an imbalance of strength at the weight bearing articulations. One approach to preventing and managing lower extremity contractures is to perform ROM and joint stretching. ROM is performed to the point of maximal stretch or a few degrees past the point of discomfort for several minutes a few times per day on joints with or prone to contractures.

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The most important muscle groups to stretch for most NMD patients are the ankle plantarflexors, the hamstrings, and the hip flexors. Occupational and physical therapists often provide education and guidance for individualized home therapy programs. There is indirect evidence that the regular use of stretching has prolonged the ability to walk for many children with NMD. Today, children with DMD appear to be able to walk longer than children managed in the 1950s before there was as much emphasis on ROM and stretching [1]. Although patients with most NMDs can benefit from daily ROM throughout life, no amount of ROM can entirely prevent contractures when muscle strength imbalance is severe.

Late Surgery

Once a contracture decreases limb function, the only way to restore full or functional ROM is to surgically stretch or "release" the joint's tightened soft tissues. The most commonly used surgical protocol to reverse lower limb contractures in NMD is one that was described for an 11-year-old "Duchenne" patient in 1845 and was redescribed in 1959 [2]. It includes the surgical release of tight flexor muscles at the hips, knees, and ankles (the Achilles tendon) and the release of the iliotibial bands at the knees at the point when the patient begins falling frequently. Following surgery, long leg bracing is required. It can also be helpful to transfer the tibialis posterior to insert into the dorsum of the foot (Fig. 16.1). This converts a plantarflexor into a dorsiflexor. This not only increases the ROM of the ankle but also balances the strength at the ankles [1].

In the 1970s, up to 40 % of MDA clinics [3] used late surgical interventions as patients "were about to lose their independent walking". Besides requiring long leg braces, this late surgical approach necessitates extensive postoperative physical therapy. Ambulation is not always prolonged in this manner; however, at times it can be prolonged for up to 5 years. Because it is not possible to predict who will benefit, and because bracing and postoperative therapy are very expensive and cumbersome, the use of this approach has fallen off over the years and is now very uncommon in the USA.

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Early Surgery

Lower limb musculotendinous releases have been performed as prophylactic rather than corrective measures for Becker, Emery-Dreifuss, DMD, and other myopathies and in SMA types 3 and 4. Patients with these conditions often have a similar pattern of muscle weakness and contractures. Early surgery can eliminate the need for ongoing physical therapy and splinting and help preserve the strength of the weaker muscles by eliminating the overdominance of their antagonists [4]. Early surgical intervention is also safer and better tolerated than late approaches. It is performed when contractures begin to appear and patients have increasing difficulty (take longer) in rising from a seated position on the floor. Iliotibial band contractures are measured by the angle that the legs take with respect to the sagittal plane with the patient supine and the legs dangling. Tibialis posterior muscle strength is examined by applying pressure laterally against inversion of the externally rotated plantar flexed foot. The interventions include wide resection of the fascia lata and iliotibial bands as well as release of muscle tendons at the hips, lateral thighs, knees, and heel cords (Fig. 16.2). People with greater hip and knee strength and minor hip or knee contractures may require only Achilles tendon lengthening and possibly tibialis posterior transfers without tendon releases at the hips and knees. Early surgical intervention can decrease a vicious cycle of weakness, muscle tightness, contracture, and abstinence from walking that leads to deconditioning and further weakness. With early intervention, free walking is permitted by the second post-op day in ankle casts, and only brief outpatient or home physiotherapy is required. Continued ambulation is free of bracing and is prolonged by a mean of 1.25 years for DMD patients and longer for patients with less rapidly progressive conditions [5].

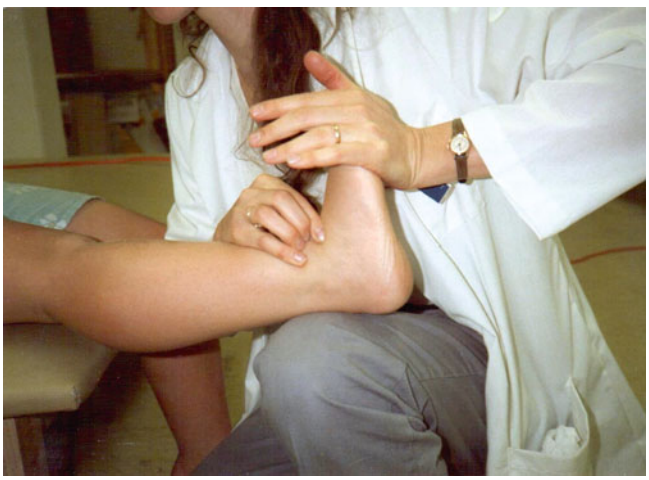

Fig. 16.1 Examining passive ankle dorsiflexion range-of-motion

Upper Extremity

Arm and hand contractures begin to develop early in pediatric NMD. Finger deformities begin by age 8 for children with DMD; they begin earlier in children with SMA or other early onset disorders. They also occur in adults with slowly progressive conditions. Ultimately, when shoulder and elbow contractures become greater than 25°, most people perceive them as hampering function, detracting from appearance, and being associated with pain and discomfort [6].

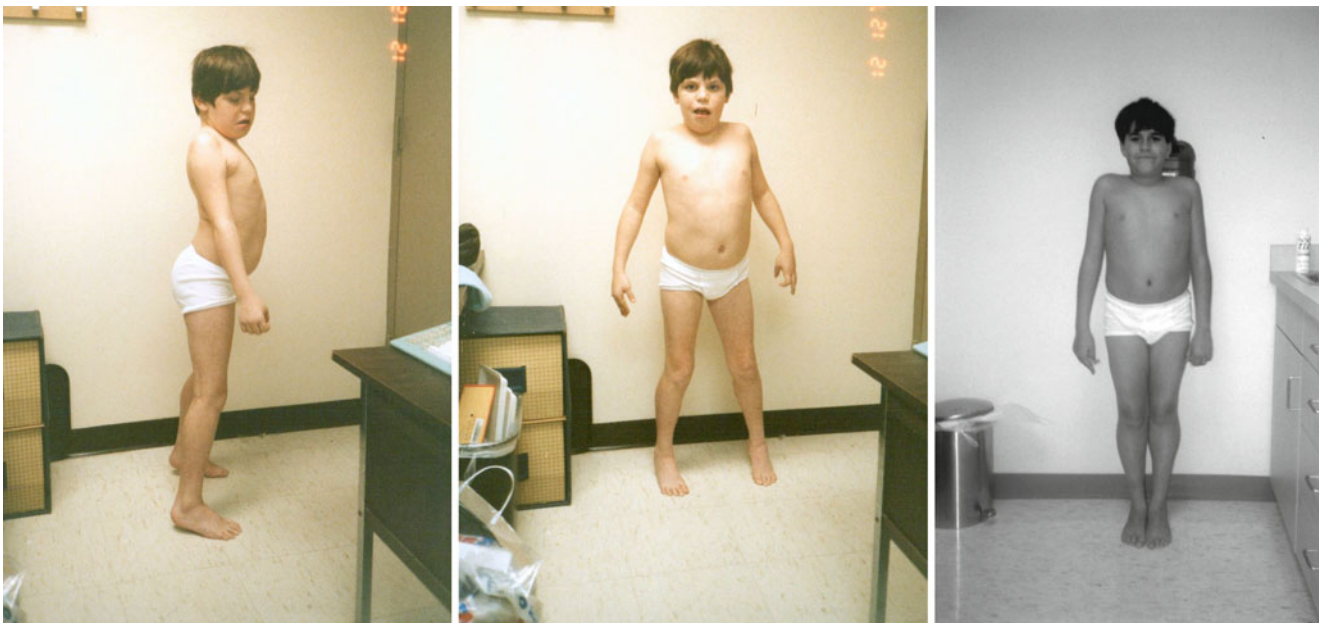

Fig. 16.2 Child with Duchenne muscular dystrophy exhibiting characteristic hip, knee, and ankle musculotendinous contractures before and their relief with surgical correction

Although an early vigorous upper extremity ROM program has been advocated, there has been no attempt at studying the effects of ROM, stretching, positioning, bracing, or surgery on the development of arm and hand contractures. At this time it may be most appropriate to recommend arm and hand ROM and stretching several times a day in an effort to prevent soft tissue contractures. The fact that a multidisciplinary approach of physical therapy, splinting, and surgery can be effective in ameliorating lower limb contractures [1] implies that effective treatment strategies may be possible for upper limb contractures as well.

Splinting and Casting

Splinting can be used to maximize joint function and hamper contracture development. Resting splints for the lower limbs and the ankles are commonly used during sleep and when the patient is confined to a wheelchair. Resting hand splints can also be used at night to impede finger and wrist contractures and during the daytime for patients without functional active movements. Resting splints provide a sustained stretch to the joint while holding it in a neutral position. They are also used after surgical releases of soft tissue contractures.

"Foot drop" is an almost ubiquitous complication of NMD. Ankle foot orthoses (AFOs) can be used to stabilize the ankle. Since it is difficult to stand from a chair with an AFO that holds the ankle in a fixed position (as it limits knee bending), dynamic components can be used. Dynamic splints permit increased movement and provide force to the movable body parts, allowing more functional use of the extremity. Static AFO's are used for individuals with flaccid ankles and little ambulation, whereas spring-loaded devices can be employed to assist ankle dorsiflexion without restricting plantarflexion.

Patients often resist using splints during sleep. Splints can be expensive and unattractive, can hamper bed mobility and sleep comfort, and may not prevent the progression of contractures. When used by growing children, fabrication of full-length lower limb splints also needs to be repeated about every 6 months.

Casting can provide a sustained stretching of the joint at the maximal angle tolerated. Casts can be reapplied every few days to increase the angle and progressively stretch the joint. This procedure is known as serial casting. Without continuous casting, however, contractures will still progress.

Standers can give support to the trunk, hips, knees, and ankles to both stretch lower extremity contractures and provide weight bearing to impede osteoporosis. These can be especially useful for children who are unable to operate standing motorized wheelchairs.

Prevention of Severe Spinal Deformity

Weak paraspinal muscles result in collapse of the spinal column and deformity of the chest. This results in scoliosis and kyphosis. For children with NMDs, spinal deformities progress rapidly once muscle weakness prevents a child from walking, and progression continues throughout life. Left untreated or braced, the spine can collapse to curves of over 100° (Fig. 16.3). Although its prevention usually yields no benefits on lung function and may even decrease vital capacity (VC) by fixing the rib cage [7], severe scoliosis can restrict heart functioning, cause intolerable unilateral back, buttock, and leg pressure, cause painful lumbar radiculopathy, necessitate expensive custom seating systems that are never very satisfactory, and can render ineffective, otherwise practical ventilatory aids like the intermittent abdominal pressure ventilator (IAPV).

Some physicians do not consider surgical options because they mistakenly think that the child has little hope of long-term survival. Surgeons often use interim bracing while applying the 40° criterion used for surgically managing idiopathic scoliosis. For children with DMD, by the time the curve reaches 40°, the VC may be below 23 % [8] and most surgeons would be reluctant to operate without prophylactic tracheotomy. This is usually refused, and because results of surgical correction are rarely curative, 75 % of scoliotic DMD patients and others with NMDs never undergo vital scoliosis correction surgery [3, 8].

The greater the degree of curvature, the less likely it is correctible. Thus, early surgery can provide a full correction and minimize cardiopulmonary risks. Late surgery, before patients have lost the ability to sit, however, can still be done safely even for patients with little or no measurable VC when using the respiratory principles noted in this chapter [7]. For people with normal muscle strength, a brace can decrease the rate of development of scoliosis because it acts as a reminder to use the paraspinal muscles to straighten the spine. Bracing does not slow scoliosis development in people with NMD because these patients cannot move away from the braces' pressure points. Although bracing does not impede curve development in children with infantile SMA and others whose scoliosis begins in early childhood, it may help maintain more curve flexibility for better surgical correction. Therefore, bracing is reasonable, at least until age 6, to allow for growth of the spine, at which point, spinal instrumentation with fusion is first justified [9–11].

There are now a variety of spinal instrumentation approaches leading to spinal fusion for correction of scoliosis. Following surgical intervention the patient is usually discharged within 4 or 5 days. To prevent respiratory complications, patients are taught noninvasive ventilation and mechanically assisted coughing (MAC) before surgery. By using these aids in conjunction with oximetry feedback

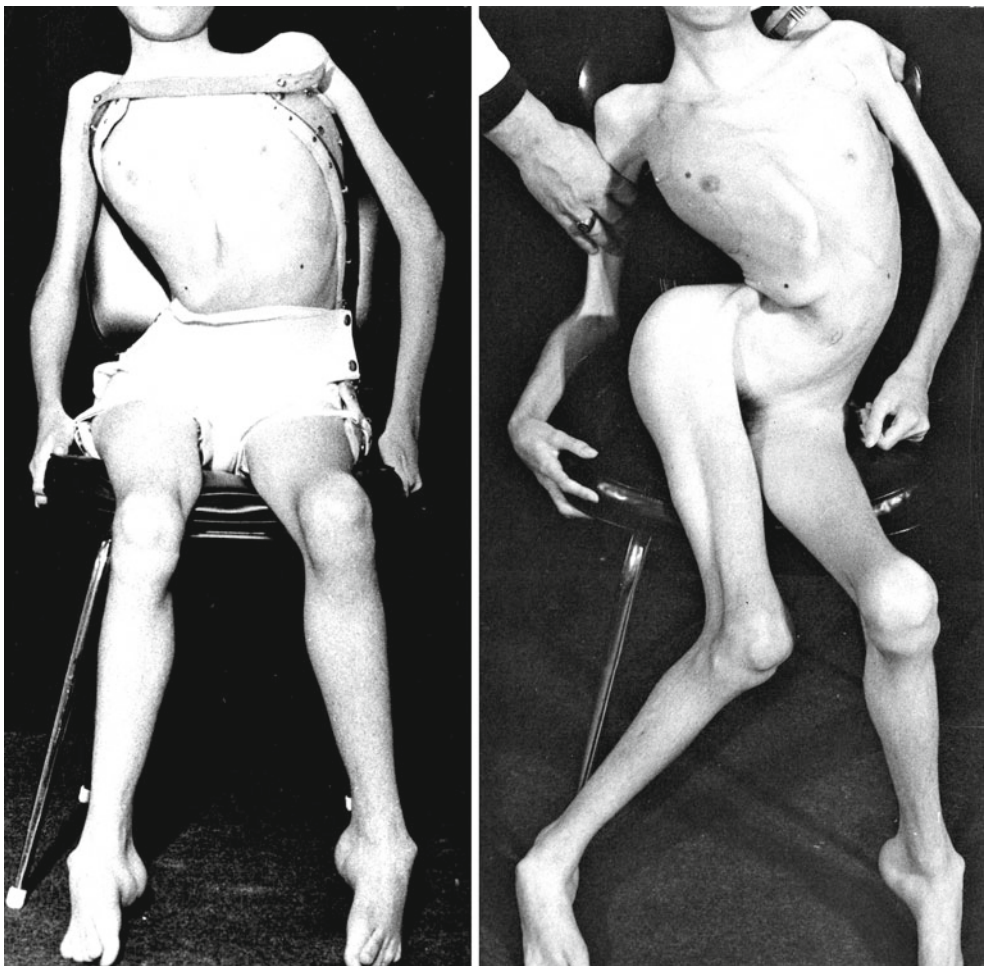

Fig. 16.3 Thoracolumbar bracing has no effect on preventing scoliosis for people with Duchenne muscular dystrophy (Republished with appreciation from Rideau et al. [4])

(to be described), they can be extubated as soon as narcotics can be discontinued, regardless of whether or not they are able to breathe.

Extremity Exercise

The muscle groups with greater than antigravity strength can be strengthened by resistance exercise training. Even with strengthening, however, their subsequent rate of strength loss, with or without continued exercise, may be even greater than without exercise. Muscles with less than antigravity strength cannot be strengthened with exercise and tend to be the muscles that lose function. Strengthening exercise does not appear to be warranted, therefore, for these muscles [12]. Nevertheless, although no harm has been demonstrated as a result of activity and exercise, patients should not be forced to exercise by overzealous parents, for example. Vignos advised patients to undertake 2–3 h/day of standing, walking, or swimming as long as they were capable and felt rested after a night's sleep [13]. This ancient recommendation is still appropriate today. All patients should be encouraged to keep as active as possible with activities they enjoy while avoiding muscle strain.

The use of nocturnal noninvasive intermittent positive pressure ventilation (NIV) while exercising has been shown to increase exercise tolerance and slow motor decline in post-poliomyelitis survivors and ALS patients with severe respiratory muscle dysfunction [14].

Respiratory Muscle Exercise

There is evidence that the use of inspiratory muscle resistive exercises can improve inspiratory muscle endurance for patients with respiratory muscle impairment. Endurance is considered to be improved when patients can breathe at 30–90 % of maximum voluntary ventilation or against greater pressures for longer periods of time. This can only occur, however, if the patient's VC is greater than 30 % of predicted normal when beginning the exercises [15]. A study of post-polio nocturnal ventilator users in which nine out of ten had VCs greater than 30 % of normal demonstrated improved endurance and generally claimed improved functioning

despite lack of better total body endurance [16]. Despite this, there is no evidence that inspiratory resistive exercise can improve VC, delay the need for ventilator use, or decrease the risk of respiratory failure during intercurrent chest infections. Indeed, patients often begin to require inspiratory muscle aids (NIV) once their VCs diminish below 30 % [17]. The failure to demonstrate respiratory benefits is in large part because episodes of respiratory failure in these patients are primarily due to expiratory (cough) muscle weakness rather than inspiratory dysfunction [18], for which there has been little attention. Therefore, it is unclear how inspiratory muscle strengthening might translate into improved clinical outcomes since respiratory failure is usually caused by ineffective coughing [18].

Respiratory Muscle Aids to Avert Tracheostomy and Prolong Survival

Pathophysiology

Respiratory function plateaus at age 19–20 then decreases by 1–1.2 %/year. Patients with neuromuscular conditions have VCs that often plateau earlier and can come to require continuous ventilatory support.

Ventilatory insufficiency is defined by hypercapnia in the presence of a normal arterial-alveolar (A-a) gradient. This hypercapnia is not caused by intrinsic lung disease or irreversible upper or lower airway obstruction, as in COPD. These patients can have airway obstruction from bronchial mucous plugging that causes an elevated A-a gradient. However, the mucous plugging is reversible by using expiratory (cough) aids. Symptomatic hypercapnic patients benefit from the use of noninvasive ventilation for at least part of the day and, more often, overnight. With progressive inspiratory muscle weakness, ventilator-free breathing ability is eventually lost.

Ventilatory muscle failure is defined by the inability of the inspiratory and expiratory muscles to sustain one's respiration without resorting to ventilator use. Ventilatory insufficiency leading to failure can be nocturnal only resulting from diaphragm dysfunction with the patient unable to breathe when supine or can result from a lack of central ventilatory drive or from severe generalized respiratory muscle dysfunction. Many patients with ventilatory insufficiency survive for years without ventilator use at the cost of orthopnea and increasing hypercapnia, associated symptoms and dangers, and a compensatory metabolic alkalosis that depresses central ventilatory drive. The alkalosis allows the brain to accommodate to hypercapnia without overt symptoms of acute ventilatory failure. Hypercapnic patients not using NIV, and especially those receiving supplemental oxygen, develop increasingly severe hypercapnia that eventually results in coma from carbon dioxide narcosis and ventilatory arrest. When symptomatic hypercapnic patients are treated with NIV, blood gasses normalize and the alkalosis resolves as the kidneys excrete excess bicarbonate ions. Because of the need to take deeper breaths to maintain normal $PaCO_2$ and blood pH levels, a nocturnal-only ventilator user can become dyspneic when discontinuing ventilator use in the morning and may require gradually decreasing NIV. Such patients eventually require NIV for increasing periods during the day until continuously NIV dependent. Some patients with ventilatory muscle failure and no measurable VC with their respiratory muscles use only a nocturnal aid and rely on glossopharyngeal breathing (GPB) to ventilate their lungs during daytime hours.

For patients with primarily ventilatory impairment, respiratory morbidity and mortality are a direct result of respiratory muscle dysfunction and can be avoided by assisting respiratory muscles. This is possible only if bulbar muscle dysfunction is not so severe that continuous aspiration of saliva causes the SpO_2 to remain below 95 %. Such patients develop essentially irreversible upper-airway obstruction and require tracheostomy tubes to protect the airway. In general, this scenario occurs for bulbar amyotrophic lateral sclerosis (ALS) patients who have lost the ability to speak and for a few other patients with NMD.

Epidemiology

Surveys in the USA, Western Europe, and Japan indicate that the use of home mechanical ventilation is increasing rapidly [19]. Most people who appear to require more than nocturnal ventilator use, however, and those who have difficulty weaning when intubated during chest infections generally undergo tracheotomy. This usually occurs because of lack of awareness of how to introduce physical medicine aids. Likewise, 90 % of episodes of acute respiratory failure for young patients with NMD occur as a result of inability to generate effective cough peak flows during otherwise benign upper respiratory infections [18]. These episodes are usually avoidable [20]. Respiratory muscle dysfunction amenable to treatment by respiratory muscle aids occurs in many people with the diagnoses listed in Table 16.1.

What Are Physical Medicine Respiratory Muscle Aids?

Inspiratory and expiratory muscle aids are devices and techniques that involve the manual or mechanical application of forces to the body or intermittent pressure changes to the airway, to assist inspiratory or expiratory muscle function. The devices that act on the body include body ventilators that create pressure changes around the thorax and abdomen.

Table 16.1 Conditions with chronic alveolar hypoventilation manageable with respiratory muscle aids

Myopathies:
Congenital, metabolic, inflammatory, and mitochondrial myopathies, myopathies of systemic disease such as carcinomatous myopathy, cachexia/anorexia nervosa, medication and ICU-associated, muscular dystrophies such as Duchenne and Becker, limb-girdle, Emery-Dreifuss, facioscapulohumeral, congenital, and myotonic
Endocrine related as with hypothyroidism, acromegaly
Mixed connective tissue disease and arthrogryposis
Anterior horn cell disorders:
Spinal muscular atrophies, motor neuron diseases, poliomyelitis
Neuropathies:
Hereditary sensory motor neuropathies
Familial hypertrophic interstitial polyneuropathy
Phrenic neuropathies
Guillain-Barre syndrome

Negative pressure applied to the airway during expiration assists coughing, just as positive pressure applied to the airway during inhalation (NIV) assists the inspiratory muscles. Continuous positive airway pressure (CPAP) does not assist ventilation and is not useful for patients with primarily ventilatory impairment.

Patient Evaluation

Patients with diminished ventilatory reserve who are able to walk commonly complain of exertional dyspnea. Eventually, morning headaches, fatigue, sleep disturbances, and hypersomnolence develop [17]. For wheelchair users, symptoms may be minimal, except during intercurrent respiratory infections when anxiety, inability to fall asleep, and dyspnea become problems.

The patient is observed for increased respiratory rate, decreased depth, or irregularity of breathing. Paradoxical breathing or asymmetric movement of the abdomen or thorax is often present. Hypophonia, nasal alae flaring, use of auxiliary respiratory musculature, peribuccal or generalized cyanosis, flushing or pallor, hypertension, difficulty controlling airway secretions, dysphagia, regurgitation of fluids through the nose, nasality of speech, cor pulmonale, confusion, and fluid retention may all be signs of ventilatory insufficiency.

Maximum inspiratory and expiratory pressures generated at the mouth correlate best with inspiratory and expiratory muscle strength. Maximum voluntary ventilation gauges respiratory muscle endurance. The VC gives an indication of both of these parameters and is simple, easy to measure, objective, and very reproducible. Because hypoventilation is often worse during sleep, the supine VC is a better indicator of ventilatory dysfunction than the sitting VC. Spirometry is also useful for monitoring progress with GPB and air stacking. A patient's maximum insufflation capacity (MIC) is determined by giving the patient the largest volume of air that can be held with a closed glottis from a manual resuscitator or a portable ventilator that is volume cycled. The patient then expels the air into the spirometer. Patients who learn GPB can often air stack consecutive GPB gulps to or beyond the MIC [21]. A nasal interface or lip seal can be used for air stacking when the lips are too weak for effective air stacking via the mouth (Fig. 16.4).

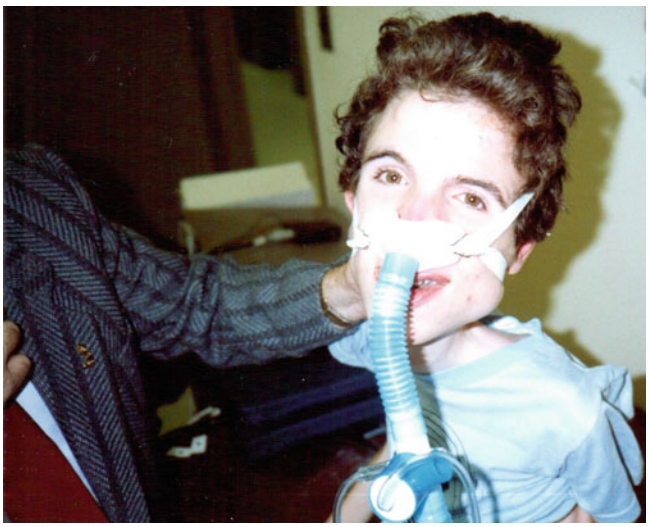

Fig. 16.4 Patient with Duchenne muscular dystrophy, continuously ventilator dependent for 7 years, air stacking via nasal interface

Cough peak flows (CPF) are measured using a peak flow meter (Access Peak Flow Meter, Healthscan Products Inc., Cedar Grove, NJ). CPF, assisted or unassisted, of 160 L/m are the minimum needed to cough effectively [22], and this is the best indicator for tracheostomy tube removal irrespective of remaining pulmonary function (Fig. 16.5) [23]. Indeed, about 40 % of patients with ALS can survive despite continuous ventilator dependence using NIV [24]. Patients with VCs less than 1,500 mL have assisted CPF measured from a maximally stacked volume of air and with an abdominal thrust delivered simultaneously with glottic opening.

For the stable patient without intrinsic pulmonary disease, arterial blood gas sampling is unnecessary. Besides the discomfort, 25 % of patients hyperventilate as a result of anxiety or pain during the procedure [22]. Noninvasive continuous blood gas monitoring, including capnography and oximetry, yields more useful information, particularly during sleep.

Nocturnal noninvasive blood gas monitoring can be performed for patients with diminished supine VC, especially for those with rapidly evolving conditions and symptoms suggestive of hypoventilation. The oximeter and the capnograph, which measures end-tidal pCO_2, must be capable of

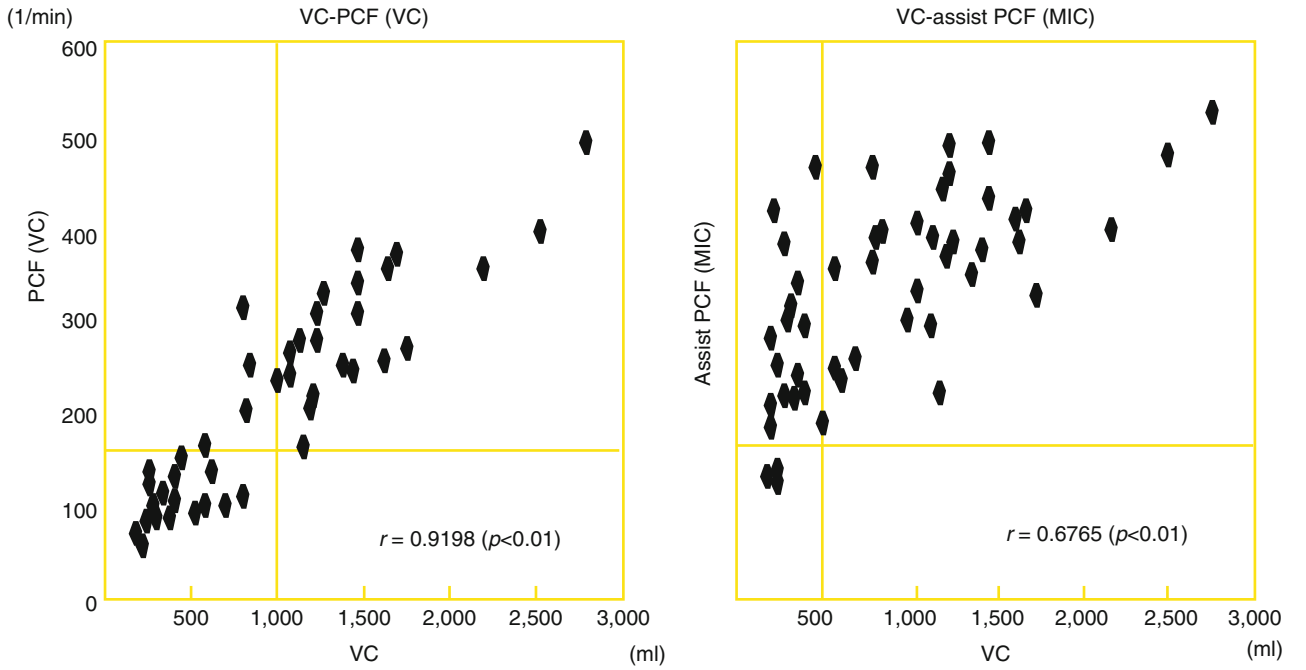

Fig. 16.5 Peak cough flows increase from ineffective levels (below 160 L/m) to effective levels by maximally insufflating the patient and then providing an abdominal thrust (With permission and appreciation to Dr. Yuka Ishikawa, Department of Pediatrics Yakumo Byoin National Sanatorium, Yakumo-cho Hikkarclo)

summarizing and printing out the data [17]. These studies are most conveniently performed in the home. When symptoms are obvious, a trial of nocturnal NIV rather than nocturnal end-tidal CO_2 and oximetry monitoring is appropriate. Any symptomatic patient with decreased VC, multiple nocturnal oxyhemoglobin desaturations below 95 %, and elevated nocturnal $PaCO_2$ requires treatment for nocturnal hypoventilation.

For symptomatic patients with normal VC, an unclear pattern of oxyhemoglobin desaturation, and no apparent carbon dioxide retention, sleep disordered breathing is suspected. This is particularly true when loud high-pitched snoring, interrupted breathing, and hypersomnolence dominate the picture [25]. These patients undergo polysomnography and are considered for CPAP therapy.

The Intervention Objectives

The intervention goals are to maintain lung and chest-wall compliance, to promote normal lung and chest-wall growth for children, to maintain normal alveolar ventilation around the clock, and to maximize CPF. The long-term goals are to avert episodes of acute respiratory failure during intercurrent chest infections, avoid hospitalizations, and prolong survival without resorting to tracheotomy. All goals can be attained by evaluating, training, and equipping patients in the outpatient setting and at home.

Goal One: Maintain Pulmonary Compliance, Lung Growth, and Chest-Wall Mobility

Pulmonary compliance is lost because the ability to expand the lungs to the predicted inspiratory capacity is lost as the VC decreases. As the VC decreases, the largest breath that one can take can only expand a small portion of the lungs. Like limb articulations and other soft tissues, regular range-of-motion (ROM) is required to prevent chest-wall contractures and lung restriction [26]. This can only be achieved by providing deep insufflations, air stacking, or nocturnal NIV. The extent to which the MIC is greater than the VC predicts the capacity of the patient to be maintained by noninvasive rather than tracheostomy ventilatory support [22]. This is because the MIC-VC difference, like assisted CPF, is a function of bulbar muscle integrity. Patients who cannot close the glottis and, therefore, cannot air stack must be passively insufflated using a Cough Assist™ (Philips-Respironics International Inc., Murrysville, Pa) or pressure-cycling ventilator at pressures of 40–70 cm H_2O. The maximum passive insufflation volume can be termed the "Lung Insufflation Capacity" or LIC [27].

The primary objectives in using air stacking or maximum insufflations for lung and chest-wall ROM are to increase the VC and MIC, to maximize CPF (see Fig. 16.5), to maintain or improve pulmonary compliance, to prevent or eliminate atelectasis, and to master NIV. In 282 spirometry evaluations of NMD patients for VC, MIC, and LIC, the authors found

mean values of 1,131 ± 744 mL, 1,712 ± 926 mL, and 2,069 ± 867 mL, respectively [27]. With the higher lung volumes by air stacking, assisted CPF were 4.3 ± 1.7 L/s by comparison with 2.5 ± 2.0 L/s unassisted. The deeper lung volumes by air stacking also permitted patients to raise voice volume as desired.

Because any patient who can air stack is also able to use NIV, if such a patient is intubated for respiratory failure, he or she can be extubated directly to continuous NIV regardless of whether the patient has regained any breathing tolerance. Before patients' VCs decrease to 70 % of predicted normal, they are instructed to air stack 10–15 times at least two or three times daily. Thus, the first respiratory equipment that is prescribed for patients with ventilatory impairment is often a manual resuscitator. In general, because of the importance of air stacking, NIV is provided via portable ventilators volume cycling on assist/control mode rather than by pressure-limiting devices.

Infants cannot air stack or cooperate to receive maximal insufflations. All babies with SMA type 1, infants with SMA type 2, and others with infantile NMD who have paradoxical chest-wall movement require nocturnal NIV to prevent pectus excavatum and promote lung growth as well as for ventilatory assistance [28]. In addition to nocturnal aid, deep insufflations can be provided via oral-nasal interfaces and manual resuscitators by timing the delivery of air to the child's breathing phases. Children can become cooperative with deep insufflation therapy by 14–30 months of age.

Goal Two: Continuously Maintain Normal Alveolar Ventilation by Assisting Inspiratory Muscles as Needed

1. The Nocturnal Inspiratory Muscle Aids
   (a) Negative Pressure Body Ventilators (NPBVs)

   The most common NPBV used today is the chest-shell ventilator. However, it is only practical for use during sleep and, like all negative pressure body ventilators and phrenic/diaphragm pacing, causes severe obstructive sleep apneas. The latter can necessitate continuous positive airway pressure or a tracheostomy, so there are few, if any, indications for the use of negative pressure body ventilators today. These devices also become less effective with aging and decreasing pulmonary compliance [29].

   (b) Noninvasive Intermittent Positive Pressure Ventilation (NIV)

   For the great majority of patients, NIV can be introduced in the clinic or home setting. It can be noninvasively delivered via mouthpieces, nasal and oral-nasal interfaces for nocturnal ventilatory support. Mouthpiece and nasal IPPV are open systems that require the user to rely on central nervous system reflexes to prevent excessive insufflation leakage during sleep; thus, it is critical to avoid supplemental oxygen and sedative medications [17, 30].

   There are numerous commercially available nasal interfaces (CPAP masks). Each interface design applies pressure differently to the paranasal area. One cannot predict which model will be most effective and preferred by any particular patient. Nasal bridge pressure and insufflation leakage into the eyes are common symptoms with several of these generic models. Such difficulties can be avoided by using nasal prong systems or custom designs [17, 31, 32]. No patient should be offered and expected to use only one nasal interface.

   Excessive insufflation leakage can be avoided by switching to the use of lip seal-nasal prong or nasal prong-oral systems that provide an essentially closed system of NIV support. Such interfaces deliver air via mouth and nose during sleep with less strap pressure than is required for oro-nasal (anesthesia) masks. This optimizes skin comfort and minimizes air (insufflation) leakage.

2. The Daytime Inspiratory Muscle Aids
   (a) Body Ventilators

   The intermittent abdominal pressure ventilator (IAPV) involves the intermittent inflation of an elastic air sac that is contained in a corset or belt worn beneath the patient's outer clothing (Fig. 16.6) (Exsufflation Belt™, Respironics Inc., Murrysville, PA). The sac is cyclically inflated by a positive pressure ventilator. Bladder inflation moves the diaphragm upward to assist in expiration. During bladder deflation, gravity causes the abdominal contents and diaphragm to return to the resting position, and inspiration occurs passively. A trunk angle of 30° or more from the horizontal is necessary for it to be effective.

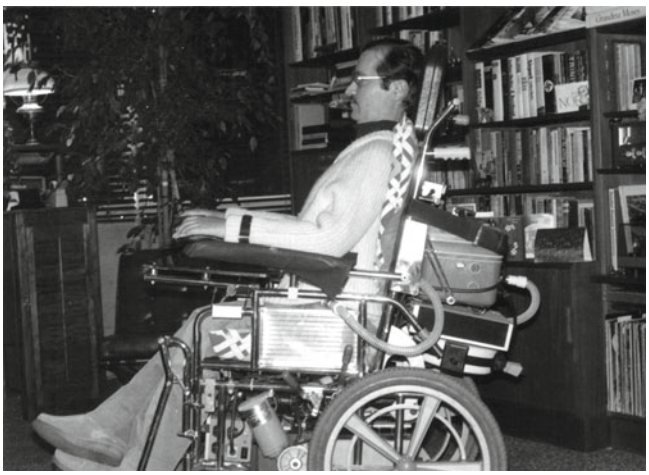

Fig. 16.6 A post-polio survivor with no measurable vital capacity since 1952 using an intermittent abdominal pressure ventilator (Exsufflation Belt™, Respironics International Inc., Murrysville, PA) during daytime hours and lip seal IPPV nightly since 1956. The air bladder inside the girdle is connected to the ventilator circuit (seen here), then the girdle is placed under the clothes and over the patient's abdomen

Fig. 16.7 Forty-eight-year-old man with Duchenne muscular dystrophy who has used 24-h mouthpiece IPPV for 25 years, now with no measurable vital capacity. The mouthpiece is fixed adjacent to the mouth by a flexible metal support arm (microphone holder)

If the patient has any inspiratory capacity or is capable of GPB, he or she can add volumes of air autonomously to that taken in mechanically. The IAPV generally augments tidal volumes by about 300 mL, but volumes as high as 1,200 mL have been reported [30]. Patients with less than 1 h of breathing tolerance usually prefer to use the IAPV rather than use noninvasive IPPV during daytime hours.

(b) Mouthpiece NIV

Mouthpiece NIV is the most important method of daytime ventilatory support. Some patients keep the 15-mm angled mouthpiece between their teeth all day. Most patients prefer to have the mouthpiece held near the mouth. A metal clamp attached to a wheelchair can be used for this purpose (Fig. 16.7), or the mouthpiece can be fixed onto motorized wheelchair controls—most often, sip and puff, chin, or tongue controls. The ventilator is set for large tidal volumes, often 1,000–2,000 mL. The patient grabs the mouthpiece with his mouth and supplements or substitutes for inadequate autonomous breath volumes. The patient varies the volume of air taken from ventilator cycle to ventilator cycle and breath to breath to vary speech volume and cough flows as well as to air stack to fully expand the lungs.

To use mouthpiece IPPV effectively and conveniently, adequate neck rotation and oral motor function are necessary to grab the mouthpiece and receive IPPV without insufflation leakage. To prevent the latter, the soft palate must move posteriorly and caudally to seal off the nasopharynx. In addition, the patient must open the glottis and vocal cords, dilate the hypopharynx, and maintain airway patency to receive the air. These normally reflexive movements may require a few minutes to relearn for patients who have been receiving ventilation via a tracheostomy tube.

(c) Nasal Intermittent NIV

Because patients prefer to use mouthpiece NIV or the IAPV for daytime use [33, 34], nasal NIV is most practical for nocturnal use. Daytime nasal NIV is indicated for infants and for those who cannot grab or retain a mouthpiece because of oral muscle weakness, inadequate jaw opening, or insufficient neck movement. Nevertheless, 24-h nasal NIV can be a viable and desirable alternative to tracheostomy, even for some patients with severe lip and oropharyngeal muscle weakness [17]. Nasal NIV users learn to close their mouths or seal off the oropharynx with their soft palates and tongues to prevent oral insufflation leakage.

Complications of Noninvasive Intermittent Positive Pressure Ventilation

Besides orthodontic deformities and skin pressure from the interface, other potential complications include very infrequent allergy to the interface, dry mouth, eye irritation from air leakage, nasal congestion, sinusitis, nose bleeding, gum discomfort and receding from nasal interface, maxillary flattening in small children, aerophagia [35], and, as for invasive ventilation, possible barotraumas although this is rare in NMD patients. Two cases of pneumothorax in over 1,000 ventilator users and over 5,000 patient-ventilator use years have been reported [36]. In addition, occasional patients experience claustrophobia. Proper interface selection eliminates or minimizes these difficulties.

Abdominal distention tends to occur sporadically in NIV users. The air usually passes as flatus once the patient gets up or is placed into a wheelchair in the morning. When severe, it can cause increased ventilator dependence. A gastrostomy may be needed to "burp" out the air.

Goal Three: Maximize Cough Flows

1. Why Are Expiratory Muscle Aids Needed?

Bulbar, inspiratory, and expiratory muscles are needed for effective coughing. The latter are predominantly the

abdominal and intercostal muscles. Clearing airway secretions and airway mucus can be a continual problem for patients who cannot swallow saliva or food without aspiration. For patients with respiratory muscle dysfunction and functional bulbar musculature, it becomes a problem during chest infections, following general anesthesia, and during any other periods of bronchial hypersecretion.

2. Manually Assisted Coughing

Assisted CPF can be greatly increased in patients receiving maximal insufflations followed by manual abdominal thrusts for assisted coughing [37]. In 364 evaluations of NMD patients able to air stack, the mean VC in the sitting position was 996.9 mL, the mean MIC was 1647.6 mL, and although CPFs were 2.3 L/s (less than 2.7 L/s or the minimum needed to eliminate airway secretions) mean-assisted CPF were 3.9 L/s. An epigastric thrust with one hand, while applying counterpressure across the chest to avoid paradoxical chest expansion, further increases assisted CPF for 20 % of patients [38]. Manually assisted coughing is usually less effective in the presence of severe scoliosis because of a combination of restricted lung capacity and the inability to effect diaphragm movement by abdominal thrusting because of severe rib cage and diaphragm deformity. When inadequate, and especially when inadequacy is due to difficulty air stacking, the most effective alternative for increasing CPF and clearing airway secretions is the use of MAC.

The inability to generate more than 2.7 L/s or 160 L/m of assisted CPF despite having a VC or MIC greater than 1 L usually indicates fixed upper-airway obstruction or severe bulbar muscle weakness and hypopharyngeal collapse during coughing attempts. Vocal cord adhesions or paralysis may have resulted from a previous translaryngeal intubation or tracheostomy [39]. Because some lesions, especially obstructive granulation tissue, can be corrected surgically, laryngoscopic examination is warranted.

3. Mechanical Insufflation-Exsufflation

(a) Introduction of Mechanical Insufflation-Exsufflation

MI-Es (Cough Assist™, J. H. Emerson Co., Cambridge, MA) deliver deep insufflations followed immediately by deep exsufflations. The insufflation and exsufflation pressures and delivery times are independently adjustable. Insufflation to exsufflation pressures of +40 to −40 cm H2O are usually the most effective and preferred by most patients. Onset of insufflation generates an insufflation flow peak and a lung insufflation of more than 2 L. Mechanical exsufflation generates two exsufflation flow notches. One occurs when the insufflation pressure stops and is due to the elastic recoil of the lung. The second one, a bit greater, is caused by the exsufflation pressure itself. Except after a meal, an abdominal thrust is applied in conjunction with the exsufflation (MAC, or mechanically assisted coughing). MI-E can be provided via an oral-nasal mask, a simple mouthpiece, or via a translaryngeal or tracheostomy tube. When delivered via a tracheostomy tube, the cuff, when present, should be inflated. The Cough Assist™ can be manually or automatically cycled. Manual cycling facilitates caregiver-patient coordination of inspiration and expiration with insufflation and exsufflation, but it requires hands to deliver an abdominal thrust, to hold the mask on the patient, and to cycle the machine.

One treatment consists of about five cycles of MAC followed by a short period of normal breathing or ventilator use to avoid hyperventilation. Insufflation and exsufflation pressures are almost always from +35 to +60 cm H_2O to −35 to −60 cm H_2O. Most patients use pressures of 40 cm H_2O for insufflations and exsufflations, as it has been shown to be most effective in animal models [40]. Insufflation and exsufflation times are adjusted to provide maximum chest expansion and rapid lung emptying. In general, 2–4 s are required. Multiple treatments are given in one sitting until no further secretions are expulsed and any secretion or mucus-induced oxyhemoglobin desaturations are reversed. Use can be required as frequently as every few minutes around the clock during chest infections.

The use of MAC via the upper airway can be effective for children as young as 11 months of age. Patients this young can become accustomed to it and permit its effective use by not crying or closing their glottises. Between 2.5 and 5 years of age, most children become able to cooperate and cough on queue with mechanical in-exsufflation. Exsufflation-timed abdominal thrusts are also used for infants.

Whether via the upper airway or via indwelling airway tubes, routine airway suctioning misses the left main stem bronchus about 90 % of the time [41]. MAC, on the other hand, provides the same exsufflation flows in both left and right airways without the discomfort or airway trauma of tracheal suctioning. Patients prefer MAC to suctioning for comfort and effectiveness, and they find it less tiring [42]. Deep suctioning, whether via airway tube or via the upper airway, can be discontinued for most patients.

(b) Efficacy of MAC

The efficacy of MAC has been demonstrated both clinically and on animal models [43]. Flow generation is adequate in both proximal and distal airways to eliminate respiratory tract debris [44, 45]. VC, pulmonary flow rates, and SpO_2 when abnormal improve immediately with clearing of airway secretions and mucus by MAC [46, 47]. An increase in VC of 15–42 % was noted immediately following treatment in 67 patients with “obstructive dyspnea,” and a 55 % increase in VC was noted following MAC in patients with neuromuscular conditions

[48]. More recently, an increase in VC of 15–400 % (200–800 mL) and normalization of SpO_2 has been observed as MAC eliminates airway mucus for ventilator-assisted NMD patients with chest infections [38].

(c) Indications for MAC

Of the three muscle groups required for effective coughing, MAC can only take the place of the inspiratory and expiratory muscles. Thus, it cannot be used to avert tracheotomy very long if bulbar function is inadequate to prevent airway collapse, as is often the case in advanced bulbar ALS, or aspiration of saliva is continuous. On the other hand, patients with completely intact bulbar muscle function, such as most ventilator users with traumatic tetraplegia, can usually air stack to volumes of 3 L or more, and, unless very scoliotic or obese, a properly delivered abdominal thrust can often result in assisted CPF of 6–9 L/s. These flows should be more than adequate to clear the airways and prevent pneumonia and respiratory failure without need for MAC. Thus, the patients who need MAC the most are those whose bulbar muscle function can maintain adequate airway patency but is insufficient to permit optimal air stacking for assisted CPF more than 250–300 L/m. This is typical of most non-bulbar ALS, NMD patients. The most typical example of patients who can consistently avoid hospitalization and respiratory failure by using MI-E during intercurrent chest infections is DMD patients [47]. Patients with respiratory muscle weakness complicated by scoliosis and inability to capture the asymmetric diaphragm by abdominal thrusting also greatly benefit from MAC.

Glossopharyngeal Breathing

Both inspiratory and, indirectly, expiratory muscle function can be assisted by GPB [21]. GPB can provide an individual with weak inspiratory muscles and no VC or breathing tolerance with normal alveolar ventilation when not using a ventilator or in the event of sudden ventilator failure day or night [21, 48]. The technique involves the use of the glottis to add to an inspiratory effort by projecting (gulping) boluses of air into the lungs. The glottis closes with each "gulp." One breath usually consists of 6–9 gulps of 40–200 mL each (Fig. 16.8). During the training period, the efficiency of GPB can be monitored by spirometrically measuring the milliliters of air per gulp, gulps per breath, and breaths per minute (Fig. 16.9). A training manual [49] and numerous videos are available [50], the best of which was produced in 1999 [51].

Although severe oropharyngeal muscle weakness can limit the usefulness of GPB, in one center 13 DMD ventilator users had no breathing tolerance other than by GPB [52]. Approximately 60 % of ventilator users with no autonomous ability to breathe and good bulbar muscle function can use

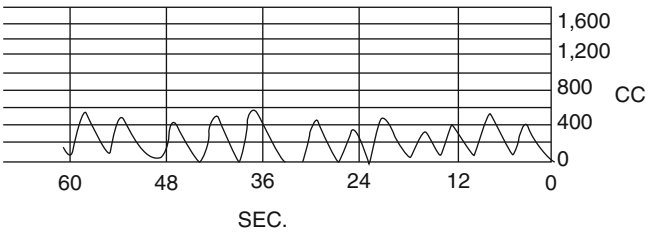

Fig. 16.8 Normal minute ventilation (60–90 mL/gulp, 6–8 gulps per breath, 12 breaths per minute for 48 mL/gulp) for 4,760 mL/min of alveolar ventilation throughout daytime hours by glossopharyngeal breathing (GPB) for an individual with no measurable vital capacity otherwise. Maximum glossopharyngeal single breath capacities can exceed 3,000 mL for such individuals

GPB and discontinue ventilator use for minutes to up to all day [48, 53]. GPB is also rarely useful in the presence of an indwelling tracheostomy tube. It cannot be used when the tube is uncapped as it is during tracheostomy IPPV, and even when capped, the gulped air tends to leak around the outer walls of the tube and out the stoma as airway volumes and pressures increase during the GPB air-stacking process. The safety and versatility afforded by GPB are additional reasons to eliminate tracheostomy in favor of noninvasive aids. Some patients with no measurable VC have awoken at night, breathing glossopharyngeally, to find that their ventilators had failed, a scenario not possible for tracheostomy ventilation users.

Oximetry Monitoring and Feedback Protocol

For a patient with chronic alveolar hypoventilation who has not been using ventilatory support or the patient being weaned from tracheostomy ventilation, introduction to and use of mouthpiece or nasal IPPV is facilitated by oximetry feedback. An SpO_2 alarm may be set to 94 %. The patient sees that by taking slightly deeper breaths, SpO_2 will exceed 95 % within seconds. He or she is instructed to maintain SpO_2 above 94 % all day [47]. This can be achieved by unassisted breathing for a period of time and, once tired, by mouthpiece or nasal NIV. With time, the patient requires increasing periods of NIV to maintain adequate ventilation (SpO_2 greater than 94 %). In this manner, an oximeter may also help to reset central ventilatory drive.

Oximetry feedback is especially important during the management of respiratory tract infections. The cough of infants and small children who can never sit is inadequate to prevent chest cold-triggered pneumonia and respiratory failure. Children who can sit are usually protected from this until after 2 years of age. Older children and adults whose assisted CPF decreases below 300 L/m are also at high risk for chest cold-triggered acute respiratory failure. Such patients require continuous SpO_2 monitoring and are taught

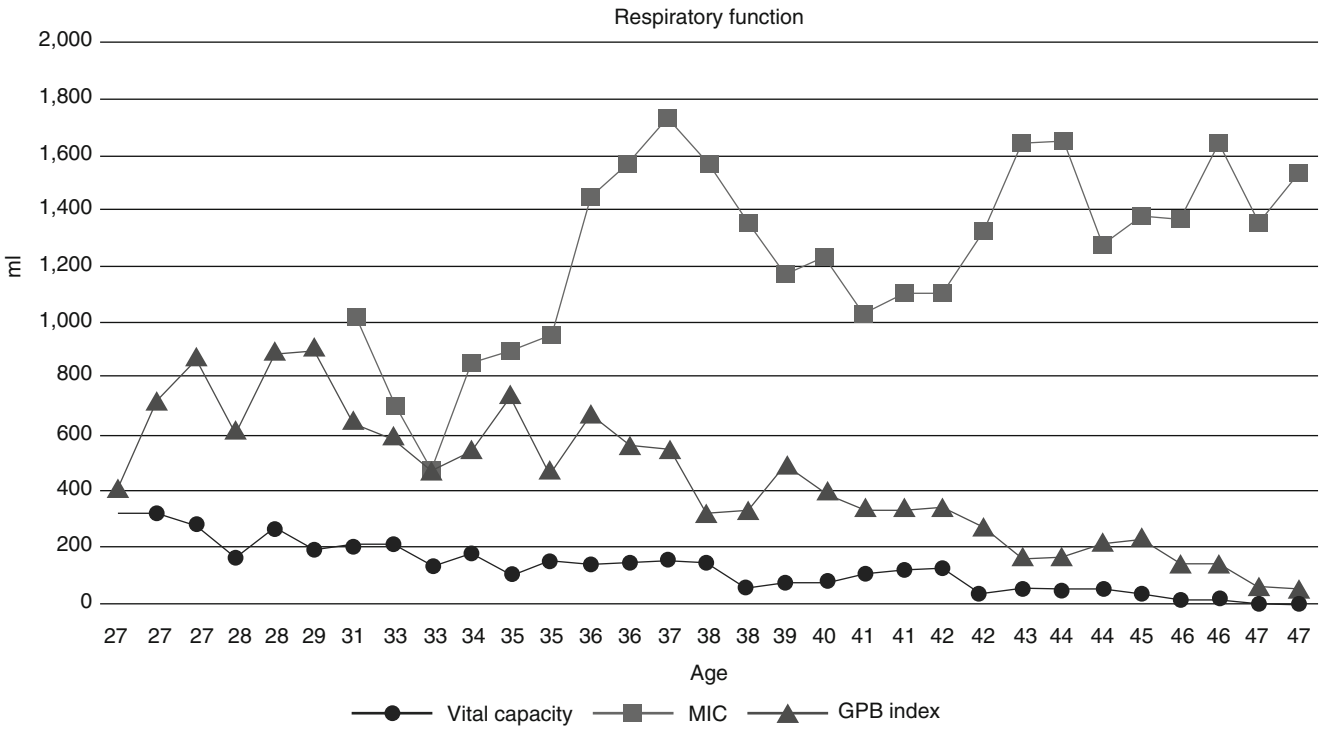

Fig. 16.9 Vital capacity, maximum insufflations capacity (*MIC*), and glossopharyngeal breathing maximum single breath capacity (GPmaxSBC) over time for 48-year old with Duchenne muscular dystrophy demonstrating relative preservation of MIC by comparison to GPmax SBC

that any dip in SpO_2 below 95 % is due either to underventilation or bronchial mucous plugging and if these two causes are not quickly addressed, may lead to atelectasis or pneumonia. They are instructed to use NIV to maintain normal ventilation and MAC to reverse mucous plug associated oxyhemoglobin desaturations. In this way, most episodes that would otherwise cause acute respiratory failure are successfully managed at home. For adults with infrequent chest colds, rapid access to this equipment may be all that is necessary.

Invasive Ventilatory Support

The use of noninvasive aids can be contraindicated by the presence of any of the following: depressed cognitive function, orthopedic conditions interfering with the application of NIV interfaces and exsufflation techniques, pulmonary disease necessitating high FiO_2, uncontrolled seizures, or substance abuse [54, 55]. Also, the presence of a nasogastric tube can hamper the fitting of a nasal interface or mouthpiece interface for NIV by interfering with both soft palate closure of the pharynx and seal at the nose. Although tracheostomy ventilation can also extend survival for these patients [56], morbidity and mortality outcomes are not as favorable as by noninvasive approaches [18, 57]. Tracheotomy is indicated for severe bulbar ALS patients [22], rarely if ever for DMD and SMA patients [20, 57], other than for an occasional patient with SMA type 1 who aspirates too much saliva to maintain normal SpO_2 [28, 58]. Patients with DMD, even those who are continuously NIV dependent, can avoid hospitalizations and pulmonary morbidity and mortality for decades and tracheotomy indefinitely when properly managed by using respiratory muscle aids [20].

Although widely thought to be fatal before age 2, SMA1, when managed according to a recently described noninvasive respiratory aid protocol, has thus far allowed many of these patients to survive into adolescence without a tracheostomy. In a recent study, 95 patients with typical, severe SMA type 1A and 7 patients with SMA type 1B who received ventilator assistance were studied. Sixty-eight of the patients without tracheostomy tubes were dependent on NIV continuously with 19 having no ventilator-free breathing capability. Sixty of the 68 individuals could communicate verbally. Twenty-seven of the patients had tracheostomy tubes; 14 of which had their tubes placed prior to referral to the clinic. Of these 27 patients, 6 were verbal prior to placement of the tubes and retained some verbalization afterward. Of the 21 individuals who had not developed speech prior to tracheostomy, none developed it after [58].

When tracheostomy ventilation is used despite the fact that oropharyngeal muscles are sufficient for swallowing, speaking, and permitting decannulation to NIV, either cuffless tubes or tracheostomy cuff deflation should be used

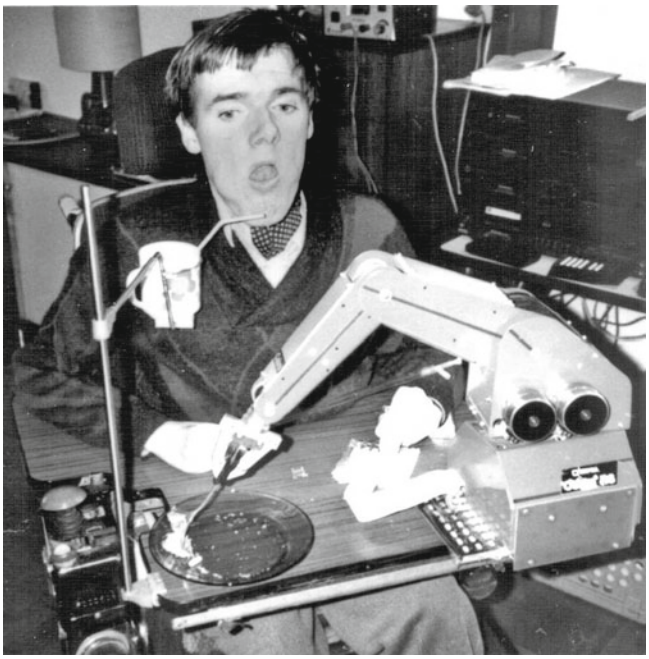

Fig. 16.10 Thirty-four-year old with Duchenne muscular dystrophy ventilated by intermittent abdominal pressure ventilator, using a robot arm for activities of daily living

up to 24 h a day [59]. Delivered air volumes are increased to compensate leak and support speech and one-way valves used to further facilitate verbal communication [60].

Quality of Life

Poor quality of life is usually given as the reason for withholding ventilator use [61]. However, no quality-of-life criteria, particularly those established by physically intact individuals, can be appropriately applied to all individuals. Life satisfaction depends, rather, on personal preferences [62] and on subjective satisfaction in physical, mental, and social situations, even though these may be deficient in some manner. Thus, not quality of life but potential satisfaction with life should be considered. It is particularly appropriate that the life satisfaction of individuals who are living the consequences of having chosen to use ventilators be considered when deciding about such ethically and financially complex matters as ventilator use for others. Interestingly, data indicate that severely disabled, long-term post-poliomyelitis, DMD, and SCI ventilator users [61] generally have very positive views of their lives and life satisfaction. These individuals find quality of life in interpersonal activities, and they are very significantly more satisfied with life than health-care professional estimates suggest [62]. Crucial for this is often the availability of personal attendant-care services and assistive equipment (Fig. 16.10). Thus, in the face of calls to limit entitlement spending, it should be noted that a society willing to provide free room, board, health care, legal and educational services, vocational training, and cable television for felons at exorbitant cost has the ethical responsibility to provide attendant-care services to those in need, some of whom are crime victims themselves.

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17 Immunotherapy in the Treatment of Autoimmune Neuromuscular Diseases

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General Principles of Immunotherapy

An increasing number of immunotherapies have been used in recent years to treat the group of neuromuscular diseases believed to have an autoimmune pathogenesis. A number of general principles should be applied when considering immunotherapy in any given patient. First, the diagnosis of an immune-mediated neuromuscular disease must be firmly established and confirmed, usually by some combination of serological and electrophysiologic testing. Once the diagnosis is established, a risk-benefit assessment for the drug under consideration must be done. This should take into account the severity of the disease manifestations, patient comorbidities and concomitant treatments, and the safety profile as well as cost of the immunotherapeutic agent. The treating neurologist should also be very familiar with the drug, its side effects, and the required toxicity monitoring. The side effects of immunosuppressive therapy can at times be worse than the disease, especially when the drugs are used for a long time, or without proper collateral measures to prevent adverse reactions. In women, pregnancy planning is critical as many immunosuppressant drugs are teratogenic. Patients must also be informed that in addition to specific short-term side effects (see below), long-term immunosuppression may increase the risk for development of infections and certain neoplasms.

The overall goal of immune-directed therapy is to induce remission or substantial improvement of symptoms in as timely a manner as possible (Table 17.1). With the exception of Guillain-Barré syndrome (GBS) – an acute, monophasic disorder – and its variants, maintenance of remission (or improvement) is then accomplished by slow and gradual tapering of medications over many months until the minimum dose of medication required to maintain disease control is identified.

The range of available immune-directed treatments is summarized in Table 17.2. Standard dosing, common side effects, basic recommendations for toxicity monitoring, and indications for use are also listed. Not all treatments have demonstrated clinical efficacy by randomized controlled clinical trials, and many of the indications are based on cohort, case control studies, or case reports.

Treatment Considerations

Assessment of Efficacy

For neuromuscular disorders, monitoring of clinical efficacy of treatment is mainly assessed by measurement of strength and sensory and/or autonomic function with appropriate

Table 17.1 General principles of immunotherapy

Initiation of therapy
Confirm diagnosis
Disease severity, likelihood of response, risk-benefit ratio
Patient features: age, concomitant diseases/medications
Drug side effects and cost
Drug dosing
Initial: use high dose to bring disease into remission
Follow-up: taper medications
Slowly
Determine minimum dose required to maintain remission
Monitor side effects
Use objective measures of drug efficacy
Quantitative strength testing
Functional testing
Activities of daily living

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Table 17.2 Immune therapies for autoimmune neuromuscular disease

Treatment	Major indications	Initial dosing/frequency	Side effects	Monitor
Plasma exchange (PE)	GBS, CIDP, PPN, MG	4–6 exchanges on alternate days	Rapid fluid and electrolyte shifts	BP, CBC, PT/PTT/INR
IVIg	GBS, CIDP, MMN, MG, LEMS, DM	1–2 g/kg (over 2–5 days)	Hypersensitivity reactions	Renal function
Prednisone	CIDP, PPN, MG, DM, PM, VN	(a) 0.75–1.5 mg/kg/day (b) 60–100 mg on alternate days	Weight gain, diabetes, osteoporosis, hypertension, cataracts	Weight, blood glucose, BP, electrolytes, DEXA scan, ocular exam
Azathioprine (AZA)	MG, CIDP, DM, PM,	2–3 mg/kg/day	Flu-like reaction (20–30 %) pancytopenia, liver toxicity, pancreatitis	TMPT (pretreatment), chronic: CBC, liver function
Mycophenolate mofetil (MMF)	MG,CIDP	2–2.5 g/day in divided twice daily doses	Leukopenia, liver toxicity, infections	CBC, liver function
Cyclosporine	MG, CIDP	4–6 mg/kg/day in divided twice daily doses	Renal insufficiency, pancytopenia	Renal function, CBC
Tacrolimus	MG	3–5 mg/day	Renal insufficiency, hyperglycemia	Renal function, CBC, blood glucose
Cyclophosphamide	CIDP, MG, VN	(a) 500 mg/m^2 (b) 50 mg/kg × 4	Pancytopenia, hemorrhagic cystitis, malignancy (total dose >75 g)	CBC, platelets, liver function, UA
Rituximab	MG, CIDP, PPN, DM	4 × 375 mg/m^2 weekly 1,000 mg IV × 2 doses (separated by 2 weeks)	Hypersensitivity, hypotension, infection (PML)	CBC, CD19 counts, JC virus Abs
Methotrexate	DM, PM, MG	7.5 mg/week in divided doses (increase to 20–25 mg weekly)	Stomatitis, hepatitis, liver and lung interstitial fibrosis	CBC, liver/renal function, CXR

GBS Guillain-Barre syndrome, *CIDP* chronic inflammatory demyelinating polyneuropathy, *MG* myasthenia gravis, *MMN* multifocal motor neuropathy, *PPN* paraproteinemic neuropathy, *DM* dermatomyositis, *PM* polymyositis, *LEMS* Lambert-Eaton Myasthenia Syndrome, *VN* vasculitic neuropathy, *CBC* complete blood count, *UA* urinalysis

clinical testing and established quantitative scores. These clinical assessments may also be supplemented by surrogate markers, such as electrophysiologic testing, antibody titers, and creatine kinase (CK) levels. Documenting improvement in muscle strength using objective measures can be a difficult problem, since the standard, commonly used assessment, the Medical Research Council (MRC) scale, is somewhat limited for the sensitive detection of mild or even moderate changes in muscle strength. Specifically, in the range of 4–5, the determinations are inconsistent, subjective, and variable among examiners. Therefore, it is desirable for the clinician to supplement the MRC scale with simple functional tests of performance. For example, using a stopwatch to time certain basic motor tasks, such as getting up from a chair, taking off a sweater, or walking across the room, and describing how a patient performs a task (e.g., the ease of movement or need for additional aids) can be very informative. Further, recording simple movements, such as how far the patient can raise each leg off the bed, elevate both hands above the ears when standing or sitting, arise from a chair with arms crossed on the chest, or step onto a stool, may often times give a more accurate picture of the disability than a vague 4, 4–, or 4+ rating on the MRC scale.

While a careful and detailed history may be extremely helpful in assessing treatment response, some patients underreport changes in strength, and others are easily persuaded that they are better or over-interpret the feeling of well-being associated with corticosteroids as an "improvement." It is more informative to ask specific questions about the performance of certain tasks at home or at work or about any change in the activities of daily living. Has there been improvement in the ability to get out of a bath, chair, or the back seat of a car? Has there been a perceptible change in shoulder girdle weakness as manifested by combing/washing hair and removing heavy objects from high shelving? For distal upper limb weakness, inquiring about problems with opening door handles and in using a key in a tight lock (patients with "grade 4" weakness may be functionally locked out of their homes), as well as button and zipper manipulation, are quite useful. It is helpful to get the patient to describe lost skills or abilities at baseline; these can give an index of the rate of evolution and in treatable disorders, regaining a lost function is a good indicator of response to treatment. Historical assessment of symptoms of weakness depends on lifestyle as much as on the pattern and severity of weakness. A bricklayer or athlete will note more subtle changes in symptoms sooner than a sedentary individual.

Without a concomitant change in the activities of daily living and objective measurement of muscle strength, there is no practical value in gauging improvement on the basis of a change in a laboratory test value, such as the creatine kinase (CK) level in inflammatory myopathy, of the nerve conduction study in neuropathy, or the titers of acetylcholine receptor antibodies in myasthenia gravis and myelin-associated

glycoprotein (MAG) antibodies in demyelinating polyneuropathies. When a patient improves, most of the laboratory test values also improve, but the opposite is not true because immunotherapy may reverse many laboratory values without clinical improvement. For example, the CK level, the acetylcholine receptor antibody titer, or the titer of MAG antibodies always drop with plasma exchange because of removal of proteins and immunoglobulins, irrespective of whether the patient improves or not. In contrast, in chronic inflammatory demyelinating polyneuropathy (CIDP), the patient often improves, but the nerve conduction velocities or the amplitudes of the evoked responses may not substantially change [1]. The main rule, therefore, is not to "chase" a laboratory value in order to establish improvement but to use these tests as supportive measures of clinical change and to understand the underlying mechanism of the disease.

Starting and Stopping Therapy

Treatment should be initiated when the diagnosis is established and all the necessary diagnostic procedures are performed. However, the start of therapy should be tailored to the needs of the individual patient. When the disease causes significant weakness and other symptoms that interfere with the patient's activities of daily living, treatment should be started as soon as possible. When the disease is mild with little functional limitations, however, the decision is more complex. It may be preferable in such cases to explain to the patient the merits of therapy with respect to anticipated outcome and adverse effects. Treatment decisions should be influenced not only by the severity of the disease but also by the patient's lifestyle, profession, finances, and family or community support. The patient needs to understand the goals of treatment and the associated risks and must agree to comply with the necessary toxicity monitoring (clinic visits and laboratory tests).

In general, therapy is usually initiated at a high dose to bring the disease into remission quickly (Table 17.1). One exception to this is the case of prednisone in myasthenia gravis (MG) where high steroid doses may precipitate a disease worsening – in these patients, either a gradual dose escalation paradigm or pretreatment with plasma exchange or intravenous immune globulin is necessary (see below). Time-to-response should also be taken into consideration since the onset of benefit may be quite delayed for some of the drugs, and the patient should be made aware of this. Sufficient time must be given for treatment to take effect, or the agent may be withdrawn after an inadequately short period of time with the patient considered "resistant" to the drug.

In a patient who responds to immune therapy, the ultimate goal is to find the lowest dose of the safest drug that controls the disease with the least adverse effects. For example, corticosteroid therapies may require the addition of a steroid-sparing drug, such as azathioprine, if there is a need to reduce or reverse adverse effects and lower the amount of steroids without breakthrough of the disease. After a favorable therapeutic response, the tapering schedule will vary depending upon the immunotherapeutic agent(s) involved. In general, stepwise reductions in the dose of prednisone may be accomplished as frequently as every 2–6 weeks, while tapering of chronic immunosuppressant drugs requires longer periods of observation since the effects of dose reduction (like the therapeutic effects) may be delayed. In certain situations (e.g., rituximab in myasthenia gravis), continued treatment after a therapeutic response may not be necessary, and careful clinical observation for disease relapse will determine the need for continued therapy.

A minority of patients will fail to improve despite appropriate and adequate standard treatments. In this situation, the patient and family may become discouraged, lose confidence, and start doubting the physician's competence and expertise. Reacting by adding another drug or therapeutic procedure, which may be of no benefit and have more adverse effects, perpetuates the vicious cycle of uncertainty and confusion. In addition, the practice of continuing an immunosuppressive agent that has not worked, with the hope that it may slow down the progression of the disease, is potentially more detrimental than beneficial. Therefore, immune drugs that are judged to be ineffective after an adequate trial should be discontinued. If the disease has improved and remains stable with only mild deficit, the patient should be reassured that overtreatment will not be of greater benefit and that a certain amount of neurologic dysfunction that does not interfere with the patient's lifestyle is not uncommon in certain autoimmune neurological diseases. Although physicians are often influenced by patients and their families to "do something," it is preferable, if the diagnosis is correct but nothing seems to work, to provide only supportive care rather than expose the patient to the dangers of prolonged immunotherapy. On the other hand, when a patient has a rapidly progressive disease and there is evidence that intense immunotherapy could make a difference, another trial of immunosuppressive or immunomodulating therapy may be considered. The lack of response to one drug does not necessarily mean the patient will not respond to others, and sequential trials with different drugs may be necessary until an effective mode of therapy is found. Clinical judgment should always prevail.

Treatment of Acute Disease or Relapses

As noted, the primary goal of treatment of a new onset or newly diagnosed autoimmune neuromuscular condition is to induce a disease remission, which is accomplished by suppressing the inflammatory immune attack or by removing pathogenic circulating antibodies or other immune factors.

The primary agents used for this purpose are corticosteroids, intravenous immune globulin (IVIg) and plasma exchange (PE). Chronic immunosuppressive drugs that have a relatively quick onset of response (e.g., cyclosporine, tacrolimus) may also be considered, typically in combination with steroids, IVIg, or PE.

Corticosteroids

Corticosteroids exert broad effects on the immune system, suppressing inflammation and innate and adaptive immune responses [2]. Corticosteroids produce a rapid depletion of circulating T cells due to a combination of effects, including the inhibition of interleukin (IL)-2 signaling and induction of T cell apoptosis [3]. Other relevant mechanism may include the inhibition of the recruitment and migration of lymphocytes to areas of inflammation and interference with the production of lymphokines [2, 4, 5]. Prednisone is the most commonly prescribed oral corticosteroid and is the most frequently used drug in the treatment of immune-mediated neuromuscular disorders, having a therapeutic role in all except Guillain-Barre syndrome and multifocal motor neuropathy.

The treatment response will often determine the need for stronger immunosuppressive drugs. An aggressive approach with high-dose prednisone (0.75–1 mg/kg/day or 60–80 mg/day as a single daily morning dose for an initial period of 3–4 weeks) beginning early in the disease course is preferred. Prednisone is then tapered over a 10–12 week period to 60–80 mg as a single daily, alternate-day dose by gradually reducing the alternate, "off-day" dose by 5–10 mg/week. This could be done faster if necessitated by side effects, though this carries a greater risk of disease relapse. If there is evidence of efficacy and there are no serious adverse effects, the dosage is reduced gradually by 5–10 mg every 3–4 weeks until the lowest possible dose that controls the disease is reached. In a patient responding to prednisone, a "maintenance" dose of 10–25 mg every other day may be needed to secure persistent improvement and stability. On the other hand, if by the time the dosage has been reduced to 60–80 mg every other day, there is no objective benefit (defined as increased muscle strength and function), the patient may be considered unresponsive to prednisone, and tapering is accelerated while the next immunosuppressive drug in the line of preference is started.

The single-dose, alternate-day program minimizes adverse effects while adequately controlling the underlying disease. We generally do not start therapy with alternate-day prednisone, without a preceding daily high-dose daily schedule, because the response may be delayed or inadequate. Furthermore, it is more difficult to induce a remission with an alternate-day program, but it is easier to maintain once achieved with a high daily dosage. It is also preferable to give prednisone as a single dose in the morning, because the higher morning concentration of natural cortisol results in a competitive decrease in metabolism of the administered prednisone, decreased clearance of the unbound (active) prednisolone, and, theoretically, a greater beneficial effect [5]. The morning dose of exogenous prednisone is also less likely to suppress the evening secretion of adrenocorticotropic hormone (ACTH), and, consequently, the endogenous cortisol secretion is anticipated to be normal the next morning.

Table 17.3 Corticosteroid side effects and prevention strategies

Side effect	Prevention strategies
Edema (sodium/fluid retention)	Sodium-restricted diet
Obesity	Low-calorie, low-fat diet; exercise
Potassium loss	Supplement (up to 40 mEq/day)
Hypertension	Monthly checks, treatment
Impaired glucose tolerance	Monitor fasting blood glucose, treat if necessary; recommend "low glycemic index" diet
Osteoporosis	Ca + (1,000 mg/day)/vitamin D (50,000 units/week), DEXA scan yearly, bisphosphonates, female hormone replacement
Steroid myopathy	Exercise, high-protein diet
Cataracts/glaucoma	At least yearly ophthalmologic examination
Growth suppression (children)	Use minimum effective dose
Peptic ulcer disease	H2 inhibitors; proton pump inhibitors
Psychosis/anxiety	Use minimum effective steroid dose; anxiolytics, antidepressants if necessary
Insomnia	Sleep hygiene, zolpidem (5–10 mg), wean off/discontinue as steroid dose is tapered

Adverse Effects of Corticosteroids

The most common adverse effects of chronic corticosteroid therapy are summarized in Table 17.3 and include the following [5, 6]: (1) abnormality of fat distribution with generalized obesity, hence the need for strict caloric restriction; (2) lipolytic action resulting in hyperlipidemia, which can rarely cause fat emboli in the femoral head and aseptic necrosis of the hip. Epidural lipomatosis resulting in spinal cord compression is rare but should be suspected if a patient on long-term steroid therapy is developing back pain and signs of myelopathy. Fatty liver, documented by ultrasound, is also common and may be responsible for increase in levels of liver enzymes; (3) glucose intolerance, hence the need for low carbohydrate diet; (4) retarded growth in children, which can be minimized with the alternate-day program; (5) menstrual irregularities; (6) edema and hypertension, hence the need for low-salt diet from the beginning of therapy; (7) osteoporosis especially in postmenopausal women, hence

the suggestion for coadministration of vitamin D, calcium supplements, or bisphosphonates; (8) gastrointestinal complaints (but rarely bleeding), which can be avoided by taking prednisone after meals and may be minimized with antacids or histamine blockers, as described earlier; (9) skin changes, including acne, ecchymosis, facial hirsutism, and stria; (10) posterior subcapsular cataracts and, rarely, glaucoma, necessitating frequent eye examinations; (11) central nervous system complications, such as insomnia, irritability, and exacerbation of the physiologic action tremor in the hands; and (12) proximal muscle weakness often referred to as "steroid myopathy" (see below). Most side effects improve with dose reduction and become minimal at less than 20 mg every other day.

Steroid Myopathy

The long-term use of prednisone may cause muscle weakness associated with a normal or unchanged CK level, referred to as "steroid myopathy" [7]. This may present a particular diagnostic/therapeutic challenge in patients with inflammatory myopathy, in whom it may be difficult to distinguish between steroid-induced myopathy and increased weakness related to disease activity. The decision to adjust the prednisone dosage in a patient with myositis who has previously responded to treatment may be aided by review of the past 2 months of strength alterations, mobility, serum CK, medication changes, and associated medical conditions. For example, a patient who recently has had increased CK levels, no new overt signs of steroid toxicity with reduced or unchanged dosage of steroids, and no evidence of a systemic illness or infection, increasing muscle weakness is most likely due to exacerbation of the disease, which may require an increase in prednisone or development of a steroid-resistant state. A useful clinical sign is worsening of the strength of neck flexor muscles with exacerbation of myositis, while these muscles remain unchanged with steroid-induced muscle weakness. Also, electromyography (EMG) may help by showing abundance of spontaneous activity when the weakness is related to myositis, while these abnormalities are absent with steroid myopathy. Steroid myopathy associated with the use of prednisone in MG is uncommon in our experience.

Intravenous Steroid Therapy

In certain autoimmune neuromuscular conditions, high doses of steroids (methylprednisolone, solumedrol) are given by intravenous pulse therapy to enhance potency and onset of benefit [8]. Typically, a dose of 500–1,000 mg methylprednisolone IV is given daily for 3–5 days. Subsequently, doses of 500–1,000 mg weekly, then every 2 weeks are administered, followed by gradual tapering, maintenance therapy, or switch to oral corticosteroid therapy. Pulsed dose intravenous steroids are typically used in the treatment of CIDP [8] and in paraproteinemic [9] and vasculitic neuropathies [10]. Similar to prednisone, IV pulsed steroids have no role in GBS or MMN and should generally be avoided in the treatment of MG because of a likely enhanced risk of steroid-associated exacerbation.

Plasma Exchange

Plasma exchange (PE) is a well-established procedure in the treatment of autoimmune neuromuscular disorders. PE temporarily reduces the levels of circulating antibodies and other circulating factors (complement, immune complexes, cytokines) and often produces clinical improvement in a matter of days [11]. It is generally used for short-term, urgent treatment of severe disease when a rapid response is needed (e.g., severe bulbar and/or respiratory muscle weakness) or in patients who do not respond to other therapies. A typical course of PE consists of 5–6 exchanges administered on an every other day schedule, during which 2–3 l of plasma are removed. Decisions regarding the total number of exchanges depend upon clinical response and tolerability, but more than six exchanges may be required in some patients.

Other immunosuppressants (see corticosteroids and below) are typically required to maintain the effects of PE in the long term, as the benefits typically wear off after 3–4 weeks although they may persist for as long as 3 months. Repeated exchanges probably do not have a cumulative benefit, and the use of PE as chronic maintenance therapy is not recommended, unless other treatments fail or are contraindicated.

Side effects during PE include paresthesias from citrate-induced hypocalcemia, symptomatic hypotension, transitory cardiac arrhythmias, nausea, lightheadedness, chills, and pedal edema. The major complications relate to the use of large-bore venous access. The risks of subclavian lines, arteriovenous shunts, or grafts for venous access include thromboses, thrombophlebitis, subacute bacterial endocarditis, and pneumothorax. Specific removal of circulating immune pathogenic factors may also be accomplished using immunoadsorption columns, some of which use immobilized antigenic proteins to remove autoantibodies from patients' serum. Further development of this technique may provide a more specific, efficient, and safer alternative to PE.

PE is a therapeutic option in severely affected patients as a short-term, temporary measure in MG, chronic inflammatory demyelinating polyneuropathy, and Guillain-Barré syndrome [11–13]. There is less experience with its use in other autoimmune neuromuscular disorders but may be effective presumably by removing autoantibodies and/or cytokines. It is not effective in multifocal motor neuropathy or in the myositides.

Intravenous Immunoglobulin (IVIg) and Subcutaneous Immunoglobulin

IVIg has emerged as a major immunotherapeutic modality in neurology [14–16] and in autoimmune neuromuscular disorders in particular. IVIg has multiple potential mechanisms of actions, including inhibition of cytokines, competition with autoantibodies, inhibition of complement deposition, effect on superantigens, interference with Fc receptor binding on macrophages or the immunoglobulins on B cells, blocking the Fc receptors on target antigens, and interference with antigen recognition by sensitized T cells via the soluble MHC class I, MHC class II, CD8, and CD4 molecules present in the IVIg preparation [17–19]. More than one of these actions are likely operant in diseases for which IVIg has shown efficacy.

The therapeutic dose of IVIg is empirically set at 2 g/kg. Although earlier practice divided the total dose for infusion into five daily doses of 400 mg/kg each, the preference now is to divide the total dose into two daily doses of 1 g/kg each especially in younger patients who have normal renal and cardiovascular function. In our experience, the 2-day infusion is not associated with more adverse reactions than the 5-day infusion as long as the rate of infusion does not exceed 200 ml/h or 0.08 ml/kg/min. Considering the drug's rapid diffusion to the extravascular space, achieving a high concentration of IVIg within 2 days may also enhance its efficacy. The half-life of IVIg is estimated at 18–32 days [19], so maintenance protocols usually call for 0.5–1 g/kg every 3–4 weeks, as dictated by the patients' clinical responses.

In general, adverse reactions to IVIg therapy are usually minor and occur in less than 10 % of patients [20]. Mild to moderate headache, chills, myalgia, or chest discomfort may develop in the first hour of the infusion and usually respond to stopping the infusion for 30 min and resuming it at a slower rate. Post-infusion fatigue, fever, or nausea may occur and last for up to 24 h. A slow rate of infusion is advisable in patients with a compromised cardiovascular system or congestive heart failure to avoid fluid overload. IVIg therapy may cause an increase in serum viscosity, which may predispose to the development of thromboembolic events, particularly in patients with high-normal or slightly elevated serum viscosity, such as those with cryoglobulinemia, hypercholesterolemia, or hypergammaglobulinemia. Rare cases of stroke, pulmonary embolism, or myocardial infarction after IVIg treatment have been reported [21–23]. Whether low-dose heparin or anti-platelet agents can prevent thromboembolic events in such patients is unknown. In patients with a history of migraine, IVIg therapy may trigger a migrainous attack, which may be prevented by pretreatment with propranolol [24]. Aseptic meningitis may rarely develop in some patients treated with IVIg, particularly those with a history of migraine [25, 26]. The symptoms respond to strong analgesia and subside in 24–48 h. Additional diagnostic testing is rarely necessary, and prophylaxis with intravenous steroids prior to subsequent infusions can be variably effective in our experience.

Acute renal tubular necrosis, mostly reversible, occurs rarely with IVIg therapy in patients who have preexisting kidney disease and volume depletion, particularly the elderly and those with diabetes or poor hydration [27, 28]. Skin reactions (urticaria, lichenoid cutaneous lesions, pruritus, and petechiae [29]) to IVIg therapy, although rare, may develop 2–5 days after the infusions and may last up to 30 days. A severe anaphylactic reaction may occur in patients with an absence or severe deficiency of IgA. Selective IgA deficiency is common (prevalence about 1:1,000) and asymptomatic. The reaction is rare, occurs mostly in patients with common variable immunodeficiency [30], and may be associated with the presence of serum IgG anti-IgA antibodies [31]. We do not routinely determine the serum IgA level before starting therapy but recommend that initial infusions be done in a hospital or outpatient setting where urgent care for an anaphylactic reaction is readily available. Finally, the IVIg preparations available in the United States are now safe with respect to the transmission of known viruses or infections. Despite this, clinicians should be watchful to ensure the early detection of any unforeseen or unexpected infectious agents (e.g., prion proteins) associated with its long-term use.

In controlled trials, IVIg was effective in Guillain-Barré syndrome [32–34], CIDP [35–40], multifocal motor neuropathy [41–45], dermatomyositis [46], Lambert-Eaton myasthenic syndrome [47], and MG [48–50]. IVIG was effective only in a small numbers of patients with IgM paraproteinemias [51, 52], and it was ineffective in inclusion-body myositis [53]. In uncontrolled studies, IVIg has been reported to be effective in some patients with polymyositis [54, 55].

Recent studies suggest that subcutaneous delivery of an immunoglobulin preparation (SCIg) may be effective and may represent an alternative to IVIg in patients with difficult venous access [56–59]. A randomized trial suggests that SCIg is safe and therapeutically equivalent to IVIg [59]. The most important limitation is the relatively small volumes that can be administered subcutaneously at a single injection site. Notably, patients commonly experience subcutaneous swelling and have found the procedure too difficult for self-administration [57, 58].

Long-Term Maintenance (Nonsteroidal) Immunotherapies

Although most patients with MG, polymyositis, dermatomyositis, and CIDP respond to steroids to some degree and for some period of time, a number of them fail to improve,

become steroid resistant, or are unable to successfully taper the steroid to an acceptable maintenance dose (≤20–25 mg every other day). The decision to start an immunosuppressive drug in these patients is based on the following factors: (a) "steroid-sparing" effect is needed since, in spite of steroid responsiveness, the patient has developed significant complications; (b) attempts to lower a high steroid dosage have repeatedly resulted in a new relapse; (c) adequate doses of prednisone for at least a 2–3 month period have been ineffective; and (d) the disease is rapidly progressive, with evolving severe limb and/or bulbar weakness or respiratory failure. The preference, however, for selecting an immunosuppressive drug is empirical. The choice is usually based on individual prejudices, experience, and assessment of the relative efficacy/safety ratio with each drug.

Azathioprine (AZA)

Azathioprine (AZA) is a purine antimetabolite that interferes with T and B cell proliferation. It is safe and inexpensive and has been used successfully in several autoimmune disorders. AZA therapy is initiated at 50 mg/day. In the absence of systemic side effects, the dose is then gradually titrated upward by 50 mg/week to a dose of 2–3 mg/kg/day. An idiosyncratic reaction, with "flu-like" symptoms, occurs within 10–14 days after starting AZA in 15–20 % of patients. This reaction requires stopping the drug. Hepatotoxicity and leukopenia are also important adverse effects [60] but are reversible if detected early, and the dose of AZA is reduced or discontinued. Blood counts and liver function tests should be followed periodically. An elevation of liver enzymes, if slight, needs only observation. Elevation of liver enzymes may be related to a "fatty liver" from long-term steroid use rather than from AZA. Patients with thiopurine methyl transferase deficiency cannot completely metabolize AZA so that a normal dose may lead to dangerous leukopenia [61]. Measurement of thiopurine methyl transferase levels is recommended by some prior to initiating AZA therapy, but is certainly advisable with early or marked AZA-associated leukopenia. Long-term use of AZA may increase the risk of developing certain malignancies [62], and the risk is likely dose and duration dependent, so the minimum effective maintenance dose of AZA should be used. Because it is usually effective after 6 months or at times longer of treatment, patience is required before it is concluded that the drug is ineffective. AZA is used in the treatment of myasthenia gravis [63], CIDP [64, 65], and the inflammatory myopathies [66, 67], mainly as a steroid-sparing drug, although with the exception of myasthenia gravis, evidence of efficacy consists mainly of uncontrolled case series.

Mycophenolate Mofetil (MMF)

Mycophenolate mofetil (MMF) selectively blocks purine synthesis, thereby suppressing both T and B cell proliferation. This drug is well tolerated, has few adverse effects, and appears to be effective for long-term therapy especially in myasthenia gravis [68]. It is a therapeutic option as a steroid-sparing agent or as a long-term immunosuppressant. Because it is less toxic than other immunosuppressant drugs (AZA, cyclosporine, cyclophosphamide), it has gained some favor as a first-line steroid-sparing agent. The typical MMF dose is 1,000 mg twice daily, but doses up to 3,000 mg a day have been used. It has a relatively slow onset of action (>3 months) and is very expensive. The main side effects are hyperglycemia, hypercholesterolemia, gastrointestinal symptoms, and electrolyte disorders [68]. Regular monitoring of the complete blood count and basic chemistries is required. Progressive multifocal leukoencephalopathy (PML) has been reported in patients treated with MMF [69], but a causal relationship is uncertain.

MMF is mainly used in the treatment of MG, based on pilot studies, and retrospective series indicating efficacy [70, 71]. Notably, two randomized, controlled trials failed to show additional benefit of MMF over 20 mg daily prednisone as initial immunotherapy of MG [72] and did not show a significant steroid-sparing effect of MMF in patients on prednisone [73], but a number of study-related issues have called these negative results into question, including the generally mild disease status of the patients, the better-than expected response to relatively low-dose prednisone, and the short duration of the studies. MMF has also been used in CIDP, MMN, and refractory PM and DM [74].

Methotrexate

Methotrexate is a folate inhibitor with a relatively safe side-effect profile that has been successfully used in rheumatoid arthritis and other autoimmune disorders [75]. Several doses and regimens have been used, but the most common is oral administration starting at 7.5 mg weekly for the first 3 weeks (given in a total of 3 doses, 2.5 mg every 12 h), increasing it gradually by 2.5 mg/week up to a total of 20–25 mg weekly [76]. When using methotrexate chronically, folic acid supplementation (1 mg daily, by mouth) is recommended. A relevant side effect is methotrexate pneumonitis, which can be difficult to distinguish from the interstitial lung disease seen in some patients with inflammatory myopathies. Other adverse effects include stomatitis, gastrointestinal symptoms, leukopenia, thrombocytopenia, renal toxicity, hepatotoxicity, and malignancies. Leucovorin rescue, in which the drug is given 24 h after administration of intravenous methotrexate, at doses of 50 mg/m^2 orally every 6 h for a total of 4

doses, may be considered to counteract the side effects of methotrexate. Methotrexate is most commonly used as a steroid-sparing drug in the inflammatory myopathies [76]. Its use in the inflammatory neuropathies or MG has been very limited, although a controlled clinical trial of methotrexate in MG is ongoing. Because it acts faster than AZA, it may be considered in appropriate clinical situations when a quicker therapeutic response is desirable.

Cyclophosphamide

Cyclophosphamide is an alkylating antineoplastic agent that is among the strongest immunosuppressive drugs. It can be given intravenously or orally at doses that vary depending upon the disease and route of administration. The intravenous route is preferred and pulsed dosing is believed to mitigate against the potentially severe side effects (0.5–1 mg/m^2 monthly × 6). Adequate hydration the day before, and antiemetics are helpful. It can be also given orally at 2.0–2.5 mg/kg (50 mg T.I.D), but it is safer intravenously. A switch to AZA or MMF is desirable once remission or substantial improvement is achieved. Adverse reactions include nausea, vomiting, alopecia, hemorrhagic cystitis, pulmonary fibrosis, bone marrow suppression, secondary malignancies, and sterility. Contraceptives are recommended for women and concomitant testosterone in men. It is critical to monitor the neutrophil count (no less than 1,500–2,000) and the lymphocyte count (no less than 1,000) at 7, 10, 14, and 21 days after intravenous infusion and perform frequent urinalysis even for several months after the drug is stopped. Cyclophosphamide has been helpful in some patients with multifocal motor neuropathy [77], CIDP [78], and vasculitic neuropathy [79] and in a subset of patients with inflammatory myopathies who also have interstitial lung disease [80].

Cyclosporine

Cyclosporine inhibits T cell proliferation via disruption of calcineurin signaling, which blocks the synthesis of IL-2 and other proteins essential to the function of T cells. It is used mainly in patients in whom AZA is either ineffective or not tolerated. The recommended initial dose of cyclosporine is 4–6 mg/kg/day in two divided doses, but maintenance doses of 3–4 mg/kg/day or less are often adequate to maintain the effect. Side effects are common and include hirsutism, tremor, gum hyperplasia, and anemia, but hypertension and nephrotoxicity are the main treatment-limiting adverse reactions [81]. CNS neurotoxicity includes tremor, convulsions, hallucinations, and a reversible leukoencephalopathy. Renal function should be also closely monitored and nonsteroidal anti-inflammatory drugs are contraindicated. When creatinine increases more than 30 %, the drug should be discontinued. There are many potential drug interactions given the fact that cyclosporine is metabolized via the P450 pathway. Cyclosporine is helpful in myasthenia gravis [82]. Uncontrolled studies have suggested benefit in dermatomyositis [80] and CIDP [83], but its use was associated with severe side effects and often led to drug discontinuation. The advantage of cyclosporine compared to azathioprine is that it acts faster, but it may be more toxic, if not monitored closely.

Tacrolimus

Tacrolimus (FK506) has a similar mechanism of action as cyclosporine, and a potential benefit in MG has been suggested by several reports [84–86], including a randomized, but unblinded, study in 36 new onset MG patients [86]. Sustained benefit has been reported in anti-ryanodine receptor-positive patients, which has been hypothesized to be due to enhancement of ryanodine receptor-related sarcoplasmic calcium release [87]. Doses of 3–5 mg/day have been used in different series, with a side effect profile suggesting that it is somewhat less nephrotoxic than cyclosporine. Despite this, potential nephrotoxicity and neurotoxicity remain the main severe side effects that limit more widespread use. Like cyclosporine, tacrolimus is metabolized via the cytochrome P450 pathway, giving rise to many potential drug interactions. Grapefruit may increase the serum tacrolimus (or cyclosporine) concentration. In addition to its use in MG, tacrolimus has also been used in small numbers of patients with refractory CIDP [88] and myositis with interstitial lung disease [80].

Biological Agents

Rituximab

Rituximab (RTX) is a human/murine chimeric monoclonal antibody (mAb) that specifically targets the B cell surface marker CD20 of B cells [89]. The binding of RTX to CD20 leads to significant depletion of peripheral B cells [89]. Based on its potential for targeting of autoreactive B cell clones, it is under investigation for its potential therapeutic role in antibody-mediated autoimmunity and has been increasingly used in the treatment of several autoimmune diseases [90, 91]. Multiple mechanisms have been proposed to for rituximab-mediated B cell depletion [89]. The main mechanism involved may be complement mediated B cell depletion, since the primary cause for resistance of malignant B cells to rituximab's effects is reported to be through enhanced expression of complement regulatory proteins [92].

There are two FDA-approved uses for RTX (B cell lymphoma and rheumatoid arthritis). Each uses a different protocol. Treatment of lymphoma patients involves four infusions of RTX at a dose of 375 mg/m^2, given on four consecutive weeks. The protocol for rheumatoid arthritis is two infusions at a dose of 1,000 mg of RTX, given 2 weeks apart. Both protocols have been used in the treatment of autoimmune neuromuscular disease, although the majority of patients in have received the lymphoma protocol. In many cases, RTX has been used in refractory disease so that concomitant therapies, usually involving corticosteroids and immunosuppressive agents, were also coadministered.

The most commonly encountered side effects are constitutional/systemic symptoms during the initial infusion. A 2005 report on the safety of RTX in patients with cancer and RA concluded that serious adverse reactions occur only in a small minority of patients but overall RTX therapy is safe [93]. Eighty-four percent of patients experience infusion related reactions including nausea, headache, fatigue, rash, and flu-like symptoms after RTX administration. The incidence of these symptoms is highest after the first infusion and decreases with subsequent infusions. These observations correlate well with the RTX use in autoimmune disease. The use of paracetamol, antihistamines, and corticosteroids is recommended as pretreatment to help control infusion related reactions.

Progressive multifocal leukoencephalopathy (PML) has been associated with the use of a number of monoclonal antibodies, including rituximab [94]. The incidence of PML occurring in patients treated with rituximab is estimated at 1:25,000 [94]. Until 2010, only patients previously treated with other immunosuppressive agents were thought to be at risk; however, at least one case of PML has been diagnosed in the absence of concomitant or prior immunosuppressive therapy [95]. The occurrence of PML in the context of B cell depletion suggests that humoral immunity may play a role in the control of JC virus replication. Despite the low risk, the associated mortality and morbidity of PML justifies a cautious approach in considering rituximab in the treatment of an autoimmune neuromuscular disease. In addition, the concomitant use of other therapeutic agents that may also enhance the risk for PML (e.g., mycophenolate mofetil, other monoclonals) should be avoided.

Rituximab has been used in the treatment of IgM paraproteinemic neuropathy [96] and in treatment-resistant CIDP [97] and MG; [98] the results of a controlled study of its use in polymyositis is pending.

Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody against the CD52 antigen, present in mature lymphocytes. Alemtuzumab potently depletes T lymphocytes, resulting in severe lymphopenia with a consequent increased risk of opportunistic infections. It was reported to have some efficacy in the treatment of IBM [99] and may be potentially useful in the treatment of refractory CIDP. Some data suggest that treated patients may be at and enhanced risk to develop other autoimmune disorders, particularly some B cell-mediated diseases, such as thyroid autoimmune disease or thrombotic thrombocytopenic purpura [100].

TNF-Alpha Antagonists (Etanercept, Infliximab)

Few reports suggest that the TNF-alpha antagonist etanercept or infliximab may be potentially useful in the treatment of the inflammatory myopathies and MG [101, 102]. Etanercept acts as a decoy receptor, binding soluble TNF and, thus, reducing TNF levels. TNF-α is upregulated in muscles of patients with inflammatory myopathies and in the nerves of patients with CIDP and is toxic to the myotubes and Schwann cells in vitro, perhaps revealing relevant mechanisms for potential benefit in inflammatory neuropathies and myopathies. The main side effects include respiratory infections, injection-site reactions, enhanced risk for infections, and headache. Tuberculosis screening must be performed prior to treatment.

Immunomodulating Procedures and Other Immunosuppressive Agents

Thymectomy

The use of thymectomy in MG was initially based on empiric observations that MG patients improved after removal of the thymus. The presumed role of the thymus in MG has provided theoretical justification for the procedure, but its precise mode of action is unclear. Acetylcholine receptor proteins are expressed in the thymus in the presence of maturing lymphocytes. Thus removal of the thymus gland may eliminate the source of autoantigen and continuous autosensitization. Thymectomy has been used as a treatment for MG for nearly 70 years. There have been no randomized controlled trials establishing efficacy in either patients with or without thymoma, and conclusions from retrospective, non-randomized studies are confounded by baseline differences between surgical and nonsurgical groups, among other things. A comprehensive meta-analysis concluded that there was probably some benefit from thymectomy in non-thymomatous MG patients and that it should be considered as a treatment option in selected MG patients [103]. Most experts consider thymectomy a therapeutic option in anti-AChR-positive, generalized MG with disease onset before

the age of 50, and some would also recommend it in patients who lack anti-AChR antibodies. An international prospective, single-blinded randomized trial of thymectomy in non-thymomatous MG is currently ongoing and will hopefully clarify this issue. At this time, the only absolute indication for thymectomy is the presence of thymoma. The role of thymectomy in anti-MuSK MG is not clear.

Hematopoietic Stem Cell Transplantation

Autologous hematopoietic stem cell transplantation has been used in the treatment of autoimmune diseases refractory to standard therapies since 1996 [104]. This procedure induces marked immunosuppression and is associated with considerable risk. Nevertheless, case series suggest effectiveness in refractory myasthenia gravis and chronic inflammatory demyelinating polyneuropathy [105, 106]. Caution should be exercised in light of the potential for serious adverse effects.

Complement Inhibitors (Eculizumab)

Complement activation is also thought to be a crucial step in the pathogenesis of MG, CIDP, and all variants of GBS and therefore represents an appealing candidate for selective immunotherapy. Eculizumab is an anti-complement agent that works by inhibiting the complement protein C5, which acts at a relatively late stage in the complement cascade. Results of a recently completed study examining the safety and efficacy of eculizumab in patients with refractory MG are pending.

Sirolimus (Rapamycin)

This drug is a macrolide antibiotic like tacrolimus that inhibits the proliferation of both T and B cells and the production of cytokines, especially IL-2. In contrast to tacrolimus that inhibits transcription of IL-2, sirolimus acts to prevent the translation of mRNA for key cytokines including IL-2 and has an effect on T cells even after their activation. There is anecdotal evidence that sirolimus was effective in some difficult cases of polymyositis.

Drug Interactions

Certain drugs can interact with the immunosuppressive drugs or immunomodulating agents and counteract or interfere with their action. Some of the more common interactions include:

(a) Anticonvulsants such as phenobarbital, carbamazepine, and phenytoin, all inducers of the hepatic microsomal enzyme system, may accelerate the elimination of prednisone. When patients are taking these drugs, a somewhat higher than anticipated steroid dose may be required to achieve a therapeutic response.
(b) Because azathioprine is metabolized by xanthine oxidase, its concurrent administration with allopurinol may be potentiated liver toxicity and myelosuppression. The combination of these drugs should be avoided.
(c) Cyclosporine, in combination with a lipid-lowering drug belonging the statin class of medications, can be myotoxic or cause myoglobinuria. If cyclosporine or tacrolimus is combined with a nonsteroidal anti-inflammatory agent, amphotericin B, or certain antibiotics, such as the macrolides, its nephrotoxicity may be enhanced. Hyperkalemia may result if cyclosporine is given together with potassium-retaining antibiotics or potassium supplements. Plasma cyclosporine level may be increased with the coadministration of cimetidine, steroids, warfarin, ketoconazole, and macrolide antibiotics (such as erythromycin and mithramycin). Its level is decreased with the coadministration of hepatic microsomal enzyme inducers, such as phenobarbital, phenytoin, carbamazepine, or the sulfonamides. Also note that St. John's wort, grapefruit, and grapefruit juice may increase cyclosporine levels.
(d) Concurrent administration of trimethoprim and methotrexate may increase risk of myelosuppression.

Specific Treatment of Autoimmune Neuromuscular Diseases

The neuromuscular disorders treated with immunosuppressive or immunomodulating agents comprise a heterogenous group of disorders that may be classified into three main groups: (1) the inflammatory neuropathies, (2) neuromuscular junction disorders, and (3) the inflammatory myopathies.

The Inflammatory Neuropathies

Guillain-Barre Syndrome (GBS)

GBS is an acute, immune-mediated polyneuropathy with a reported incidence of 1–2 per 100,000 population [107]. The main features of GBS are rapidly progressive, relatively symmetric weakness of the limbs usually accompanied by areflexia, with or without involvement of respiratory muscles or cranial nerve-innervated muscles. By definition, maximum weakness is reached within 4 weeks, but most patients reach their maximum weakness within 2 weeks. Thus, immune-directed treatment is focused on short-term therapy of acute disease, and chronic immunosuppression is not indicated. The current established treatments of GBS are plasma exchange (PE) and intravenous immunoglobulin (IVIg) [107].

PE is beneficial when given within the first 4 weeks of disease onset in GBS, but the largest effect is seen when started early (within the first 2 weeks) [108–110]. The usual regimen is PE five times every other day over 10 days to 2 weeks, with a total exchange of about five plasma volumes. Patients treated with PE have been shown to have a significantly reduced disability at 1 month using the Guillain-Barre Syndrome Disability Scale, and treated patients ambulate independently in less time than untreated patients [110].

The first randomized controlled clinical trial on the use of IVIg in GBS was published in 1992 and showed that IVIg was as effective as PE [34]. In subsequent studies, no difference was found between IVIg and PE with respect to the improvement in disability grade after 4 weeks, the duration of mechanical ventilation, mortality, or residual disability [111]. The combination of PE followed by IVIg has been found not to be significantly better than PE or IVIg alone [33]. However, because of its greater ease of administration and better tolerability, IVIg (2 g/kg divided over 2–5 days) has replaced PE as the preferred treatment in many centers.

Oral or intravenous steroids are not beneficial in GBS [112, 113], and the combination of IVIg and intravenous methylprednisolone is not more effective than IVIg alone [113]. Despite treatment (IVIG or PE), GBS continues to have a mortality of up to 9 % and severe disability of 17 % [107]. Both treatments are associated with potential complications (see above), and clinical trials have shown that not all patients are able to complete the full course of therapy.

The easy access of IVIg and its administration without need for a central venous access has made IVIg the treatment of choice in children with GBS, even though its effectiveness in this population is based on uncontrolled trials or small series of patients.

Treatment Guidelines

Most published clinical trials have included only patients who are treated within the first 2 weeks from onset of weakness and who are unable to walk without assistance. If these criteria are met, there is no doubt that patients with GBS should be treated with IVIg or PE. If no contraindication exists for either, IVIg is the preferred therapy as it is associated with fewer complications and is cheaper overall. Patients with rapidly progressive limb weakness, impaired pulmonary function, severe swallowing difficulties, or autonomic dysfunction should also be treated with IVIg. Treatment outside of 2 weeks from symptom onset is also indicated for patients in these groups, particularly if symptoms are progressive at the time of treatment, but it is likely that outcomes are worse. IVIg is also preferable in small children or patients who have poor venous access, sepsis, or unstable hemodynamics. PE may be preferred in patients with known anaphylaxis to IVIg or vaccinations and for those who have history of hypercoagulable or hyperviscosity states. No randomized trials have assessed the effect of PE or IVIg in mildly affected patients with GBS, "mildly affected" arbitrarily defined as being able to walk (with or without assistance). A retrospective study showed that these patients may have residual disabilities, perhaps justifying therapy [114].

Some patients with GBS continue to deteriorate after PE or a standard course of IVIg [115]. Whether these patients need PE after they have been treated with IVIg has not been investigated. As noted, there is evidence that the combination of PE followed by IVIg is no better than PE or IVIg alone. PE after IVIg is also not advised, because PE would likely wash out the previously administered IVIg. A second course of IVIg in unresponsive patients with GBS may be effective and is the recommended strategy [116, 117]. Similarly, about 5–10 % of patients with GBS deteriorate after initial improvement or stabilization following IVIg treatment. In this situation, it is common practice to give a second IVIg course (2 g/kg in 2–5 days), because these patients are likely to improve after reinitiating this treatment. Some patients with GBS might even have several episodes of deterioration. This often raises the question of whether these patients might have chronic inflammatory demyelinating polyneuropathy with acute onset (see next section).

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

CIDP is characterized by symmetric weakness and distal sensory loss with areflexia. It develops in either a relapsing-remitting or chronic progressive course. The goal of therapy is to promote recovery of strength, improve gait and balance, and lessen sensory loss and paresthesias. Data from controlled clinical trials indicate that corticosteroids, IVIg, and PE result in short- or long-term clinical improvement in about two-thirds of patients [118]. Long-term maintenance therapy is needed in most patients.

Corticosteroids

CIDP is historically described as a "steroid-responsive" polyneuropathy. While corticosteroids have been widely used for CIDP treatment, only one randomized, unblinded trial showed effectiveness at 12 weeks [119]. Additional case series and extensive experience suggests that steroids are effective in CIDP treatment. Therapy is usually started with high-dose (60–100 mg) daily therapy, and the dose is then slowly tapered to a low-dose daily or alternate-day regimen. Onset of response is as early as 2 weeks but requires as long as 2 months. Studies have suggested similar effectiveness and lower side effects when using pulsed intravenous dexamethasone or methylprednisolone, compared to standard oral steroid regimens [8, 120], but there is no convincing data that this is any safer than chronic oral therapy. A recent study has shown that cure or long-term remission can be achieved in about one-quarter of patients with CIDP after 1 or 2

courses of pulsed dexamethasone or 8-month daily prednisolone [121]. A subset of patients with CIDP, particularly those with pure motor forms of CIDP, may worsen with steroids, and this should be taken into account in patients experiencing an acute treatment-related deterioration.

Plasma Exchange

PE has shown efficacy in the treatment of CIDP in controlled trials [122, 123]. Typically, a standard treatment course consists of 5–6 exchanges administered every other day. Maintenance therapy of at least one exchange every 6–8 weeks in combination with steroids or other immunosuppressant drugs may be considered. The need for large-bore venous access limits the feasibility of PE as a maintenance therapy. Because of this, IVIg is generally the preferred therapy.

IVIg

A number of controlled studies support the use of IVIg in CIDP [35–39]. Most recently, a large randomized controlled study confirmed the efficacy of IVIg in the treatment of CIDP and also demonstrated that maintenance IVIg doses of 1 g/kg administered every 3 weeks can sustain improvement and prevent further axonal degeneration [40]. These results argue for the use of IVIg as a first-line therapy. Although controlled studies have not been done, IVIg is also efficacious in childhood CIDP [60]. Multiple courses of IVIg appear to secure continuous efficacy. We have found that a combined alternate-day prednisone regimen combined with IVIg therapy in difficult cases has considerable success and minimal toxicity.

A number of patients who respond to IVIg may show a less consistent response in subsequent infusions, and others may not respond fully at the onset of therapy. In some of these patients, we have found that the combination of IVIg with prednisone (or intravenous steroids) may be effective. In general, CIDP may be more difficult to treat if axonal changes are extensive, regardless of the regimen used. On the other hand, patients with less severe axonal changes improve much better, hence the need to initiate therapy early.

In practice, the choice of initiating therapy with prednisone, IVIg, or PE (all effective in controlled trials) is determined on the basis of cost, long-term side effects, patient age, venous access, disease severity, and concurrent illnesses. While IVIg has become the treatment of choice for CIDP because of its demonstrated efficacy and safety profile, some patients may not respond. Patients may respond only to IVIg, others respond only to prednisone, and a third group benefit from combination therapy. Only after conducting a controlled comparative trial can it be determined which of these drugs (or combinations) is superior. The question is also important considering the disparities in the cost of steroids compared to IVIG or PE.

Other Immunosuppressant or Immunomodulating Agents

Up to one-third of CIDP patients will not respond adequately to steroids, IVIg, or PE [118]. Azathioprine, cyclosporine, and mycophenolate mofetil have all been used in CIDP mainly as steroid- or IVIg-sparing agents, although there are no controlled studies supporting their use. Nevertheless, these agents should be considered in patients who are intolerant or have an inadequate response to standard therapies. A trial of methotrexate in CIDP showed no difference in the treatment vs. placebo group in the ability to lower IVIG or steroid doses by more than 20 % [124]. In small uncontrolled studies, rituximab has shown favorable results in CIDP, with up to 50 % of treated patients improving after 2–12 months [125]. In selected cases, particularly when CIDP co-occurs with hematologic diseases, it may be considered as an early option.

Treatment Guidelines

After a diagnosis of CIDP is confirmed, if symptoms are mild and not significantly functionally limiting, no treatment is given. If significant symptoms or disability are present, a course of IVIg (2 g/kg) is administered. If this is effective, the patient is followed to observe the evolution of the CIDP, and, at the first sign of symptom recurrence, another course of IVIg is given, and then, serial IVIg treatments at a set frequency (1 g/kg every 3–6 weeks) are initiated. If IVIg infusions are required frequently, a second drug is started, usually prednisone at 1 mg/kg daily for a month, which is then tapered and maintained at low doses (below 25 mg every other day). We then start reducing IVIg frequency and/or dose to the minimum required. PE is best reserved for patients in whom IVIg therapy is ineffective. We use other immunosuppressant drugs, usually cyclosporine, mycophenolate mofetil, or azathioprine as steroid-sparing agents or in those patients in whom either steroids are contraindicated or an unacceptably high dose of steroids is required to maintain disease control. If there is no response IVIg, steroids, or PE, we try rituximab (2 g 15 days apart or 375 mg/m^2 in 4 weekly infusions) or cyclophosphamide (1 g/m^2 monthly) taking into consideration patient age and degree of disability.

Multifocal Motor Neuropathy (MMN)

MMN is a purely motor neuropathy characterized by slowly progressive, asymmetric, predominantly distal weakness of the limbs. It is characterized electrophysiologically by the presence of multifocal motor conduction block and immunologically by the detection of anti-GM1 antibodies in the serum of approximately 50 % of patients [126]. IVIg is the treatment of choice in light of four double-blind placebo-controlled trials confirming its efficacy and safety [41–44]. Approximately 70–90 % of patients improve with this therapy [127, 128]. It appears that more recently affected nerves

respond better to IVIg treatments, possibly because there is less axonal loss. The majority of patients require multiple regularly scheduled treatments [45]. Clinical parameters including muscle strength measures and patient perceptions have shown consistent improvement in response to IVIg treatment [45], and reinnervation and remyelination with reversal of conduction block has been demonstrated [129].

Prednisone and PE are ineffective in most patients with MMN and may even exacerbate symptoms [130, 131]. Cyclophosphamide was the first drug used to treat MMN and is reported to be effective in case series [77], but the substantial risk for severe adverse reactions restricts its use. Uncontrolled studies have suggested benefit with the use of cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil [126]. In a randomized controlled trial, mycophenolate mofetil failed to demonstrate any additional benefit as an adjunct to IVIG [132]. Treatment with eculizumab, a monoclonal antibody directed against complement factor C5, did not allow dose reduction of IVIg in most patients, although some improvements in objective motor performance measures were observed after treatment in an open-label study of 13 patients [133]. The effectiveness of rituximab in small patient series has been inconsistent [126].

Treatment Guidelines

The initial IVIg course is usually given at 2 g/kg over 2–5 consecutive days. Only 20–30 % of patients treated with a single IVIg achieve full remission [126], and the beneficial effects of IVIg only last a few weeks, so repeated infusions are necessary. Nevertheless, after IVIg-induced improvement, patients are typically followed carefully, and a subsequent deterioration is treated with second course of IVIg (2 g/kg), and plans for serial therapy are made. As is the case for CIDP, the optimal dose and interval for IVIg maintenance therapy has not been established, but must be determined based on the patient's response and careful monitoring of muscle strength testing and self-evaluation of disability and quality of life. Typically, 0.4–1.0 g/kg once every 4 weeks is required. Regular reevaluation of the maintenance regimen is recommended as many patients require an increase in the IVIg dose over time [45]. If there is no response to IVIg, the diagnosis should be reconsidered, and if the disease process is still believed to be most consistent with MMN, an additional IVIg course should be given, followed by consideration of treatment with cyclophosphamide or rituximab

It is important to note that there is no correlation between anti-GM1 levels and treatment efficacy. However, patients with high serum titers of this antibody may be more likely to respond to IVIG therapy [134]. Anecdotal evidence from observations of our own and others suggests that the efficacy of IVIg in MMN (and also in CIDP) might be restored in occasional patients if a short course of PE precedes the next IVIg infusion.

Paraproteinemic Immune Polyneuropathies

Coexistence of an immune polyneuropathy and a monoclonal gammopathy represents a heterogeneous group of disorders. The paraprotein may be a monoclonal gammopathy of uncertain significance (MGUS), or it may occur in the context of a malignancy such as multiple myeloma or Waldenstrom's macroglobulinemia. In the case of an established hematologic malignancy, this should take precedence over treatment of the polyneuropathy. In some of the IgM MGUS-associated neuropathies, the IgM paraproteins bind to myelin-associated glycoprotein (MAG) in peripheral nerve, thereby establishing a direct link between the paraprotein and the neuropathy. Patients with IgM MGUS-associated neuropathies and anti-MAG antibodies typically have a predominantly distal usually very slowly progressive demyelinating neuropathy with prominence of sensory symptoms and sensory ataxia [135]. They are often poorly responsive to therapies, so it is important to recognize this particular clinical phenotype and tailor treatment accordingly.

In IgM MGUS neuropathies with anti-MAG antibodies, there is some evidence that both PE and steroids may be effective mainly in combination with other immunosuppressants (chlorambucil) [136]. A small randomized controlled trial of IVIg in IgM MGUS neuropathy showed only a modest benefit in no more than 18 % of patients but included patients without anti-MAG activity [51]. A randomized controlled trial of rituximab in IgM anti-MAG neuropathy showed evidence for mild efficacy both clinically and on anti-MAG antibody levels [137]. The most improved patients were those with high anti-MAG titers and most severe sensory deficits at baseline. It is also important to remember that a number of patients with anti-MAG IgM MGUS have mild or chronic disease with prolonged periods of stability that may not require treatment.

Patients with IgM- (without anti-MAG antibodies), IgA-, or IgG MGUS-associated neuropathies may resemble idiopathic CIDP clinically, and treatment in these cases should be based on recommendations for CIDP (see above). However, because elevated serum levels of monoclonal proteins may cause high serum viscosity (which can be further increased with IVIg), caution is required when IVIg is infused in such patients to avoid precipitating thromboembolic events. Patients with IgM-, IgG-, and IgA MGUS-associated axonal neuropathies often have distal sensorimotor dysfunction with slow progression, not requiring treatment. Monoclonal gammopathy associated with cryoglobulinemia is often associated with hepatitis C infection and manifests as a multifocal axonal neuropathy. Management usually involves treatment of the underlying hepatitis C infection, although PE may be helpful in severe cases [138]. The coexistence of MGUS with an axonal neuropathy should indicate the possibility of amyloidosis, particularly when there is coexistent pain, weight loss, organomegaly, or

cardiomyopathy. Prognosis in these cases is usually not good, and patients with confirmed amyloidosis require a tertiary care referral for appropriate management, including possibly peripheral stem cell transplant.

Vasculitic Neuropathy (VN)

The classic presentation of vasculitic neuropathy is acutely evolving motor and sensory dysfunction in the distribution of multiple peripheral nerves, but it may also present as overlapping mononeuropathies or rarely as a distal symmetric polyneuropathy. The vasculitis may be part of a systemic inflammatory disease affecting the peripheral nerves or may be nonsystemic affecting the peripheral nerves without associated systemic features [9]. Once the diagnosis is made, most patients require prompt treatment. In general, the primary initial consideration is whether the patient requires monotherapy with corticosteroids alone vs. combination therapy with a cytotoxic agent [9, 139]. The presence of rapidly progressive weakness and/or multiorgan involvement in systemic vasculitis should lead to consideration of combination therapy – prednisone 1–1.5 mg/kg/day or methylprednisolone plus cyclophosphamide usually administered as intravenous pulsed doses. A typical protocol for cyclophosphamide administration is 0.6 g/m^2 every 2 weeks × 3, followed by 0.7 g/m^2 every 3 weeks × 3–6. The dose may be decreased in the elderly or in patients with renal insufficiency. Combination therapy is also advised for rapidly progressive nonsystemic vasculitic neuropathy and for patients who progress on corticosteroid monotherapy [139]. Patients are switched from cyclophosphamide to a less toxic immunosuppressive drug after induction therapy (typically after 6 months). First-line immunosuppressive options for maintenance therapy include methotrexate AZA, cyclosporine, and MMF.

Neuromuscular Junction Disorders

Myasthenia Gravis (MG)

Patients with MG respond fairly well to the available immunotherapies, such as thymectomy, corticosteroids, azathioprine, cyclosporine, tacrolimus, plasmapheresis, and IVIg [140]. Patients with mild or purely ocular MG may be initially treated symptomatically with anticholinesterase drugs. Corticosteroids are generally the first line of immunotherapy and are used when symptoms of MG are not adequately controlled by anticholinesterase drugs alone. In four large retrospective series of steroid treatment for generalized MG, administered at various doses, more than 73 % of the 422 patients treated achieved either "marked improvement" or remission [141–144]. Prednisone is the primary steroid drug used and may be administered at high doses (0.75–1.0 mg/kg/day) initially and then gradually tapered off or continued at low doses for many years. Approximately one-third of patients have a temporary exacerbation after starting prednisone; this usually begins within the first 7–10 days with high prednisone doses and lasts for several days [140, 141]. In mild cases, cholinesterase inhibitors may manage this worsening. In patients with oropharyngeal or respiratory involvement, PE or IVIg may be given before beginning prednisone to prevent or reduce the severity of corticosteroid-induced exacerbations.

Nonsteroidal Immunosuppressant Drugs

Nonsteroidal immunosuppressant medications are typically used in combination with prednisone as either steroid-sparing agents or as add-on drugs to enhance treatment response in those patients with a partial or minimal response to prednisone. Retrospective studies indicate that AZA is effective in 70–90 % of MG patients, but the onset of benefit may be delayed for as long as 12 months [63, 145]. The efficacy of mycophenolate mofetil (MMF) in MG has been suggested by retrospective analyses [70, 71]. The standard MMF dose used in MG is 1,000 mg twice daily, but doses up to 3,000 mg a day may be used. Two recently completed controlled trials of MMF in MG failed to show additional benefit of MMF over 20 mg daily prednisone given as initial immunotherapy [72] or a significant steroid-sparing effect of MMF in patients on prednisone [73]. A number of factors have been cited to explain these negative results, including the generally mild disease status of the patients, the better-than expected response to relatively low-dose prednisone, and the short duration of the studies. While the clinical efficacy of MMF in MG remains an open question, it continues to be widely utilized in the treatment of MG.

The efficacy of cyclosporine in MG has been suggested by a small, randomized, placebo-controlled clinical trial [82], and retrospective studies have supported its use as a steroid-sparing agent [81]. Cyclosporine is used mainly in patients in whom AZA is either ineffective or not tolerated. Tacrolimus (FK506) has a similar mechanism of action as cyclosporine, and potential benefit in MG has been suggested by several reports [84–86], including a randomized, but unblinded, study in 36 de novo MG patients [86]. Sustained benefit has been reported in anti-ryanodine receptor-positive patients, which has been hypothesized to be due to enhancement of ryanodine receptor-related sarcoplasmic calcium release [87].

A percentage of MG patients are refractory or develop intolerable side effects to treatment with corticosteroids in combination with one or more of the immunosuppressive

agents described above. Agents that may be considered in these refractory patients include cyclophosphamide and rituximab. Pulsed doses of intravenous cyclophosphamide (500 mg/m^2) given to patients with refractory MG improved muscle strength and lowered steroid requirement [146]. Remarkable therapeutic responses have also been reported in refractory MG patients receiving a one-time, high-dose (50 mg/kg) intravenous course of cyclophosphamide for 4 days followed by rescue therapy, with benefit persisting for several years without relapse [147]. As previously noted, side effects of cyclophosphamide are common and potentially serious, including myelosuppression, hemorrhagic cystitis, and an increased risk for infection and malignancy.

Rituximab is a chimeric monoclonal antibody directed against the B cell surface marker CD20. It effectively reduces circulating B cell counts and based on its potential for targeting of autoreactive B cell clones, may have a therapeutic role in antibody-mediated autoimmune diseases. Case reports have suggested benefit in refractory MG patients, particularly in MuSK MG [148, 149]. Further investigation is needed to determine its role in MG therapy, but it appears to be a less toxic alternative to cyclophosphamide in refractory cases and may be appropriate to consider early in the course of anti-MuSK patients since there is some evidence of induction of long-lasting therapeutic benefit without need for serial treatment in some patients.

PE and IVIg are used for short-term treatment of MG exacerbations and when it is desirable to achieve a rapid clinical response. PE temporarily reduces the levels of circulating antibodies and produces improvement in a matter of days in the most patients with acquired MG [140]. Typically one exchange, removing one to two plasma volumes, is performed every other day, up to a total of four to six times. IVIg is widely used for exacerbating MG. Support for its use comes from RCTs that show efficacy comparable to PE [48, 50] and a double-blind, placebo-controlled trial in MG patients with worsening weakness [49]. A number of issues regarding IVIg in the treatment of MG remain unanswered. First, we do not know if IVIg has a synergistic effect with the other drugs; second, it is unclear if IVIg has a role as a steroid-sparing agent, especially in children or the elderly; third, it is uncertain whether it works as fast as PE or affects the acetylcholine receptor antibody titers; and fourth, we are not clear if it is as effective as plasmapheresis in myasthenic crisis.

Thymectomy

The use of thymectomy in MG is based on empiric observations that MG patients improve after removal of the thymus. The presumed role of the thymus in MG has provided theoretical justification for the procedure, and thymectomy has been used as a treatment for non-thymomatous MG for nearly 70 years. There have been no randomized controlled trials, and conclusions from retrospective, non-randomized studies are confounded by baseline differences between surgical and nonsurgical groups, among other things. A comprehensive meta-analysis concluded that there was probably some benefit from thymectomy and that it should be considered as a treatment option in selected MG patients [103]. Most experts consider thymectomy a therapeutic option in anti-AChR-positive, generalized MG with disease onset before the age of 50, and some would also recommend it in patients who lack anti-AChR antibodies. An international prospective, single-blinded randomized trial of thymectomy in non-thymomatous MG is currently ongoing and will hopefully clarify this issue. At this time, the only absolute indication for thymectomy is the presence of thymoma. The role of thymectomy in anti-MuSK MG is not clear.

Treatment Guidelines

The treatment of patients with MG must be individualized according to the clinical presentation and requires a comprehensive assessment of the patient's functional impairment and its effect on daily life. The therapeutic goal is to return the patient to normal function as rapidly as possible while minimizing the side effects of therapy. Cholinesterase inhibitors may be sufficient in a minority of patients with restricted ocular or mild generalized disease (with or without prior thymectomy). In those not adequately treated with cholinesterase inhibitors alone, immunotherapy should be initiated promptly, starting with prednisone and adding the other immunomodulating drugs discussed above as needed (first-line agents include MMF and AZA). In a patient with relatively mild disease and a complete or near complete remission with prednisone, the addition of MMF or AZA can be considered if the prednisone cannot be tapered to an acceptable level. In patients with more severe disease or an incomplete response to prednisone, the addition of MMF or AZA should occur early in the therapeutic course. It is important to recognize that the effects of MMF and AZA can be quite delayed, so tapering of the prednisone dose should be done cautiously during the first 4–6 months. In patients treated with immunotherapies, the lowest effective dose should always be determined in regular follow-up clinic evaluations. In patients refractory to prednisone and MMF/AZA, treatment with tacrolimus or rituximab (particularly if anti-MuSK positive MG) should be considered.

Many case series report short-term benefit from PE and IVIg in myasthenic crisis. We recommend PE in the treatment

of crisis except when there is hemodynamic instability, sepsis, or coagulopathy or during the first trimester of pregnancy.

Thymectomy is indicated in patients with imaging evidence of a thymoma and should be considered in non-thymomatous MG patients with generalized, anti-AChR-positive disease and onset prior to age 50. Thymectomy is never an urgent procedure, and MG symptoms should be adequately controlled with immunomodulating agents (including PE or IVIg) prior to thymectomy or any surgical procedure.

Lambert-Eaton Myasthenic Syndrome (LEMS)

Once the diagnosis of LEMS is established, an extensive search for underlying malignancy, especially small cell lung cancer, is mandatory. Chronic smokers should undergo bronchoscopy and/or PET scan if chest-imaging studies are normal. Weakness may improve after effective cancer therapy, and some patients require no further treatment. Therefore, in "paraneoplastic LEMS," the target of initial treatment is the underlying malignancy. Patients with LEMS may have a gratifying symptomatic response to 3,4 diaminopyridine (3,4 DAP) [150–152], and although this is not an immunotherapy, it is generally considered the first-line treatment. Immunotherapy should be considered in LEMS patients who remain significantly symptomatic despite 3,4 DAP and should be tailored to the individual, based on the severity of weakness, underlying (malignant) disease, life expectancy, and response to previous treatment. Treatments, such as PE, corticosteroids, and immunosuppressive agents, including rituximab [153], may be of benefit in some patients but have not been tested in controlled trials. Both PE and IVIg provide short-term improvement in some patients with LEMS [154]. If these treatments are not effective, it must be determined if weakness is sufficiently severe to warrant immunotherapy with prednisone, AZA, cyclosporine, or rituximab. In patients with severe weakness, it may be advisable to give IVIg or PE first before considering adding prednisone or other immunosuppressant drugs. Maintaining improvement may require repeated courses of treatment.

Along these lines, a controlled study comparing IVIg to placebo showed a statistically significant increase in muscle strength compared to placebo, which peaked at 2–4 weeks and declined by 8 weeks. The effectiveness of IVIg was associated with a statistically significant reduction of antibodies against voltage-gated calcium channels [47]. On the basis of this controlled study alone, along with anecdotal case reports, it seems that IVIg is useful in treatment-resistant cases of LEMS, perhaps in lieu of steroids, and as an alternative to chronic immunosuppression.

The Inflammatory Myopathies

The inflammatory myopathies are a group of disorders characterized by immune-mediated muscle injury. The three most commonly mentioned subtypes are dermatomyositis (DM), polymyositis (PM), and inclusion-body myositis (IBM).

Dermatomyositis (DM)

DM is a multisystem disease predominantly affecting skeletal muscle (myopathy) and skin (skin rash – dermatitis) that can affect both adults and children. DM may be associated with interstitial lung disease or malignancy, so the appropriate work-up to evaluate for these conditions should be performed prior to instituting immunotherapy. Well-designed randomized controlled clinical trials in DM have been limited. DM is typically treated with high-dose oral prednisone, usually starting at a dose of 1 mg/kg/day [155]. Steroid therapy may also be initiated using intravenous methylprednisolone 500–1,000 mg IV per day for 3–5 days followed by oral prednisone. Oral prednisone is continued until the patient's weakness resolves, plateaus, or side effects are intolerable, usually 1–3 months. Steroid tapering is then initiated slowly with careful monitoring for any relapse or worsening. In general, the taper should proceed no faster than a decrease of 5–10 mg/day every 6 weeks, continuing until there is breakthrough of symptoms which indicates the minimal effective dosage for maintenance of remission.

While prednisone is effective in most patients with inflammatory myopathies, relapses are common when it is tapered, limiting its long-term use as a stand-alone drug. Steroid-sparing or second-line agents for the immunotherapy of DM include IVIg, AZA, methotrexate, and rituximab. Methotrexate is commonly used for its steroid-sparing effects in DM [155]. It is given once weekly in divided doses. A commonly used regimen initiates therapy with 7.5 mg weekly (2.5 mg every 12 h × 3), and the dose is increased by 2.5 mg/week to as much as 20 mg/week. Folate (1 mg four times daily) is coadministered [76]. The efficacy of AZA has been suggested in open-label studies and case series in the treatment of refractory DM [76, 155]. Approximately 75 % of patients treated with AZA appear to demonstrate improvements in strength [156]. Doses of 1.5–2 mg/kg are commonly used, but it is preferable to use doses up to 3 mg/kg for more effective immunosuppression. Because AZA is usually effective after 6 months of treatment, patience is required before concluding that the drug is ineffective.

In patients with severe weakness, myositis with interstitial lung disease (ILD), or concomitant osteopenia or

osteoporosis, methotrexate or AZA is typically started concomitantly with prednisone. Because methotrexate can cause pulmonary fibrosis, it is best avoided in patients who already have ILD. In these patients, MMF may be an alternative to AZA. In very weak patients, sometimes a short course of intravenous methylprednisolone is helpful prior to initiating prednisone or other immunosuppressant therapies.

In a double-blind study of IVIg therapy in 15 patients with refractory DM, strength improved in the IVIg randomized patients [43]. IVIg therapy may be used as an initial treatment (in combination with steroids) in severely affected patients with a goal of more rapid improvement. As a chronic or maintenance treatment, it may be considered in steroid-resistant patients or as an add-on therapy in patients who are not adequately controlled with combination of steroids and methotrexate or AZA, with a goal of reducing long-term steroid exposure. In some patients, IVIg infusions can lower the prednisone dose required for maintenance, demonstrating the most effective (although most expensive) steroid-sparing effect [7].

The IVIg-induced improvement in strength does not last more than 4–8 weeks, and repeated infusions are required periodically to maintain it. Patients who initially benefit from IVIg continue to respond to it in conjunction with low-dose steroids. They may need periodic infusions to maintain a reasonably good response or show less impressive improvement, possibly due to further progression of the disease. Overall, however, low-dose prednisone appears to enhance the benefit of IVIg. It has also been observed that some patients with DM who had become unresponsive to steroids may respond again to prednisone after a few IVIg infusions [7].

The efficacy of rituximab has also been suggested in the treatment of refractory DM. Case series have suggested significant improvements in muscle strength and functionality with concomitant reductions in serum CK and LDH [157, 158]. These effects have been sustained for more than 2 years in some patients [158]. An ongoing double-blinded placebo-controlled trial is underway to evaluate the benefit of rituximab in refractory DM.

Polymyositis

The diagnosis of PM encompasses a range of different disease associated with "inflammatory changes" on muscle biopsy. Patients present with subacute progressive proximal weakness without a skin rash. As with DM, there may be an association with interstitial lung disease, although there is no established association with malignancy. Treatment is essentially as described for DM above.

Inclusion-Body Myositis (IBM)

There is no treatment that has been shown to be effective in IBM, and most experts choose not to treat with immunosuppressant drugs because of this and the associated risks of adverse effects. IVIg is not effective [159]. In a small study, alemtuzumab infusions were shown to slow disease progression in IBM patients by up to 6 months and improved the strength of some patients and reduced endomysial inflammation on repeat muscle biopsy [99]. These encouraging results remain to be confirmed.

Immune-Mediated Necrotizing Myopathy

Immune-mediated necrotizing myopathy refers to a subset of inflammatory myopathies characterized by rapid onset and severe proximal weakness which tends to be refractory to immunotherapy [160]. While previously considered a form of polymyositis, pathological evaluation of muscle specimens revealed significant necrotic, degenerating, and regenerating muscle fibers with scant inflammatory cells. Many of these patients may have antibodies to the signal recognition particle complex (anti-SRP) [161]. In general, these patients should be treated aggressively with a combination of intravenous corticosteroids and IVIg or PE at disease onset. Steroid-sparing agents should be used as for DM and PM; refractory patients may respond to rituximab although there is little experience. A distinct form of autoimmune necrotizing myopathy has been reported in association with the use of statin drugs, with patients commonly relapsing when immunotherapy is tapered even with discontinuation of the statin agent [162]. An autoantibody targeting 3-hydroxy-3-methylglutaryl-conenyzme A reductase (anti-HMGCR), the target for statin therapy, has also been found in patients with this disorder [163]. This may represent an example of an environmental trigger for sustained autoimmunity, meriting further study.

A Step-by-Step Approach to Therapy

A "recipe" for treating each disease may be attractive but is not universally applicable because many of the treatment modalities are based on uncontrolled trials, and in some cases the immunosuppressive drugs are used empirically. Consequently, formulation of a step-by-step method of treatment may be considered an oversimplified approach. Nonetheless, it is useful to offer practical guidelines, drawn from our experience and that of others, for a step-by step approach to the use of immunotherapies (Table 17.4). These are not meant to be firm prescriptions, and modifications should be made according to the patient's needs or disease status or in response to new developments as appropriate.

Table 17.4 General treatment recommendations for immune-mediated neuromuscular disorders

Guillain-Barré syndrome
Step 1. IVIg or PE
Note: Both of these modalities are equally effective. IVIg is easier to administer, available worldwide, and may be initiated with minimal delays. Steroids are of no benefit and should not be used
Step 2. If early relapse occurs, repeat the treatment
Chronic inflammatory demyelinating polyneuropathy
Step 1. IVIg or prednisone
Step 2. IVIg and prednisone (if one treatment alone is not adequate)
Also may consider IV methylprednisolone 500–1,000 mg given with each IVIg
Step 3. PE (if two agents are ineffective)
If the need for a "steroid-sparing" agent arises with the use of prednisone, try MMF, cyclosporine, or cyclophosphamide
Step 4. Rituximab (particularly if associated IgM paraprotein – see below)
Multifocal motor neuropathy
Step 1. IVIg
Step 2. Adjust dose/frequency of IVIg (if effect of IVIg lessens)
Step 3. Cyclophosphamide (if IVIg is ineffective or loses its effect)
IgM paraproteinemic neuropathies with anti-MAG antibodies
Step 1. No treatment (if mild or pure sensory)
Step 2. Prednisone + chlorambucil for at least 3 months
Step 3. IVIg or PE alone or combined with prednisone and chlorambucil (if Step 2 ineffective) but the results are overall disappointing
Step 4. Rituximab
Demyelinating MGUS polyneuropathies
Step 1. Prednisone
Step 2. PE (if prednisone is ineffective or loses its effect)
Step 3. IVIg (if PE is ineffective)
If the neuropathy is axonal, it usually does not respond to therapy, but a trial of the therapies outlined is justified
Myasthenia gravis
Step 1. Pyridostigmine
Step 2. Prednisone (if pyridostigmine does not adequately control weakness)
Step 3. MMF or AZA (if prednisone does not control weakness or as steroid-sparing agent)
Step 4. Thymectomy for patients 12–50 years
Step 5. Tacrolimus or cyclosporine (if prednisone does not control weakness or as steroid-sparing agent, when azathioprine, mycophenolate ineffective)
Step 6. Rituximab (for refractory disease, particularly anti-MuSK MG)
Step 7. PE or IVIg. Both offer short-term benefit and may be used intermittently between steps 1 and 6 until the other therapies become effective. PE preferred for myasthenic crisis
Lambert-Eaton myasthenic syndrome
Step 1. 3,4-Diaminopyridine (available in compounding pharmacies and via compassionate use protocols in US)
Step 2. IVIg (patients with moderate to severe symptomatic weakness)
Step 3. Prednisone (patients with symptomatic weakness); combine with IVIg
Step 4. Azathioprine (if prednisone and IVIg do not control weakness or as steroid-sparing agent)
Step 5. PE or rituximab (if not controlled by Steps 2–4 and if weakness is severe)
Dermatomyositis and polymyositis
Step 1. Prednisone
Step 2. Methotrexate (if prednisone does not control weakness or as steroid-sparer)
Step 3. IVIg (to induce rapid improvement in severe disease and as a steroid-sparer)
Step 4. Cyclophosphamide (if refractory with interstitial lung disease)
Step 5. Other immunomodulators (azathioprine, mycophenolate mofetil, rituximab) (if steps 1–3 do not control weakness or as steroid-sparer)
Inclusion-body myositis
No pharmacologic treatment. Patients may benefit from a graded resistance exercise program (mild/early disease). A trial with IVIg may be considered if there is acute worsening, life-threatening dysphagia, or very prominent inflammatory endomysial infiltrates on muscle biopsy

Table 17.4 (continued)

Immune necrotizing myopathy
Step 1. High-dose steroids (IV or oral) + PE or IVIg
If statin-associated, stop statin drugs
Step 2. Methotrexate, azathioprine, or mycophenolate mofetil (steroid-sparing)
Step 3. Rituximab (for refractory disease)
Vasculitis of the peripheral nervous system
Step 1. Treat underlying tumor, infection, inflammatory disorder if present
Step 2. Prednisone or methylprednisolone (for more rapidly progressing disease)
Step 3. Steroids plus cyclophosphamide (when weakness moderate to severe and evidence for multiorgan involvement)

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Critical and Respiratory Care in Neuromuscular Disorders

18

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Introduction

The specialty of critical care medicine arose largely from the practical need to develop mechanisms of ventilatory support for patients with neuromuscular disorders (NMD), particularly poliomyelitis, and advances in respiratory care and the introduction of mechanical ventilation, as we know it today, dramatically decreased mortality in patients with NMD. In recent years, the implementation of critical care concepts and accessibility to specialized intensive care units have further improved morbidity and outcome [1, 2].

Knowledge of basic critical care principles and changes in pulmonary function are vital for providing optimal medical care. Managing NMD patients extends beyond the simple identification of various cardiorespiratory abnormalities and available treatment modalities in the intensive care unit (ICU). It involves prompt recognition and management of the natural progression of a disease, side effects of treatments, and comorbid illnesses that commonly occur in the ICU setting. Thus, all intensivists and physicians caring for patients with NMD should be familiar with the pathophysiologic changes associated with these disorders. The most common primary and secondary neuromuscular disorders seen in the ICU are shown in Table 18.1.

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Pulmonary Function in Neuromuscular Disorders

Patients with respiratory muscle weakness have a restrictive pattern on pulmonary function testing, based on static and dynamic lung volume indices [3, 4]. The vital capacity (VC), total lung capacity (TLC), and functional residual capacity (FRC) tend to be lower than predicted values, while the residual volume (RV) and the ratio of forced expiratory volume in 1 s to forced vital capacity (FEV_1/FVC) are normal. The diffusion capacity in NMD patients is preserved, which helps distinguish them from patients with restrictive defects related to parenchymal lung disease.

One expects significant loss of muscle strength to cause reductions in the VC, based on the normal pressure-volume curve of the respiratory system [5]. However, the VC is frequently reduced because of the concomitant reduction in respiratory apparatus compliance. This reduction in static lung compliance, which is usually about 30 % and improves with deep breathing, is due to increased alveolar surface tension as a result of breathing at low lung volumes [6]. The exact mechanism is unknown, but it is likely multifactorial in nature. Chest wall compliance and lung elasticity are altered [7, 8]. The low level of stress on the elastic tissue, due to chronic small tidal volumes and alveolar collapse, may be a factor in this process. Atelectasis and microatelectasis have unclear roles in the pathogenesis, since patients may have low compliance and elasticity without evidence of complete or partial collapse. Also, chest computerized tomography fails to show an association between microatelectasis and reduced lung compliance in patients with generalized NMD or traumatic tetraplegia [9]. Although daily use of intermittent positive-pressure ventilation (IPPV) is an effective method for improving lung compliance and preventing atelectasis formation, a true cause and effect relationship has not been established [10].

Respiratory muscle strength and reserve are indirectly measured by (1) negative inspiratory force (NIF) (synonymous with maximum inspiratory pressure, MIP),

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Table 18.1 Neuromuscular disorders encountered in ICU

Primary neuromuscular disorders		Secondary neuromuscular disorders
Muscle		Muscle
Congenital myopathies		Necrotizing myopathy
Mitochondrial myopathies		Paraneoplastic
Inflammatory myopathies		Sarcoidosis
Muscular dystrophies: Duchenne's,		Critical illness myopathy
Muscular dystrophies		Steroid and septic myopathy
Channelopathies		Malignant hyperthermia
NMJ		NMJ
Myasthenia gravis		Botulism
Lambert-Eaton syndrome		Tick, snake, scorpion, and spider bites
Congenital myasthenic syndromes		Electrolytes/antibiotics/infection
Nerves, roots, plexus, and autonomic		Nerves, roots, plexus, and autonomic
GBS, CIDP	Channelopathies	Metabolic/toxic: diabetes, uremia, hepatic
Porphyria	Primary dysautonomia	Critical illness polyneuropathy
Anterior horn cells		Anterior horn cells
Motor neuron disease		Paraneoplastic
Spinal muscular atrophy		Toxins
Poliomyelitis syndromes (polio or West Nile viruses)		
Spinal cord		Spinal cord
Demyelinating disease		Infectious
		Traumatic
		Infarction

Table 18.2 Useful respiratory physiologic variables in the respiratory management of patients with neuromuscular disease

Variable	Normal values	Consider ICU admission (or noninvasive measures in chronic NMD)	Consider intubation and assisted ventilation	Consider weaning off ventilator
Vital capacity (VC)	50–70 ml/kg	25–30 ml/kg	10–15 ml/kg	>15 ml/kg
Negative inspiratory force (NIF)[a]	>60 cm H_2O	−30 to −40 cm H_2O	<20 cm H_2O	>25 cm H_2O
Maximum expiratory pressure (MEP)	>100 cm H_2O	<50 cm H_2O	<40 cm H_2O	>40 cm H_2O

[a]Also called maximum inspiratory pressure (MIP)

which reflects inspiratory muscle and diaphragm strength and is usually less than −60 cm H_2O; (2) maximum expiratory pressure (MEP), which measures expiratory muscle strength and is usually greater than 100 cm H_2O; and (3) forced vital capacity (FVC), with a usual normal value of 50–70 ml/kg (Table 18.2). Monitoring these physiologic parameters helps identify patients with impending respiratory failure. Inability to cough and clear secretions occurs when MEP is less than 40 cm H_2O and FVC is less than 30 ml/kg, while ventilatory failure develops when NIF is less than 20 cm H_2O and FVC is less than 10 ml/kg [11]. NIF measurement correlates well with diaphragmatic fatigue and has the highest predictive value for initiation and weaning from mechanical ventilation [12, 13]. Other parameters of diaphragmatic function such as maximum transdiaphragmatic pressures and tidal volume (Vt) are severely diminished in the acute and recovery phases of primary NMD such as Guillain-Barre syndrome (GBS) and myasthenia gravis (MG). Although these variables improve during recovery, they do remain abnormally low [12, 13].

Abnormalities in the thoracoabdominal pattern of breathing include decreased contribution of thoracic and abdominal compartments to Vt, due to paradoxical rib cage and abdominal movements [14, 15]. Perez et al. quantitatively studied the effect of IPPV and an abdominal binder on Vt, the thoracic contribution to Vt, the phase angle changes between thoracic and abdominal volumes, and the labored breathing index in 31 patients with spinal muscular atrophy (SMA) and myopathy [15]. In SMA, a motor neuron disease, the paresis mainly involves the intercostal muscles sparing the diaphragm, while in myopathies, the diaphragm is partially paralyzed sparing the intercostal muscles. Thus, in myopathies, the intercostal muscles contribute mainly to thoracic cage movement during inspiration leading to the paradoxical inward abdominal movement and asynchrony between the thoracic and abdominal motion. On the other hand, motor neuron disease involvement of the intercostal muscles hinders expansion of the thoracic cage during inspiration, leading to smaller thoracic contribution to the Vt when compared to myopathies [14, 15]. This may explain

Table 18.3 Respiratory abnormalities associated with neuromuscular disorders

Physiologic abnormalities
Reduced chest wall compliance
Reduced static and dynamic lung volumes
Decreased ability to sigh and yawn
Reduced ability to clear secretions
Hypercapnia when muscle strength drops below 30 % of its predicted value
Clinical consequences
Atelectasis and microatelectasis
Aspiration pneumonia
Difficulty weaning from mechanical ventilation
Abnormal thoracoabdominal breathing pattern
Obstructive sleep apnea
Hypersomnolence

the more frequently abnormal thoracoabdominal breathing pattern and labored breathing seen in patients with motor neuron disease. These abnormal breathing patterns improve with institution of IPPV of 25–30 cm H_2O, particularly in patients with SMA [15], and reappear after its discontinuation [10]. Abdominal binding also increases thoracic contribution to the Vt. This is more noticeable in motor neuron disease than in myopathies [14, 15]. Observing a paradoxical pattern of thoracoabdominal breathing that is more pronounced in the supine position or measuring FVC in supine and sitting positions may alert the examiner to diaphragmatic dysfunction. However, this technique is rather insensitive and should not be solely relied upon in clinical practice.

Other findings in patients with NMD include inability to clear secretions and absent sighs and yawns, which are believed to help distribute surfactant evenly and, thereby, prevent alveolar collapse. Furthermore, NMD increase both the resistive and elastic loads on respiratory muscles, leading to an increase in work of breathing. The latter cannot be adequately accomplished by the weakened respiratory apparatus, causing fatigue and, ultimately, failure. In NMD with bulbar muscle involvement, the detection of abnormalities on pulmonary function tests, particularly abnormal contour of the flow-volume loop, may be apparent before any clinical evidence of bulbar muscle weakness [16–18]. This may signify involvement of the upper airway musculature and suggests an increased risk for developing respiratory complications related to the upper airway. In addition, patients with NMD have blunted responses to carbon dioxide and variable degrees of hypoxia [12, 19, 20]. Both of these changes account for the increased incidence of sleep-disordered breathing in this patient population. A summary of impairment of respiratory function and mechanics in NMD patients is outlined in Table 18.3.

Basic Critical Care Approach in NMD

As with all critically ill patients, the basic assessment and management of patients with neuromuscular disease require particular attention to airway, breathing, and circulation. Respiratory musculature weakness in patients with NMD renders them more vulnerable to respiratory compromise that may progress to failure. Those with bulbar involvement are at risk for upper airway obstruction and aspiration, whereas those with generalized weakness are prone to developing atelectasis, lobar or lung collapse. These phenomena are due to inability to protect the upper airway, cough, sigh, or clear secretions. All these considerations are important when a patient with a primary NMD presents, not only with an exacerbation, but also with any acute stressor. Both situations require prompt institution of incentive spirometry, chest physical therapy, and nasotracheal suction. Once a clinical assessment is made, the patient's ability to maintain adequate ventilation should be determined and monitored closely [21–23]. Standard respiratory parameters including FVC, MEP, and NIF measurements are inexpensive and easily performed at bedside and correlate well with respiratory derangement, as described above.

Evaluation and management of confounding systemic abnormalities is paramount to decreasing morbidity and mortality in patients with NMD. For example, electrolyte imbalances that may induce muscle weakness have devastating consequences in patients with primary muscle or neuromuscular junction disorder. Infections, local or systemic, may lead to neuropathies, muscle necrosis, and weakness. Concurrent illnesses, such as pulmonary embolism, ischemic heart disease, thyroid dysfunction, and renal dysfunction and hypovolemic states, may precipitate acute decompensation. In disorders that affect the autonomic nervous system (Table 18.4), cardiac and hemodynamic monitoring should be instituted at the onset of any sign of dysfunction or instability, since fluctuations in blood pressure and arrhythmias may be fatal. Prophylaxis against gastrointestinal stress ulcers, reflux, dysmotility syndromes, and venous thromboembolic disease should be introduced early in the course of the illness in all critically ill patients. Nutritional support, preferably enteral feeding, should be started as soon as possible to prevent cachexia and secondary weakness. In addition, medications known to induce myopathies and weakness must be avoided whenever possible.

Pain control is a vital adjunct to the overall care of these patients. Since most ICU patients are unable to communicate or express themselves verbally, objective parameters, such as abrupt rise in systolic blood pressure, tachycardia, and diaphoresis, are useful measures to gauge distress. Steroids, nonsteroidal anti-inflammatory drugs, or codeine is usually a good choice for pain management. Other common

Table 18.4 Neuromuscular disorders associated with autonomic dysfunction

Acquired diseases
Guillain-Barre syndrome
Botulism
Diabetic neuropathy
Paraneoplastic syndromes
Amyloid neuropathy
Alcoholic neuropathy
Drug induced: vincristine, metronidazole, heavy metals, clonidine, prazosin
Infections: West Nile virus, diphtheria
Inherited
Acute intermittent porphyria
Fabry's disease
Tangier disease
Familial dysautonomia (Riley-Day syndrome)

Table 18.5 Neuromuscular disorders associated with pulmonary dysfunction in patients requiring ICU care (in order of frequency)

Critical illness polyneuropathy
Critical illness myopathy
Toxic, metabolic (including steroid myopathy, rhabdomyolysis), septic, and electrolyte disturbances
Mixed pathology
Guillain-Barre syndrome
Myasthenia gravis (rarely Lambert-Eaton myasthenic syndrome)
Motor neuron disease
Spinal cord: traumatic, epidural mass, or transverse myelitis
Botulism
Tick paralysis
Inflammatory myopathies
Inherited myopathies: Duchenne's, myotonic dystrophies, glycogen storage diseases (Pompe's, McArdle's, and Tauri's), nemaline myopathy, mitochondrial, periodic paralysis
Porphyria
Vasculitic neuromuscular diseases

conditions that occur in ICU patients include sleep deprivation, delirium, and frank psychosis. After excluding an organic cause of altered mental status, these processes may be remedied by restoring patients' sleep-wake cycle and increasing adequate external environmental stimuli such as radio, television, family visitations, and rooms with windows that permit daylight. In addition, rehabilitation is usually started in the ICU as soon as the clinical situation allows. Devices to prevent contractures may be applied, and range of motion exercises started at bedside and advanced as tolerated.

Last, but equally important, are the ethical dilemmas that patients and their families face. The majority of patients are unfamiliar with their disease, its potential complications, and short- and long-term management issues at hand. Devoting adequate time for individual and group counseling through family meetings in order to answer questions and concerns is invaluable and must be a priority for the treating physicians. Maintaining a constant line of communication between the treating team, patient, and family helps patients cope with the stress of an intensive care environment. It is important to discuss a patient's and family's values and expectations, and when appropriate, palliative care should be introduced, and the palliative care team consulted.

Acute Ventilatory Management

Respiratory failure in NMD is the leading indication for admission to the ICU (Table 18.5). Disorders with an acute onset have a relatively predictable course. Many patients, who appear to be stable, lapse into respiratory failure within hours. Others, who are discharged prematurely from the ICU, are readmitted with ventilatory failure. Since the primary goals are to prevent, detect, and manage respiratory failure, close monitoring of simple respiratory indices is warranted in order to institute elective ventilatory support as dictated by the clinical setting [21–24]. The clinician must decide when to admit a patient to the ICU, establish an artificial airway, mechanically ventilate, and begin weaning and discontinue ventilatory support (Fig. 18.1) [24–32].

The maintenance of a patent, well-protected airway is the most important initial task for an intensivist in any clinical scenario. Upper airway compromise is clinically suspected if there is excessive drooling, difficulty swallowing oral secretions, use of accessory muscles, or stridor. In less severe cases, subtle changes on the flow-volume curve during spirometry may suggest airway compromise. Hence, an artificial airway should be established, regardless of gas-exchange abnormalities, with any sign of upper airway compromise.

Patients with acute or chronic NMD who present with an upper respiratory illness, even without obvious ventilatory failure, need frequent repeated measurements of respiratory parameters (FVC, NIF, and MEP) to guide therapy. The first step is to prevent any further pulmonary function compromise by immediately instituting chest physical therapy accompanied by nasotracheal suctioning, incentive spirometry, and IPPB. Management of the underlying disease affects outcome and, therefore, immediate initiation of therapy to arrest the disease process and, hopefully, halt further deterioration in respiratory function should be instituted. Equally important, aggressive correction of other factors that may compromise neuromuscular function, such as electrolyte imbalance, medications, fever, infection, and dehydration, should be carried out. Medications should be reviewed for any possible toxic effect on nerve, muscle, and neuromuscular junction. Keeping patients in a partially upright sitting

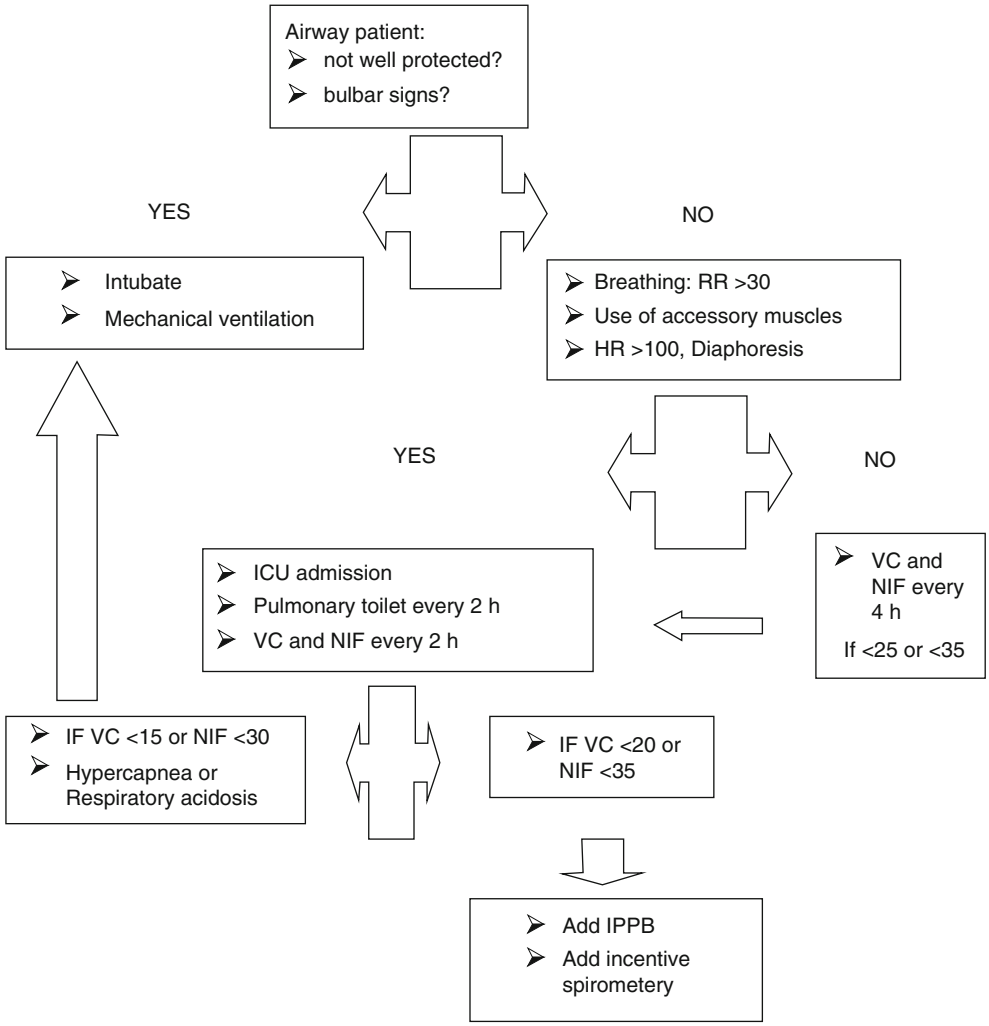

Fig. 18.1 Neuromuscular disease: acute presentation. Management algorithm (*RR* respiratory rate, *HR* heart rate, *ICU* intensive care unit, *VC* vital capacity, *NIF* negative inspiratory force, *IPPB* intermittent positive pressure breathing)

position at a 30° angle can help optimize diaphragm position and therefore its function.

The next step is to decide when to transfer a patient to the ICU. There are several suggested criteria for ICU admission [24–32]: (1) clinically ominous signs such as bulbar involvement with stridor, use of accessory muscles, a paradoxical respiratory pattern, diaphoresis, and autonomic instability; (2) any patient with NMD presenting with acute respiratory symptoms and weak proximal muscles; and (3) reduction in physiologic measures, namely, FVC of 25–30 ml/kg, NIF of 30–40 cm H_2O, and MEP <50 cm of H_2O (Table 18.2). All the above correlate well with respiratory failure and need for assisted ventilation.

Once in the ICU, more frequent bedside measurements of physiologic measures should be performed, along with around-the-clock IPPB, incentive spirometry, and chest physical therapy to optimize bronchial clearing. We strongly recommend early intubation, particularly in patients with increased secretions, which may lead to a less traumatic course and prevent further formation of atelectasis and pneumonia [27, 28].

Criteria for endotracheal intubation in patients with NMD are well addressed in the literature, and several recommendations have been made [27–32]. We usually perform orotracheal intubation; others advocate nasotracheal intubation [27, 28]. Mechanical ventilation in patients with an acute NMD is best initiated prior to the development of hypercapnic respiratory failure, since hypercapnia is a late manifestation of respiratory muscle weakness. *Thus, assisted ventilation should be started when FVC is between 10 and 15 ml/kg, NIF <20 cm H_2O, and/or MEP <40 cm H_2O* (Table 18.2) [24–32].

The optimal mode of ventilation is one that provides enough pressure and volume to prevent and reverse alveolar collapse, allows patients to participate and use their respiratory muscles without fatigue, and is associated with the least work of breathing. Unfortunately, there are no controlled studies comparing outcome of the various modes of mechanical ventilation in this setting [33–35]. Hence, the mode of mechanical ventilation used is dependent mainly on the physician's preference, experience, and availability. In our institution, the most commonly used technique is the *assist-control*

mode (AC). The ventilator delivers a positive-pressure breath at a preset Vt and rate. If a voluntary inspiratory effort is sensed, a similar machine breath will be delivered assisting the patient in his effort. *Synchronized intermittent mandatory ventilation (SIMV)* in combination with pressure support is also used. In this mode, the ventilator again delivers a preset Vt and rate, allowing the patient to breathe spontaneously in between machine breaths. If pressure support is added, the airway pressure rises to a set level augmenting the patient's spontaneous efforts. The Vt (6–8 cc/kg of ideal body weight/breath) and respiratory rate are adjusted to match the patient's minute ventilation requirements. Sighs and pauses may be added along with PEEP between 5 and 15 cm H_2O, to help reverse atelectasis and maintain normal airway peak and plateau pressures.

Weaning starts as soon as muscle strength improves and the comorbid illnesses and physiologic imbalances are reversed. If the patient is awake enough to protect the airway (MEP >40 cm H_2O), with low oxygen requirements (FiO_2 <45 %) and good strength (FVC >15 ml/kg and NIF >25 cm H_2O), a weaning trial may be started (Table 21.2) [24–32]. Several weaning methods have been studied [33–35]. We use daily spontaneous breathing trials (SBT) of continuous positive airway pressure (CPAP) with pressure support and carefully assess for signs of distress such as tachycardia, tachypnea, agitation, and diaphoresis [30–35]. Initially nocturnal rest on assisted ventilation is allowed. If the patient tolerates CPAP with minimum pressure support (less than 5 cm H_2O); has FVC greater than 30 ml/kg, NIF of >40, and MEP of >50; and has adequate gas exchange, extubation may be performed. We usually like to try patients for 2 h or more on SBT before we remove the endotracheal tube. The traditional teaching is that if patients are not able to wean off assisted ventilation in 2 weeks, a tracheostomy be performed. In practical terms, patients with NMD who are not been successfully weaned from mechanical ventilation by 7–10 days are likely to require tracheostomy and prolonged support. The advantages of tracheostomy include easy access for suctioning secretions, decreased dead space, reduction of laryngotracheal injury, and, to some degree, improved patient comfort.

Chronic Ventilatory Management

Chronic respiratory failure (CRF) is a common occurrence in patients with advanced NMD such as Duchenne muscular dystrophy (DMD) or amyotrophic lateral sclerosis (ALS). Since many of these disorders are irreversible, patients may elect long-term mechanical ventilation [36–40]. With the advances in noninvasive techniques in assisted ventilation, many chronically ill patients are surviving longer with improved quality of life [37, 38, 41]. Patients with DMD, SMA, post-poliomyelitis syndrome, and ALS are the most likely candidates for long-term mechanical ventilation [41–46]. In the United States, almost all patients with DMD and 50 % of those with post-poliomyelitis or ALS are chronically ventilated [2, 45–48]. Most patients can be supported at home initially with noninvasive nocturnal ventilation. As the disease advances, handling secretions becomes difficult and the need for continuous ventilatory support becomes a necessity to maintain life [47–52].

The use of noninvasive ventilation is as old as the poliomyelitis epidemics. It started with negative-pressure ventilators, like the iron lung, cuirass, and wraps, and later evolved into abdominal displacement devices such as the pneumobelt and rocking bed [53, 54]. The iron lung is a large pressurized apparatus that encloses a patient's body below the neck, generating subatmospheric pressures around the thorax, allowing air to flow into the lungs. Pressures then return to normal, causing passive deflation. The iron lung is probably of historic value only nowadays, although it was lifesaving during the poliomyelitis epidemics. The rocking bed, on the other hand, uses gravity to displace abdominal viscera by changing the angle of the bed between 10° and 30° several times each minute to assist in diaphragmatic excursion in patients with quadriplegia and bilateral diaphragmatic paralysis [53]. The pneumobelt is placed on the abdomen with automatic cyclical inflation and deflation provided by a positive-pressure source, which aids in diaphragmatic movement [55, 56]. Negative-pressure ventilation using cuirass and a body-wrap ventilator may be acceptable in some patients, who cannot tolerate the mask used in positive-pressure ventilation. However, it is contraindicated in patients with bulbar muscle weakness, because of the potential precipitation of upper airway obstruction [42, 43].

Noninvasive positive-pressure ventilation is the mode of choice in patients with NMD due to its efficacy, portability, and ease of use [43, 44]. It can be volume limited or pressure limited and applied via a tightly fitted nasal, facial, or oral mask. The main disadvantages are poor tolerance, infraorbital leak, nasal congestion, skin lacerations, and sinusitis. The clinical picture dictates choosing between volume- and pressure-limited assisted ventilation. Patients who are ambulatory, with relatively stable lung compliance, yet require nocturnal ventilatory support and tend to benefit from pressure-limited devices. *Bi-level positive airway pressure (BiPAP)* is the most commonly used device. Others with more progressive disease and unstable lung compliance tend to do better with volume-limited ventilation. In patients with upper airway muscular weakness, the use of *continuous positive airway pressure (CPAP)* helps prevent upper airway collapse by pneumatically splinting the airway, leading to a decrease in obstructive apnea events. CPAP also augments the patient's functional residual capacity, thus reducing the incidence of atelectasis [42–58].

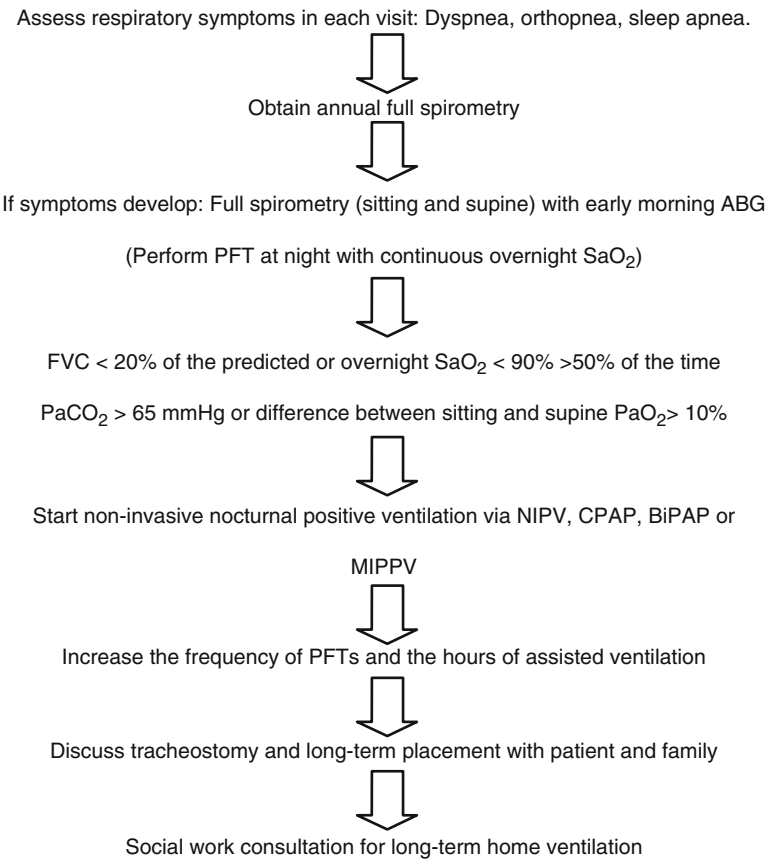

Fig. 18.2 Chronic respiratory care in patients with neuromuscular disease. Chronic respiratory care in patients with neuromuscular disease (*ABG* arterial blood gas, *PFT* pulmonary function tests, SaO_2 oxygen saturation, $PaCO_2$ partial pressure of carbon dioxide, *NIPV* negative intermittent pressure ventilation, *CPAP* continuous positive pressure ventilation, *BiPAP* bi-level positive airway pressure, *MIPPV* mechanical intermittent positive-pressure ventilation)

Recently, diaphragmatic pacing has been reevaluated, with increasing interest and research on its applications in patients with spinal cord injury and NMD [59, 60]. Obstacles to its use include the availability of immediate care in case of malfunctioning and the need for an educated and responsible patient, family, or caregiver. However, more experience has been accumulated in the past 10 years making this technique easier and safer to implant even in patients with pacemakers [61].

Strengthening exercises for inspiratory muscles and upper airway musculature is a mainstay of treatment. Although this may only produce minimal benefit, the need for ventilatory support may be delayed [62]. Eliminating and treating conditions that may worsen respiratory status, such as surgical correction of thoracic cage skeletal deformities, may help augment lung volumes [63]. Ultimately, the need for ventilatory support supervenes. We suggest to begin with several hours of nocturnal noninvasive ventilation, which improves the quality of life in patients with progressive NMD. With disease progression, the length of time needed for assisted ventilation increases, and difficulty handling secretions becomes more evident. At this point, discussion with the family regarding long-term goals and elective tracheostomy is advisable (Fig. 18.2). In addition, in home-ventilated NMD patients, caregivers must assess the efficiency of mechanical ventilation to allow for subsequent adjustments. Concomitant pulse oximetry and transcutaneous CO_2 monitoring are recommended to investigate this [64]. The choice of assisted continuous ventilatory mode and tracheostomy is usually made on an individual basis and discussed with the patient and their family using a team approach [41, 49, 51]. In this setting, tracheostomy along with continuous mechanical ventilation is labor intensive. Subsequently, delivering adequate home care may become difficult for the family and the caregivers. The need for institutional care may be necessary, and facilities with health professionals familiar and well trained in the care of patients with NMD should be considered. Several social, ethical, and economical factors are encountered and may complicate decision making regarding initiation of chronic ventilation and placement issues. It is of the utmost importance that the patient and family be involved in all decisions relating to the overall care. Discussing immediate and long-term goals and plans and taking into account the progressive irreversible nature of the disease and its impact on the patient and family's quality of life are of paramount importance.

Cardiovascular Aspects in NMD

Cardiac manifestations in neurologic diseases are common. Acute and chronic NMD may lead to various types of cardiovascular complications. In GBS, cardiac arrhythmias and

Table 18.6 Indications for cardiac pacing in NMD

Disorders of conduction
Complete heart block
Mobitz type II atrioventricular block
New bifascicular block
Asystole
Disorders of heart rate
Symptomatic sinus bradycardia
Recurrent ventricular tachycardia unresponsive to medical treatment
Junctional rhythm with atrioventricular dissociation
Medically refractory supraventricular tachycardia

dysautonomia are common and are the current leading causes of death. Various types of arrhythmias are encountered including sinus bradycardia, variable heart blocks, asystole, supraventricular, and ventricular tachycardia [65–67]. Also, variation in heart rate and blood pressure with orthostatic hypotension and diaphoresis may occur [65–67]. All patients with GBS and cardiovascular manifestations are at high risk of sudden death and should be monitored in the ICU. Hydration is the mainstay of treatment, but some patients may require vasoactive drugs, cardioversion, and even temporary pacemakers [65–67] (Table 18.6). Other NMDs that may involve the heart include periodic paralysis (related to potassium imbalance), mitochondrial myopathies, and toxic and alcoholic myopathies. Although some antiarrhythmic medications such as procainamide and quinidine may unmask or worsen MG, cardiac manifestations are not clearly associated with MG [68, 69].

Chronic NMD frequently involve cardiac muscle. DMD leads to rhythm disturbances, such as inappropriate sinus tachycardia, abnormal atrial rhythm, and rarely ventricular arrhythmia [70–72]. The electrocardiogram (EKG) may show tall right precordial R wave, increased R/S ratios with deep Q waves in V1 and V5–V6, short PR interval, and multifocal premature atrial and ventricular complexes indicative of cardiac involvement [73–76]. Asymptomatic women carriers may also show similar EKG findings [77]. Mitral regurgitation due to both papillary muscle involvement and dilated cardiomyopathy may lead to heart failure [78–83]. Dilated cardiomyopathy may also occur in women [84]. In Emery-Dreifuss and facioscapulohumeral (FSH) muscular dystrophies, there is a peculiarly high susceptibility to atrial flutter or fibrillation with atrial paralysis, requiring immediate cardiac electrophysiologic studies and possible pacemaker placement [85–87]. Myotonic dystrophy preferentially involves the Purkinje-His system, with fatty infiltration leading to intraventricular conduction abnormalities with right or left bundle branch block. This may culminate in Stokes-Adams episodes which can be prevented by placing a pacemaker [88–93]. Heart failure occurs in less than 10 % of these patients due to the rarity of myocardial involvement [94, 95]. Friedreich's ataxia may be associated with heart failure due to dilated and hypertrophic cardiomyopathies, the latter being far more common [96–98]. Charcot-Marie-Tooth disease may cause dilated cardiomyopathy and heart failure, cardiac arrhythmias, and conduction abnormalities [99]. Centronuclear myopathy is associated with myocardial fibrosis, dilated cardiomypathy, and sudden death due to cardiac involvement [100].

In summary, cardiac involvement is common in acute and chronic NMD leading to heart conduction abnormalities and cardiomyopathies. Recognizing these abnormalities early in the disease leads to timely medical management, and a low threshold should be maintained for placing a pacemaker when necessary.

Electrodiagnostic Testing in Intensive Care

Electrodiagnostic (EDX) testing in the ICU environment of critically ill patients with suspected acute NMD is often difficult. Limitations and pitfalls to performing these studies in the ICU are well recognized by most electromyographers [101]. Reviewing the history and discussing the testing plan with the ICU team often is beneficial to avoid possible pitfalls. Particular attention should be given to the patient's skin temperature since peripheral vasoconstriction is common and may lower skin temperature. A core temperature of <36 °C, muscle <34 °C, or skin <32 °C is associated with slowing of distal latencies and conduction velocities and an increase in motor and sensory amplitudes. Excessive tissue edema and subcutaneous fat may prevent supramaximal stimulation [101]. Some patients may have a bleeding diathesis, excessive sweating, skin breakdown, central lines, pacemakers, monitoring devices, or communicable diseases, which affect the choice of the procedure, the particular site, and the extremity tested. In spite of these limitations, EDX testing, including needle electromyography (EMG), nerve conduction studies (NCS), and repetitive nerve stimulation, may be performed and provide significant aid in arriving at an accurate diagnosis and prognosis [102, 103].

Testing of the respiratory system is another important part of the application of EDX testing that has not been used frequently [104]. Its major role is to investigate the cause of respiratory insufficiency by testing components of the central and peripheral nervous system involved in ventilation, including the diaphragm, phrenic nerve, spinal cord, and cerebral cortex. Phrenic motor NCS by surface stimulation, recording from the skin over the diaphragm, may be readily and easily performed in the ICU setting [104]. Repetitive nerve stimulation may be performed on the phrenic nerve as well, which may shed light on the pathogenesis of the neuromuscular weakness [104]. Diaphragmatic needle EMG examination may be performed but is cumbersome in the ICU, and patients may not be alert enough to cooperate with

testing [104]. Central causes of respiratory depression may be studied by transcortical magnetic stimulation of the motor cortex while recording from the diaphragm and by phrenic nerve somatosensory-evoked potentials [104].

In general, most EDX studies may be performed safely and with enough details in the ICU to provide sufficient information to guide diagnosis and therapy. Serial studies are often helpful in diagnosis and prognosis.

Plasmapheresis and Intravenous Immunoglobulin in the ICU Setting

Plasmapheresis and intravenous immunoglobulin (IVIG) are the most commonly used treatments in acute neuromuscular paralysis requiring ICU admission, since they are effective in GBS and MG [105, 106]. Other uses for IVIG and plasma exchange include some inflammatory myopathies, paraneoplastic syndromes, and Lambert-Eaton myasthenic syndrome. The usual dose of IVIG is 2 g/kg divided into two to five daily infusions. During plasma exchange, about 40–50 cc/kg of plasma is removed using a continuous flow machine, replacing the plasma with albumin or saline [105, 106]. A series of four to six exchanges on a daily or alternate-day regimen are often administered.

Although IVIG is usually well tolerated by ICU patients with impaired hemodynamics, recognizing its side effects is very important. The most commonly encountered side effects are a flu-like illness with headache, myalgia, malaise, fever, and chills, which respond to the administration of acetaminophen or ibuprofen, diphenhydramine, and intravenous steroids prior to each IVIG infusion [107, 108]. The headache may be so severe and intolerable requiring discontinuing the treatment, although it may occasionally respond to migraine drugs, such as sumatriptan or intravenous dihydroergotamine, prior to IVIG infusion or immediately afterward. More serious adverse reaction may include arterial thrombosis, deep venous thrombosis, pulmonary embolism, stroke, retinal necrosis, aseptic meningitis, leukopenia, and renal failure in patients with baseline renal insufficiency [107, 108]. Hyponatremia is also observed in some patients who received IVIG. More commonly, worsening of hyponatremia, from syndrome of inappropriate secretion of antidiuretic hormone associated with GBS, occurs upon institution of the IVIG. Anaphylaxis due to presence of IgA in IVIG preparations may rarely occur in patients with selective IgA deficiency [107, 108]. It is our practice, as well as some others, to obtain a quantitative serum IgA measurement prior to IVIG therapy. Reversible encephalopathy due to hypertensive crisis or vasculopathy is reported in GBS patients treated with IVIG [108]. Cortical blindness, seizures, and delirium may occur as soon as the first dose of IVIG is completed, and magnetic resonance imaging of the brain during these episodes may show a transient increase in signal intensity in the posterior aspects of the brain. Viral transmission is uncommon, but it may occur and usually the risk is highest for hepatitis C. New methods of preparing IVIG have reduced the risk of transmission of hepatitis C. There are no reported cases of HIV transmission.

Plasma exchange may be associated with a viral-like illness as well, especially in patients with reduced immunoglobulin levels. Hemodynamic instability may occur, more frequently when the patient has unstable blood pressure or autonomic dysfunction. Lightheadedness, dizziness, and cardiac arrhythmias may also occur. Impaired coagulation tests with thrombocytopenia, prolonged prothrombin, and partial thromboplastin time (due to depletion of coagulation factors) are not uncommon [109, 110]. This increases the risk of gastrointestinal bleeding in ICU patients who are usually malnourished, have vitamin K deficiency, and harbor stress gastritis. Electrolyte abnormalities, in particular hypocalcemia and hypomagnesemia, need to be monitored closely since they may worsen the underlying NMD. Complications related to venous access, including infection, bacterial endocarditis, pneumothorax, or thrombosis and thrombophlebitis, are common. Adverse reactions of both plasma exchange and IVIG are summarized in Table 18.7.

Table 18.7 Adverse reactions associated with plasmapheresis and IVIG in ICU

IVIG	Plasmapheresis
Flu-like symptoms: fatigue, malaise	Flu-like symptoms
Severe vascular-like headache	Cardiac arrhythmias
Arterial and venous thrombosis: DVT, pulmonary embolism, stroke, and retinal necrosis	Orthostatic symptoms
Hypertensive encephalopathy	Venous access complication
Aseptic meningitis	Bleeding
Renal failure (if renal function is impaired)	Thrombophlebitis, thrombosis
IgA anaphylaxis	Infection: line sepsis or bacterial endocarditis
Rarely hepatitis C	Pneumothorax, arterial puncture
Electrolyte imbalance: hypocalcemia and hyponatremia	Electrolyte imbalance (mainly Ca^{2+})
	Coagulopathy

Selected Primary Neuromuscular Disorders

NMD requiring admission to the ICU are numerous. Some of these conditions, such as GBS and MG, may present acutely with respiratory failure. Others, such as DMD patients, require hospitalization for intercurrent illness or aspiration pneumonia, which may be related directly to the underlying respiratory muscle dysfunction. Other reasons

for ICU admission include postoperative care (surgical ICU) or cardiac dysfunction (telemetry and cardiac ICU). Critical care aspects of selected NMDs are discussed in the following sections. MG and GBS, common diseases requiring ICU admission, and ALS, a common disease treated with chronic ventilation, are discussed in detail in other chapters.

Inflammatory Myopathies

Critical care issues arise when either the lung or heart is involved in inflammatory myopathies. Dermatomyositis and polymyositis occasionally present with respiratory failure, but more frequently weakness of the intercostals and diaphragm musculature occurs in the course of the disease leading to pulmonary distress and aspiration pneumonia. Moreover, pulmonary fibrosis and pneumonitis or fibrosing alveolitis is reported in 10–30 % of patients. It often occurs when an associated collagen vascular disease is present or in mixed connective tissue disease. Respiratory involvement responds usually only to steroid therapy, but only in half of patients, if instituted early. Pulmonary fibrosis carries a poor prognosis [111]. Overall, inflammatory myopathies associated with pulmonary involvement tend to be more severe and extensive, carrying a poor outcome, and may necessitate early tracheostomy and IPPV.

Cardiomyopathy, myocarditis, or pericarditis may be associated with polymyositis or dermatomyositis. This occasionally leads to congestive heart failure and may aggravate a preexisting respiratory compromise leading to ventilatory failure. Various cardiac conduction abnormalities including atrioventricular heart block, and brady- or tachyarrhythmias, may be seen; some may require pacemaker placement [112]. Close attention to gastrointestinal motility is crucial. Although bulbar muscles are rarely involved, esophageal and gastrointestinal motility may be impaired, leading to dysphagia, malnutrition, and aspiration pneumonia [111, 113, 114].

Muscular Dystrophies

Duchenne muscular dystrophy (DMD) is the most common childhood neuromuscular disorder [115]. Critical care may be needed when patients develop cardiac or respiratory complications. The onset of pulmonary dysfunction is around 17 years of age, but cardiac complications may start earlier. NIF (MIP) is the first parameter reduced on pulmonary function testing, while VC remains normal until late in the course of the disease [1–4, 19, 23]. Maximum static expiratory pressure may correlate with the severity of impaired respiratory mechanics. Pulmonary function test abnormalities may lag behind clinical deterioration, leading to a false sense of security. Nocturnal hypoventilation with hypercarbia and hypoxia is an early manifestation of respiratory compromise, resulting in daytime fatigue, tachypnea, and headache. Management of nocturnal hypoventilation includes preventive measures, such as weight loss, changing sleeping position, and suctioning at home, or the use of noninvasive ventilatory methods. Negative-pressure ventilation to correct nocturnal breathing problems may be poorly tolerated, increase the risk of aspiration pneumonia, and intermittently obstruct the upper airway. Intermittent nasal positive-pressure ventilation or via a mask (IPAP and BiPAP) may not be the optimal treatment but is effective in preventing core pulmonale and delaying tracheostomy. Since structural deformities of trunk, such as kyphoscoliosis, may cause further lung compromise and restrict ventilation, surgical correction often delays the decline in pulmonary function. Treatment of Duchenne muscular dystrophy with prednisolone (0.75 mg/kg/day) may help limb and respiratory muscle strength as evidenced by improvement of pulmonary function tests [115, 116]. Unfortunately, as the disease progresses, continuous mechanical ventilatory support via tracheostomy is the only hope for survival. Occasionally, nocturnal mechanical positive ventilation may suffice.

Cardiac involvement including fibrosis and cardiomyopathy may lead to conduction defects and congestive heart failure. Occasionally, cardiomyopathy is lethal and resistant to medical treatment. EKG abnormalities are present in all patients and include deep narrow Q waves in left precordial leads with increased amplitude of R waves in the V1 lead as discussed earlier.

Gastrointestinal complications due to gastric dysmotility are rare. Acute gastric dilatation may require immediate deflation with gastric and rectal tubes to prevent perforation; constipation and megacolon are uncommon. In advanced stages of the disease, feeding tube and enteral feeding may be required. Complications of enteral feeding and malnutrition further compromise muscle strength and cardiopulmonary function. Measuring total protein, albumin, and prealbumin in peripheral blood on a timely schedule may be necessary to monitor optimal nutrition. Following general anesthesia patients with Becker and DMD may be at risk of developing myoglobinuria, which may mimic malignant hyperthermia (see below) [117].

Limb-girdle muscular dystrophy is a heterogeneous group of muscular dystrophies characterized by progressive proximal muscle weakness in the second and third decades of life [118]. Mutations in the sarcoglycan complex, a cytoskeletal muscle glycoprotein, have been implicated as the cause of muscle dysfunction in about 10 % of patients [119].

Respiratory dysfunction, which rarely requires assisted ventilation, occurs usually late in the disease and parallels the progression of limb weakness. Selective diaphragmatic involvement may occur early in the disease. Scoliosis and kyphosis may also contribute to pulmonary dysfunction.

Sleep apnea, nocturnal hypoventilation, and pneumonia are the most common complications [120]. When respiratory failure occurs, patients may elect tracheostomy with assisted positive ventilation. Cardiac involvement is uncommon, but when present, it is usually manifested by mild congestive heart failure and, rarely, conduction defects [121, 122].

Myotonic dystrophy is the most common adult form of muscular dystrophy, with autosomal dominant inheritance (chromosome 19q13.1 with a CTG trinucleotide repeat) [123]. Pulmonary dysfunction is common but is not as severe as in other forms of muscular dystrophies. Sleep apnea and daytime hypersomnolence may occur, the latter being the most common pulmonary presentation [124]. An abnormal respiratory breathing pattern may present with ataxic, periodic, or Cheyne-Stokes breathing [123, 124]. Reduced sensitivity to hypercapnia and hypoxia with alveolar hypoventilation may be due to a central mechanism.

Patients may present to the ICU with respiratory, cardiac, or gastrointestinal complications or for postoperative care [88]. The combination of respiratory muscle weakness, poor cough and atelectasis, central hypoventilation, and mild bulbar muscle weakness may precipitate acute respiratory failure and aspiration pneumonia. This may require positive-pressure mechanical ventilation via tracheostomy with a lengthy weaning period. Older age and rapidity with which respiratory failure develops predicts poor outcome [88].

Cardiac abnormalities are common, and almost all patients may have EKG abnormalities [88–95]. Malignant bradyarrhythmias may lead to sudden death or recurrent episodes of syncope that require permanent pacemaker placement [88–95]. Phenytoin and quinidine, used to treat myotonia, are associated with lethal arrhythmias particularly if cardiac conduction abnormalities are present, such as heart block and other bradyarrhythmias [94].

Close observation for electrolytes imbalance, including magnesium, is mandatory as part of the ICU care, since such an imbalance may be associated with deleterious cardiopulmonary complications in patients with myotonic dystrophy. Gastrointestinal atony may lead to gastric dilatation and megacolon [123]. Placement of gastric and rectal tubes may be lifesaving. In postoperative care, a gastric tube for decompression is recommended.

In summary, cardiac and pulmonary complications should be monitored closely, with routine pulmonary function tests and EKG yearly. Epidural rather than general anesthesia should be used whenever possible. Careful postoperative care of patients with myotonic dystrophy should include continuous cardiac monitoring as well as gastric decompression until bowel sounds are well established [125, 126].

Emery-Dreifuss muscular dystrophy (EDMD) is a rare form of muscular dystrophy. Patients often have bradycardia, heart block, and other abnormal rhythms which may require permanent pacemaker placement [127–129]. Congestive heart failure and sudden death due to cardiomyopathy are less common [130]. Although respiratory compromise has not been reported in EDMD, this may occur in *rigid spine syndrome*, an entity that resembles EDMD with contractures mainly affecting the paraspinal muscles [131, 132]. Skeletal deformities are common, leading to scoliosis and kyphosis. Subsequently restrictive lung diseases ensue, causing respiratory failure and cor pulmonale [132]. In rigid spine syndrome, death from ventilatory failure occurs. Other patients have been maintained successfully on intermittent positive-pressure ventilation [132].

Respiratory muscle involvement is uncommon and cardiac complications are rare in *facioscapulohumeral muscular dystrophy*. Respiratory complications have been described in two situations [120]: (1) when the weakness is severe or advanced involving the diaphragm, as in aggressive childhood cases, and (2) if the bulbar muscles are weak, leading to aspiration pneumonia [120]. Cardiac arrhythmia may occur leading mainly to atrial bradycardia or standstill [133].

In summary, p*ostoperative care* is of paramount importance in patients with muscular dystrophies, mainly myotonic, limb-girdle, and Duchenne muscular dystrophies [125, 126]. Complications range from gastrointestinal atony to difficulty weaning off mechanical ventilation and cardiac arrhythmia with or without congestive heart failure. Aspiration pneumonia is a common risk in the postoperative period that may further compromise ventilation [125, 126]. Difficulty weaning and respiratory muscle weakness postoperatively may be the first manifestation of muscular dystrophy. If nutritional status is compromised postoperatively, it may be related to poor absorption secondary to gastrointestinal dysmotility. Poor gastrointestinal absorptive function decreases the bioavailability of oral medications, which are more effective if given parenterally. Preoperative assessment becomes even more important in this group of patients with mandatory EKG or 24 h Holter monitoring and pulmonary function tests at baseline. During anesthesia induction, awake intubation is preferable to provide a trigger-free anesthetic and to avoid succinylcholine and halothane. Since these patients are susceptible to malignant hyperthermia, judicious use of opioids and neuromuscular blocking agents is recommended to avoid intractable postoperative complications and a prolonged ventilatory course and complications.

Malignant Hyperthermia

Malignant hyperthermia has been described as a pharmacogenetic disorder of skeletal muscle involving dysregulated myoplasmic calcium, hypercontracture, and hypermetabolism in response to potent volatile anesthetics and depolarizing muscle relaxants [134, 135]. Other precipitating

factors are exertion or heat stress without any clear pharmacologic exposure. Susceptibility to malignant hyperthermia is usually transmitted in an autosomal dominant manner with incomplete penetrance and variable expressivity. The ryanodine receptor (RyR1) gene is the primary, but not only, site for mutations in individuals who are susceptible to malignant hyperthermia. The skeletal muscle RyR1 is located in the membrane of the sarcoplasmic reticulum, and its major function is the release of calcium necessary for contraction. The clinical presentation may be dramatic with a rapid increase in body temperature, widespread muscular rigidity, myoglobinuria, and metabolic acidosis [134, 135]. The risk of developing malignant hyperthermia increases with a positive family history and the presence of central core congenital myopathy (which has also been mapped to chromosome 19) [135]. Lethal malignant hyperthermia may also occur in patients with myotonic and limb-girdle muscular dystrophies. The caffeine contracture injection test may be used to predict susceptibility by exposing fresh muscle fibers from a biopsy and measuring muscle tension. Alternatively, genetic testing can be carried out in high-risk groups [117, 135]. Treatment is usually disappointing and is mainly supportive in addition to the use of intravenous dantrolene at a dose of 2.5 mg/kg. Dantrolene inhibits calcium release from the sarcoplasmic reticulum, which may lead to the relaxation of hypercontracted muscle fibers [134, 135]. Supportive therapy includes fever control, fluid resuscitation, and mechanical ventilation with dialysis if needed.

Acid Maltase Deficiency

Adult-onset glycogen storage disease type II is a metabolic disease caused by 1,4-glucosidase deficiency and manifests with pelvic girdle and truncal weakness. Respiratory symptoms, such as orthopnea, or frank respiratory failure as its initial manifestation is common [136]. Sleep disturbances, including sleep apnea, and frequent pulmonary infections may occur prior to diagnosis. Mechanical ventilation with positive intermittent ventilation may be required. Negative-pressure ventilation, nocturnal ventilation, and rocking bed have been used [136]. Physical therapy is useful in strengthening respiratory muscles.

Periodic Paralysis

Periodic paralysis (PP) is a clinically heterogenous group of disorders characterized by recurrent attacks of weakness and impairment of electrolyte channels transport in muscle membrane [137]. These include hypokalemic and hyperkalemic PP and paramyotonia congenita. Hyperthyroidism and thyrotoxicosis can precipitate severe attacks of weakness with hypokalemia that occurs primarily in oriental adults.

Respiratory involvement is uncommon in hyperkalemic PP and paramyotonia congenita [138], while cardiac involvement with frequent premature ventricular contractions, bigeminy and tachycardia may occur [139]. Treatment includes glucose and insulin infusion. Prevention is aimed at maintaining serum potassium concentration within the normal range to avoid cardiac arrhythmias and muscle weakness. This can be accompanied by increased ingestion of carbohydrates. In contrast, hypokalemic PP may involve respiratory muscles that leads to ventilatory failure and death [140]. Cardiac monitoring is recommended during attacks to evaluate EKG changes associated with hypokalemia, including flattening of T waves and the presence of U waves [140]. Acute treatment during the attack includes close respiratory and cardiac monitoring and potassium supplementation, which may be enhanced by use of 5 % mannitol diluent [137]. Avoiding carbohydrates and taking acetazolamide and oral potassium supplements can prevent attacks.

Secondary Neuromuscular Disorders

Several NMDs manifest following an admission to the ICU (Table 18.8). Secondary NMD are more frequent than the primary disorders and are more likely to be reversible and respond to treatment [141, 142].

Electrolytes and acid–base disturbances are frequent occurrences in critically ill patients. Muscle weakness is common with hypokalemia, hypophosphatemia, and hypomagnesemia. Hypocalcemia and acidosis are associated with muscle weakness and tetany. The latter may contribute to difficult weaning from artificial ventilation [141, 142]. Correcting electrolyte abnormalities is crucial in critically ill patients who are already at risk for neuromuscular complications.

Some medications administered to severely ill patients may be toxic to muscles, neuromuscular junction, and nerves (Table 18.9) [143]. Cyclosporine and cholesterol-lowering agents may lead to a myopathy with mitochondrial disruption. Antipsychotics including phenothiazines are associated with necrotizing myopathy and CK elevation [143]. Procainamide and beta-blockers, commonly used to control arrhythmias and blood pressure, may affect neuromuscular junction. Antibiotics including aminoglycosides, polypeptide antibiotics (colistin and neomycin), and quinolones may compromise the function of neuromuscular junction. Anticonvulsants may interfere with neuromuscular transmission and exacerbate the muscle weakness in MG. Carbamazepine overdose may cause reversible neuromuscular disease with respiratory failure [103]. Chronic steroid myopathy may cause quadriplegia and lead to respiratory

Table 18.8 Secondary neuromuscular disorders in intensive care

Muscle	Neuromuscular junction	Nerves	Spinal cord
Cachectic myopathy	Hyper-/hypomagnesemia	Critical illness polyneuropathy	Postoperative infarction[a]
Hyper-/hypomagnesemia	Hypophosphatemia	Nutritional deficiency: thiamine	Nutritional
Hypokalemia	Neuromuscular blockers	Hepatic dysfunction/uremia with uncontrolled diabetes[a]	Traumatic
Hypophosphatemia	Calcium channel blockers	Drug induced[a]	Drug induced[a]
Critical illness myopathy	Aminoglycosides	Paraneoplastic[a]	Paraneoplastic[a]
Steroid myopathy	Quinolone antibiotics	Sepsis with chronic polyneuropathy	
Drug-induced myopathy[a]	Antiarrhythmic: procainamide		
Septic myopathy	Beta-adrenergic blockers		
Rhabdomyolysis[a]			

[a]Disorders that may be the primary presentation to the ICU or secondary complications that occur after admission

Table 18.9 Agents that may be associated with neuromuscular weakness in ICU patients

Antimicrobials
Aminoglycosides
Fluoroquinolones
Nitrofurantoin
Metronidazole
Isoniazid
Antimalarial
Amphotericin B
Antineoplastics
Vincristine
Cis-platinum
Taxol
Anticonvulsants
Phenytoin
Phenobarbital
Carbamazepine
Antiarrhythmic and cardiac medications
Amiodarone
Procainamide
Beta-blockers
Diuretics

Table 18.10 Common causes of acquired rhabdomyolysis

Toxic/drugs
Drugs: epsilon aminocaproic acid, neuroleptic drugs, clofibrate, lovastatin, plasmacytoid, barbiturates, propofol
Toxins: alcohol, toluene, heroin, amphetamine, cocaine, and phencyclidine
Traumatic
Head injury
Fall, crush syndrome
Convulsions
Electric shock, lightning stroke
Prolonged myoclonus
Burns
Vascular
Disseminated intravascular coagulation
Compartment compression syndromes
Ligation of vena cava
Metabolic
Diabetic ketoacidosis
Hypothermia/hyperthermia
Hypokalemia
Infections: toxic shock syndrome, viral, bacterial

muscle weakness. Supportive treatment and discontinuation of steroids would restore muscle strength and facilitate weaning process [141, 142].

Rhabdomyolysis may represent an inherited or acquired susceptibility to necrosis of striated muscles. In the ICU, this condition is seen in association with neuroleptic drug administration, prolonged coma, and head injury [144]. Other precipitating factors include hypernatremia, increased osmolality, hypokalemia, alcohol, propofol and hypoxia during artificial ventilation [145]. A list of common causes of rhabdomyolysis is presented in Table 18.10. Clinical features include myalgias, malaise, generalized muscles weakness, respiratory muscle weakness, fever, myoglobinuria, elevated CK, anuria, hyperkalemia, hypercalcemia, azotemia, and renal failure. Weakness may outlast other symptoms. Supportive care is the mainstay of treatment, with forced diuresis using mannitol or hemodialysis whenever electrolyte abnormalities occur. Recurrence may occur and is usually triggered by increased physical activity [144].

Sepsis is common in the ICU and may cause widespread muscle weakness in patients not exposed to any myotoxic agents and with normal electrolytes [146, 147]. Respiratory failure and difficult weaning may accompany muscle weakness. The risk of sepsis-induced myopathy becomes quite high with multiple organ failure. Rarely, isolated ventilatory failure occurs, although needle EMG may reveal subclinical widespread muscle involvement [146]. Specific organisms that have been incriminated include *Escherichia coli*, Leptospira, Legionella, and *Staphylococcus aureus* [146]. Muscle enzymes may be normal or mildly elevated; needle EMG shows myopathic pattern and occasionally a mixed picture of axonal neuropathy and myopathy. Histological findings on muscle biopsy occasionally reveal microabscesses. The disease mechanism is unclear, but interference with energy utilization of muscle is suspected. Other

contributing factor may include an increase in muscle necrosis by increased muscle catabolism and proteolysis [146, 147]. Treatment involves therapy for the underlying conditions and use of supportive measures, in addition to avoiding, if possible, neuromyotoxic agents, and correcting electrolyte disturbances.

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Part IV

Neuromuscular Disorders: Neuronopathies (Motor Neuron and Dorsal Root Ganglion Disorders)

Poliomyelitis and Post-poliomyelitis Syndrome

19

Kanokwan Boonyapisit

Introduction

Poliomyelitis is a highly contagious systemic infection caused by a virus of the enterovirus subgroup. The poliovirus is transmitted by fecal-oral route and causes systemic symptoms characterized by fever and malaise. In a small proportion of patients, the virus infects the central nervous system producing meningitis and acute progressive lower motor neuron weakness. Epidemics of poliomyelitis were common in the first half of twentieth century, but with the introduction of effective polio vaccination in 1955, poliomyelitis epidemics are no longer seen in developed countries but still occur in parts of sub-Saharan Africa and the Indian subcontinent.

In the last two decades, a syndrome characterized by slowly progressive weakness, fatigue, and pain, which develops decades after acute paralytic poliomyelitis, has been described. The condition is now a widely accepted entity and is known as post-poliomyelitis syndrome or post-polio syndrome.

Poliomyelitis

Etiology and Pathogenesis

Poliomyelitis is caused by the poliovirus, one of the single-stranded RNA viruses in the enterovirus subgroup of the picornaviruses [1–4]. All three serotypes of poliovirus can cause acute paralytic poliomyelitis. Poliovirus is transmitted through fecal-oral route with high infectivity rate. The virus enters the lymphatic system in the pharynx or intestine and then spreads to the central nervous system by a hematogenous route [4]. The typical clinical presentation begins with prodromal symptoms of fever and malaise, followed by manifestations of meningitis. In a small proportion of patients, the poliovirus affects the anterior horn cells and brain stem nuclei causing acute progressive lower motor neuron weakness of limb and bulbar muscles and generalized hyporeflexia [1–3].

Poliomyelitis epidemics usually occur in late summer. Before the development of polio vaccine, epidemics occurred most frequently in northern countries and primarily affecting children older than 6 months, teenagers, and young adults [1, 2]. Poliomyelitis has now nearly been eradicated. The majority of cases derive from the Indian subcontinent and some African countries [5–8]. All poliomyelitis infections that occur now in North America and European countries are due to the oral polio vaccine (OPV), which carries a risk of one active infection per 2.5 million doses. Immunocompromised patients and persons with incomplete vaccination may develop poliomyelitis from close contact with vaccine-induced poliomyelitis patients [9–11].

Clinical Manifestations

The clinical manifestations of acute poliomyelitis start after an incubation period of 3–6 days after ingestion of the poliovirus. For vaccine-induced poliomyelitis, the incubation period is longer with manifestations 2–3 weeks after vaccination [3]. Among immunocompromised patients, the time between vaccination and development of disease can be up to 6 months or longer [9, 10].

After exposure to the virus, the virus multiplies in the pharynx and lymphatic tissue of the intestine for few weeks before it is contained by immune response. Ninety percent of patients will only have viremia without symptoms. Fever, malaise, sore throat, headache, and diarrhea occur in 10 % of patients and last typically 2–3 days without progression to central nervous system infection. In a few percent of patients, the virus enters the central nervous system causing meningi-

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tis, which usually resolves spontaneously in 1–2 weeks [1–3]. The infection progresses to anterior horn cell involvement causing acute paralytic poliomyelitis in 0.1–1 % of all individuals infected with the poliovirus [1, 2, 12, 13].

Acute progressive weakness often occurs after the prodromal symptoms subside or few days after the onset of clinical meningitis but can occur as late as 2–3 weeks after initial symptoms [3, 13]. The weakness progresses over hours to days to severe weakness of the extremities, which often is asymmetric, accompanied by areflexia. Prominent neck and back pain is common prior to the onset of weakness. Bulbar weakness causing dysphagia and dysphonia occurs in 10–15 % of the patients, although facial weakness is less common [1]. The common distribution of weakness differs among age groups. Severe weakness of the lower extremities is more common in young children, whereas weakness of upper and lower extremities is more common in older children and young adults. Autonomic dysfunction, which is the result of involvement of brain stem nuclei, can be found in small proportion of the patients [3]. Respiratory failure occurs in patients with severe general weakness.

Neurological examination reveals weakness, decreased muscle tone, and hypoactive deep tendon reflexes in the affected extremities. Fasciculation can sometimes be seen even early in the course of weakness. Muscle atrophy develops in a few weeks. Sensory examination is normal, although some patients may have complaints of sensory disturbance.

Improvement of muscle strength begins a few weeks after infection and maximal recovery is seen in 6–9 months. Up to 60–70 % of the patients with acute paralytic poliomyelitis have prominent residual weakness [1–3].

Differential Diagnosis

The differential diagnosis for acute poliomyelitis includes neurological conditions that present with acute progressive lower motor neuron weakness such as Guillain-Barre syndrome, acute transverse myelitis, botulism, tick paralysis, and myopathies (Table 19.1) [1, 2, 14, 15]. Acute progressive weakness associated with other viral infections such as other enteroviruses (e.g., enterovirus 71, coxsackievirus A7) and flaviviruses (e.g., Japanese encephalitis) can mimic symptoms of acute paralytic poliomyelitis [16]. The emergence of West Nile virus, which also belongs to the flavivirus family and can affect anterior horn cells, needs to be considered in North American and European countries [17].

Diagnostic Evaluation

Cerebrospinal fluid examination in poliomyelitis shows increased protein and pleocytosis, which is neutrophil predominance followed by lymphocytic predominance. An abnormal CSF examination differentiates poliomyelitis from several causes of acute progressive flaccid paralysis in particular Guillain-Barre syndrome [1–3].

Isolation of the poliovirus from throat culture, stool culture, and CSF culture can provide confirmation for the diagnosis. The throat culture and stool culture are more sensitive than CSF culture for viral isolation. Serum antibody titers for poliovirus can also be used for confirmation of the diagnosis, if there is a fourfold elevation in the titers between acute and convalescent specimens.

The electrodiagnostic studies in poliomyelitis reveal changes consistent with acute neurogenic process, involving only motor component and sparing the sensory. Sensory conduction studies are all normal. Motor conduction studies often show reduced compound motor action potential (CMAP) amplitudes in weak muscles. Needle electromyography (EMG) reveals reduced recruitment of motor unit action potentials (MUAP) in the affected muscles, although the morphology of MUAP is still normal, which reflects the acute process. Prominent fibrillation potentials can be seen in the affected muscles few weeks after the onset of weakness [1, 18].

Table 19.1 Differential diagnosis of acute paralytic poliomyelitis

Spinal cord
Acute transverse myelitis
Spinal cord compression
Other acute spinal cord syndromes, e.g., spinal cord infarction
Anterior horn cells
Viral infection
Enterovirus: poliovirus, enterovirus 71, coxsackievirus A7
Flavivirus: West Nile virus
Nerve
Infection
Diphtheria
Rabies
Guillain-Barre syndrome
Critical illness neuropathy
Porphyria
Heavy metal poisoning: arsenic, thallium
Neuromuscular junction
Botulism
Myasthenia gravis (severe cases)
Muscle
Inflammatory myopathy (severe cases)
Critical illness myopathy

Treatment and Prognosis

There is no specific treatment for acute poliomyelitis. Patients with symptoms of CNS infection or acute paralysis should be hospitalized under close observation for signs of respiratory insufficiency or autonomic dysfunction. Patients

with respiratory failure will need respiratory support in the intensive care unit. Good supportive care to prevent complications from prolonged immobilization and early rehabilitation is essential. Rehabilitation is important during the recovery period to improve physical strength and minimize deformities and contractures in affected limbs [1–3].

Mortality from poliomyelitis has improved over time due to advances in critical care. The mortality rate is often greatest in the first week due to respiratory failure and presence of circulatory insufficiency secondary to autonomic failure. Other causes of mortality are related to hospital-acquired infection and complications from prolonged immobilization [1, 2].

Prevention

In 1956, Jonas Salk introduced the trivalent inactivated polio vaccine (IPV). The Salk vaccine is administered by injection and stimulates serum IgM, IgG, and IgA directed against the virus. However, the Salk vaccine is less effective for stimulating secretory IgA, which is an important defense when the poliovirus enters the oropharynx.

Albert Sabin developed the oral live-attenuated polio vaccine (OPV), which replaced the Salk vaccine in 1962. The Sabin vaccine contains live-attenuated strains of polioviruses 1, 2, and 3, which are grown in cell culture. Multiple dosages of vaccination are required to ensure the development of immunity to all strains. The Sabin vaccine is more effective in stimulating the local secretary IgA, and the virus is excreted in the feces for 6–8 weeks after vaccination, which can also lead to immunity in close contacts. However, viral shedding carries a risk of vaccine-associated poliomyelitis in contacts who are immunocompromised [2, 3].

After the introduction of both vaccines, the polio epidemics from wild-type poliovirus have been nearly eradicated. The last major poliomyelitis outbreak in the USA occurred in 1952 prior to vaccine development [19–25]. Despite the effort of the WHO global eradication initiative since 1988 [26–28], cases continue to occur in the Indian subcontinent or African nations due to inadequate immunization programs [5–8]. All poliomyelitis reports from North America and Europe have been vaccine-associated poliomyelitis secondary to the live-attenuated polio vaccine [9, 11, 25, 27].

Currently the inactivated polio vaccine used in western countries is an enhanced potency inactivated poliovirus vaccine (IPV-e), which causes less viral shedding and provides better immunity against poliovirus compared to the OPV [3]. IPV-e is indicated in immunocompromised patients and children with immunocompromised close contacts. The IPV-e should be used in adults, since adults are generally more susceptible to vaccine-associated poliomyelitis after receiving OPV. In many countries in the North America and Europe, Australia, New Zealand, and Japan, the IPV-e is now replacing the OPV or is used in conjunction with OPV in the immunization schedule for children to enhance the efficacy of disease prevention and to reduce the occurrence of vaccine-associated paralytic poliomyelitis [29–31].

Post-poliomyelitis Syndrome

This syndrome is characterized by new weakness, fatigue, and pain, which develops several years after acute paralytic poliomyelitis in the region previously affected by acute poliomyelitis [32–40]. Patients may also have several other symptoms, sometimes outside the affected region including dysphagia, dysarthria, muscle cramps, fasciculation, generalized fatigue, and sleep abnormalities [34–40]. After first description by Cornil and Raymond in 1875, post-poliomyelitis was subsequently named "post-poliomyelitis syndrome" or "post-polio syndrome." The existence of the syndrome had first been questioned, but the post-polio syndrome is now generally accepted as a well-defined clinical entity. Epidemiologic studies of post-polio syndrome have been difficult due to poorly established diagnostic criteria. Estimates of prevalence of post-polio syndrome vary from 20 to 85 % of patients with prior poliomyelitis [33, 41–45]. Understanding of post-polio syndrome has expanded over the past two decades [46], but many aspects of clinical aspects, pathogenesis, optimal treatment, and quality of life are lacking.

Etiology and Pathogenesis

The primary underlying pathogenesis for weakness in post-polio patients is ongoing denervation of the motor units; however, the exact pathogenesis of post-polio syndrome is unclear. A widely accepted mechanism for denervation [47–50] is distal axonal degeneration in the enlarged motor units after the extensive reinnervation process that occurs after acute poliomyelitis. Terminal axonal degeneration at the motor nerve terminals can explain several clinical features in post-polio syndrome. The degeneration of distal motor axon results in slowly progressive weakness in the previously affected muscle groups. Dysfunction of motor nerve terminals, which causes defects in the neuromuscular transmission, may explain the symptoms of fatigability [50, 51].

In the patients with a history of poliomyelitis and no deterioration, the reinnervation process is effective due to sprouting of distal axons. The motor unit size may be seven to eight times greater than the normal motor unit, and muscle fiber grouping occurs but the size of muscle fibers is normal. Although the denervation process occurs within these large motor units, reinnervation also occurs by sprouting from neighboring axons. This continuous remodeling occurs in all enlarged motor units among patients with prior poliomyelitis. When the denervation process exceeds the reinnervation

process, distal axonal degeneration occurs, and followed by reduction of the motor unit size, atrophy of muscle fibers and symptoms of post-polio syndrome develop [35, 49]. The proposed theory of terminal axonal degeneration in the enlarged motor units in post-polio patients is supported by electrodiagnostic studies that demonstrate defects in neuromuscular transmission, such as increased jitter on single-fiber electromyography and abnormal decremental responses on repetitive nerve stimulation [36, 49–54]. However, the evidence of active denervation is also seen in the stable post-polio patients, which is contrary to the hypothesis that states that active denervation occurs to a greater extent in newly weak muscles [49].

Besides distal axonal degeneration, there are other less well-accepted theories for pathogenesis of post-polio syndrome [37–39]. One theory proposes motor neuron loss due to normal aging, but because of limited amount of motor neuron reserve due to prior poliomyelitis, weakness develops. Old age was found as one of the risk factors for post-polio syndrome [55]. However, other studies have found that age was only a confounding factor for the development of post-polio syndrome [43]. The studies estimating motor unit number in post-polio patients offer conflicting results. A significant reduction of motor units over a 2-year follow-up was found [56] when compared to motor unit loss among normal, age-matched subjects, and another did not show significant loss of motor units over a 15-year period [57].

Immunological mechanisms have been proposed, but support is limited for such a pathophysiology. Pathologic evaluation has shown evidence of inflammation in the spinal cord [58]. However, the etiology of inflammation is uncertain [59]. There is also conflicting evidence of whether an intrathecal immune response is present among patients [60–62].

Clinical Manifestations

The frequency of post-polio syndrome has been estimated to be as high as 64–85 % of patients with a history of poliomyelitis [43], but significant disability is estimated to occur 20–40 % of patients [33, 41, 42, 45]. The onset of symptoms typically occurs several decades after acute poliomyelitis [32] with a range of 8–71 years (mean interval of 36 years) and tends to be shorter in patients with severe weakness [34]. Patients with post-polio syndrome often have a variety of new symptoms, but the most frequent are weakness, fatigue, and pain [33–43]. Fatigue in post-polio syndrome can be generalized or limited to the affected muscles and appears to be the most disabling symptom [32, 33]. Fatigue can occur in up to 90 % of patients and can lead to significantly compromised quality of life. Generalized fatigue is often described as exhaustion, similar to that of flu-like illness [63]. Fatigue usually is worse after physical activities and in some individuals associated with increased sleep requirement and decreased concentration. Muscular fatigue is described as reduced endurance and increased weakness in the affected muscles after exertion, which improves with rest [64–67]. New weakness in patients with post-polio syndrome most commonly involves the previously affected muscles but can also involve the normal muscles, which may have been subclinically affected by acute poliomyelitis. Weakness typically progresses gradually. Episodic weakness is described by some patients, which is likely related to fatigue and reduced muscle endurance [34, 35, 39, 40].

Pain in the muscles and joints is common [68–70]. Muscle pain is described as aching after physical activity and muscle cramps. Some patients have a fibromyalgia-type syndrome [71]. Joint pain is often secondary to osteoarthritis, tendinitis, or bursitis after chronic overuse of the affected limbs.

Muscular atrophy, dysarthria, dysphagia, respiratory insufficiency, cold intolerance, muscle cramps, and fasciculation are also observed among some patients. Dysarthria and dysphagia occur in many regardless of whether there was bulbar involvement at the time of acute poliomyelitis [72]. Detailed testing of oropharyngeal function has shown abnormalities, although aspiration is rare and weight loss secondary to dysphagia usually does not occur. Respiratory dysfunction are described in up to 40 % of patients and appear to be more common in patients with prior history of respiratory failure during acute poliomyelitis [73]. Cold intolerance, probably secondary to decreased heat production in the atrophic limbs due to poorly developed circulation, is described in 30–60 % of the patients. Increased stress, anxiety, and insomnia are common. Depression is associated with greater pain and overall poor medical status [74].

Patients with significant weakness gradually become more inactive and disabled. Many patients gain weight. Ambulation especially climbing stairs is affected, and activities of daily living (e.g., cooking, writing, driving) are compromised. Adaptation in lifestyle and assistive devices may be needed in this group of patients.

Differential Diagnosis and Evaluation

There is no specific laboratory investigation that confirms the diagnosis of post-polio syndrome. In 1997, the Post-Polio Task Force developed diagnostic criteria, which required several specific clinical features and exclusion of medical, orthopedic, or neurological conditions that may cause similar weakness, fatigue, and pain [75, 76](Table 19.2). Diagnostic criteria for post-polio syndrome has not been well validated. A detailed clinical history of prior paralytic poliomyelitis is crucial and should first be confirmed in each patient. If a previous history poliomyelitis is uncertain, the examination should reveal evidence of motor neuron loss (muscle atrophy,

Table 19.2 Proposed diagnostic criteria for post-polio syndrome

1. A history of prior episode of paralytic polio with residual motor neuron loss, which can be confirmed through a typical patient history, a neurologic examination, and an electrodiagnostic examination
2. A period of neurologic recovery followed by an interval (usually 15 years or more) of neurologic functional stability
3. A gradual onset of new weakness and/or abnormal muscle fatigability and decreased endurance, with or without generalized fatigue, muscle atrophy, and/or pain
4. Exclusion of medical, orthopedic, and/or neurologic conditions that may be causing the symptoms mentioned in step 3

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Table 19.3 Differential diagnosis of post-polio syndrome

Adult spinal muscular atrophy
Amyotrophic lateral sclerosis
Multiple sclerosis
Spinal cord tumor
Spinal stenosis
Radiculopathy
Cauda equina syndrome
Multifocal motor neuropathy with conduction block
Chronic inflammatory demyelinating polyneuropathy
Entrapment neuropathy
Heavy metal toxicity
Myasthenia gravis
Inflammatory myopathy

weakness, decreased or loss of deep tendon reflexes), and the other possible clinical conditions that may mimic post-polio syndrome should be excluded, such as hypothyroidism, rheumatoid arthritis, polymyalgia rheumatica, and inflammatory myopathies. Neurological disorders, which may be confused with post-polio syndrome, are shown in Table 19.3.

Appropriate laboratory investigation to exclude other disorders (Tables 19.2 and 19.3) should be performed. Serum creatine kinase is often mildly elevated among post-polio patients, but those with significant elevations require evaluation for a myopathy [77, 78].

Electrodiagnostic study (EDX) is a useful tool for exclusion of other neurological conditions. However, conventional EMG and single-fiber EMG cannot differentiate between stable post-polio patients and those with new weakness. Nerve conduction studies usually reveal decreased amplitude of compound motor action potential with preserved latencies and conduction velocities. Sensory nerve action potentials are normal. Needle EMG generally reveals evidence of ongoing denervation (e.g., fibrillation potentials) and chronic reinnervation (e.g., large motor unit action potentials with reduced recruitment). Fasciculations can be seen in affected muscles, although usually are not prominent. These EDX findings can be seen in several chronic progressive neurologic condition affecting anterior horn cells (e.g., amyotrophic lateral sclerosis, adult spinal muscular atrophy) and are not specific to post-polio syndrome. However, EDX can be used to exclude several neurologic conditions (e.g., chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy with conduction blocks, entrapment neuropathy, myasthenia gravis, and inflammatory myopathy). Single-fiber EMG shows increased jitter and blocking in post-polio syndrome, but these abnormalities are not specific and may be seen in many other neurological diseases [49, 50, 79–82].

All patients with breathing complaints should undergo pulmonary function evaluation, since even patients without respiratory complaints may have respiratory insufficiency [83]. Patients with a vital capacity below 55 % of normal should have more extensive evaluation such as measurement of vital capacity in sitting and supine position and arterial blood gas [84, 85]. The presence of hypercapnia is a predictor of poor outcome and increased risk of respiratory failure [85, 86].

Patients with excessive daytime sleepiness and other symptoms suggestive of obstructive sleep apnea (e.g., snoring, morning headache) should undergo a polysomnogram, since obstructive sleep apnea can be found in up to 7.3 % of polio survivors [87]. Disturbance of sleep in post-polio syndrome can be secondary to primary obstructive sleep apnea or hypoventilation or both [87, 88].

Swallowing evaluation is required in patients with complaints of dysphagia [89–91]. Laryngeal and voice assessment may also be necessary for such patients [90].

Plain X-ray of the spine and joints assists in evaluation of scoliosis and joint dysfunction. Assessment with CT or MRI may be indicated in some patients to exclude other causes of back, neck, or limb pain including spinal stenosis, cervical myelopathy, and radiculopathy.

Treatment

Currently, there is no specific treatment for post-polio syndrome. Management of weakness, fatigue, pain, and other physical disabilities is best performed through interdisciplinary programs [35, 39, 40]. An investigation of 70 post-polio patients followed on average for about 2 years demonstrated improvement or resolution of symptoms, and manual muscle testing confirmed increased strength in 30 patients with good compliance to treatment protocols, while in the partial complier group ($n=32$) and noncompliant group ($n=15$), there is no change or a decline in strength with worsening of symptoms [92].

An interdisciplinary team usually involves the primary care physician, neurologist, physical therapist, psychiatrist, orthopedist, rheumatologist, pulmonologist, occupational therapist, social worker, dietician, occupational therapist, orthotist, nurse, and respiratory therapist. Education for

patients on how to keep their activities and exercise program in balance and avoid muscle overuse is required. Sections below focus on specific major issues in the care of patients [35, 39, 40, 93–97].

Management of Weakness

Exercise for post-polio patients had been a controversial subject, because of concerns that overuse would increase weakness; however, beneficial effects of various types of exercise programs have been shown. Controlled studies have shown the benefits of aerobic exercise such as bicycling, treadmill walking, and aquatic exercise in post-polio patients [98–103]. Uncontrolled studies demonstrate benefit for isotonic, isokinetic, and isometric exercises. The isotonic exercise may strengthen muscles that are mildly affected, whereas isometric exercise may strengthen muscles over painful joints [104–108]. Stretching maintains or even improves range of motion. Therapists should monitor to ensure that exercise is performed appropriately. Muscle overuse should be avoided and can be avoided by pacing, reduction of activities, and energy conservation techniques [35, 39, 40, 95–97, 109].

Orthosis and assistive devices are useful for improving mobility and activity of daily living and can be beneficial to reduce pain, joint deformities, and gait difficulties [110, 111]. Assistive devices aid in conservation of energy [112]. An ankle-foot orthosis will improve function related to ankle dorsiflexion weakness, while a locked knee orthosis or a locked knee-ankle-foot orthosis will benefit patients with quadriceps weakness [113, 114]. Crutches and wheelchairs will also improve mobility.

Management of Fatigue

Excessive fatigue is helped through energy conservation techniques: reduction of activities, resting periods during daytime, relaxation techniques, and improvement of sleep quality. Energy conservation methods involve modification of environments and activities by living on one floor, use of automatic machines for household activities, handicapped parking, and electric scooter use for a long distance. A balance must be struck between activity and prolonged muscle use that leads to fatigue. A rating scale, such as the Borg Rating Scale of Perceived Exertion (RPE), can be used to evaluate patients' perception of fatigue. RPE is a 15-point scale, which ranges from 6 to 20, with 6 indicates the lowest effort and 20 indicates the highest effort to perform activities. Patients are generally instructed to keep their daily activities or exercise below the RPE level of 14 to avoid excessive fatigue [115, 116].

Pain Management

Muscle overuse is probably the most common cause of pain. In patients who walk, pain occurs primarily in the lower extremities and low back and associated with increased exertion and faster walking speed [117]. Muscle pain in post polio is usually described as deep aching sensation within the muscles. Pain from muscle cramps, fasciculation, and fibromyalgia also occurs. Cramps and fasciculation are often related to muscle overuse and can be managed by reduction of activities, pacing, and using orthosis or assistance devices. Pain of fibromyalgia usually requires interdisciplinary approaches [71].

Other frequent causes of pain in post-polio patients occur from joint and soft tissue abnormalities. Osteoarthritis, tendinitis, and bursitis can occur secondary to joint deformities or prior history of joint fusion. Osteoarthritis of wrist and hand is common in older patients especially those who require assistance devices for walking [118]. Joint pain in post-polio patients can be managed by physical therapy, strengthening exercises of the surrounding muscles, orthosis to control deformities, and nonsteroidal anti-inflammatory drugs. Steroid injection and surgery are rarely required.

Superimposed neurological disorders, which may result from overuse, may also produce pain. Entrapment neuropathy (e.g., carpal tunnel syndrome, ulnar neuropathy) and radiculopathy occur in a good portion of post-polio patients, and each condition requires specific treatment for the particular disorders [80, 119].

Other Treatment Issues

Respiratory insufficiency is caused by muscle weakness and further exacerbated by sleep-disordered breathing, scoliosis, and kyphosis [83, 84]. Central hypoventilation rarely occurs. Problems with respiration often occur among patients who had required ventilation during acute poliomyelitis. Noninvasive ventilation may be indicated in those with significant hypoventilation [73, 120–122]. Obstructive sleep apnea should also be monitored for and treated. All post-polio patients should receive pneumococcal and influenza vaccinations.

Up to 20 % of post-polio patients have complaints of dysphagia [123], which can occur even without history of previous bulbar polio [72, 124]. Formal speech therapy provides advice regarding swallowing techniques and diet modification including purees or thickened liquids for those with severe swallowing difficulties [35, 96].

Psychosocial Issues

Many polio survivors are high achievers. Studies from several countries indicate that individuals with a history of polio have higher educational levels and higher rates of employment and marriage than other disabled populations [125–127]. Patients with post-polio syndrome may need to adjust to the added disabilities caused by the syndrome. Attitude toward the disability and family support are important influencing factors for overall life satisfaction. Depression, which is not common in patients with previous poliomyelitis, may occur

with post-polio syndrome [74, 128–130]. Interdisciplinary support through psychiatrist, psychologist, social worker, and patient groups is beneficial.

Lifestyle changes and adaptation are important. Weight reduction or stabilization program can reduce fatigue and increase mobility in overweight patients [95–97]. Modification in lifestyle may reduce symptoms from muscle overuse [131], but this should be balanced with an active lifestyle to support psychological well-being [132]. Occupational and vocational rehabilitation may be needed in some individuals [133].

Pharmacotherapy

Controlled trials of various pharmacological treatments have been performed. Challenges exist in performance of the clinical trials in post-polio syndrome. Disease progression is slow leading to the need for long evaluations. Also, there is great variation in clinical presentations, and measurement of outcome at times depends on the patients' subjective assessment.

The Cochrane Neuromuscular Disease Group reviewed the randomized and quasi-randomized trials of pharmacological treatment for post-polio syndrome and concluded that there is inadequate evidence to support the effectiveness of treatment options [134]. The pharmacologic agents reviewed were modafinil, intravenous immunoglobulin (IVIG), pyridostigmine, lamotrigine, amantadine, and prednisone. Two randomized controlled trials of modafinil found no benefit for reduction of activity limitation, fatigue, and pain compared to placebo [135, 136]. Pyridostigmine at doses of 180–240 mg/day was no different than placebo in a study of 126 subjects although there was benefit shown in some secondary outcome measures [137]. Pyridostigmine did not reduce fatigue subsequent smaller trials [138]. Lamotrigine has shown some positive effects on activity limitation and pain in an open-label study [139]. High-dose prednisone was not effective for fatigue in a small placebo-controlled trial of 17 subjects [140], and amantidine in a randomized controlled trial of 25 subjects did not demonstrate effectiveness [141]. IVIG in two randomized controlled trials using two infusions of 90 g or one infusion of 2 g/kg showed no beneficial effects on activity limitations. For muscle strength and pain, the two studies were contradictory [142, 143], therefore, more studies are needed to investigate the efficacy of IVIG in this patient population. Other pharmacologic treatments evaluated in small case series are carnitine, neurotrophic factor recombinant human insulin-like growth factor I [144], growth hormone [145], bromocriptine [146, 147], and coenzyme Q10 [148]. None showed benefit.

Prevention of Complications

Post-polio patients are at increased risk for osteopenia, osteoporosis, and fractures [149–151]. Bone density evaluation should be performed, and treatment of osteoporosis should be initiated if significant bone density reductions exist [152]. Patients with a prior history of polio also are at higher risk of falls and injuries [151]. Advice from physical therapy regarding fall precaution is essential and can help preventing serious injuries from falls.

Prognosis

Progression of post-polio syndrome is generally slow [153–155]. In some cases, disability can stabilize [57, 156, 157]. Associated conditions such as depression, entrapment neuropathy, and orthopedic or rheumatologic complications can cause functional deterioration in patients with post-polio syndrome, which with proper therapy of these conditions should have beneficial effects on their clinical outcome.

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Amyotrophic Lateral Sclerosis

20

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Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder that primarily affects motor neurons. The characteristic form of this devastating disorder features the simultaneous presence of both upper and lower motor neuron signs with progression from one region of the neuraxis to the next and eventual death, typically from respiratory compromise. This condition first appeared in the literature in 1850 when François Aran reported a family of 11 patients of the ALS subtype, progressive muscular atrophy (PMA) [1]. Amand Duchenne first described progressive bulbar palsy (PBP) a decade later [2]. In 1869, Jean Martin Charcot, professor of neurology at the Salpêtrière, comprehensively described both the clinical and pathological features of classic ALS, and, a few years later, Heinrich Erb first described primary lateral sclerosis (PLS), a condition felt to be a subtype of ALS rather than a distinct separate entity [3, 4]. The term *motor neuron disease* was coined by Brain in 1933 to unify PMA, PBP, PLS, and ALS under one name [5]. Lou Gehrig, an American baseball player named "Iron Horse," was diagnosed with ALS in 1939, although the eponym "Lou Gehrig's disease," perhaps in response to efforts to increase public awareness of the condition, did not come into popular use for another 35 years [6]. In the 1950s, epidemiological studies identified the presence of a condition characterized by a combination of ALS, parkinsonism, and dementia in several distinct regions of the Western Pacific including the Marianas Islands, the Kii Peninsula of Japan, and the Irian Jaya region of New Guinea [7–9]. A great breakthrough in the understanding of ALS came when, in 1993, Rosen et al. showed that 15–20 % of familial ALS patients manifest a mutation in the Cu/Zn superoxide dismutase (SOD1) gene located on chromosome 21 [10]. Since then, multiple different SOD1 mutations have been discovered [11] along with mutations in other "ALS" genes including FUS, optineurin, dynamin, and C9ORF72.

There has always been some confusion regarding the terminology of ALS. In Europe it is better known as Charcot's disease or *motor neuron disease*, whereas, in the USA, the terms amyotrophic lateral sclerosis, ALS, and Lou Gehrig's disease are in more common use. Perhaps the most important distinction to be made is whether to call the disease ALS or motor neuron disease; the former is considered to be more specific. The World Federation of Neurology Research Group on Neuromuscular Diseases has grouped sporadic ALS, PMA, and PBP together as disorders of motor neurons of undetermined etiology [12].

Epidemiology

The incidence and prevalence rates for non–Western Pacific ALS are similar across the globe. The annual incidence of ALS is roughly 2 per 100,000 population with a prevalence rate of about 6 per 100,000. Differences in methods of case identification, database maintenance, death certification, and treatments may account for the variations seen from region to region [13, 14]. Several different risk factors such as race, age, sex, and occupation have been analyzed separately with a view to better understanding the disease. The incidence and prevalence rates appear to be higher in Caucasians than in non-Caucasians in western countries although this may be a reflection of underreporting rather than a true racial predisposition [15]. Age is the single most important risk factor for ALS with an age-related increase in mortality up until the

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eighth decade and peak mortality rate between the approximate ages of 65 and 75 years [13, 16]. Men develop ALS more often than women, the male-to-female sex ratio being 1.4:1–2.5:1. On the other hand, most studies show that bulbar-onset ALS displays a female predominance [17–20]. Epidemiological studies identified an increased mortality risk from ALS among electrical utility workers, the risk being greater with more prolonged exposure to electromagnetic fields [21, 22]. An increasing body of evidence indicates an association between higher levels of physical fitness and ALS, which appears to be independent of physical trauma or actual muscle strength [23–25]. Somewhat paradoxically, however, smoking also appears to be an independent risk factor [26]. Rarely, one encounters reports of "ALS clusters" (including conjugal ALS) which provide tantalizing evidence that local environmental or toxic factors play a significant part in the pathogenesis of the disease, but there is insufficient evidence to associate ALS with pesticides, heavy metals, or solvents despite interesting studies suggesting that they may play a pathogenic role [27, 28]. However, certain toxins have gained particular attention, namely, β-N-oxalylamino-alanine (BOAA) and cycasin. BOAA is the cause of *lathyrism* in India, a condition characterized by UMN signs, occurring in individuals who have consumed chickling pea flour. A similar condition, *konzo*, seen in East Africa, may be related to ingestion of insufficiently prepared cassava roots which yield an aminothiazolidine carboxylic acid which is similar to BOAA. Cycasin is a cycad nut-derived toxin found in high concentration in certain foodstuffs of the Chamorro Indians of Guam, but the exact role of cycasin in the pathogenesis of *ALS–parkinsonism–dementia complex* remains uncertain.

Clinicoanatomic Correlation

Both the classic and familial forms of ALS feature a combination of upper motor neuron (UMN) and lower motor neuron (LMN) signs (Table 20.1) affecting limb, trunk, and bulbar musculature. The UMN syndrome is the result of an interruption of the corticospinal and corticobulbar tracts occurring over a protracted time. These tracts originate in the primary motor cortex, premotor areas, temporal cortex, and sensory cortex; converge in the internal capsule; pass through the ventral midbrain; and separate into bundles in the basis pontis (Fig. 20.1). At this level, the corticobulbar tract separates off and bilaterally projects to the motor neurons of cranial nerves V, VII, IX, X, and XII. In the medulla, some of the corticospinal bundles coalesce ventrally to form the pyramids with 75–90 % of these fibers decussating at the level of the lower medulla to form the lateral corticospinal tracts [29]. The latter project to ipsilateral motor neurons, innervating the extremities, and associated interneurons in

Table 20.1 Signs in ALS

Upper motor neuron	Lower motor neuron	Others
Weakness	Weakness	Dementia [b]
Spasticity	Atrophy	
Poor dexterity	Fasciculations[a]	Atypical/rare:
Pathologic reflexes	Cramps	Sensory loss
Hyperreflexia	Hyporeflexia	Sphincter dysfunction
Pseudobulbar signs		Extraocular dysmotility
Retained reflex in atrophic limb		

[a]Debate as to origin of fasciculations (see text)
[b]Dementia is no longer considered rare or atypical (see text)

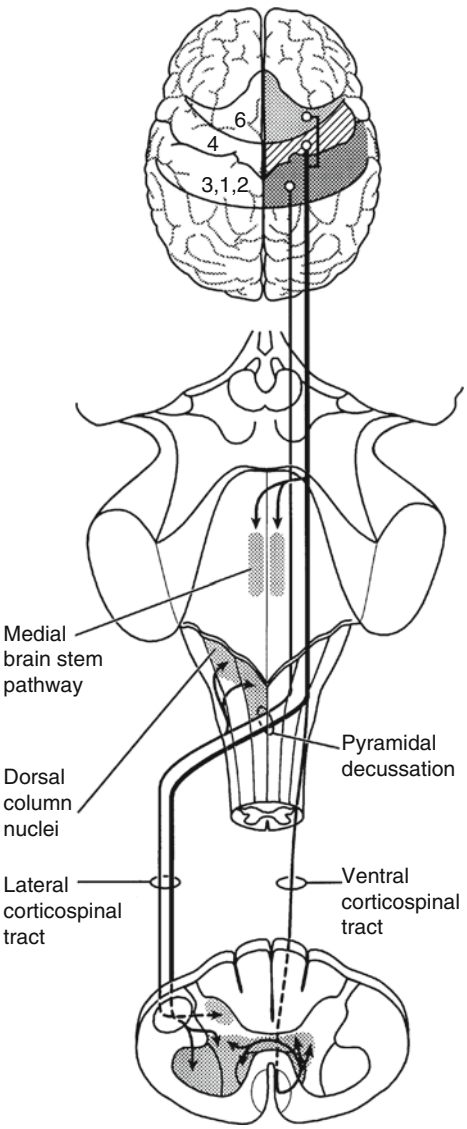

Fig. 20.1 Anatomic pathways involved in amyotrophic lateral sclerosis. The corticospinal tracts originate from multiple areas of the cortex (Brodmann's areas *1*, *2*, *3*, *4*, and *6*), pass through the brainstem, and emerge as both crossed and uncrossed corticospinal tracts that synapse upon alpha motor neurons and interneurons in the anterior horns of the spinal cord. The corticobulbar tracts (not illustrated) also originate from a broad region of cerebral cortex including connections to the limbic system

the lateral anterior horn. The remaining corticospinal fibers descend as the uncrossed anterior corticospinal tracts to project onto ventromedial motor neurons and interneurons which innervate axial and postural muscles. Recent electrophysiological evidence suggests that there is preferential involvement of the fast-conducting direct corticospinal tracts in ALS while sparing the slower, polysynaptic pathways [30]. Axons within these tracts provide excitatory input to alpha motor neurons, gamma motor neurons, and Ia inhibitory interneurons. Brainstem nuclei are intimately connected to the motor neurons in the anterior horn via the vestibulospinal, tectospinal, and reticulospinal tracts. In addition, an independent limbic motor system with medial, lateral, and periaqueductal gray components influences somatic motor neurons together with emotional, autonomic, endocrine, and visceral functions [31].

The lower motor neurons in the spinal cord are centered in the anterior horns forming longitudinally arranged columns extending from one to four spinal segments. Motor neurons that innervate the distal muscles of the extremities are more dorsally located in the anterior horn, whereas those innervating proximal muscles are more ventrally positioned. The individual cells are composed of large alpha motor neurons, medium-sized beta motor neurons, gamma neurons (fusimotor neurons), and interneurons. The alpha motor neurons are among the largest neurons in the nervous system and possess long axons together with broad dendritic receptive fields.

Clinical Presentation

Typical Features

The classic form of ALS is characterized by the coexistence of both UMN and LMN signs (see Table 20.1). Weakness, the most common presenting complaint, typically begins in the limbs, is asymmetric, and progresses over time to adjacent myotomes in the same limb and thence to the opposite side. It has recently been reported that onset in the upper limb is usually in the dominant limb, but the same cannot be said of the lower limb, where "footedness" appears not to play a role [32].

The UMN syndrome comprises those abnormalities attributable to involvement of the corticospinal and corticobulbar tracts which include loss of dexterity, weakness, spasms, spasticity, hyperreflexia, and pseudobulbar palsy. Poor dexterity is often described as clumsiness or slowness of certain activities, such as buttoning clothing or tying shoelaces. Complaints of muscle slowness, fatigability, or stiffness are common. Spasticity, the defining feature of the UMN syndrome, is thought to arise from increased excitability of the lower motor neurons caused by denervation hypersensitivity of the anterior horn cell interneuron population in the setting of damage to the integrity of the corticospinal tract [33].

With loss of inhibitory pathways in the spinal cord, muscle stretch reflexes become exaggerated so that even the slightest of hammer taps may elicit a response. A deep tendon reflex may spread to muscles that should not be involved in the tested reflex arc (i.e., "pathologic spread"). Easily elicitable reflexes in the setting of a flaccid, atrophic limb should also be considered an UMN sign. A study comparing the corneomandibular reflex in ALS to that in stroke (with resulting pseudobulbar palsy) showed that this reflex is a sensitive indicator of ALS [34].

Primitive reflexes may become disinhibited as a result of loss of UMN control. The most important is the Babinski sign whose presence correlates well with corticospinal tract involvement but which may be masked by muscle atrophy (in such a situation one should look for contraction of the tensor fascia lata when one stimulates the sole of the foot) [35]. Hoffmann's and Tromner's signs may be present, although these primitive reflexes may be seen in some normal individuals and, thus, should be interpreted as definitely pathologic only if there are associated UMN signs.

Compared to the UMN type, weakness in the LMN syndrome is more pronounced and often associated with significantly greater degree of muscle atrophy. Additionally, the reflexes are hypoactive or even lost. Weakness is typically focal in onset, is painless, and subsequently spreads to contiguous muscles. The most common site of onset is the distal extremity, the intrinsic muscles of the hand being more frequently affected than elsewhere. One should assess for clinical evidence of the "*split hand*," a phenomenon whereby the muscles of the lateral aspect of the hand are more severely involved than those of the medial aspect (see the electrodiagnostic examination below). When onset presents as foot drop, wrist drop, or claw hand alone, the presentation is said to be "pseudoneuritic" (although some prefer to restrict this term to lower limb onset, also known as "flail leg"). Involvement of cervical paraspinal musculature can present as head drop, whereas involvement of thoracic and lumbar paraspinal muscles can lead to bent spine and marked camptocormia [36]. As motor units continue to be lost, muscle atrophy occurs, which, in ALS, is most commonly seen in the form of intrinsic hand muscle wasting or sharpening of the tibial border. With severe degrees of atrophy, loss of muscle stretch reflexes, palpable flaccidity, and trophic joint changes occur. The latter may be associated with painful contractures and pericapsulitis.

Fasciculations are an important sign in ALS, presenting as involuntary, painless, rapid twitches in muscles of the limbs and the trunk. They represent spontaneous contractions of muscle fibers belonging to a particular motor unit. It is postulated that fasciculations arise from hyperexcitable

distal motor axons, although there is some evidence in support of a supraspinal origin. While a relatively uncommon presenting symptom, they are eventually seen in almost all ALS patients, and accordingly, their absence should prompt one to carefully rethink the diagnosis. Cramps or "charley horses" are often described by patients with ALS and occur in a far more widespread distribution than that seen in the normal population. These sudden, involuntary, painful, sustained muscle contractions can arise at rest and may awaken the patient from sleep. Yet again, they are rarely the presenting complaint but are frequently seen as the disease progresses.

The bulbar palsy syndrome in ALS typically involves damage to both upper and lower motor neurons. The patients present with dysarthria, dysphagia, sialorrhea, aspiration, and pseudobulbar signs. As in limb involvement, there are both UMN and LMN syndromes referable to the bulbar region. The UMN syndrome may present with spastic dysarthria characterized by a slowness of oral and tongue movement and a strained vocal quality. Dysphagia, initially more for liquids than solids, may also occur. There may be a hyperactive gag reflex and a brisk cough reflex. One may also elicit a brisk snout reflex and jaw jerk, which may even become clonic. UMN involvement affecting the muscles of mastication may lead to a slowness and stiffness of chewing (patients complain of taking a long time to eat) or jaw pain after prolonged chewing. The pseudobulbar affect is a feature peculiar to the UMN bulbar syndrome that presents as inappropriate, spontaneous, forced crying, laughing, or yawning. It is thought to arise from disruption of the bilateral corticobulbar pathways bearing fibers of the limbic motor control system [37].

Compared to the UMN bulbar syndrome, LMN bulbar impairment leads to greater degrees of weakness affecting the face (particularly the perioral region), palate, and tongue. In the earlier stages, the patient may have a horizontal smile, be unable to pucker the lips or whistle, and may have difficulty holding air in the cheek. With more advanced bulbar weakness, there is additional difficulty elevating the palate, the gag and jaw jerks disappear, and the tongue becomes increasingly, and often somewhat asymmetrically, atrophic and flaccid (Fig. 20.2). Fasciculations may also be seen on the surface of the tongue. It is important to differentiate these pathologic movements from the twitches that may be seen in normal, anxious individuals and view the tongue while at rest on the floor of the mouth as protrusion may exaggerate normal surface undulations.

Excessive drooling (sialorrhea) is a frequent complaint caused by impaired automatic swallowing and clearance of oral secretions. When neck extensor weakness coexists, this disturbing problem is worsened. Both silent and symptomatic aspiration, a major concern in ALS, may present as frequent bouts of mealtime choking and coughing, nocturnal awakenings, or even fatal laryngospasm.

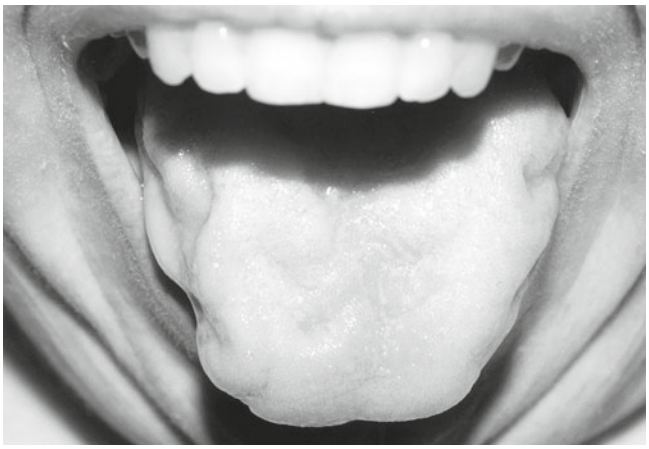

Fig. 20.2 Tongue atrophy in amyotrophic lateral sclerosis. Note the scalloping of the lateral tongue surface

Diaphragmatic and intercostal muscle involvement is frequent in ALS, albeit rarely at disease onset [38–40]. Patients may complain of sleep disturbance, orthopnea, dyspnea on exertion, dyspnea at rest, or morning headaches. Thus, one should look for use of accessory muscles of respiration, paradoxical abdominal movements, and signs of CO2 retention such as cyanosis, chemosis, papilledema, and bounding pulses. The voice may become softer and weaken at the end of long sentences, and frequent sighs may be observed. Many abnormalities of sleep architecture are described in ALS, including increased sleep latency, persistence of EMG activity during REM sleep, frequent awakenings, and a reduction in total sleep time. It has been postulated that both bulbar and diaphragmatic weaknesses may result in increased hypopneas and apneas, even at an early stage, that may lead to excessive daytime sleepiness and increase the amount of perceived muscle fatigue. In fact, fatigue similar to that seen in neuromuscular transmission disorders is a common complaint in ALS and is associated with disease severity [41]. The pathogenesis of this fatigue is unclear with evidence implicating sources from the level of cerebral cortex to beyond the neuromuscular junction [42], but it is important to consider the possibility that fatigue may be a side effect of riluzole, the most commonly used therapeutic drug in ALS. Many of the common symptoms and signs of ALS, such as sighing, fatigue, frequent crying, sleep disturbance, and weight loss, are also seen in and may actually represent depression [41]. Weight loss may be severe in ALS. It does not appear to be simply related to reduced caloric intake, and there is evidence that some patients suffer from a form of "ALS cachexia" [43, 44].

Atypical Features

It has become clear that a spectrum of cognitive impairment, once considered uncommon in ALS, often accompanies

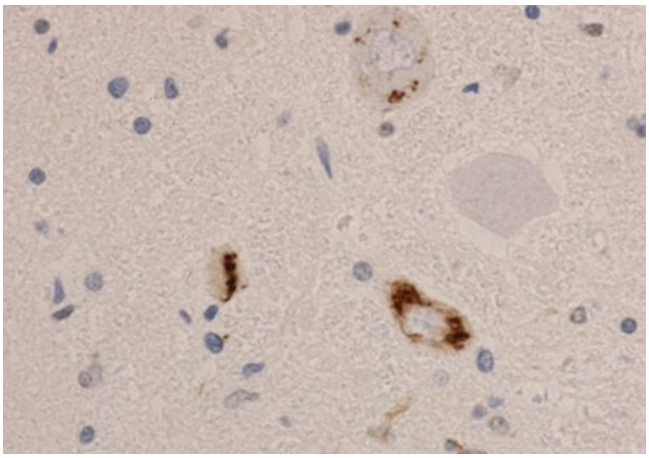

Fig. 20.3 Pathological TAR DNA-binding protein, TDP-43 (*brown*), in the hippocampus of a patient with sporadic ALS (Courtesy of Professor M Farrell, Beaumont Hospital, Dublin, Ireland) (For a more detailed discussion, see Neumann et al. [54])

motor neuron degeneration [45–50]. The range of cognitive syndromes reflects frontotemporal dysfunction, including a cognitive-behavioral syndrome, a dysexecutive syndrome, and a frank frontotemporal dementia. Both sporadic and familial variants of ALS can be affected. Neuroimaging, neuropsychological, and pathological studies demonstrate abnormalities beyond the primary motor cortex with evidence that language deficits, especially anomia, may be relatively frequent in ALS patients but are often masked by dysarthria. A recent prospective population-based study of cognitive function identified that comorbid dementia occurs in approximately 14 % of patients with a new diagnosis of ALS. Cognitive impairment, predominantly but not exclusively in the form of executive dysfunction, was present in more than 40 % of ALS patients without overt evidence of dementia [51]. Thus, although cognitive impairment in ALS is not a universal feature, it may previously have been underreported and its manifestations may be more heterogeneous than previously recognized. In addition to motor-onset ALS presentations, a subgroup of patients (maybe up to 30 %) may initially present with FTD, later developing ALS symptoms [52]. The clinical overlap in most cases of FTD with ALS is reflected by significant pathologic overlap between clinically pure FTD and those with classic ALS—i.e., underlying frontotemporal lobar degeneration (FTLD) with linear spongiosus, atrophy, neuronal loss, and pathological TDP-43(transactive response DNA-binding protein) ubiquitinated inclusions in astrocytes and neurons [53] (Figs. 20.3 and 20.4). Thus, recent pathologic findings suggest that FTD–ALS is part of a clinicopathologic spectrum of TDP-43 proteinopathy. The inheritance of ALS and FTD as a single trait has been recently described, confirming an intronic expansion of the GGGGCC hexanucleotide repeat within the C9ORF72 gene as the cause of a large proportion of familial ALS–FTD, in addition to apparently sporadic disease [55, 56]. C9ORF72 cases show features of a relatively rapidly progressive, but otherwise typical, variant of ALS associated with familial and sporadic presentations. All show classical ALS pathology with TDP-43 inclusions along with extra-motor pathology in the frontal cortex and the hippocampal CA4 subfield [57–59]. Better understanding of the pathological subtypes and clinical phenotypes of these ALS–FTD overlap syndromes is essential to inform development of effective targeted therapies, particularly as these conditions are often the most rapidly progressive neurodegenerative diseases.

The extraocular muscles and those muscles subserving bladder and bowel functions are relatively spared in ALS although advanced patients maintained on ventilators may eventually develop overt dysfunction in these areas. If one performs quantitative testing of saccades, one may detect a reduction of saccade velocities and smooth pursuit movements [60, 61]. A recent study replicated findings that visual acuity, gaze impersistence, voluntary upgaze restriction, eyelid opening apraxia, and saccadic horizontal smooth pursuits are more frequent in patients with ALS than in similar-aged controls. These ocular motility abnormalities are potential clinical markers of neurodegeneration beyond upper and lower motor neuron disease in ALS, suggesting dysfunction of supranuclear control. Several autopsy studies demonstrated neuronal loss in many subcortical regions subserving eye movement control. Further study is required regarding their application to disease categorization and outcomes assessment [62].

Within the sacral cord, the motor neurons of Onufrowicz that control the muscles of the pelvic floor, anal sphincter, bladder, and urethra are essentially spared in ALS. However, while frank urge incontinence and bowel dysfunction are rarities, mild urgency of micturition and urinary retention may occur [63].

The sensory system is also characteristically spared which perhaps contributes to the rarity of decubitus ulcers in this population of immobilized patients (local autonomic reflexes being intact). Despite an overall absence of objective signs, some patients do report vague sensory complaints in the distal extremities; detailed quantitative sensory testing and somatosensory evoked potential studies identified objective sensory disturbances in a small proportion of patients, suggestive of a disruption of the ascending afferent system [64]. There appears to be specific changes in the skin composition in ALS patients. Studies have revealed increased levels of type III procollagen in the skin and serum of ALS patients as compared to controls with excessive deposition of β-amyloid protein and increased dermal ciliary neurotrophic factor and insulin-like growth factor I (IGF-I) suggesting that a metabolic alteration growth factors may take place in the skin of patients with ALS. Perhaps this helps explain the low incidence of pressure sores in immobilized patients with ALS [65]. Extrapyramidal involvement may occur in about 5 % of

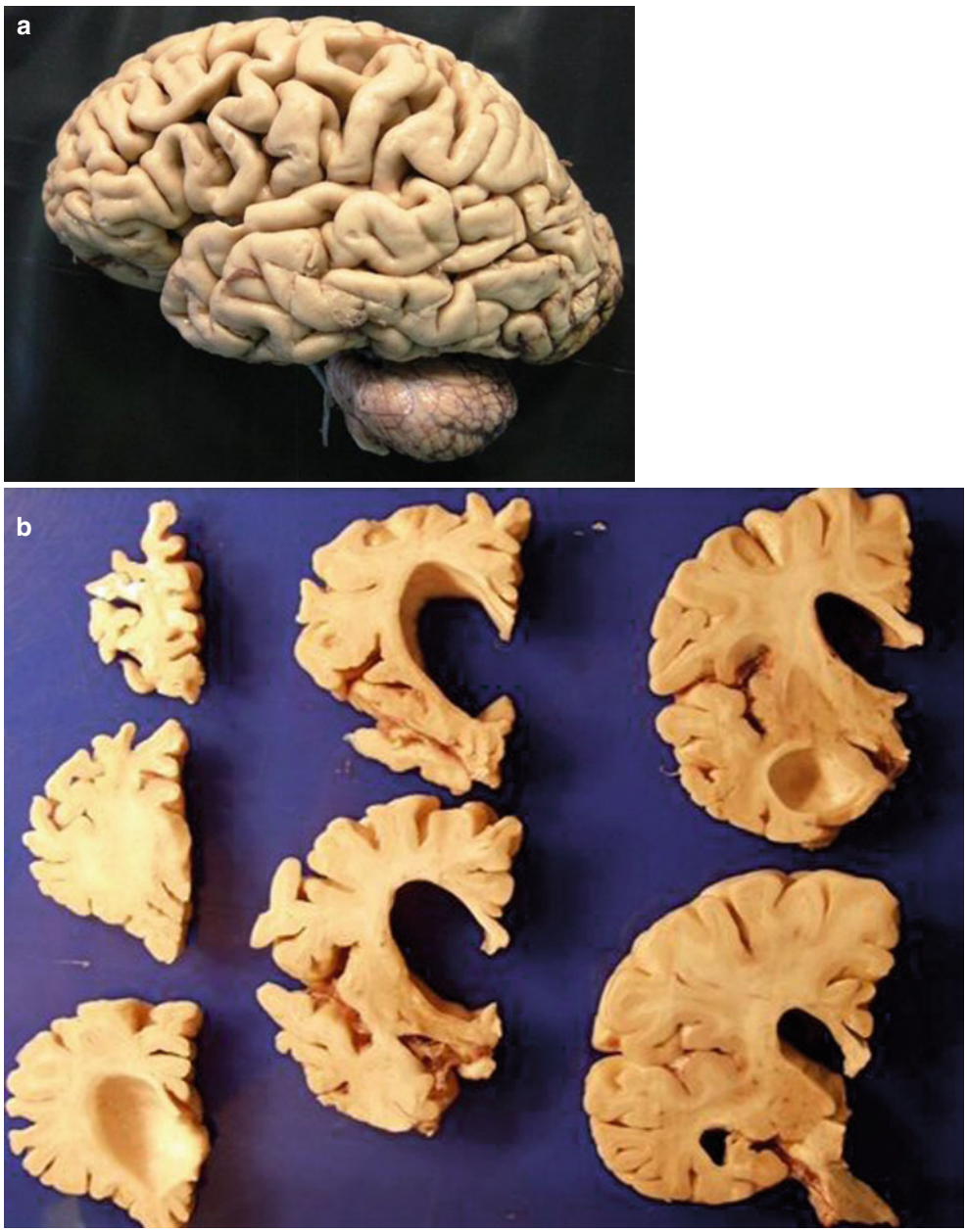

Fig. 20.4 (**a**) Pathology in ALS-FTD: Gross frontal and anterior temporal atrophy (Courtesy of Professor M Farrell, Beaumont Hospital, Dublin, Ireland) (For further detail, please see "Pathology" section in main text). (**b**) Marked frontal and temporal lobe atrophy in ALS-FTD (Courtesy of Professor M Farrell, Beaumont Hospital, Dublin, Ireland) (For further detail, please see "Pathology" section in main text)

ALS patients and may present as an impairment of postural reflexes or retropulsion during attempted ambulation [66].

When one considers these facts, it appears reasonable to conclude that ALS is a widespread, multisystem disorder rather than a pure "motor neuron disease," although it does appear that the motor neuron pool is particularly vulnerable to damage from the injurious processes involved.

ALS Subtypes

Bulbar palsy can be the initial symptom in ALS (Table 20.2). It is most commonly seen in postmenopausal women and may

Table 20.2 Presentations of ALS

Spinal (classic, sporadic)
Primary lateral sclerosis
Progressive muscular atrophy
Progressive bulbar palsy
Familial
Monomelic
Flail-leg syndrome (pseudoneuritic)
Flail-arm syndrome
Mills' (hemiplegic) variant
ALS–FTD (ALS–frontotemporal dementia)
ALS–parkinsonism–dementia complex

portend a worse prognosis. Various studies report that bulbar-onset ALS accounts for 19–28 % of all presentations. Clinically, affected individuals present with dysarthria and dysphagia. The pattern of speech impairment may be more strained, as seen in the UMN predominant presentation, or more slurred as seen in the LMN pattern. Combinations of tongue weakness, wasting, fasciculations, slowness, and lower facial weakness are seen. Often there is coexistent UMN jaw jerk exaggeration and a hyperactive gag (although the LMN type may have no gag at presentation). Emotional lability is frequent and can be embarrassing for the patient. There is often a history of recurrent cough during meals, and there may also be weight loss and aspiration events. This disturbing condition advances locally first and spreads first to the lower cervical/upper thoracic region and thence to lumbosacral myotomes by which time the patient has increasing difficulties with speech and swallowing. Very rarely, the disease does not advance beyond the bulbar region at all; this is true *progressive bulbar palsy (PBP),* an exceedingly rare disease.

Between 2 and 3.7 % of all ALS patients present as a pure UMN syndrome called *primary lateral sclerosis (PLS)* that never goes on to involve the lower motor neurons. Age of onset is typically between 50 and 55 years and the rate of progression may be very slow. A common presentation is that of spastic paraparesis progressing rostrally over many years to eventually cause pseudobulbar palsy. The most recent natural history study suggests that clinically pure PLS can be defined by isolated UMN signs 4 years after symptom onset and is a syndrome of slow progression with high levels of function and longer survival compared with ALS [67]. Diagnosis of PLS cannot be made with certainty before the fourth year of symptoms because many patients develop LMN signs within that time frame (this rendering a diagnosis of upper motor neuron–onset ALS) [68, 69]. Although detailed neuropsychological test batteries may reveal subtle cognitive changes in PLS, overt dementia is uncommon [70, 71].

Progressive muscular atrophy (PMA), the rarest "ALS" presentation (2.4 %), presents as a pure LMN syndrome and tends to harbor a more favorable outcome. Clinically, it is characterized by signs of lower motor neuron dysfunction. By definition, the condition must be pure LMN before designation as PMA, but, as with PLS, one must continue to reevaluate patients for later development of UMN signs [72]. Comparison of survival of patients with PMA or ALS and analysis of clinical features that influence survival in PMA suggest that, although patients with PMA tend to live longer than those with ALS, shorter survival in PMA is associated with the same risk factors that predict poor survival in ALS. Additionally, PMA, also a TDP-43 proteinopathy, is progressive, and UMN involvement can eventually occur. For these reasons, PMA should be considered a form of ALS [73].

Mention should be made of three distinctive presentations of ALS: Mills' (hemiplegic) variant, flail-arm syndrome and flail-leg syndrome. *Mills' variant* is a well-recognized, hemiplegic presentation featuring a combination of UMN and LMN signs isolated to one side [74]. The *flail-arm syndrome*, also known as brachial amyotrophic diplegia, occurs in about 10 % of patients and presents as relatively symmetric proximal and distal bibrachial wasting with additional evidence of corticospinal tract involvement (positive Babinski sign). *Flail-leg syndrome* represents a pseudopolyneuritic variant of ALS and occurs in approximately 6 % of all patients. Survival in both syndromes is significantly better than in classical ALS [75].

Familial ALS

Familial ALS (fALS) describes the 5–10 % of all cases in whom ALS is known to be an inherited trait. The true frequency of fALS is probably higher, and reduced penetrance may account for apparently sporadic disease. There are autosomal dominant, autosomal recessive, and X-linked dominant forms, some juvenile, and others adult, onset. Familial ALS-known genes and phenotypes are outlined in Table 20.3.

Familial ALS should be suspected when family members of successive generations are definitely affected by the disease. However, family history may be incomplete, and phenotypic variability abounds so that few clinical features separate sporadic from familial forms. Overall, fALS has a younger age at presentation, lacks male predominance, and has shorter disease duration and a predilection for lower extremity onset. Most ALS research in the past has focused on the neurotoxicity of mutant SOD1, and this has directed therapeutic research. More recently, TDP-43 has been identified as the major pathological protein in sporadic ALS, ALS–FTD, and *SOD1*-negative familial ALS [10, 83–85].

Up to 20 % of fALS patients are associated with a mutation in the Cu/Zn superoxide dismutase 1 (SOD1) gene on chromosome 21, and since its discovery, many different mutations have been described in all five exons [10, 86]. Cumulative evidence suggests that a toxic gain of function rather than a loss of function is conferred by the mutations. The most common is an alanine for valine substitution at codon 4 (shortened to A4V) that seems to correlate with shorter patient survival (mean 1.5 years). Usually SOD-1 fALS is autosomal dominant, but aspartate for alanine substitution in exon 4 (D90A,) seen most commonly in Scandinavians is recessive. The alsin mutation on chromosome 2q33 (known as ALS2) and affecting predominantly Tunisians, Saudi Arabians, and Kuwaitis has a mean age of onset of 12 years and progresses very slowly. Both PLS and ALS presentations occur. The disorder is proposed to occur

Table 20.3 Familial ALS: genes and features

ALS	Gene mutation	Chromosome and gene product function	Inheritance	Details
ALS 1	SOD1	21q21; oxidative stress	AD (rarely AR)	Late onset >30 years, 15–20 % all familial ALS (1–2 % all ALS) [10]
ALS 2	ALSIN	2q33; trafficking and signaling	AR	Rare, juvenile ALS; loss of function of gene product
ALS 3	Not identified	18q21	AD	
ALS 4	(SETX) Senataxin	9q34, RNA processing	AD	Juvenile onset, slowly progressive, distal amyotrophy, and UMN signs, not bulbar
ALS 5	Spatacsin	15q15-q22	AR	Juvenile onset
ALS 6	FUS–TLS	16q21; RNA processing	AD	5 % non-SOD1 familial ALS, 1 % sporadic ALS [76]. FUS is immunoreactive with TDP43 and ubiquitin [56]. Associated with FTD and hallucinations
ALS 7	Not identified	20ptel-p13	AD	Rare, late onset
ALS 8	VAPB (vesicle-associated membrane protein)	20q13.3; trafficking and signaling	AD	Heterogenous phenotype [77]
ALS 9	Angiogenin	14q11.2; RNA processing	AD	Adult onset
ALS 10	TDP-43 (transactive response DNA-binding protein)	1p36.2; RNA processing	AD	ALS with limb/bulbar onset. Although not specific to ALS, the frequency of TDP-43 inclusions in familial (2–5 %) and sporadic ALS suggest pathogenic role [78, 79]
ALS 11	FIG-4	6q21; trafficking and signaling	AR	ALS/PLS onset. Familial and sporadic ALS [80] FIG-4 mutation also causes CMT4J
X-linked AD	Ubiquilin 2	Xp11; protein turnover	X-linked AD	Combined UMN/LMN
ALS12	OPTN; optineurin	10p13; trafficking and signaling	AR, AD	[81]
Dynactin	Dynactin (p150 glued subunit) (Puls et al. 2005)	2p13; trafficking	AD	Distinctive phenotype: early bilateral vocal cord paralysis, then intrinsic hand muscles, legs, face. Other mutations: ALS or FTD
FTD–ALS overlap				
ALS–FTD 1	Not identified	9q21-q22	AD	
ALS–FTD 2	Not identified	9p21.3	AD	
ALS–FTD 3*	CHMP2B	3, trafficking and signaling	AD	ALS, ALS–FTD, PMA [82]
*Autosomal-dominant ALS–FTD		9q21-22	AD	
C9ORF72 hexanucleotide repeat expansion	GGGGCC hexanucleotide repeat within the *C9ORF72* gene	9		Familial and sporadic ALS. Associated with TDP-43 proteinopathy. Classic ALS and extra-motor pathology [57]
FTD with some ALS features—progranulin	Progranulin (PGN)	17		Neuronal and glial TDP43-positive, tau-negative ubiquitinated inclusions
DDPAC (disinhibition–dementia–parkinsonism–amyotrophy complex)	TAU	17	AD	Tau-immunoreactive inclusion bodies in affected regions of CNS

through loss of function of the gene product (which is important in cell trafficking) [87]. Autosomal dominant ALS 10, associated with a TDP-43 (transactive response DNA-binding protein) mutation, is characterized by ALS with limb/bulbar onset and is not reliably distinguishable from sporadic ALS aside from family history [78, 79]. Most recently, the gene underlying inheritance of ALS and FTD as a single trait within the same family has been described, with confirmation that a hexanucleotide expansion on chromosome 9 underlies a large proportion of familial ALS and FTD, in addition to apparently sporadic disease [57]. Other implicated genes include FUS–TLS (chromosome 16q21) [76], ubiquilin [56], senataxin [88], FIG-4 (chromosome 6q21) [80], and optineurin/OPTN [81]. As outlined in a later section of this chapter, these various genes have overlapping functions, some associated with RNA processing, some concerned with endosomal trafficking/cell signaling, and others involved in oxidative stress responses. Intracellular inclusion bodies are found in many of these genetic disorders including SOD1, TDP-43, FUS/TLS, and optineurin [89].

Western Pacific ALS

A combination of ALS and Parkinsonism on the island of Guam was first described by Mulder et al. in 1954. This was followed by Hirano's first complete pathological description of the syndrome of Guamanian ALS–Parkinsonism–Dementia Complex [90]. Subsequently, the incidence of ALS was noted to be particularly higher in West New Guinea and the Kii Peninsula of Japan, being between 50 and 150 times, than elsewhere [7–9, 90]. Clinically, about 5 % of patients develop a predominantly ALS type of disorder, whereas 38 % manifest principally with a combination of parkinsonism and dementia. The pathology is similar to that of Alzheimer disease, with prominent loss of CNS neurons and the presence of abundant tau-immunoreactive neurofibrillary tangles. However, the characteristic pathology of Guamanian ALS and PDC also includes TDP43-positive inclusions in neurons and glial cells. α-Synuclein pathology also is detectable in the amygdala of affected brain tissue [91]. Various environmental substances, including cycad seeds, aluminum, and silicon, have been studied with regard to its pathogenesis, but their roles, including that of cycad seeds in neurotoxicity, is still subject to debate [92–94]. The cycad seed has many uses: in West Papua and Guam as a topical medicine for skin lesions and in Japan as an oral medicine [95, 96]. Cox and Sacks (2002) proposed a process of biomagnification of cycad toxins in Guam through the Chamorro practice of eating flying foxes, which themselves feed on cycad seeds. ALS–parkinsonism–dementia complex is beginning to disappear from the endemic regions, and it has been proposed that this may be due to altered exposure to an unidentified trigger as well as changes in social/cultural practices in endemic regions. The cycad-derived BMAA (beta-methylamino-L-alanine) neurotoxin hypothesis has wider implications for research in SALS worldwide. It has been recently shown that protein-bound BMAA is present in the brains of North American patients dying with ALS and Alzheimer disease, and it has been hypothesized that such patients may be genetically susceptible to BMAA-induced neurodegeneration [97, 98].

Etiology and Pathogenesis

The cause of ALS remains unknown, but there are several intertwining strands of evidence that together suggest multiple molecular mechanisms that may ultimately combine to effect loss of motor neurons and their support systems. Much of this evidence stems from research in the field of fALS. As the first ALS-associated gene, superoxide dismutase 1 (SOD-1) is an antioxidant protein. One of the most studied areas in this regard is *oxidative stress* wherein overproduction of, or failure to clear, potentially harmful oxygen free radicals in aging motor neurons may precipitate eventual cell failure (probably in concert with other pathogenic processes). Markers of free-radical damage are elevated in tissue samples of patients with ALS, and signs of oxidative stress have been identified in the organelles of cells from fALS cases (notably SOD 1-associated diseases) and in animal models of fALS [99, 100]. *Excitotoxicity* is another mechanism whereby overstimulation/activation of glutamate receptor subtypes (most notably amino-3-hydroxy-5-methylisoxasole-4-propionic acid, AMPA receptors) leads to disordered calcium homeostasis and triggers intracellular protein breakdown and generation of harmful levels of oxygen free radicals. Evidence to support this theory includes elevated glutamate levels in cerebrospinal fluid levels of ALS cases and reduced activity/expression of the major excitatory amino acid transporter EAAT2 not only in ALS cells but also in animal model studies [101–103]. Most recently, a new ALS-associated gene has been identified: the gene product (D-amino oxidase, DAO) is a protein involved in oxidative deamination of amino acids involved in glutamate receptor activation [104].

A burgeoning theory in ALS pathogenesis is that of *altered cellular energy* [43]. Motor neurons have particularly high energy requirements as they pertain to cell soma size, axonal transport, and activation of large terminal arborizations. As mentioned earlier in this chapter, there appears to be an association between higher metabolic rate/physical fitness and ALS. Furthermore, upper limb onset is more often in the dominant limb. Mitochondria play a major role in the energy production in cells, and there is evidence to implicate dysfunction of these organelles in the pathogenesis of the disease. Oxidative damage impairs respiratory chain function in the mitochondria of patients with ALS, and mutant SOD1 protein can adhere to the mitochondrial membrane and disrupt chaperone-assisted organelle folding [103, 105, 106]. There may be abnormal transport, and therefore reduced numbers, of mitochondria in the terminal axons, thus depriving them of vital energy at a site of high energy requirement [107]. An ALS presentation with ragged-red fibers has been reported in five families and is associated with mtDNA mutations in some patients [108–110].

Other organelle systems under scrutiny in the molecular pathogenesis of ALS are endosomes and neurofilaments. Endosomes are a cargo delivery system from the cell surface to the interior. Recently discovered mutations in genes such as Alsin (ALS2), VAPB (vesicle-associated membrane protein-associated protein B) [77], VCP (valsolin-containing protein) [111] FIG4 (polyphosphoinositide phosphatase) [80], optineurin [81], and CHMP2B (charged multivesicular protein 2B) [82] support a theory of altered endosome mobility within cells in ALS. Motor soma and axons are rich in neurofilaments, microtubules, kinesins, and dyneins, all of which are critical in bidirectional axonal transport. However,

this system can be impaired in ALS not only via oxidative stress but also through (rare) mutations in genes for neurofilament heavy chains, peripherin, and tau. This process may precipitate a form of axonal strangulation that disrupts transport of cargo and indeed energy to where it is required both proximally and, especially, distally.

An *inflammatory process* likely plays an important role in the cell injury process in ALS. Studies of mutant SOD1 models have yielded evidence of early activation of microglial cells, astrocytes, and an overall pro-inflammatory T-cell response [112]. Furthermore, it is known that certain viral infections and paraneoplastic inflammatory disorders can selectively damage motor neurons and cause an ALS-like presentation (polioviruses, HIV, West Nile virus, anti-Hu antibody syndrome). This body of evidence suggests some promising therapeutic targets despite the fact that anti-inflammatory therapeutic trials have disappointed to date.

The pathological hallmark of ALS is the presence of the ubiquitinated intracellular inclusion body in motor neurons and glial cells; TDP-43 (43 kDa transactive responsive sequence DNA-binding protein) is normally a largely nuclear protein and is important in transcription, splicing, and micro RNA processing. TDP-43 is the major protein in sporadic ALS but it is mislocalized so that it mostly lies in the cytoplasm in the form of a *protein aggregates*. This type of protein mislocalization has been observed in many other neurodegenerative disorders such as Huntington's disease and the dominantly inherited spinocerebellar ataxias. It is also seen in some forms of familial ALS including those related to TDP-43, SOD-1, FUS, and ubiquilin (see "Familial ALS"). The accumulation of misfolded cytoplasmic proteins into aggregates may, at least initially, be a normal cytoprotective process in the cell mediated via the endoplasmic reticulum unfolded protein stress response. How these protein aggregates cause ALS is still unclear, but it is likely through an imbalance in lost nuclear function in concert with disruption in cytoplasmic function.

Many of the recent studies in ALS report genetic disorders that involve RNA regulatory genes such as TDP-43, FUS, ANG [113], and SETX which in turn support an evolving theory of *aberrant RNA metabolism* in the pathogenesis of this disease (see Table 20.3 with genetic mutations and their gene functions). Various processes may be involved from regulation of transcription to alternative splicing and mRNA transport.

Pathology

Gross pathologic specimens may exhibit atrophy of the motor cortex together with grayness and atrophy of the ventral spinal roots. There may be a gray appearance to the lateral columns of the spinal cord suggesting sclerotic changes caused by gliosis. In addition, there may be gross muscle atrophy. Microscopically, there is evidence of both upper and lower motor neuron loss. As such, there is some degree of loss of large motor neurons of the anterior horns of the spinal cord and/or brainstem motor nuclei (V, VII, IX, X, and XII) and loss of large pyramidal cells in the motor cortex and/or large myelinated axons of the corticospinal tracts. Degeneration of the corticospinal tracts occurs at the same level, and both normal and abnormal neurons are intermixed, reflecting different stages of neuronal degeneration. Lipofuscin accumulation and loss of Nissl substance is seen in degenerating neurons.

At the cellular level, ALS is characterized by the abnormal accumulation of insoluble ubiquitinated proteins in the cytoplasm of degenerating motor neurons [91, 114, 115]. These ubiquitin-immunoreactive inclusions, most common in lower motor neurons, are a highly sensitive and specific marker for ALS. In the past 5 years, the TAR DNA-binding protein, TDP-43, has been identified as a major component of the neuronal inclusions in sporadic ALS (see Fig. 20.3), as well as in the most common pathological subtype of frontotemporal dementia (frontotemporal lobar dementia with ubiquitinated inclusions [FTLD-U]) [54].

In combination with recent studies showing both clinical and pathological overlap between ALS and frontotemporal dementia, these findings support the view that sporadic ALS and some FTD represent a spectrum of neurodegenerative disease linked mechanistically to pathological TDP-43 (see Fig. 20.4 a, b).

A recently described hexanucleotide intronic expansion of the GGGGCC hexanucleotide repeat within the *C9ORF72* gene on chromosome 9 underlies a large proportion of familial ALS and FTD in addition to apparently sporadic disease [55]. These *C9ORF72* cases demonstrate features of a relatively rapidly progressive, but otherwise typical, variant of amyotrophic lateral sclerosis associated with familial and sporadic presentations. All show classical amyotrophic lateral sclerosis pathology, but extra-motor pathology in the frontal cortex and the hippocampal CA4 subfield neurons distinguishes *C9ORF72* cases. Inclusions in CA4 neurons, absent in non-*C9ORF72* cases, indicate that this pathology predicts mutation status [57, 116]. Although the mechanism is not clear, phenotype is determined by initial location and spread of degeneration [59].

Diagnosis

The Clinical Examination

The diagnosis of ALS is largely made on the basis of the clinical examination, with ancillary testing used to confirm the clinical suspicion and to refute alternative diagnoses.

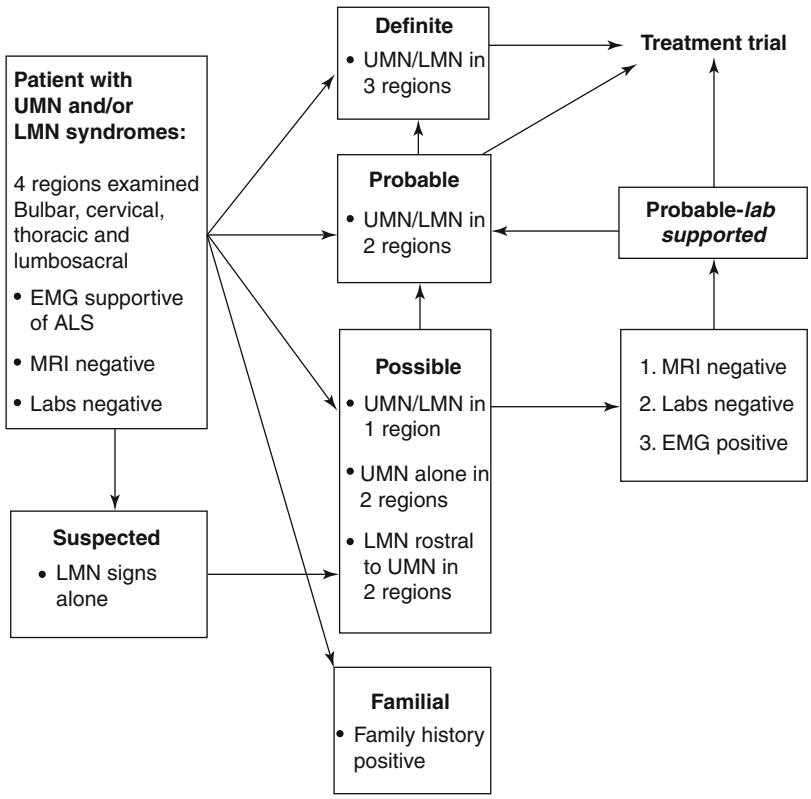

Fig. 20.5 Simplified diagnostic algorithm for the diagnosis of amyotrophic lateral sclerosis. Currently, neuroimaging and blood testing are used as tests to exclude other diagnoses. The electrodiagnostic examination is an ancillary test to aid in making the diagnosis. Regular reexamination is critical (For a detailed review, see Ref. [117] (World Federation of Neurology, Revised Criteria))

A meeting of the World Federation of Neurology at El Escorial, Spain, provided a set of clinical, electrodiagnostic, and pathological criteria for the diagnosis of ALS. The clinical criteria divide candidates into those with *definite, probable, possible,* and *suspected* ALS, based upon the particular pattern of LMN and UMN signs seen in bulbar, cervical, thoracic, and lumbosacral regions (Fig. 20.5). A further review of the criteria, carried out at Airlie House, includes the criterion of spread of disease from region to region and spread within a region [118]. In addition, these criteria demand an absence of electrodiagnostic, pathologic, or radiologic evidence in support of other diseases that may mimic ALS. These criteria have proved important in research and clinical fields, allowing accurate research trial selection and assistance in the day-to-day management of patients.

Definite ALS implies that both UMN and LMN signs are seen together in at least three separate central nervous system regions. *Probable* ALS refers to the presence of UMN and LMN signs in only two regions wherein the UMN signs lie rostral to the LMN signs. If only one region is affected or UMN signs are seen alone in one region with additional electromyographic (EMG) evidence of LMN dysfunction in two regions, the clinician may use neuroimaging and clinical laboratory testing to exclude alternative diagnoses and classify the patient as *probable-laboratory-supported* ALS. Clinically suspected ALS refers to a pure LMN presentation and is regarded as insufficient to allow patient inclusion in a research study.

The revision of the original criteria was implemented to allow earlier access of patients into clinical trials and highlights the importance of EMG and ancillary testing in the diagnostic work up of the candidate patient. There are occasions when UMN and LMN signs are found in only one region and ancillary tests fail to support a diagnosis of ALS. Such patients fall into the *clinically possible* category but follow-up evaluation must be performed to assess for disease progression at which time the patient may be upgraded to a probable or definite category.

Electrodiagnostic Studies

The electrodiagnostic (EDX) examination is an indispensable part of ALS evaluation, essentially serving as an extension of the clinical examination and most useful in identifying LMN dysfunction. Not only may EDX reveal characteristic changes in those regions clinically manifesting signs but also serves to disclose asymptomatic areas of involvement. Since the 1960s, the "Lambert criteria" have aided the electrodiagnostician in making the diagnosis of ALS [119]. These criteria include (1) normal sensory nerve action potentials (SNAPs), (2) motor conduction velocities no less than 70 % of the lower limit of normal values for age, and (3) fibrillation and fasciculation potentials in bulbar and/or limb muscles with reduced number of motor unit action potentials (MUAPs) and increased duration and amplitude.

However, only more advanced patients may meet such criteria, potentially excluding some patients from therapeutic trials. Thus, new criteria were devised at a meeting in El Escorial, Spain, in 1990, which, upon critical review, were later modified [118].

Motor and sensory conduction studies are part and parcel of the EDX examination in ALS and are principally used to exclude alternative diagnoses. Characteristically, the SNAPs are normal. However, coexistent entrapment neuropathies, peripheral polyneuropathies, and the normal effects of aging may reduce SNAP amplitudes. With significant axon loss, low compound muscle action potential (CMAP) amplitudes with modest degrees of slowing may be found. When widespread, this "generalized low motor-normal sensory" pattern is characteristic of more advanced ALS and often portends a worse prognosis [119, 120]. However, it is not specific for the diagnosis and may be seen in spinal muscular atrophies, diffuse myelopathies, certain neuromuscular transmission disorders, polyradiculopathies, and myopathies. Of interest is the finding of the "split hand," i.e., low-amplitude median and ulnar CMAPs recorded from the thenar eminence and first dorsal interosseous muscles, respectively, with a normal or near normal ulnar CMAP amplitude recording from the hypothenar eminence. A possible explanation for this pattern is relative increased cortical representation of the thenar eminence musculature, but it is also possible that the neurons innervating these muscles are more liable to oxidative stress [121]. Median distal motor latencies may also be prolonged out of proportion to the degree of axon loss, which probably reflects the relatively slow conduction along the terminal axons of collateral sprouts. As with conventional motor conduction studies, F-wave latencies remain within normal limits until significant degrees of axon loss have occurred, and, with progressive motor axon loss, they may disappear altogether.

On needle EMG of affected muscles, features of both active and chronic denervation must be observed. Active denervation consists of fibrillation potentials and positive sharp waves, whereas chronic denervation consists of MUAPs that are increased in duration, occasionally increased in amplitude, and often polyphasic. In addition, these MUAPs usually fire at a rapid rate (>10 Hz) unless there is significant upper motor neuron disease, wherein slower rates of firing may occur. Moment-to-moment MUAP amplitude variation, representing motor unit instability, may often be appreciated. Fasciculation potentials are a characteristic feature, seen in almost all patients; they typically occur in a widespread distribution and often have an abnormal configuration (depending on the motor unit generating them). If fasciculation potentials are not readily detected during the EDX examination, considerable doubt must be cast upon the diagnosis. The Awaji algorithm has been devised to increase the importance of fasciculation potentials in the diagnosis of suspected ALS and is particularly helpful in the early diagnosis of bulbar-onset disease. The algorithm uses fasciculations as evidence of active denervation as long as the muscle that is being studied shows additional chronic neurogenic change [122–124]. Neither fibrillation nor fasciculation potentials are easily appreciated in the tongue, as it is difficult to achieve adequate relaxation, and the MUAPs normally appear rather similar to fibrillation potentials in terms of both their size and configuration. Ultrasound of the tongue may prove to be a useful test to diagnose fasciculations not only in the tongue but also in other muscles [125]. Repetitive discharges, also known as doublets, are a particularly frequent finding in ALS where the interval between the first and second waveform is short but variable suggesting that both are derived from the same cell soma. It is postulated that they represent hyperexcitability of the cell membrane.

As in the clinical examination, the EDX features must be observed in a certain topographical distribution. In fact, none of the previously described EDX findings are specific for ALS. Rather, it is the widespread pattern of involvement that is characteristic, affecting multiple segments of the neuraxis with progression over time. Changes should be found in at least two of the four regions (bulbar, cervical, thoracic, and lumbosacral regions). In cervical and lumbosacral regions, at least two muscles derived from different roots and peripheral nerves must be involved. Abnormalities in the opposite limb should only be included if they involve a separate spinal cord segment. When the bulbar region is assessed, changes must be observed in at least one muscle (including tongue, jaw muscles, and facial muscles). Similarly, if one examines the thoracoabdominal segments, one should demonstrate EDX changes in abdominal muscles or in a paraspinal muscle at or below the T6 level. Evaluation of higher thoracic segments may be misleading as denervation changes derived from cervical segments may manifest as far caudally as the T6 level. The EDX examination should ideally be performed on three or more regions and should assess all the major segments in the limbs examined. In conjunction with the inclusive criteria as described previously, there are a number of EDX findings considered incompatible with the diagnosis of ALS, including marked conduction slowing, conduction block and abnormal sensory responses otherwise unexplained by advanced age or coexisting neuropathy.

A number of special EDX techniques may be employed in the evaluation of patients with suspected ALS; these techniques have been helpful as outcome measures in the assessment of efficacy in therapeutic trials. Manual and computer-based motor unit number estimation (MUNE) techniques have been used to monitor disease progression (see Chap. 9) and can help distinguish subtypes of ALS [126]. Swash and de Carvalho devised the Neurophysiological Index derived from the CMAP, distal motor latency, and

F-wave frequency to determine rapid from slowly advancing disease [127]. Repetitive stimulation studies, although not routinely performed, may show a decrementing response (albeit usually less dramatic than that seen in myasthenia gravis) that is likely due to impaired neuromuscular transmission at the immature nerve terminals of collateral sprouts. Similarly, increased fiber density, abnormal jitter, and blocking may be detected during single-fiber EMG [128]. Macro-EMG refers to the use of a specialized recording electrode that samples all muscle fibers within a single motor unit and estimates the degree of motor unit loss and the extent of collateral reinnervation. Other methods for evaluating chronic partial denervation include turns/amplitude analysis, EMG decomposition, and quantitative motor unit potential analysis (see Chap. 9). Transcranial magnetic stimulation (TMS) studies can provide useful information in assessing the central motor pathways in ALS. Many, but not all, patients with sporadic ALS have low motor evoked potential amplitudes on TMS, with prolongation of both the response threshold latencies and central motor conduction times. A gradual reduction in the motor evoked potential amplitudes over time is a particularly useful way to determine upper motor neuron system involvement in apparently pure lower motor neuron disease and also is a valuable technique to monitor disease progression [129].

Neuroimaging

The most important role for neuroimaging remains exclusion of structural, inflammatory, or infiltrative disorders that may mimic ALS. All patients should undergo brain and spinal cord imaging. However, in addition, more sophisticated techniques may allow discernment of abnormal signal in the motor tracts in ALS. In patients with more severe disease, signal change reflecting wallerian degeneration may be visualized on proton density-weighted MRI (Fig. 20.6). FLAIR and T2-weighted fast-spin echo sequences are less specific in detection of such corticospinal tract signal changes. Nonspecific atrophy of the frontal and parietal cortex may also be seen. Surface-based cortical morphology analyses performed on structural 3T MRI data reveal cortical thinning of the primary motor cortex, which may be a diagnostic marker for upper motor neuron degeneration in ALS; relative thinning in temporal regions has been associated with a rapidly progressive disease course [130]. The search for ALS biomarkers has led to the investigation of other imaging techniques such as magnetization transfer ratio (MTR) imaging, magnetic resonance voxel-based morphometry, magnetic resonance spectroscopy, and diffusion tensor MRI (DTI). The latter demonstrates that corpus callosum involvement is a consistent feature of ALS, with extension of reduced fractional anisotropy in primary motor cortices, supplementary motor regions, and in temporal lobe regions. Whole brain-based and DTI tractography analysis can define a distinct white-matter pathoanatomy of different MND geno-/phenotypes [131]. Furthermore, DTI of white-matter tracts has also demonstrated structural differences between ALS and PLS [132], and differences in intracerebral corticospinal tract changes of patients with familial and apparently sporadic ALS have facilitated study of genotype/phenotype interactions [133]. FDG-PET studies reveal frontal and temporal hypometabolism (parietal hypometabolism often also present), with relatively preserved perirolandic metabolism [134].

Although functional imaging with blood oxygenation level–dependent (BOLD) functional MRI and magnetoencephalography may reveal abnormal activity in motor and non-motor areas in ALS, further studies are needed to determine their role in UMN assessment [135, 136]. Additional research is also necessary to clarify the role of transcranial magnetic stimulation (TMS), alone or in combination with DTI, in the evaluation of the UMN system.

Laboratory Testing

There is no serologic test to diagnose sporadic ALS. Indeed, normal results are supportive of the diagnosis. Testing of serum, urine, and CSF is primarily performed to exclude alternative diagnoses, the array of tests being tailored to each particular presentation (see section on "Differential Diagnosis"). Nevertheless, there are certain blood tests performed at initial evaluation. These include complete blood count, chemistry panel (including calcium, phosphate, and magnesium), creatine kinase (CK), VDRL, HIV, erythrocyte sedimentation rate, serum protein immunofixation or immunoelectrophoresis and anti-GM1 antibody assay, angiotensin-converting enzyme (ACE) and glycosylated hemoglobin (HbA1c), thyroid function studies including thyroid-stimulating hormone, serum parathormone (if calcium is raised), and vitamin B12 levels. Anti-neuronal antibody testing, to exclude a paraneoplastic syndrome, should be considered, as paraneoplastic encephalomyelitis may present as myelopathy with motor neuron symptoms alone, resembling ALS (although sensory and autonomic features may occur later). Associated anti-neuronal antibodies, including anti-amphiphysin, anti-Hu, anti-Ma, and anti-CRMP5, may be detected [137, 138]. By definition, these tests should be normal except for possible modest elevation of CK which commensurate with the degree of muscle atrophy in early disease in active males.

Patients older than 50 years and smokers of any age should have a chest radiograph and fecal occult blood testing. If any chest lesion is identifiable, or if the presentation is subacute with atypical features such as sensory loss, a

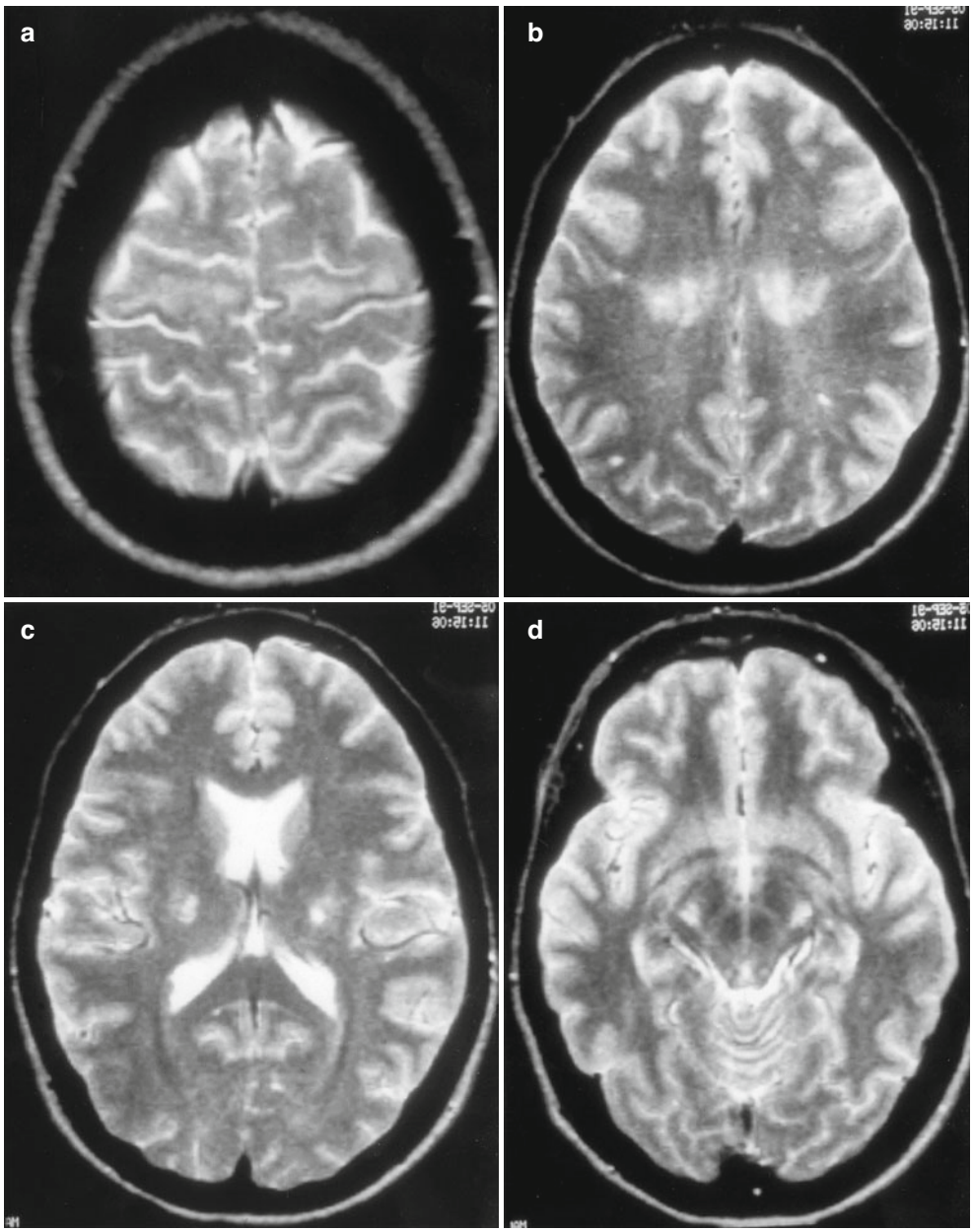

Fig. 20.6 (**a**–**d**). T2-weighted cerebral magnetic resonance images at four levels in a female patient with rapidly progressive amyotrophic lateral sclerosis. Note the increased signal intensity in the corticospinal tract as it extends from the motor cortex to the brainstem

paraneoplastic anti-neuronal antibody screen, particularly anti-Hu antibody levels, should be performed. Some patients may have clinical features suggesting a neuromuscular junction disorder and should have testing for antibodies against the acetylcholine receptor or voltage-gated calcium channel. If there is biochemical evidence of adrenal insufficiency, it is prudent to obtain a very long-chain fatty acid (VLCFA) assay to investigate for possible adrenomyeloneuropathy. Young-onset ALS with atypical clinical features such as early dementia, cramps, and tremor should prompt the physician to obtain a leukocyte hexosaminidase-A assay. Young age at onset, with perioral fasciculations and gynecomastia, should prompt genetic assessment for the trinucleotide repeat expansion on the androgen receptor gene associated with Kennedy's disease (spinobulbar muscular atrophy). If there is a positive family history of ALS or frontotemporal dementia in otherwise typical ALS, it is important to counsel the patient in preparation for appropriate mutation analysis. Reserve cerebrospinal fluid examination for cases with features suggestive of an infectious or infiltrative process such as lymphoma or basal meningitis or suspected CIDP. No specific features on muscle biopsy distinguish ALS from other neurogenic disorder. (It may reveal changes of chronic denervation and muscle fiber regeneration and, in long-standing patients, replacement of muscle fibers by fibro fatty tissue.) Thus, reserve biopsy for cases that are more suggestive of a myopathy.

Differential Diagnosis

Many diseases, both neurologic and systemic, may mimic ALS, making the differential diagnosis rather extensive. Depending upon the particular study, the misdiagnosis rate varies between 27 and 42 %, with more misdiagnoses occurring in patients over 60 years [139]. One may approach the differential diagnosis in terms of the anatomy, symptoms, or clinical presentation. For this discussion, we discuss the differential in terms of nervous system anatomy (Table 20.4).

Brain

Certain early manifestations of *Parkinson's disease* bear resemblance to ALS such as increased tone, hypophonia, sialorrhea, and dysarthria. However, tremor and response to levodopa help to distinguish the two conditions. Furthermore, the EMG fails to show widespread changes of denervation. Similarly, *multiple system atrophy (MSA)* may present with long tract signs and amyotrophy. However, ataxia, dysautonomia, sphincter disturbance, and oculomotor disturbances are common in MSA and rare in ALS. Also, there is evidence of external anal sphincter chronic denervation in MSA on needle EMG. *Spinocerebellar ataxia type 3 (Machado Joseph disease)* may exhibit spasticity and distal extremity wasting, usually with prominent extrapyramidal and oculomotor signs. Rarely, mild phenotypes of *Huntington's disease*, particularly when lacking a family history, may resemble ALS with increased tone and dysarthria. However, the progression of both disorders is dissimilar, and there are characteristic basal ganglionic MRI findings seen in Huntington's disease. *Stroke* with multiple subcortical ischemic lesions may produce marked pseudobulbar affect, weakness, and corticospinal tract signs, but MRI, especially T2-weighted and FLAIR images, should readily demonstrate these changes.

Polyglucosan body disease is a rare, late-onset, slowly progressive disorder characterized by combined UMN and LMN signs, cognitive decline, distal sensory loss, and disturbances of bladder and bowel function. MRI of the brain may reveal diffuse white-matter signal increase on T2-weighted images, but diagnosis is based on characteristic pathological changes in tissue from peripheral nerve, cerebral cortex, spinal cord, or skin. Axons and neural sheath cells contain non-membrane-bound cytoplasmic periodic acid–Schiff-positive polyglucosan bodies. Ultrastructural examination shows inclusions consisting of 6–8-nm branched filaments, most abundant in myelinated nerve fibers. In Ashkenazi Jewish patients (and one reported non–Ashkenazi Jewish patient), the disorder was caused by mutations of the glycogen-branching enzyme (GBE) gene, with subsequent deficiency of the protein product. However, adult polyglucosan body disease occurs in many different populations, and considerable molecular heterogeneity has been observed, with otherwise typical cases lacking GBE mutations despite deficiency of enzyme activity [140, 141]. Incidentally, two types of polyglucosan body may be seen in typical ALS—Lafora bodies and corpora amylacea—although neither could be considered characteristic pathological features.

Brainstem and Spinal Cord

Cervical spondylosis is probably the most important consideration in the differential diagnosis of ALS, and may closely mimic ALS, potentially presenting with asymmetric weakness of all extremities and UMN signs due to spinal cord compression and LMN signs due to foraminal stenosis. Lesions at the foramen magnum and various medullary lesions, such as infarct, syrinx, demyelination, and neoplasm, may simulate the bulbar presentation of ALS, rendering neuroimaging essential in the evaluation. Although *syringomyelia* may present with weakness and wasting, a characteristic pattern of dissociated sensory loss typically occurs and the disease progresses at a much slower pace in a generally younger population than ALS. A combination of UMN and LMN signs may be seen in *multiple sclerosis* in the setting of plaque formation at root exit zones. Characteristic MRI and CSF findings help to differentiate multiple sclerosis from ALS. Another consideration, in patients presenting in their third or fourth decade, is *adrenomyeloneuropathy*, a peroxisomal disorder caused by a defect in beta-oxidation of very long-chain fatty acids. Patients present with spastic paraparesis, areflexia, sphincter disturbance, and sensory loss. The diagnosis is established by demonstrating increased plasma levels of very long-chain fatty acids [142]. The prominence of sensory findings usually distinguishes ALS from subacute combined degeneration due to *vitamin B12 deficiency*. However, since patients may occasionally lack sensory features, it is prudent to routinely measure a vitamin B12 level to exclude this eminently treatable condition.

"Four-A" syndrome (Allgrove syndrome), a very rare autosomal recessive disorder that derives its name from the combination of achalasia, alacrima, adrenocorticotrophic insufficiency, and amyotrophy, can manifest from the first decade of life with dysphagia and adrenocortical insufficiency. A broad range of neurological problems can arise later in life including cognitive deterioration, optic atrophy, seizures, autonomic disturbance (dry mouth, postural hypotension, and syncope), and bulbospinal amyotrophy (amyotrophy of limbs and tongue, with tongue fasciculations and pyramidal signs) [143]. The AAAS gene is located on chromosome 12q13 and encodes *aladin* in the neuroendocrine system with

Table 20.4 Differential diagnosis of ALS

Anatomical location	Disorder	Test
Brain	Parkinson's disease	Levodopa
	Huntington's disease	MRI, CAG repeat
	Cerebrovascular disease	MRI brain
	Prion disease, HIV	EEG, CSF, biopsy
	Multiple systems atrophy	Autonomic testing
	Spinocerebellar atrophy	Genetic testing
Brainstem and spinal cord	Brainstem glioma, plaque, infarct	MRI
	Foramen magnum mass	
	Syringobulbia	
	Kennedy's disease	CAG repeat
	Spondylosis, syringomyelia, MS, SCDC, HTLV-1/2, HIV/2	MRI, EMG, CSF
	Adrenomyeloneuropathy	Serology, B12 levels
	Hereditary spastic paraparesis	VLCFAs Gene tests
Anterior horn cell	Spinal muscular atrophy	
	Kennedy's disease	CAG repeat, EMG
	Monomelic amyotrophy	
	Hexosaminidase A deficiency	Hexosaminidase A assay
	Post-polio syndrome	
	West Nile virus	WNV IgM serum and CSF
	Paraneoplastic	
		Anti-Hu, Anti-Ma, anti-amphiphysin
Root, plexus, and nerve	Radiculopathy	EMG, MRI
	Diabetic polyradiculoneuropathy	EMG, glucose
	Polyradiculopathy (CIDP, GBS, porphyria, HIV, CMV, lyme, syphilitic, postradiation)	EMG, labs, serology
	Neuralgic amyotrophy	
	POEMS, MMNCB, mononeuropathies	EMG
		EMG, SPI, anti-GM1
Neuromuscular Junction	Lambert–Eaton syndrome	Repetitive stimulation
	Myasthenia gravis	EMG, SFEMG, AchR AB assay
Muscle	Inclusion body myositis	Biopsy
	Oculopharyngeal dystrophy	GCG repeat, biopsy
	Myotonic dystrophy	CTG repeat,
	Isolated neck extensor myopathy	EMG
	Metabolic and congenital myopathies	EMG, Biopsy
Systemic	Hyperthyroidism	TSH, T4
	Hyperparathyroidism	$Ca^{++,}$ PTH assay
	Benign fasciculations	EMG
	Cramp–fasciculation syndrome	EMG
	Paraneoplastic syndrome	Anti-neuronal Abs, imaging, CSF

HIV human immunodeficiency virus, *MS* multiple sclerosis, *SCDC* subacute combined degeneration of the cord, *CK* creatine kinase, *HTLV-1* human T-lymphotropic virus, *VLCFAs* very long-chain fatty acids, *CIDP* chronic inflammatory demyelinating polyneuropathy, *GBS* Guillain–Barré syndrome, *CMV* cytomegalovirus, *SPI* serum protein immunofixation, *AchR AB* acetylcholine receptor antibody, *PTH* parathormone, *anti-neuronal Abs* anti-neuronal antibodies, *CSF* cerebrospinal fluid

roles in regulation of the cell cycle, cell signaling, and the cytoskeleton.

Both *hereditary spastic paraparesis* (HSP) and *tropical spastic paraparesis* should be considered in the differential diagnosis of slowly evolving spastic paraparesis. However, the former is differentiated by a family history together with very slow progression, sphincter disturbance, and an absence of LMN, bulbar, or respiratory involvement [144]. Tropical spastic paraparesis, a chronic myelopathy associated with human T-lymphotropic virus type 1 (HTLV1), presents in the third or fourth decade with UMN signs involving the bladder and lower extremities. Human T-cell leukemia virus

type 1 (HTLV-1) is a replication-competent human retrovirus associated with two distinct types of disease only in a minority of infected individuals: the malignancy known as adult T-cell leukemia (ATL) and a chronic inflammatory central nervous system disease HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). HTLV-2 may also cause a similar myelopathy [145]. Antibodies against HTLV1 may be detected in serum and CSF, and MRI often shows evidence of demyelination. Another virus that should be considered is human immunodeficiency virus (HIV) which may present with a vacuolar myelopathy in the setting of a low CD4 count. However, both sensory and sphincter complaints are much more prominent in HIV myelopathy than in ALS.

Anterior Horn Cell

Although most *spinal muscular atrophies* (SMAs) are disorders of childhood and youth, some crossover with the ALS population exists in the form of juvenile-onset ALS and adult-onset SMA. Overall, the SMAs usually manifest with slowly progressive, symmetrical, proximal muscle weakness and atrophy without additional UMN signs (see Chap. 21). *Kennedy's disease*, or X-linked bulbospinal neuronopathy/spinal and bulbar muscular atrophy (SBMA), is a rare X-linked trinucleotide polyglutamine disorder, caused by an abnormally large expansion of tandem CAG (cytosine–adenine–guanine) repeats in exon 1 of the androgen receptor (AR) gene on chromosome Xq11-12 (see Chap. 22). It is characterized by degeneration and loss of lower motor neurons in brainstem and spinal cord and typically presents in males in the third or fourth decade with weakness and wasting of bulbar, facial, and limb girdle muscles; tremor; perioral fasciculations; mild cognitive impairment; sensory disturbance; and signs of endocrine dysfunction such as diabetes mellitus, gynecomastia, and testicular atrophy [146]. In normal individuals, the CAG repeat ranges in size between 9 and 36, and expansion over 38 and up to 62 is pathogenic [147]. Additional useful features that help to separate Kennedy's disease from ALS include a moderately high CK and low SNAPs. To confirm the diagnosis, a genetic test that detects the CAG repeat expansion of the androgen receptor gene is available.

ALS rarely occurs in an individual with a history of poliovirus infection.

A separate anterior horn cell disorder, the *post-poliomyelitis syndrome* (PPS), is a late consequence of prior infection with poliovirus (see Chap. 19). It typically presents, after a prolonged stable course following the original paralytic illness, as worsening of weakness in previously affected muscles and ill-defined pain in the low back, neck, and many joints together with significant fatigue, dizziness, and somnolence. While many of these complaints are shared with ALS, there is a paucity of UMN signs and the rate of progression in PPS is very slow. Criteria for the diagnosis of PPS include a history of paralytic poliomyelitis, partial or complete recovery of neurological function followed by a period of stability (usually decades), persistent new muscle weakness or abnormal muscle fatigability, and exclusion of other causes. The condition is thought to occur as a result of distal degeneration and premature neuronal dysfunction of preexisting, enlarged polio-affected motor neurons. Potential contributing factors include aging (with motor neuron loss), overuse, and disuse. Although no specific treatment exists, a multidisciplinary management program can be useful in modifying symptoms [148]. West Nile arthropod-borne flavivirus infection can cause epidemics of meningitis and encephalitis. A small proportion of patients (<1 % overall but 10–50 % with neuroinvasive disease) develop a polio-like, and sometimes painful, disorder characterized by acute asymmetrical flaccid paralysis, due to viral infection of anterior horn motor neurons in the spinal cord that can precipitate respiratory failure and even death [149].

Acidic-hexosaminidase deficiency, or Hex A deficiency, a GM2 gangliosidosis that causes a recessively inherited progressive neurologic disorder, may present from childhood to the fifth decade and may resemble ALS. It is most often, but not exclusively, seen in the Ashkenazi Jewish population [150]. The enzyme has two subunits, alpha and beta, and hydrolyzes lysosomal GM2 gangliosides in neuronal membranes. Complete absence of the alpha polypeptide results in Tay–Sachs disease, which manifests in infancy with encephalopathy, myoclonic seizures, macular cherry-red spots, and death. Compound heterozygotes with less severe mutations in one of the alpha subunits resulting in a deficiency of the enzyme develop later-onset disease characterized by elements of LMN weakness, dysarthria, cerebellar ataxia, cramps, spasticity, cognitive deterioration, and tremor. EDX studies may reveal prominent complex repetitive discharges on needle EMG and abnormal SNAPs. Overall, this rare disorder should be considered in atypical cases of ALS, in particular in a young person. It can be confirmed by serum analysis of Hex A activity in leukocytes and Hex A gene mutation analysis [151].

It may be difficult to differentiate monomelic-onset ALS from benign *monomelic amyotrophy* (MMA), a condition originally reported in Japan and India, which typically presents as focal atrophy of one limb, or part thereof, predominantly affecting young men in their second and third decades. Segmental anterior horn cell involvement causes wasting and weakness of predominantly one upper or lower limb, without evidence of sensory dysfunction. Reflexes may be either reduced or normal, and fasciculations are prominent. Progression may occur for a few years with eventual stabilization [152]. Needle EMG may reveal relatively sparse

fibrillation potentials in affected muscles along with neurogenic changes in both affected and clinically uninvolved limbs. MRI may reveal focal cervical cord segmental atrophy and ventral root atrophy if performed late in the disease.

Paraneoplastic disease particularly that associated with lymphoma may present subacutely with LMN manifestations arising typically in the lower extremities, although there are rare patients that present with a combination of both UMN and LMN signs, thus bearing close resemblance to ALS. One should consider this diagnosis if a paraprotein is detected in the blood. Apart from lymphoma, a similar motor neuron disease may be the presenting manifestation of Waldenstrom's macroglobulinemia and myeloma. Paraneoplastic encephalomyelitis may present as a transverse myelopathy with motor neuron symptoms alone, resembling ALS (although sensory and autonomic features and ataxia may occur later). Associated anti-neuronal antibodies, including anti-amphiphysin, anti-Hu, anti-Ma, and anti-CRMP5, may be detected. The anti-amphiphysin presentation is usually PLS-like, but with rapid deterioration (thus unlike true PLS) and the anti-Ma, associated disorder varies but can be like PMA [137, 153]. The association of ALS with solid malignancy is somewhat unclear; one study reported a frequency of tumor in ALS patients more than twice that of controls, but patients with both ALS and cancer do not differ clinically from patients with ALS without cancer. Furthermore, with rare exceptions, ALS does not respond to tumor treatment [154–156].

Radiculopathies, Polyradiculoneuropathies, and Polyradiculopathies

Compressive radiculopathy must be considered in the differential diagnosis of any patient presenting with focal LMN signs in a limb. Foot drop may either be the first symptom of ALS or an L5 radiculopathy, and hand interosseous wasting may occur in both ALS and C8 radiculopathy. While pain and sensory loss may serve as clues to the presence of a nerve root lesion, some patients with radiculopathy present with weakness alone. EDX studies reveal changes restricted to a particular root distribution, and MRI or CT myelography reveals nerve root compromise in the clinically manifesting root distribution. *Neoplastic* (such as lymphoma, or leukemia related), *radiation-induced,* and *infectious* (viral and spirochetal) *polyradiculopathies* may superficially mimic ALS. Additional historical clues and characteristic signs such as skin or retinal changes may point to alternative diagnoses, with appropriate serology and CSF analysis required to identify the specific cause. *Diabetic polyradiculoneuropathy* is a rare condition that may present as progressive asymmetric weakness in the proximal lower extremities thus simulating PMA (see Chap. 31). In its most severe form, diabetic cachexia, multiple roots extending from the cervical to sacral areas are involved, but pain and sensory loss are typically prominent findings and EDX often reveal associated polyneuropathy.

Neuropathies and Plexopathies

Multifocal motor neuropathy with conduction block (MMNCB) is a rare disorder (see Chap. 22), characterized by onset of focal motor weakness, usually in a distal upper extremity. Those sites typically involved in entrapment neuropathies are spared and both fasciculations and cramps are common. Progression is very slow, over months or even years. An important clue to the diagnosis is the absence of muscle atrophy despite very significant weakness, until late in the disease course. The pattern of motor weakness is typically restricted to multiple separate peripheral motor nerves with a striking absence of sensory involvement. As the name implies, MMNCB is defined by demyelinating conduction block in affected motor nerves [157]. A variable percentage of patients have a high titer of serum antibodies against GM1 ganglioside, a neuronal membrane glycolipid present in high concentrations at nodes of Ranvier. However, these antibodies are not specific for MMNCB and their absence does not rule out the diagnosis.

Up to 10 % of ALS patients have a monoclonal gammopathy in the absence of any disease association, such as neoplasm or motor neuropathy with conduction block, although only about half of these patients have high titers. Of particular interest, however, is the motor neuropathy seen with *POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)* (see Chap. 30). This disorder can lead to a wasted appearance as seen in ALS, but may have tremor, papilledema, but no UMN features. One should perform a skeletal survey to seek out an osteosclerotic myeloma lesion, and CSF analysis may reveal elevated protein levels (often in excess of 100 mg/dl). The EDX studies are invaluable in revealing a sensory and motor polyneuropathy pattern characterized by generalized slowing of motor conduction velocities. Because of their demyelinating features on EDX, POEMS and MMNCB may closely resemble *chronic inflammatory demyelinating polyneuropathy (CIDP),* albeit with less sensory phenomena. CIDP may be difficult to distinguish clinically from ALS, although it classically features hypo-/areflexia and sensory changes and also is associated with elevated CSF protein concentrations. Yet again, performing EDX studies is essential to identify the characteristic changes of CIDP. In general, differentiating *Guillain–Barré syndrome (GBS)* from ALS poses less of a problem; there are unusual patients that lack sensory features and progress asymmetrically in a manner similar to PMA. Also, there are acute axonal variants of GBS that affect predominantly motor fibers (acute motor axonal neuropathy). However, the fast rate of progression of GBS

and reflex loss serve as diagnostic clues, and ancillary testing with EDX studies and CSF clarifies the issue.

Neuralgic amyotrophy or Parsonage–Turner syndrome, also known as brachial neuritis, may resemble limited forms of ALS such as monomelic-onset disease. This disorder, however, is classically preceded by significant deep, aching pain in the affected limb and shoulder that lasts several days and then fades away only to be replaced by motor weakness. The nerves involved are all largely motor in nature, often including one or more of the following: the long thoracic, suprascapular, axillary, anterior interosseous, and phrenic nerves. The EDX examination may reveal bilateral upper limb neurogenic changes on needle EMG, even in the presence of unilateral symptoms, but they are not as widespread as seen in ALS. In fact, involvement of motor nerve fibers can be curiously patchy, such as severe changes in infraspinatus but sparing of supraspinatus, although both muscles are innervated by the same nerve. This disorder usually improves spontaneously, but recovery can take months and there is recent evidence that early treatment with immune therapy may help speed recovery [158, 159].

Disorders of the Neuromuscular Junction

Myasthenia gravis (MG), an autoimmune disease characterized by antibodies directed against the acetylcholine receptor, may present with weakness of bulbar and neck extensor muscles without extraocular manifestations, thus mimicking bulbar-onset ALS (see Chap. 48). Patients may also present with significant respiratory compromise. Clues to the diagnosis of MG include the absence of UMN signs and fasciculations. One can confirm the diagnosis of MG by checking acetylcholine receptor antibodies and performing repetitive nerve stimulation looking for a decremental response and/or single-fiber EMG studies looking for abnormal jitter. However, in more severe patients of ALS, a decremental response may occur, albeit to a lesser extent than typical of MG. Similarly, single-fiber EMG studies may reveal increases in jitter and in fiber density in ALS just as in MG. To further blur the picture, edrophonium testing may be positive in both conditions. On the other hand, it is very rare to detect fibrillation potentials in MG, and fasciculations are not a feature of MG unless patients are overtreated with cholinergic agents. *Lambert–Eaton myasthenic syndrome* (LEMS) is an autoimmune disorder, caused by antibodies directed against voltage-gated calcium channels on the presynaptic nerve terminal (see Chap. 49). It typically presents with limb girdle weakness without atrophy or fasciculations and often with associated signs of autonomic dysfunction such as dry mouth and impotence. One of the characteristic features of LEMS is the transient increase in muscle strength and deep tendon reflexes after a brief contraction. On EDX examination, there may be generally low-amplitude CMAPs as may be seen in advanced ALS. However, EDX studies distinguish LEMS from ALS by the demonstration of post-tetanic facilitation and by the absence of fibrillation and fasciculation potentials [160].

Myopathies

Inclusion body myositis (IBM) may mimic ALS, sharing distal muscle involvement, painless asymmetric weakness, and difficulty swallowing. However, fasciculations are conspicuously absent and there are no UMN signs [161]. The CK levels are often similar in both conditions (slightly elevated or normal), but needle EMG features predominantly myopathic rather than neurogenic changes in IBM. Muscle biopsy is required to confirm the presence of rimmed vacuoles and intranuclear inclusions, the characteristic abnormalities of IBM. In addition to IBM, there are *sporadic and inherited distal myopathies* that appear between the ages of 40 and 60 years and present as weakness and wasting of distal upper and lower extremities; they may be diagnosed by EMG and muscle biopsy. Distal muscle weakness is also characteristic of *myotonic dystrophy,* but there are several clinical features such as a distinctive facial appearance, myotonia, and systemic abnormalities including cataracts, frontal balding, and diabetes mellitus, which help to lead to the correct diagnosis. Needle EMG reveals prominent myotonic discharges. Testing for the presence of an abnormally large expansion of the CTG trinucleotide on the serine–threonine protein kinase gene located on chromosome 19 confirms the diagnosis. *Oculopharyngeal muscular dystrophy*, an uncommon myopathy caused by a trinucleotide repeat expansion, may mimic progressive bulbar palsy (see Chap. 60). Indeed, as the disease advances, weakness spreads to the shoulder girdle, but the condition usually involves the eyelids and extraocular muscles, thus setting it apart from ALS and its variants. A muscle biopsy may be required to confirm the diagnosis, especially in those rare patients that present with dysphagia and subtle extraocular manifestations. Another interesting disorder, *isolated neck extensor myopathy*, presents in older individuals with dropped-head syndrome and is associated with signs of active denervation in cervical paraspinal muscles. This may be initially mistaken for ALS, but the weakness does not spread to other regions.

Systemic Disease

Hyperthyroidism may present with corticospinal tract signs, fasciculations, weight loss, and weakness, thus simulating ALS. However, there usually are additional signs such as heat intolerance, anxiety, tremor, tachycardia, insomnia, and goiter that lead to the correct diagnosis. It is prudent to include a thyroid-stimulating hormone assay in the screening

evaluation of ALS. *Hyperparathyroidism* may present with clinical weakness and even a myopathy and as such may mimic the PMA form of ALS. There may be a high level of ionized calcium, and the diagnosis is confirmed by elevated serum parathormone.

Benign fasciculations typically occur in people under the age of 30 years, and often have a relapsing–remitting course over months or years without any other abnormalities. They occur in a wide variety of disorders and are frequent in the normal population. Fatigue, stress, alcohol, caffeine, and vigorous exercise exacerbate them. Similarly, one must be able to recognize *cramp–fasciculation syndrome*, a benign condition that may be sporadic or inherited, manifests as cramps and fasciculations in the calves, and responds to carbamazepine. There are certain features on needle EMG that reportedly serve to differentiate benign from ALS-associated fasciculations. The latter tend to have a more complex waveform and may be induced by joint displacement, and benign fasciculations, as suggested by the name, are not associated with clinical and EDX features of a widespread disorder of anterior horn cells.

As already outlined, motor neuron disease may rarely occur as a paraneoplastic phenomenon. Patients present with features typical of pure ALS or manifest as PMA or PLS. Other motor neuron manifestations may represent only one part of a larger paraneoplastic syndrome, such as anti-Hu antibody–associated encephalomyelitis, presenting initially as a transverse myelopathy with motor neuron symptoms alone, resembling ALS. Atypical features (sensory and autonomic features and ataxia) may occur later on, and associated anti-neuronal antibodies, including anti-amphiphysin, anti-Hu, and anti-CRMP5, may be detected. Most paraneoplastic motor disorders are typically unresponsive to treatment of the underlying malignancy.

HIV infection may also mimic ALS clinically. A retrospective review of 1,700 cases of HIV-1-infected patients with neurological symptoms identified six cases presenting as a reversible ALS-like syndrome representing a 27-fold increased risk of developing an ALS-like disorder in that particular HIV-1 patient population [162]. Overall, patients were younger than the typical ALS population, and onset was characteristically in a monomelic pattern followed by rapid spread to other regions over a period of weeks, characterized by UMN and LMN involvement, with fasciculations, cramps, and bulbar symptoms. Two patients also had rapidly progressive dementia, suggesting an additional diagnosis of AIDS–dementia complex. Sensory and sphincter disturbances were not apparent. CSF protein levels were sometimes mildly increased, and lymphocytic pleocytosis was evident in three patients, but all remaining laboratory results (HIV-1 seropositivity apart) were negative. EDX revealed widespread anterior horn cell disorder in the absence of demyelinating conduction block, and MRI in one patient showed diffuse white-matter signal increase suggestive of AIDS–dementia complex. In each case, antiretroviral therapy was beneficial either in stabilizing or curing the disease, but subsequent cases have been described that failed to recover despite treatment [117]. Another case report found similar clinical features in a 32-year-old HIV-positive patient who responded to antiretroviral therapy, and resolution of motor symptoms coincided with a lack of detectable HIV in plasma and CSF. MRI abnormalities also resolved almost completely [163]. Flail-arm ALS-like variants have also been described in HIV, with MRI signal changes in the anterior cervical spinal cord.

Table 20.5 Prognostic indicators in ALS

Better prognosis	Worse prognosis
Younger (<50 years)	Older
Spinal onset	Bulbar onset
Progressive muscular atrophy	Dyspnea onset
Primary lateral sclerosis	Some familial forms
Flail arm	
Slow deterioration	Rapid deterioration
Normal compound muscle action potentials	"Low motor–normal sensory"
No decrement on repetitive nerve stimulation	Decrement on repetitive nerve stimulation
Mild at diagnosis	Severe at diagnosis
Long duration from onset to diagnosis	Short duration from onset to diagnosis
Well nourished	Malnourished
Psychological well-being	Psychological distress
Normal serum chloride	Low serum chloride
Fasciculations mild or absent	Fasciculations widespread
Attends multidisciplinary care	

Natural History and Prognosis

Despite the recent advances in understanding the natural history of ALS, it remains difficult to accurately predict the course and prognosis in individual patients (Table 20.5) [16]. Up to 30 % of anterior horn cells may be lost by the time a patient with ALS actually presents with weakness, which suggests that ALS may be subclinical for months or even years before symptom onset. During this preclinical stage, the rate of denervation may be balanced by the rate of collateral reinnervation, but the rate of denervation eventually supercedes. Original thinking was that the pattern of decline was linear from onset (Fig. 20.7) [6, 16], but recent work has shown that deterioration in ALS is nonlinear: the early and late phases of the illness show the most rapid rates of decline. Older age and bulbar signs are associated with a steeper decline and, along with more rapid initial rate of decline, predict survival [164]. When onset is in one arm, the progression of disease is typically to the contralateral arm, then the ipsilateral leg,

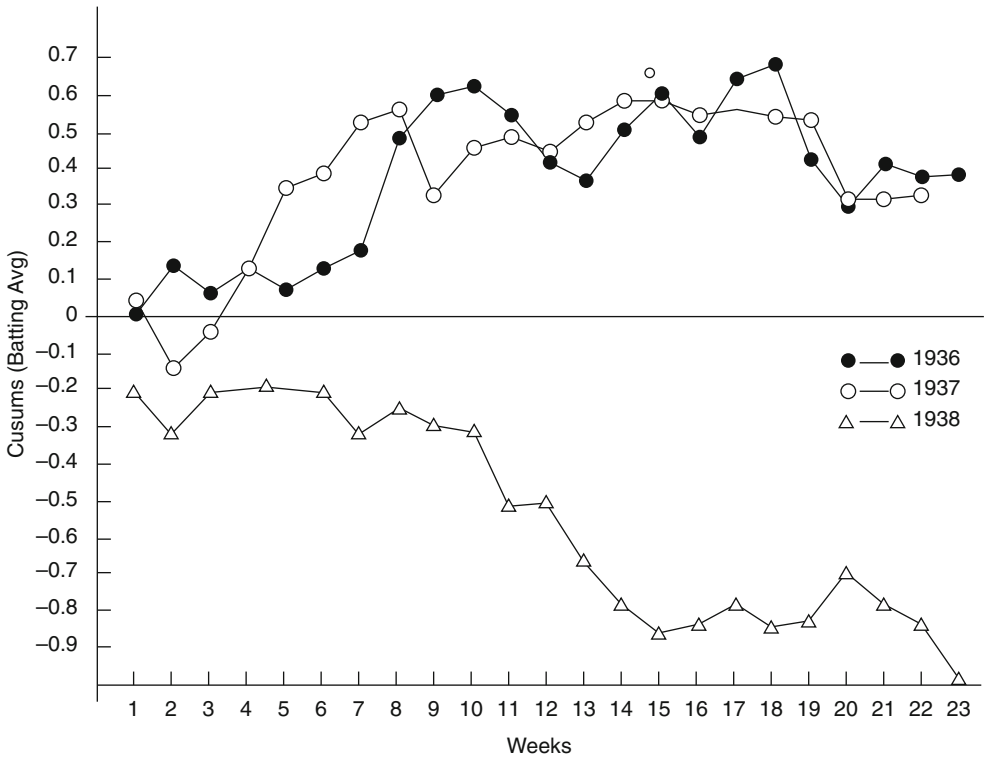

Fig. 20.7 Decline in function over time in amyotrophic lateral sclerosis as depicted by this graph representing cumulative sum (CUSUM) statistical analysis of Lou Gehrig's batting average on a weekly basis from 1936 to 1938. Note the linear decline in function in 1938 (Reproduced with kind permission from Kasarskis and Winslow [6]) (Note: a recent study suggests that progression is nonlinear. Gordon et al. [164])

contralateral leg, and, finally, the bulbar region. With lower extremity onset, a similar pattern of progression follows, the bulbar region being affected last. Bulbar-onset ALS progresses first to the arms and then to the legs [17, 165]. Mean duration of the illness from symptom onset to death is approximately 3 years (mean duration ranges from 23 to 43 months). Roughly 20 % of patients live 5 years and 10 % of patients follow a more benign course, surviving for more than a decade [16].

When one analyzes the cumulative data from several different studies using mean survival times, it is evident that PLS harbors the best prognosis of all types of ALS, with a mean survival time of 224 months in one study and 168 (14 years) in another [17, 166, 167]. By definition, PMA indicates a disorder limited to lower motor neurons for more than 4 years and thus harboring a relatively good prognosis with one series of patients living a mean of 159 months from clinical onset [17, 72]. There are conflicting data on the prognosis of bulbar-onset ALS; while it is often associated with a shorter survival (disease duration has been reported to be between 12 and 27 months), it is argued that one must factor in the generally older age and many patients may be referred to inappropriate clinics prior to diagnosis. A recent study showed that the time to anarthria predicted loss of ambulation which in turn predicted a further 3-month survival [18]. The many forms of familial ALS do not portend a uniform prognosis: it is important to try to identify the causative mutation to allow more accurate prognostication. Both the flail-leg (pseudoneuritic) and flail-arm presentations are associated with longer survival [75].

When dyspnea is the presenting feature of ALS, there is a statistically significant shortening of disease duration. Moreover, a decline in pulmonary function, as tested by serial forced vital capacities, is a strong predictor of a poor prognosis [16, 40]. The severity and duration of disease at presentation also have prognostic implications, with more severe disease portending a worse prognosis and a long interval between onset and diagnosis being more favorable [16]. The ALS CNTF Treatment Study Group identified low serum chloride as a poor prognostic indicator, reflective of a compensatory metabolic response to respiratory acidosis that occurs in the later stages of the disease [168]. The role of psychological well-being on survival has also been investigated with indicators that psychological distress significantly predicts a less favorable prognosis [16]. A "generalized low motor–normal sensory" pattern seen on nerve conduction studies, a decremental response on repetitive nerve stimulation, and a rapid rate of decline of MUNE (motor unit number estimation) are all associated with poorer prognosis. There is limited evidence to support the lack of fasciculations as being prognostically favorable. Malnutrition with low body mass index is an independent risk factor for poor outcome [169].

Treatment and Clinical Trials

The past two decades have yielded theories of ALS pathogenesis each with potential for translation into future therapeutics. Interventions to counter nuclear protein

mislocalization may show promise as may agents involved in cell trafficking/signaling, inflammatory responses, excitotoxicity, and mitochondrial regulation. Clinical trials in ALS have examined a broad spectrum of drugs for their potential anti-glutamatergic activity (e.g., talampanel, lamotrigine, branched-chain amino acids, topiramate, dextromethorphan, and gabapentin) and neuroprotective and/or antioxidant effect (vitamin E, L-deprenyl, *N*-acetylcysteine, xaliproden Sanofi SR57746A), most with negative results. In addition, several recombinant neurotrophic factors (including ciliary neurotrophic factor, brain-derived neurotrophic factor, insulin-like growth factor (IGF-1, myotropin), and glial cell–derived neurotrophic factor) have been studied in well-designed trials, but without significant clinical efficacy. A phase III trial of IGF-1 polypeptide is underway. Other agents, ultimately non-efficacious in ALS, include creatine, coenzyme Q10, minocycline, rapamycin, ceftriaxone, celecoxib, glatiramer acetate, tamoxifen, minocycline, TCH346, ONO 2506 PO, and lithium. Further details regarding ongoing trials are available at www.wfnals.org.

Despite high cost and modest efficacy, riluzole, with a modest effect on prolonging life in ALS patients, remains the only approved agent (Fig. 20.8) [172]. Its mechanism of action is not completely clear, but may include modification of N-methyl-D-aspartate (NMDA) receptor-mediated responses, stabilization of the inactivated state of voltage-dependent sodium channels, and inhibition of glutamate release from presynaptic terminals while increasing extracellular glutamate uptake. When taken for 18 months (in patients with clinically probable or definite El Escorial ALS, with symptoms less than 5 years, FVC >60 % and age <75 years), 100 mg (taken as 50 mg twice daily) probably prolongs median survival by 2–3 months [173]. Preliminary developments in areas of stem cell therapies, RNA interference, viral vector-mediated gene therapy, and immunotherapy offer promise of novel therapeutic strategies. Based on the likely role of mitochondrial dysfunction in ALS pathogenesis, dexpramipexole, the putative mitochondrial modulator (KNS-760704) has undergone preliminary trials (http://clinicaltrials.gov), which suggest safety and tolerability and possible attenuation of ALS functional rating scale decline, thus supporting further testing [174].

Although it is difficult, care must be taken to break the diagnosis of ALS in such a way that the patient and the family understand the diagnosis and its implications but do not feel that hope has been taken away. Thus, one should provide sufficient information regarding the disease itself, including treatment trials and research progress.

It is vitally important to maintain patient autonomy in all decision-making processes and, at the appropriate time, to adequately discuss difficult topics, such as advance directives and issues regarding terminal care. Those patients with more recent diagnoses and with more rapid declines in pulmonary function are more likely to seek interventions such

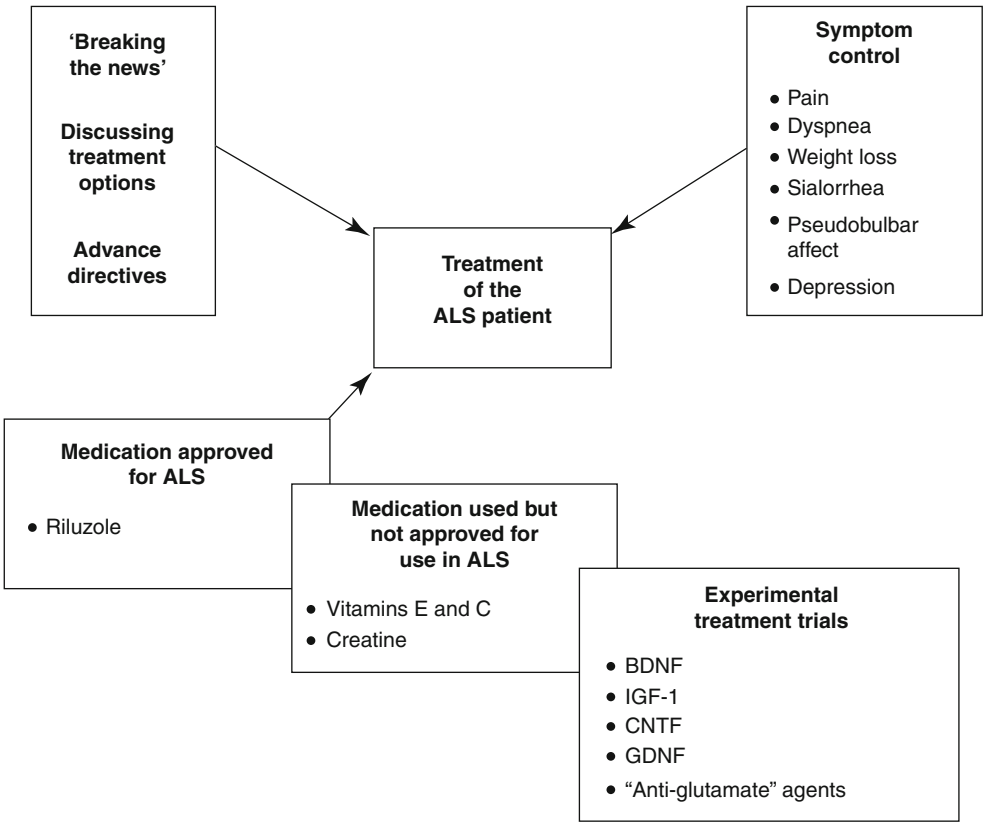

Fig. 20.8 Simplified algorithm for the treatment of amyotrophic lateral sclerosis (For a more detailed discussion, see Refs. [170, 171])

as ventilatory assistance and enteral feeding tubes. Overall, it is best to impart information, particularly that pertaining to prognosis, in a stepwise manner and not to overwhelm the patient as soon as the diagnosis is made. There is no specific treatment currently available that halts or reverses the disease, but there are several paths to optimally manage the many distressing symptoms of ALS. The recommendations for the symptom management of ALS are clearly defined in the practice parameter report by the Quality Standards Subcommittee of the American Academy of Neurology [170, 171].

Symptom Management

Sialorrhea, Pseudobulbar Affect and Depression

Daytime sialorrhea may be treated with anticholinergic preparations such as benztropine, transdermal hyoscine, glycopyrrolate, trihexyphenidyl, and atropine or, as is more commonly practiced, by utilizing the anticholinergic properties of the tricyclic antidepressants (TCADs). In order to reduce thick mucus, adding a beta-blocker, such as propranolol, may be helpful. Mechanical insufflation–exsufflation further enhances clearance of mucous plugs. Alternative approaches include injection of botulinum toxin A into the parotid glands which, by blocking autonomic cholinergic fibers subserving secretomotor function, may lead to a substantial reduction in saliva production and parotid irradiation [175, 176].

Pseudobulbar affect may be effectively controlled with tricyclic antidepressant (TCAD) treatment although one may also use a selective serotonin reuptake inhibitor (SSRI), such as fluvoxamine or quinidine/dextromethorphan. Depression, with or without anxiety, may be treated with a variety of antidepressant preparations such as the TCADs and SSRIs, whereas isolated anxiety may be responsive to benzodiazepines or buspirone. Patients may have pseudobulbar, depressive, and sialorrheic symptoms simultaneously, and it is often possible to treat all complaints with one medication.

Nutrition

Attention must be paid to the nutritional needs of the patient. Particularly with advancing dysphagia, assessment of swallow at the earliest possible stage is advised, in order to devise strategies to maximize caloric intake, prevent dehydration, and reduce aspiration risk. Initial management should focus on appropriate forward head positioning, chin tuck, thickening of liquids, and dietary supplementation. As dysphagia worsens and the patient loses more weight, the physician should recommend a percutaneous endoscopic gastrostomy (PEG), a procedure that may help maintain weight [171], enhance patient quality of life, and also prolong survival by 1–4 months. To minimize risks, evidence suggests that PEG should be performed before vital capacity (VC) falls below 50 % of predicted [177]. Although it may be possible to insert PEG with noninvasive ventilator (NIV) assistance, radiologically inserted gastrostomy (RIG) or percutaneous radiological gastrostomy (PRG) may be a safer alternative in some patients [178]. Importantly, patients who receive a PEG or RIG tube can continue to eat by mouth: the purpose of enteral feeding is to provide calories and fluid. Aspiration is a continued risk to the patient even after PEG tube insertion, and if recurrent aspiration of PEG contents becomes a persistent problem, one can either recommend percutaneous enteral jejunostomy (PEJ), which further reduces (but still does not eliminate) the risk, or a tracheostomy. In aphonic patients with recurrent aspiration, one could also consider conservative laryngectomy or laryngeal diversion. Most guidelines state that supplementary enteral feeding should be considered when body weight falls by > 10 % of the pre-diagnostic or baseline weight [179].

Pain, Spasticity, and Muscle Cramps

Pain, commonly from pericapsulitis, bursitis, cramps, or spasticity, may pose a significant problem in advanced stages of ALS, and the physician must be aggressive in controlling such discomfort. This should start with physical therapy, using passive joint-stretching techniques, followed by treatment with nonsteroidal anti-inflammatory drugs (NSAIDS). Various heating agents, including diathermy and ultrasound, are useful in pain management and in performance of range-of-motion exercises. In addition, transcutaneous electrical nerve stimulation (TENS) is often effective in relieving joint and connective tissue–related pain. Lancinating pains may be responsive to carbamazepine, phenytoin, clonazepam, and amitriptyline, but if pain remains poorly controlled, the physician should not be hesitant to use opioids and, particularly in the preterminal stages, morphine or a fentanyl patch. Several agents, such as baclofen, tizanidine, benzodiazepines, and dantrolene either alone or in combination, may be effective in managing spasticity although patients may experience additional weakness as a troublesome side effect. When cramps are severe, one may employ muscle-stretching exercises in combination with quinine sulfate, baclofen, carbamazepine, diazepam, or phenytoin. In the preterminal phase of ALS, the patient may suffer considerably from distressing dyspnea which can be managed using benzodiazepines, opiates, supplemental oxygen, and, for terminal restlessness, chlorpromazine.

Mobility and Assist Devices

With advancing disease, it is important to continually make adjustments so as to maximize patient function and independence. A number of adaptive devices are available to assist in this regard, including AFO braces for foot drop, specialized neck-support collars for head drop, and various hand/wrist

splints. Increasingly sophisticated communication assist devices are becoming available to aid anarthric patients. Likewise, there are many kinds of wheelchairs, including motorized models that may be customized for each patient's needs. Home assessments by nurses, occupational therapists, and physical therapists are of great benefit when choosing the optimal equipment. Apart from assist devices, it is important that the patient initiates an appropriate program of therapeutic exercise with particular focus on range-of-motion stretching maneuvers. There is some concern that excessive exercise to the point of fatigue may be deleterious and may even be an underlying precipitant of the disease itself, although this has not been borne out in the literature.

Respiratory Function

Dyspnea-onset ALS and a progressive decline in pulmonary function portend a poorer prognosis, but visible signs of early pulmonary compromise may go unnoticed until an adverse event, such as aspiration pneumonia, occurs. Measuring the FVC at regular intervals serially assesses declining pulmonary function and assists the patient and the physician in appropriately projecting ahead. Whether or not the patient wishes for mechanical ventilation should be planned as early as possible. Most patients and physicians prefer the noninvasive approach.

Erect forced vital capacity (FVC) is the most commonly measured index of pulmonary function in ALS, but supine FVC provides a more accurate assessment of diaphragmatic weakness. To detect nocturnal hypoventilation, maximal inspiratory pressure (MIP) and nocturnal oximetry may be more effective. Trans-diaphragmatic sniff pressure (sniff Pdi) and the Sniff nasal inspiratory pressure (SNIP) are also useful indicators of hypercapnia and nocturnal hypoxemia [171]. SNIP is a good measure of diaphragmatic strength and is probably more accurate than vital capacity, although both measurements underestimate respiratory function in patients with bulbar impairment. A SNIP of 32 % (~25 cm H2O) or less is highly predictive of respiratory failure [180–183]. Observational studies and a randomized controlled trial show that NIV improves survival and quality of life. In patients with severe bulbar impairment, NIV improves sleep-related symptoms, but is unlikely to confer a large survival advantage [184]. Sociocultural factors (age, gender, marital status) influence the probability of receiving NIV, and these obstacles should be addressed to encourage NIV use in all ALS patients with respiratory failure [185].

Although evidence exists that NIV improves quality of life and may prolong survival in ALS, it does not prolong life indefinitely, and patients still face the difficult decision of whether to use an invasive ventilator. While invasive ventilation may prolong a patient's life for many years, the patient may develop additional "atypical" signs of disease such as overt cognitive decline, extraocular muscle palsies, and sphincter disturbance, which may later place a great burden upon patient and family. When initiating ventilatory therapy, there should be an agreement as to when, or if, it should be withdrawn. Decisions regarding withdrawal of ventilatory support, or augmentation when noninvasive means of ventilatory assistance are insufficient, must be based on effective and compassionate end-of-life care. In the event of initiating ventilatory withdrawal, sufficient opiates and anxiolytics should be used to minimize patient discomfort.

Because ALS is a progressive neurodegenerative disease with a predictable clinical course, palliative care should be initiated at, or soon after, diagnosis. The majority of skeletal muscles are eventually affected, and multiple ensuing problems require multidisciplinary input, including symptomatic therapy, rehabilitation to maintain muscle function, nutritional and respiratory support, communication device introduction, and psychological support for both patient and family or caregivers. Social, ethical, financial, and legal issues, including advance directives, should be addressed long before decisions regarding enteral feeding and assistive ventilation are required. Management goals must be reassessed regularly [186]. Hospice care, at home or in a residential hospice, provides highly effective palliative services to patients and families. Its philosophy strongly affirms life, promoting maintenance of independence and dignity as much as possible [187].

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Spinal Muscular Atrophies

21

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Introduction

The spinal muscular atrophies (SMAs) are a heterogeneous group of disorders affecting the lower motor neurons leading to muscle weakness and atrophy. Though the term SMA has traditionally been applied to both inherited and acquired disorders, its use should be restricted to disorders related to a genetic defect. Classification of the different forms of genetic SMA is by the mode of inheritance and the clinical phenotype (i.e., whether the predominant weakness is proximal or distal) (Tables 21.1 and 21.2). Several different causative genes have been identified for various types of SMA, but by far the most common is related to the survival motor neuron (SMN) gene on chromosome 5q11.12–13.3. This is an autosomal recessive disorder that usually presents in infancy or early childhood and is associated with predominantly proximal muscle weakness and atrophy.

The initial clinical description of childhood SMN-related SMA was made over a century ago by Werdnig and Hoffmann [1, 2]. Werdnig reported two patients with early infantile hereditary progressive muscular atrophy presenting as a dystrophy but on a neurogenic basis. Hoffman first coined the term spinal muscular atrophy [3]. Autopsy of their cases revealed atrophy of the ventral roots and loss of motor neurons in the anterior horn [1, 2]. Subsequently, others described later-onset patients of variable severity, including an adult-onset form of the disease [4–7]. Dubowitz highlighted the relationship between disease severity and age of onset [6]. Several attempts to classify the common autosomal recessive proximal SMAs were made [8, 9], culminating in the adoption of a widely used consensus classification by an International SMA Consortium based on the age of symptom onset and maximal motor milestone achieved [10]. This scheme embraced the wide spectrum of childhood SMA phenotypes that ranged from infants with severe disease and early death to children and adolescents with milder weakness and a normal life span (SMA types 1–3). Subsequent modifications to this scheme recognized a type 4 with adult onset (and generally mild weakness) and a type 0 which is present at birth and associated with very early death (Table 21.3).

Table 21.1 Classification of the proximal spinal muscular atrophies

Autosomal recessive	*Locus*	*Gene*
SMA 1–4	5q	Survival motor neuron (SMN1)
Congenital with arthrogryposis	5q	Survival motor neuron (SMN1)
Congenital axonal neuropathy	5q	Survival motor neuron (SMN1)
SMA with pontocerebellar hypoplasia	14q32.2	Vaccinia-related kinase 1 (VRK1)
SMA with congenital fractures	Unknown	Unknown
Autosomal dominant	*Locus*	*Gene*
Adult proximal SMA (Finkel type)	20q13.22	Vesicle-associated membrane protein-associated protein B (VABP)
Benign congenital with contractures	Unknown	Unknown
SMA with lower extremity predominance	14q32	Unknown
Scapuloperoneal syndromes	12q24	Vanilloid transient receptor protein (TRPV4)
X-linked	*Locus*	*Gene*
Bulbospinal muscular atrophy (Kennedy's)	Xq12	Androgen receptor gene
Infantile SMA with arthrogryposis	Xp11.3	Ubiquitin-activating enzyme1 (UBE1)

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Table 21.2 Classification of the distal spinal muscular atrophies (non-SMN variants)

Autosomal dominant	*Locus*	*Gene*	*Onset*	*Clinical features*
Distal SMA 1	Unknown	Unknown	Juvenile	Symmetric distal leg weakness and atrophy, slow progression, pes cavus, hammer toes
Distal SMA 2a	12q24	HSPB8/heat shock protein 22	Age 14–35	Early extensor hallucis longus involvement, complete paralysis of distal leg muscles, and some thigh weakness after 10 years. Young adults with rapid progression
Distal SMA 2b	7q11	HSPB1/heat shock protein 27	Age 21–54	Early distal leg involvement with progression to the arm and proximal leg in 5–10 years
Distal SMA 2c	5q 11	HSPB3/heat shock protein	Mid 20s	Distal leg, slow progression
Distal SMA 5a	7p14	GARS	Age 5–20	Weakness and atrophy of the hands, occasional upper motor neuron findings, very slow progression
Distal SMA 5b	11q12	BSCL2	Age 2–40	Hand amyotrophy and spastic paraparesis (Silver syndrome)
Distal SMA 7a	2q14	Unknown	First to second decade	Early vocal cord paralysis, hand weakness and atrophy, legs later
Distal SMA 7b	2q13	DCTN1	Early adulthood	Early VC paralysis causing breathing difficulty, face and distal limb weakness and atrophy, hands (thenar predilection) > legs
Distal SMA with UMN signs	9q34	SETX6	Juvenile	Distal leg atrophy and weakness, later arm Variable upper motor neuron findings
Autosomal recessive	*Locus*	*Gene*	*Onset*	*Clinical features*
Distal SMA 6 (SMARD1)	11q13	IGHMBP2	Infant	Severe diaphragmatic paralysis, cardiomyopathy, and lactic acidosis
Distal SMA 3	11q13	Unknown	Juvenile	Slow progression
SMA (Jerash type)	9p21.1–p12	Unknown	Age 6–10	Weakness and atrophy of the legs associated with pyramidal features, arms involvement 2 years after onset
Distal SMA 4	P36	PLEKHG5	Juvenile	Severe diaphragmatic and distal limb weakness
Distal SMA 2b	7q11	HSPB1/heat shock protein 27	Age 21–54	Early distal leg involvement. In 5–10 years, arm and proximal leg

GARS glycyl tRNA synthetase, *BSCL2* Berardinelli-Seip congenital lipodystrophy 2, *DCTN1* dynactin, *SETX6* sentaxin, *IGHMBP2* immunoglobulin mu-binding protein 2, *PLEKHG5* pleckstrin homology domain-containing, family G, *UMN* upper motor neuron

Table 21.3 Classification of SMN-related spinal muscular atrophy [10]

Type	Eponyms	Onset	Course	SMN2 copy number
0	–	Prenatal	–	1
1	Werdnig-Hoffman disease	0–6 months	Never sits independently Life expectancy <2 years	2
2	Intermediate form; chronic Werdnig-Hoffman disease	<18 months	Able to sit independently but not walk. Life expectancy into third or fourth decade	3 or 4
3a	Kugelberg-Welander disease	<3 years	Able to walk. Normal life expectancy	3 or 4
3b	Kugelberg-Welander disease	>3	Able to walk. Normal life expectancy	4
4	Adult SMA	>20 years	Able to walk. Normal life expectancy	4–8

The understanding of the molecular genetics of SMA began in 1990 with the linkage of the disease to the long arm of chromosome 5 [11]. Five years later, the causative gene was identified as the *survival motor neuron* (*SMN*) *gene* [12]. Since that time, major advances in the field have provided significant insights into the molecular pathogenesis of SMA and better understanding of the disease severity and phenotypic variability. These discoveries have also led to identification of possible therapeutic targets and resulted in acceleration of research to explore multiple potential therapeutic strategies [13].

Epidemiology

SMA is the second most common autosomal recessive disorder after cystic fibrosis and is the leading genetic cause of infant mortality. The incidence is estimated to be 1 in 6,000–10,000 live births leading to approximately 600 new cases of SMA per year in the USA [14–17]. The carrier frequency is approximately 1 in 40 with about six to seven million carriers in the USA. There is unexplained slight male preponderance [18, 19]. Because of the high rate of mortality for type 1 disease, the relative frequency of the

different types is somewhat difficult to state precisely, with prevalence figures understating the frequency of SMA 1. Overall figures suggest that the relative prevalence of the disease is that approximately 45 % of cases are type 1, 23 % are type 2, 30 % type 3 (16 % 3a and 14 % 3), and only 2 % type 4.

Clinical Manifestations

SMN-Related Spinal Muscular Atrophy

SMA Type 1

Type 1 SMA presents in the first 6 months of life; mothers often describe decreased fetal movement during pregnancy in the third trimester. Infants usually present with profound hypotonia, impaired head control, weak cry, poor feeding, severe diffuse weakness affecting predominantly the proximal muscles, and respiratory distress (Fig. 21.1) [20]. By definition, affected patients are never able to sit independently [10]. Because of absent or minimal facial involvement, patients appear surprisingly alert for their degree of weakness [21]. The patients do not exhibit signs of extraocular muscle or cerebral involvement, and children with SMA typically have a normal IQ. In fact, older children with SMA as a group have a higher verbal IQs compared to controls, possibly because the development of cognitive skills may be compensatory for their physical restrictions [22]. Other findings include tongue atrophy and fasciculations, which are observed in 50 % of cases [5, 21]. Patients also assume a "frog-leg" appearance with externally rotated and abducted thighs with flexed knees (Fig. 21.2). Deep tendon reflexes are absent. Paradoxical breathing with flattening of the upper chest and flaring of the lower chest with abdominal protrusion during inspiration (bell-shaped chest) is noted because of weakness of the intercostals with relative sparing of the diaphragmatic muscles (Fig. 21.3). In addition to dysphagia, constipation is common [21, 23]. Mild contractures at the knees and rarely the elbows may occur late in the course, but severe early contractures should suggest another diagnosis. There are rare reports of various cardiac abnormalities and digital vascular necrosis and thrombosis in severe SMA [24, 25].

Historically, children with SMA 1 usually die in the first 2 years of life from respiratory complications [26–28]. However, survival has increased in recent years due to advances in proactive pulmonary, nutritional, and supportive care [29, 30]. A modification of this basic phenotype is seen with so-called type 0 disease. These babies have a more severe phenotype with a prenatal onset of symptoms, a requirement of respiratory support, and early death by the age of 1 month.

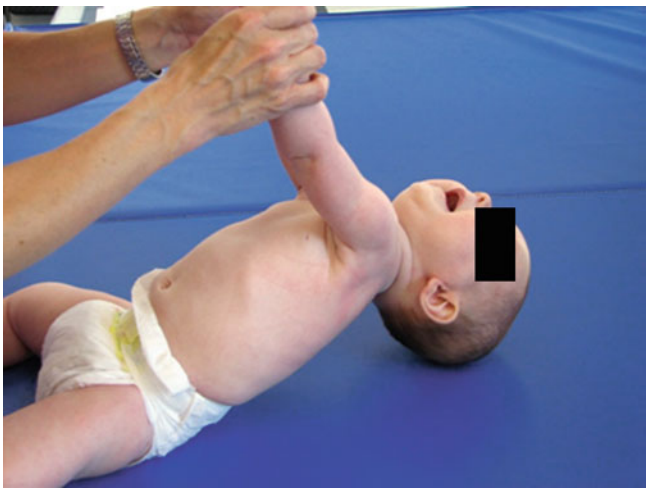

Fig. 21.1 Eight-month-old infant with SMA 1 being pulled to a sit. There is marked proximal weakness and head lag

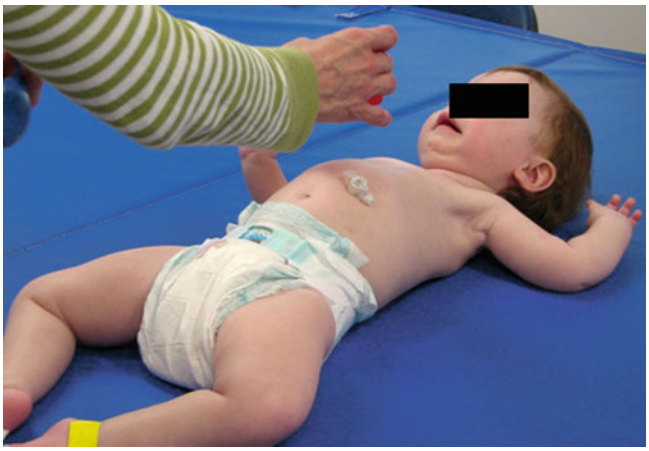

Fig. 21.2 Eighteen-month-old with SMA 1 showing classic "frog-leg position" with externally rotated and abducted thighs and knee flexion

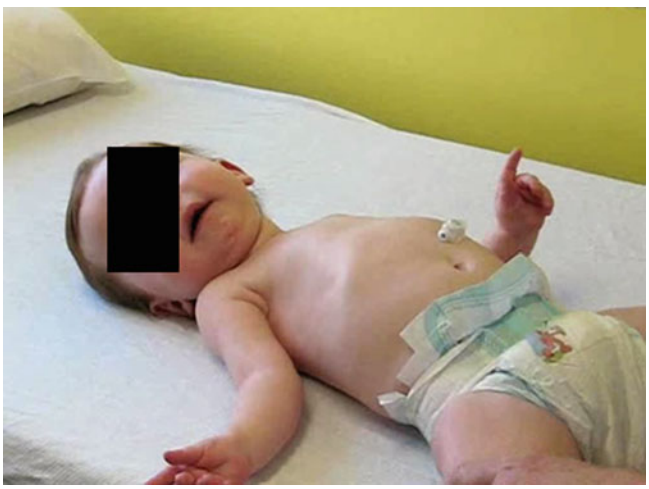

Fig. 21.3 Eighteen-month-old with SMA 1 showing paradoxical breathing and "bell-shaped" chest with inspiration. Note the slight flaring of the lower rib cage with retraction of the upper chest and protrusion of the abdomen

SMA Type 2

These patients usually present between the ages of 6 and 18 months with decreased tone and delayed motor milestones, but eventually they are able to sit unsupported. In one study, 73 % of 175 patients with SMA 2 achieved the ability to sit within a normal age range (i.e., up to 9 months); the remaining 27 % sat by age 10–30 months [31]. The strongest patients in this category sometimes are able to stand using a long leg brace or standing frame, but they are never able to walk independently (Fig. 21.4). Weakness is invariably more severe in the legs. The facial and extraocular muscles are spared. Tongue atrophy and fasciculations are often noted. The majority (~70 %) will have no deep tendon reflexes, although retained reflexes can be seen in stronger muscle groups. Patients have normal sensation. Patients sometimes develop a fine tremor of the fingers referred to as minipolymyoclonus [32]. Dysphagia and restrictive lung disease can occur, but respiratory compromise is proportional to the degree of weakness and thus less common and severe than in SMA 1 [33–35]. In type 2 patients, however, other factors often contribute to further compromise in pulmonary status, including scoliosis, recurrent aspiration, and infections as well as sleep-disordered breathing [36, 37]. Joint contractures (Fig. 21.5), kyphosis, and scoliosis worsen overtime. Osteopenia and a tendency to be overweight are also common in this population [38, 39]. Usually, there is an accelerated phase of strength decline followed by long plateau period [40].

SMA Type 3

This is a relatively mild form of the disease with onset after age 18 months. Two subtypes have been identified on clinical grounds basis, SMA 3a and SMA 3b, with the latter presenting after 3 years of age and generally having milder disease. By definition, **a**ll patients achieve the ability to stand and walk; in 10 %, this is delayed until after 18 months of age [29, 31]. Patients usually present with recurrent falls and difficulty arising from the floor or going up steps. The weakness is predominately proximal with legs more involved than the arms. A peculiar feature of some SMA 3 patients is their retained ability to ambulate despite severe weakness. This might be related to the segmental distribution of weakness allowing for compensatory mechanisms [41]. Patients have a waddling gait and protuberant abdomen related to weakness of the hip abductors and abdominal muscles, respectively. This group also shares with other SMA types minimal to absent facial involvement, normal extraocular muscle movement, normal sensation, decreased to absent deep tendon reflexes, and minipolymyoclonus [32]. Fasciculations in limb muscles can be seen. Calf hypertrophy is noted in some patients, leading to a mistaken diagnostic impression of Duchenne or other type of muscular dystrophy [42, 43]. Pulmonary function is often normal in this group, but restrictive lung disease and sleep-disordered breathing are noted in those with more severe weakness.

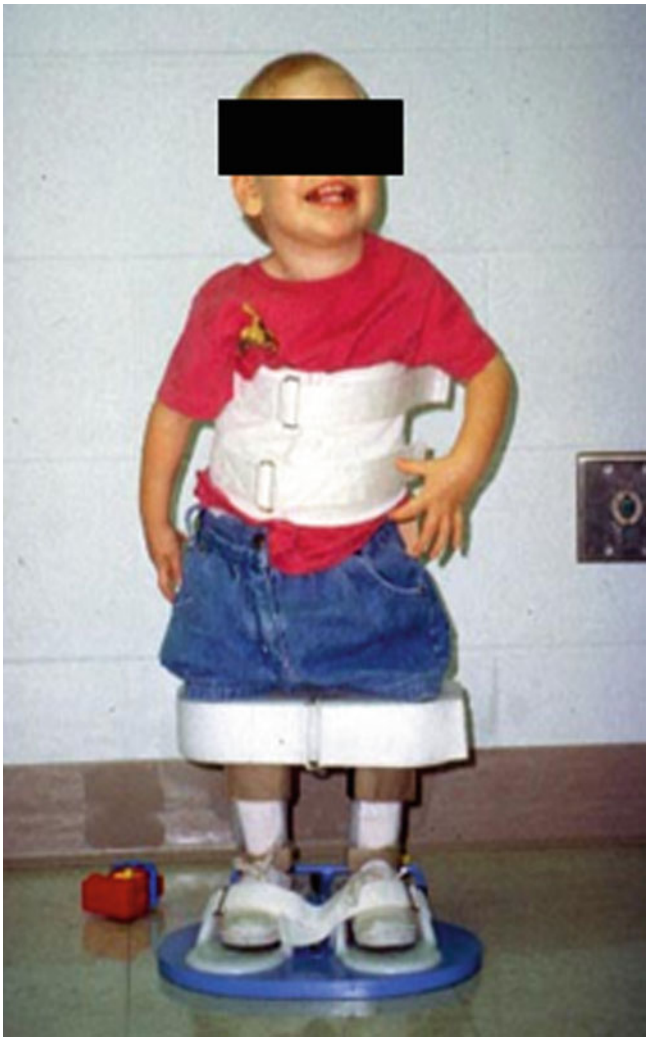

Fig. 21.4 Thirty-month-old girl with SMA 2. She could sit unassisted but could stand only with the aid of the parapodium

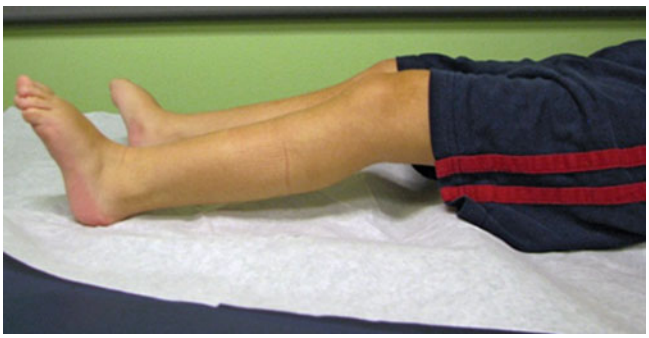

Fig. 21.5 Supine view of 6-year-old boy with SMA 2. There are obvious contractures at the hips and knees, as well as less obvious ankle contractures

Although SMA 3 is a progressive disease, the disorder is similar to SMA 2 in that there are periods of disease

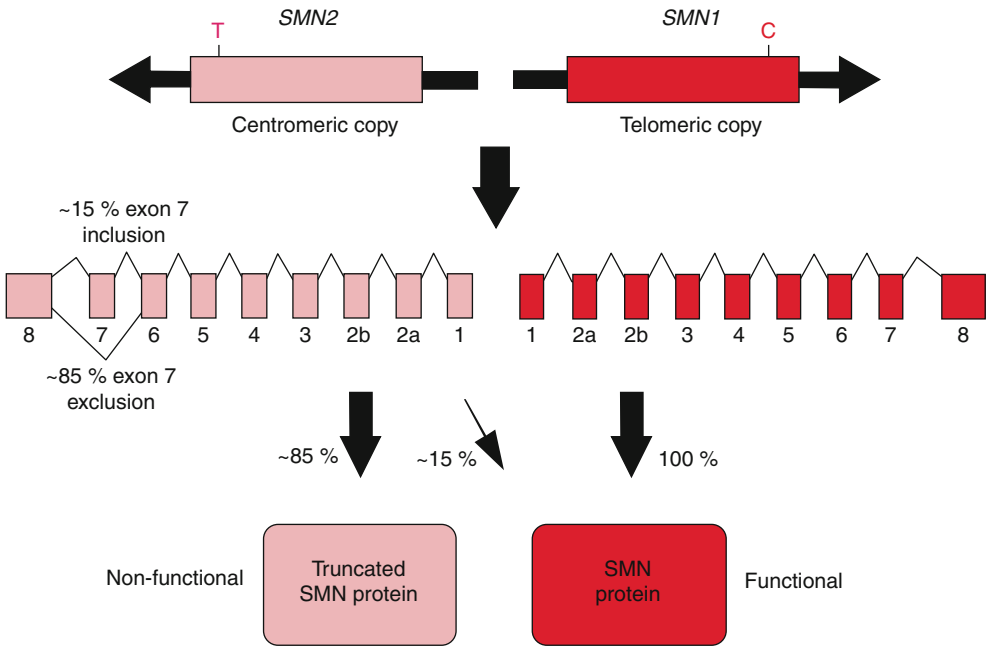

Fig. 21.6 Schematic diagram of the human SMN genes and the resultant pre-messenger RNAs transcribed from these genes. Patients with SMA have deletions or mutations in both SMN1 genes. SMN2 gene is expressed in these patients, although most of this SMN2 lacks exon 7 because of a C-to-T transition at position 6 of exon 7. The truncated SMN protein is unstable, nonfunctional, and rapidly degraded. A proportion of full-length messenger RNA containing exon 7 is produced by the SMN2, however, resulting in full-length and functional SMN protein (Reproduced with permission from Kolb and Kissel [13])

progression followed by long plateau periods that may last for years [40]. The distinction between types 3a and 3b is clinically significant in this regard in terms of prognosis. In one study, for example, 58 % of SMA 3b patients were ambulatory at the age of 40 compared to only 22 % of 3a patients [27].

SMA Type 4

Patients with type 4 disease present with the insidious onset of muscle weakness in adult life, with a mean age of onset in the 30s [44]. The majority of adult-onset SMA represents autosomal recessive disease although some non-SMN-related cases are inherited as autosomal dominants [45, 46]. The pattern of weakness is similar to that of limb girdle muscular dystrophy, and patients usually present with difficulty getting up from the floor, rising from a chair or going up steps with or without rail assistance. Fasciculations in the limb muscles are common and sometimes lead to a mistaken diagnosis of amyotrophic lateral sclerosis. Pulmonary involvement, dysphagia, and scoliosis are rare. Patients with SMA 4 tend to remain ambulatory.

Pathogenesis and Pathology

SMN-related SMA results from a genetic defect on chromosome 5; other types of SMA and most of the variants are linked to other chromosomes (Tables 21.1 and 21.2) [11, 47]. The survival motor neuron (*SMN*) gene exists in two almost identical forms: a telomeric (*SMN1*) and centromeric (*SMN2*). The *SMN2* gene differs from *SMN1* by a single cytosine to thymidine substitution in exon 7 that results in its exclusion during transcription, due to either disruption of an exonic splice enhancer or creation of an exonic splice silencer (Fig. 21.6). *SMN1* produces predominately a full-length transcript, whereas *SMN2* produces an alternatively transcribed product lacking exon 7, which results in low-level production of a rapidly degraded, unstable protein. Due to alternative splicing, however, about 10–15 % of the protein produced by the *SMN2* gene is full length [13].

SMN1 is homozygously deleted in 95 % of all SMA 1, 2, and 3 patients and in approximately 70 % of SMA type 4 patients [12, 45]. Most of the other 5 % are compound heterozygotes involving an *SMN1* deletion on one chromosome and an *SMN1* intragenic mutations (either a missense or frameshift mutation) on the other chromosome. There is no known clinical sequel for *SMN2* mutations, and the *SMN2* gene is actually absent in 10–15 % of the normal population. In the setting of homozygous *SMN1* deletion that occurs in SMA, the presence of one or more copies *of SMN2* is necessary for survival and is the major determinant of the phenotype. Thus, the number of SMN2 copies is inversely related to the disease severity and correlates with SMA type [48–53]; SMA type 0 typically has one SMN2 copy, SMA 1 has two copies, SMAs 2 and 3a have three to four copies, SMA 3b has four copies, and SMA 4 has four to eight copies (Table 21.3).

Although SMN2 copy number is clearly the most important determinant of severity, other modifiers have been identified. A second gene, the neuronal apoptosis inhibitory protein (*NAIP*), was initially felt to be a modifier gene, but subsequent studies did not confirm this [54]. More recently, several patients have been identified with a second

c.859 G > C mutation in exon 7 that resulted in a marked increase in full-length SMN protein production and a milder phenotype in three adults with SMA type 3b reported who had only two copies of *SMN2* [55, 56]. Another gene mutation, *plastin 3*, was also found to be a possible protective modifier of SMA in females [57–59].

The function of the SMN gene and thus the pathogenesis of SMA are not yet fully understood. The SMN protein is found as part of a multi-protein complex, the SMN complex. It is present in the cytoplasm and in the nucleus; in the latter it is present in structures called "gems" [60, 61]. The most accepted function of SMN protein is that it plays a key role in spliceosomal small nuclear ribonucleoprotein (sNRP) assembly. The deficiency of the ubiquitously expressed SMN protein results in motor neuron degeneration [62, 63]. The reason behind the selective vulnerability of the motor neuron remains to be fully elucidated, as does a possible role for SMN protein at the neuromuscular junction and other sites in the motor unit. The emerging theory hypothesizes downstream deleterious impact of defective RNA processing on motor neurons' development, survival, or both [64]. Of note lately there is emerging evidence of possible involvement of other organ systems in SMA [24, 25].

Differential Diagnosis

The differential diagnosis for SMA 1 includes all other causes for a floppy and hypotonic infant (see also Chap. 77) [65]. The most frequent causes of a hypotonic infant are central involving the cerebral hemisphere, basal ganglia, brain stem, or cerebellum. Clues to such diagnoses are altered level of consciousness, seizures, and persistence of infantile reflexes such as continued presence of Moro, tonic neck, or grasp reflexes after 6 months of age. Spinal cord injuries are suspected in the setting of traumatic birth, breech presentation, or bowel and bladder dysfunction.

Peripheral causes of neonatal hypotonia like the congenital myopathies (e.g., nemaline myopathy, central core myopathy, myotubular myopathy, multicore disease, and congenital fiber-type disproportion) should be considered when facial and extraocular muscle weakness are prominent or dysmorphic features, ptosis, and high arch palate are present. Congenital myotonic dystrophy and other congenital dystrophies are associated with mental retardation, seizures, and facial and extraocular muscle weakness. Examination of the mother can provide clues to the diagnosis of congenital myotonic dystrophy. Similarly, an established diagnosis of myasthenia gravis in the mother provides a clue to the diagnosis of transient neonatal myasthenia. Congenital myasthenic syndromes and infantile botulism cause floppiness as well. Ptosis and extraocular muscle weakness are common to both, whereas constipation and dilated unreactive pupils suggest botulism. Metabolic myopathies such as Pompe's disease cause hypotonia with clues such as hepatomeglay, macroglossia, and cardiomyopathy.

Chromosomal disorders, such as Prader-Willi syndrome, result in hypotonia, mental retardation, obesity, short stature, and hypopigmentation. Peroxisomal disorders such as Zellweger's disease, neonatal adrenoleukodystrophy, and infantile Refsum's disease are associated with dysmorphic features, mental retardation, retinopathy, and hearing deficits.

The differential diagnosis for proximal weakness in older children and adolescents (i.e., SMAs 2 and 3) includes congenital and metabolic myopathies, dystrophinopathies, limb girdle dystrophy, and inflammatory myopathies. Electrodiagnostic studies and muscle biopsy help distinguish this group. Similarly, myasthenia gravis is distinguished based on additional features such as ptosis and extraocular muscle weakness as well as serology and electrodiagnostic studies. Immune-mediated peripheral neuropathies, Guillain-Barre syndrome and childhood chronic inflammatory demyelinating polyradiculoneuropathy, characterized by proximal predominant weakness and areflexia are distinguished from SMA by the prominent demyelinating features on the electrodiagnostic studies and the high CSF protein. Other motor neuron processes such as hexosaminidase A deficiency can resemble SMA; however, cognitive decline, developmental regression, personality change, ataxia, spasticity, and seizures are additional clues.

Prevention

Prenatal diagnosis of SMA is available using amniotic fluid or chorionic villous sampling [66–69]. Carrier detection testing using quantitative PCR-based assay also allows carrier detection by determination of the number of *SMN1* copies, with a carrier usually having only one copy of *SMN1*. As with all genetic testing, however, caution must be exercised in the interpretation of results, since in 2 % of carriers, both copies of SMN1 are present in the same chromosome (cis configuration). An individual with such an arrangement would therefore test as a noncarrier (i.e., two copies of *SMN1*) while still harboring a chromosome lacking SMN1. In addition, routine SMA carrier testing also does not detect intragenic mutations [70]. Patients or their parents should only have such testing in the context of formal genetic counseling [70]. Newborn and carrier screening is feasible, and despite the absence of effective treatment at this stage, there appears to be a significant value for presymptomatic and early detection to explore effective treatments before irreversible neuronal loss occurs [71, 72].

Diagnosis and Laboratory Evaluation

Diagnosis of SMA depends on molecular genetic testing, and the availability of such testing has made muscle biopsy, and in many cases electrodiagnostic testing, unnecessary. Homozygous deletion of SMN1 is detected by demonstrating an absence of exon 7. The test is commercially available and it has 95 % sensitivity and near 100 % specificity [12]. As already discussed, 2–5 % of SMA patients are compound heterozygotes for *SMN1* deletion and *SMN1* intragenic mutation [69]. The role of electrodiagnostic testing and muscle biopsy is substantial in those with negative genetic testing or with variants.

As in most motor neuronopathies, electrodiagnostic studies in SMA typically reveal normal sensory nerve action potentials; however, they can be reduced in some patients [28]. The compound muscle action potential amplitudes are reduced, and the conduction velocities are usually normal but can be reduced in some patients [28]. Needle electromyography demonstrates active denervation and reinnervation as evidenced by fibrillation potentials and positive sharp waves, fasciculations, and large-amplitude, long-duration, fast-firing motor unit action potentials. Regular spontaneous motor unit action potentials occur in SMA type 1 [73, 74].

Mild to moderate creatine kinase elevation is frequently seen, sometimes leading to a false suggestion of underlying muscle disease [75]. Muscle biopsy in SMA type 1 is almost never needed but if performed in difficult to diagnose cases shows intermixed hypertrophic type 1 fibers and sheets of atrophic round fibers. The muscle biopsy of newborns with SMA 1 reveals universally small fibers, with type 1 fibers being smaller than type 2, making the histological diagnosis difficult [76, 77]. In SMA 2 the findings are similar to type 1 in some patients, and in others hypertrophic type 2 fibers and fiber-type grouping are noted. The latter is common in SMA 3; in addition, secondary myopathic features including fiber splitting, increased internal nuclei, and endomysial connective tissue can be seen [28]. Similar changes can be seen in non-SMN-related SMA.

Management

The presence of multiple animal models (including several murine, zebrafish, and Drosophila models) that closely mimic the human disease has not only increased the understanding of the pathogenesis of SMA but also has permitted effective screening for various therapeutic agents [78, 79]. Despite success in these animal models with several compounds, numerous human therapeutic trials over the past decade have not identified an effective agent. To date, there is therefore no drug treatment for SMA that has been proven to have significant efficacy [80, 81]. Among the several strategies explored include efforts to enhance neuroprotection (gabapentin and riluzole), anabolic effects (albuterol), and energy metabolism (creatine and carnitine) and, most notably, to increase *SMN2* expression or stability (valproic acid, hydroxyurea, phenylbutarate) [82–92]. In addition, other strategies being tested include gene therapy, stem cell therapy, and antisense oligonucleotide-based therapy aimed at either replacing the SMN1 gene entirely or genetically converting SMN2 message into SMN1 [13, 93, 94].

The mainstay of treatment for SMA is therefore focused on aggressive supportive care with emphasis on a multidisciplinary team approach. The published guidelines by the international SMA Standard of Care Committee establish an expert consensus approach to practice guidelines for clinical care of SMA patients [95].

Pulmonary Management

Pulmonary complications are the major source of morbidity and mortality in SMA 1 and 2 and for a small percentage of SMA 3 patients. The standard of care consensus statement recognized the key respiratory problems in SMA as weak cough, reduced clearance of secretions, recurrent infections, poor development of the chest wall and lungs, and sleep-disordered breathing [95]. Early referral for respiratory care cannot be overemphasized. Breathing effectiveness can be assessed by observing cough ability, breathing pattern, respiratory rate, work of breathing, and presence of cyanosis. The clinical observations and pulse oximetry are invaluable tools, particularly in young children who cannot participate in pulmonary function testing [96].

Airway clearance can be achieved using manual cough assist or insufflation-exsufflation devices. Chest physical therapy and postural drainage are also useful [95–97]. Education of the parents and caregivers on the evaluation methods, use of home pulse oximetry, and providing a treatment strategy using clearly outlined protocols are the cornerstone for optimal pulmonary management [96]. Other recommended therapies include routine vaccinations, adequate hydration, nutritional support, and gastroesophageal reflux management [95]. There is no evidence to support the chronic use of mucolytic drugs. There should be a low threshold for treatment of pulmonary infections. Overall goals of care should be discussed with the family, and respiratory support provided accordingly. Respiratory support is indicated for carbon dioxide retention, for sleep-disordered breathing, or as a palliative measure to decrease the work of breathing. Noninvasive ventilation using bi-level positive airway pressure machines (BiPAP) results in fewer hospitalizations, prolongs life, alters chest wall deformity, and may improve lung development and function [98–100]. It is most helpful in combination with airway clearance measures. The

use of tracheotomy and chronic ventilation is an ethical dilemma and somewhat controversial in SMA 1 [101]. The decision making should be a process that involves explanation and discussion with the family about the expected outcome and quality of life as well as exploration of other options such as palliative care.

Gastrointestinal and Nutrition Management

The major gastrointestinal and nutritional complications of SMA are related to bulbar dysfunction causing dysphagia and increased aspiration risk, gastroesophageal dysmotility leading to constipation, delayed gastric emptying, gastroesophageal reflux, and undernutrition in the non-sitters and overnutrition in the sitters and walkers [21, 23, 95]. Chewing and mouth opening difficulties also occur in some patients, especially type 1 patients [102]. Swallowing evaluation early in the course is mandatory for essentially all patients. This is usually done by speech or occupational therapist. Video fluoroscopic swallow studies are often helpful in identifying the type and extent of dysphagia. Changing food consistency by thickening liquids can be beneficial. The option of considering gastrostomy tube for feeding is individualized, and decision should be part of overall goal of care and should follow extensive discussions with family of patients with poor intake early in the course. Most infants will benefit from Nissen fundoplication, usually done concomitantly with the placement of gastric feeding tube using a laparoscopic approach [103, 104]. However, some physicians reserve this procedure for those who fail medical treatment for reflux with H2 blocker and proton pump inhibitors. Delayed gastric emptying can be helped by use of metoclopramide or erythromycin. It is important to establish a bowel regime early in the course to avoid chronic constipation and fecal impaction. The majority of SMA patients with constipation will respond to dietary management by increasing fiber and water content [20].

There are many challenges when it comes to proper assessment and treatment of growth and nutritional status in SMA because of the paucity of quality data and the vast amount of undocumented information available on the Internet and similar resources. However, history, examination, growth charts, and 3-day dietary records and 24-h food recall are usually useful to capture data to help nutritional decisions [95, 105]. Non-sitters and some of the sitters are at risk of failure to thrive, whereas sitters and walkers are at risk of becoming overweight or frankly obese [95]. Caution must be exercised when using body mass index (BMI) as the sole parameter because of the risk of underestimation of body fat content. One study showed evidence of increased fat mass and high incidence of SMA patients being overweight despite the low BMI [39]. Currently, there is no hard evidence that high or low protein or fat content in the diet is beneficial for the underlying disease and no evidence to support the use of specific vitamins or minerals. Evaluation and follow-up by a dietitian familiar with the disease are essential, and dietary regimens must often be individualized.

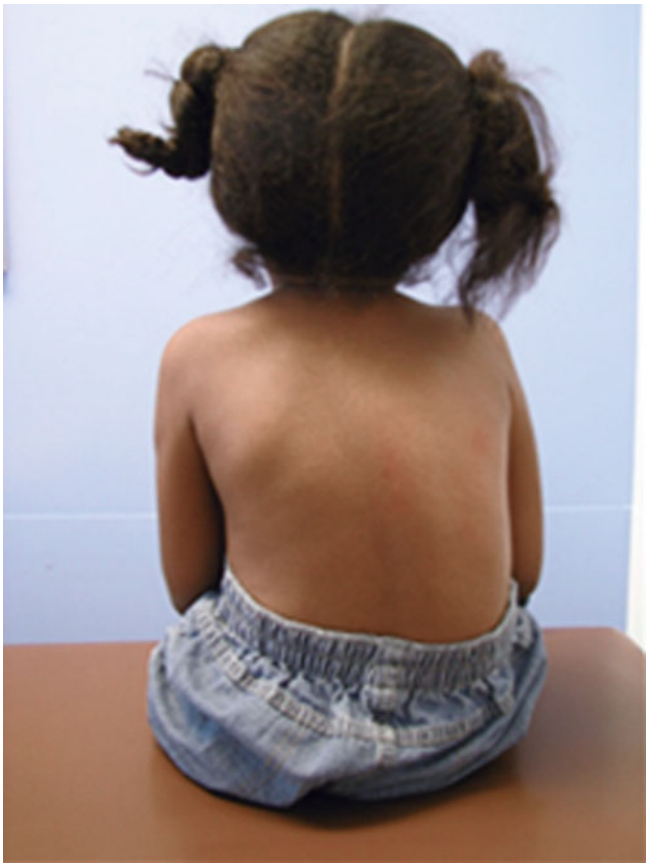

Fig. 21.7 Posterior view of 5-year-old girl with SMA 2. There is significant thoracolumbar kyphoscoliosis

Orthopedic Care and Exercise

The major orthopedic complications in SMA are related to scoliosis, kyphosis, contractures, mobility impairment, osteopenia, and fractures [95]. In addition to deformity, scoliosis results in decreased function, impairs sitting ability, and contributes to pain and respiratory impairment (Fig. 21.7) [65]. Overall, development and progression of spinal deformity correlates with weakness, and scoliosis is more severe in sitters than walkers. It is usually noticed in the SMA 2 patients between the ages of 2–5 years and at later ages in the type 3 patients, particularly after the loss of ability to walk [20, 65]. Use of back bracing provides symptomatic relief of back pain in some of the patients, and it can allow for a better seated position, but there is no evidence that it limits or prevents progression [65]. Surgical correction results in improvement in sitting, balance, comfort, and appearance and delays

decline of pulmonary function [106–110]. Timing of surgical correction must take into account the degree of curve, child growth, and pulmonary function.

A variety of assistive devices are available to help maximize function, prolong independency, and improve quality of life for both patients and caregivers. Proper selections are individualized based on specific patient needs and should be done under the guidance of the physical and occupational therapist. This further emphasizes the need for multidisciplinary team approach. Lightweight orthotics, walking frames, and power wheelchairs are examples of such devices.

There is paucity of human data when it comes to the role of exercise in SMA. There is a theoretical concern that excess exercise can accelerate the loss of motor neuron, but animal studies demonstrate that regular running in SMA mice led to better motor function, a longer life span, and more surviving motor neurons [111]. The consensus guidelines encouraged routine exercise such as swimming and adaptive sports to maintain and optimize fitness and endurance [95].

Palliative Care

In patients with SMA 1, early and extensive discussions with families should include the option of palliative care [112]. There is lack of consensus as to the appropriate level of care as well as there are conflicts regarding interventions that may prolong life without necessarily impacting the quality of life [95]. Families are entitled to an honest and unbiased opinion to help them through the decision-making process [112]. This can only be achieved with appropriate input from a multidisciplinary team, including experts in palliative care. Lay and family support organizations can also be indispensable in providing information and emotional support during this process.

Prognosis

Historically children with SMA 1 usually die in the first 2 years of life because of respiratory complications [26–28]. Survival in SMA 1 has increased in recent years due to proactive care with advances in pulmonary care and aggressive nutritional support [29, 62]. In 1997, Zerres and colleagues published an analysis on the natural history of 569 clinically diagnosed SMA patients. They reported that 68 % of SMA 2 patients are alive at the age of 25 and SMA 3 patients have normal life expectancy. They also found that ambulation was retained after 10 years in 70 % of SMA 3a compared to 96 % of SMA 3b but after 20 years in only 33 % of SMA 3a compared to 84 % of SMA 3b. After 40 years, 22 % of SMA 3a patients were still ambulatory compared to 58 % with SMA 3b [28].

SMN-Related SMA Variants

Congenital SMA with Arthrogryposis

Arthrogryposis is characterized by multiple contractures and is usually nonfamilial and nonprogressive. It can be caused by any process that limits intrauterine movements, including congenital myopathies, congenital muscular dystrophies, and anterior horn cell disorders. Rarely, and for reasons not entirely clear, SMN-related SMA can present with prominent arthrogryposis at birth. Several reports however have linked SMN1 deletion mutation to infants presenting with neurogenic arthrogryposis [113, 114]. These cases need to be differentiated from the X-linked form of SMA described below.

Congenital Axonal Neuropathy

This is an unusual and severe form of SMA caused by a large deletion of the *SMN* gene and loss of markers Ag1-CA and C212 in the paternal haplotype. The three siblings described all died in the first 3 weeks of life after presenting with generalized weakness, asphyxia, facial diplegia, and external ophthalmoplegia [115]. Electrodiagnostic studies revealed unexcitable sensory and motor nerves, and autopsy showed loss of myelinated fibers and axonal damage in sensory and mixed nerves. Though the anterior horn cell number was normal, many of the neurons showed chromatolytic changes [115].

Non-SMN-Related SMA

SMA with Pontocerebellar Hypoplasia

This autosomal recessive disease has been linked to a mutation in vaccinia-related kinase 1 (*VRK1*) gene mapped to chromosome 14 q32.2 [116]. It is described as one of the so-called SMA-plus syndromes, a term used to identify a group of disorders that manifest as SMA but with additional or atypical features. The group includes SMA with respiratory distress (SMARD), infantile X-linked SMA with arthrogryposis and congenital fractures (SMAX2), and SMA 1 with arthrogryposis and bone fractures, in addition to SMA with pontocerebellar hypoplasia (PCH type1). SMA patients with PCH1 have variable disease severity that combines features of anterior horn cell and cerebellar deficits [117, 118]. Some patients have symptom onset within 6 month and a life span of 2–4 years, while others have more severe forms with onset in the prenatal period or immediately after birth and death within months [119]. The mutation in *VRK1* was first identified in three children

from consanguineous family of Ashkenazi Jewish decent with early features of microcephaly, poor sucking, delayed motor development and subsequent development of upper limb ataxia, equinovarus, and brisk deep tendon reflexes. Another study using deep sequencing to identify novel genes for recessive cognitive disorders identified *VRK1* homozygous missense mutation in four siblings with moderate to severe intellectual disability and pontocerebellar hypoplasia phenotype [120].

SMA with Congenital Fractures

This is an autosomal recessive SMA variant without an identified linkage to date. Patients have normal *SMN* genes. In addition to the severe weakness, hypotonia, and respiratory difficulty, patients have osteopenia and congenital fractures [121, 122]. Additional features reported in some of the patients include hypertrichosis and congenital heart defects. Electrodiagnostic studies show evidence of active denervation, and autopsy studies show generalized type 1 and 2 fiber atrophy and loss of the anterior horn cells [123, 124].

Adult Proximal SMA (Finkel Type)

Approximately 30 % of adult-onset proximal SMAs are autosomal dominant disorders not linked to the SMN protein [125]. There are no distinctive phenotypic features when compared to the autosomal recessive form. Patients present after the third decade with slowly progressive weakness and atrophy of the proximal leg muscles with later involvement of the arms. Generalized areflexia and fasciculations are typical. Overall patients have a benign course [8, 126–128]. Linkage to chromosome 20q13.3 and missense mutation in vesicle-associated membrane protein (*VAMP*)/synaptobrevin-associated membrane protein B gene (*VAPB*) was described in a large white Brazilian family [129]. The same mutation was identified in other family members with atypical and typical amyotrophic lateral sclerosis phenotypes [129].

SMA with Lower Extremity Predominance

This is one of the rare autosomal dominant proximal forms of SMA that is linked to chromosome 14q32. The symptoms onset is in early childhood with a static or slowly progressive course. The patients described has a peculiar pattern of weakness that is confined to the legs mostly affecting the quadriceps and hip muscles and is associated with severe atrophy of the quadriceps muscles [130].

Scapuloperoneal Syndrome

Scapuloperoneal syndromes are characterized by weakness of the shoulder girdle and the leg anterior compartment muscles. The phenotype is seen in both myopathic and neurogenic processes, most commonly in association with muscle diseases such as facioscapulohumeral muscular dystrophy and limb girdle muscular dystrophy. An autosomal dominant SMA scapuloperoneal syndrome linked to chromosome 12q24.1 has been reported in large New England kindred of French Canadian descent [131]. In addition to progressive scapuloperoneal atrophies, the patients have distinctive features of congenital absence of muscles and laryngeal palsy. Males are more severely affected than females, and there is increase disease severity in successive generations [132]. The responsible mutation is identified in the vanilloid transient receptor potential cation-channel gene TRPV4 [133]. The condition is allelic to the axonal sensory motor neuropathy form of Charcot-Marie-Tooth disease (CMT2C).

X-Linked Bulbospinal Muscular Atrophy (Kennedy Disease SMAX1)

This is an X-linked recessive disease caused by CAG trinucleotide repeat expansion in the androgen receptor gene [134, 135]. The symptoms start in the fourth decade with insidious slowly progressive atrophy and weakness of the bulbar and proximal limb muscles. Rarely, a rapid progressive course is noted [136]. Facial and perioral grouped fasciculations are a characteristic feature. Tongue atrophy and fasciculations are often noted. Jaw drop with prominent temporalis and masseter muscles weakness can be a presenting feature [137]. Dysarthria and dysphagia may occur. Additional features include gynecomastia, testicular atrophy, infertility, and diabetes mellitus. Asymptomatic sensory neuropathy is a common finding. Muscle cramps, fatigue, and mild CK elevation can be early symptoms in young males and rarely seen in female carriers [138, 139]. Overall the neurologic impairment is usually mild without major bulbar or respiratory dysfunction, and the long-term survival is only mildly reduced [140]. Several trials in patients with Kennedy disease have showed no effect. Recently, androgen-reducing treatment with dutasteride, a 5-alpha-reductase inhibitor, had no effect on progression of muscle weakness [141]. Also, leuprorelin, which suppresses the accumulation of the pathogenic androgen receptors, has no effect on

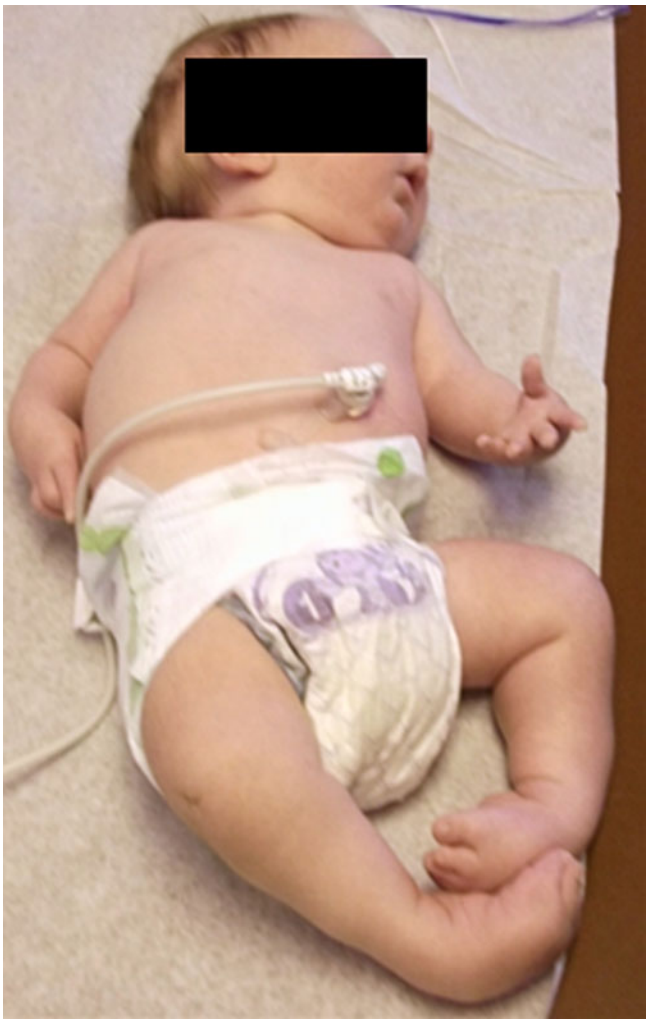

Fig. 21.8 Eight-month-old boy with presumed infantile SMA with arthrogryposis. Note the severe lower extremity contractures

swallowing function [142]. The disorder is described in more detail in Chap. 22.

Infantile SMA with Arthrogryposis

This is an X-linked recessive disease associated with mutation in the ubiquitin-activating enzyme 1 (*UBE1*) gene [143–145]. The presentation is at birth with severe hypotonia, areflexia, and multiple congenital contractures [144] (Fig. 21.8). The phenotype resembles that of SMA with additional features, including congenital or early-onset proximal and digital contractures, facial weakness and other facial dysmorphic features, and urogenital abnormalities [146]. Death usually occurs in infancy from respiratory compromise.

Distal Spinal Muscular Atrophies (Hereditary Motor Neuropathy)

This term identifies a heterogeneous group of inherited disorder characterized by distal symmetric weakness without clinical or electrodiagnostic evidence of sensory loss [147]. The latter defines the group compared to the hereditary sensory and motor neuropathies (or CMT group), and the term "distal" defines the group in contrast to proximal SMA. The terms hereditary motor neuropathy and distal SMA are often used synonymously; however, the pathology of distal SMA in theory is related to anterior horn cell degeneration [148]. Harding classified the group into seven phenotypes according to age at onset, mode of inheritance, and presence of additional features [142]. Additional groups are identified in the last decade as well advances in molecular genetics led to identification of several causative genes (Table 21.2) [47, 149–165].

The distal SMAs (see below) tend to mimic CMT, with the important difference being the absence of clinical or electrophysiologic evidence of sensory involvement in the distal SMAs. In some of the entities, however, the distinction is not clear or absolute. For instance, certain heat shock protein mutations have been described in both CMT2 and distal SMA (see also Chap. 26). The distal myopathies are group of hereditary disorders characterized by distal leg or arm muscle weakness and atrophy and should be distinguished from distal SMAs. Creatine kinase elevation, myopathic changes on the electrodiagnostic studies, and vacuolar changes on muscle biopsy help distinguish the two groups. Hirayama disease should be considered in the differential diagnosis of distal SMA. This is a transiently progressive motor syndrome with resultant asymmetric atrophy and weakness of the distal upper extremity. The pathogenesis of this disorder is uncertain; however, chronic intermittent lower cervical cord compression and ischemia during neck flexion are implicated in the majority. Flexion and extension cervical spine MRI could show a crescent-shaped signal posterior to the cord caused by engorged venous plexus.

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Atypical Motor Neuron Disorders

22

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Introduction

There are several disorders that primarily affect the motor nervous system and mimic amyotrophic lateral sclerosis (ALS) (Table 22.1) [1, 2]. These disorders are often referred to as *atypical motor neuron disorders*. While many of the atypical motor neuron disorders have several features in common with ALS, they may be differentiated by their specific clinical, laboratory, electrophysiologic, and pathologic characteristics.

ALS is characterized by the degeneration of upper motor neurons in the brain and lower motor neurons in the brainstem and spinal cord, including anterior horn cells and cranial nerve nuclei (see Chap. 20). Patients with ALS typically manifest with a combination of focal limb atrophy, weakness, and more widespread muscle wasting and fasciculations. Upper motor neuron signs, including spasticity and pathologically brisk muscle stretch reflexes, are often present in the same spinal segments as the muscle atrophy. If upper motor neurons signs are not present at the time of presentation, they usually develop later in the disease course. In contrast to ALS, the atypical motor neuron disorders often lack upper motor neuron signs. Furthermore, few of these disorders are presumed immune-mediated, and weakness is secondary to motor nerve pathology, rather than anterior horn cell disease. The motor nerve pathology may be demyelinating, axonal, or a combination of both. Some of the atypical motor neuron disorders present with weakness in association with cerebellar, extrapyramidal, sensory, and cognitive dysfunction. Atypical motor neuron disorders may be seen as a remote effect of some neoplasms or secondary to various toxins, drugs, metabolic disorders, or as a result of electrical injuries, radiation, or infections, previous poliomyelitis, or spinal cord lesions. Recognition of these atypical motor neuron disorders is important because several are potentially treatable or may not carry the same grave prognosis as ALS. Others may be inherited, emphasizing the importance of early recognition for genetic counseling and family planning.

Clinical Clues That Suggest an Atypical Motor Neuron Disease

Although each disorder has distinctive clinical features, there are several clues that help differentiate patients with atypical motor neuron disorders from those with ALS (Table 22.2). Several important clues on the neurological examination may suggest an atypical disorder. The first clue is a *non-myotomal pattern of weakness*, whereby patients develop weakness in the distribution of individual named peripheral nerves, rather than in the distribution of myotomes. This pattern of weakness suggests that the pathology lies in peripheral nerves rather than at the level of the anterior horn cells. The second clinical clue is *weakness out of proportion to muscle wasting in affected limbs*, which suggests that the weakness is secondary to demyelination, such as conduction block within peripheral motor nerves (see below), a finding uncharacteristic of ALS. With initial demyelination, the axon remains intact, and early-stage muscle wasting is either absent or minimal. *Non-regional spread of weakness* is another clinical clue that suggests an atypical motor neuron

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Table 22.1 Atypical motor neuron diseases

Immune-mediated motor neuropathies
Multifocal motor neuropathy with conduction blocks
Other presumed immune-mediated lower motor neuron syndromes
Nonimmune-mediated lower motor neuron syndromes
Spinal muscular atrophy
X-linked bulbospinal muscular atrophy (Kennedy disease)
Monomelic amyotrophy (Hirayama disease)
Brachial amyotrophic diplegia (flail arm syndrome)
Progressive muscular atrophy
Progressive bulbar palsy
Fazio-Londe disease and Brown-Vialetto-Van Laere syndrome
Hereditary spastic paraplegia
Autosomal dominant
Autosomal recessive
X-linked
Multiple system disorders with prominent motor signs
Adult-onset hexosaminidase A deficiency (Late-Onset Tay-Sachs Disease)
Spinocerebellar degenerations
Autosomal dominant cerebellar ataxias
Autosomal recessive cerebellar ataxias
Adult polyglucosan body disease
Other multiple system disorders
Shy-Drager syndrome (multiple systems atrophy)
Guamanian Parkinson-amyotrophic lateral sclerosis
Hallervorden-Spatz disease (pantothenate kinase-associated neurodegeneration)
Creutzfeldt-Jakob disease
Huntington's disease
Pick's disease
Other atypical motor neuron diseases
Hyperparathyroidism
Electrical injury associated with motor neuron disease
Infectious/post-infectious
Retroviral-associated motor neuron syndrome
Post-radiation motor neuron disease
Paraneoplastic disorders with motor neuron dysfunction
Toxins/drugs
Post-poliomyelitis syndrome

disorder. Whereas weakness in patients with ALS tends to spread in a regional fashion, for example, right arm to left arm, rather than right arm to left leg, this is not necessarily the case in the atypical motor neuron disorders. The *lack of upper and lower motor neuron signs in the same spinal segments* may also suggest an atypical disorder. While patients with ALS generally have brisk or at least preserved reflexes in the same distribution as weak atrophic muscles, this pattern is not characteristic of many of the atypical motor neuron disorders. Failure to find upper and lower motor neuron signs in the same spinal segments should therefore prompt a search for an atypical disorder.

Table 22.2 Clinical clues that differentiate atypical motor neuron diseases from typical ALS

Non-myotomal pattern of weakness
Insignificant muscle wasting in chronically weak limbs
Non-regional spread of weakness
Lack of concurrent upper and lower motor neuron signs in the same spinal segments
Associated sensory symptoms or signs or both
Bladder or bowel dysfunction
Extraocular movement dysfunction
Cerebellar, extrapyramidal, cognitive or psychiatric dysfunction or both
Duration of illness longer than 5 years
Lack of bulbar involvement after 1 year
Onset of illness before age 35
Positive family history
History of spontaneous remissions
History of malignancy, radiation, old poliomyelitis, or electrical injury

Likewise, any evidence of extraocular muscle weakness, significant bladder or bowel dysfunction, sensory alterations, cerebellar, extrapyramidal, cognitive, or psychiatric dysfunction should question the diagnosis of ALS. Clues in the medical history that may suggest an atypical disorder include duration of illness greater than 5 years, lack of bulbar involvement after 1–2 years, onset before age 35, family history of a similar disorder (although a small percentage of ALS is familial), and a history of malignancy, radiation, previous poliomyelitis, or electrical injury.

Immune-Mediated Motor Neuropathies

Multifocal Motor Neuropathy with Conduction Block

Multifocal motor neuropathy with conduction block (MMN) is a disorder of motor nerves characterized by slowly progressive, asymmetric, primarily distal upper extremity limb weakness, although proximal weakness may predominate. Upper motor neuron signs are notably absent [3–5]. Two key laboratory features are associated with this disorder, distinguishing it from ALS. First, electrodiagnostic (EDX) testing shows *conduction blocks* along motor nerves exclusive of entrapment sites [6–8] (Fig. 22.1). Second, highly elevated levels of antibodies to GM1 gangliosides are found in the serum in 30–60 % of patients, supportive of an immune-mediated pathogenesis (see below) [3–5]. Lewis and Sumner first described the disorder in their case series in 1982, but the association with anti-GM1 antibodies was not described until 1988 by Pestronk [3, 9–11].

Fig. 22.1 Conduction block in a patient with multifocal motor neuropathy. Motor nerve conduction of the median nerve recording from abductor pollicis brevis muscle, stimulating at the wrist (*top tracing*) and antebrachial fossa (*bottom tracing*). Note the significant drop in area and amplitude of the compound motor action potential between stimulating sites (sensitivity = 2 mV/div; sweep speed = 5 ms/div)

Etiology and Pathogenesis

The pathogenesis of MMN is generally presumed to be autoimmune, based on its association with antibodies to GM1 gangliosides in many cases, and marked clinical improvement following immune-modulating therapy. However, the specific pathogenic role for antibodies against GM1 gangliosides in MMN and other lower motor neuron syndromes is not well defined. Gangliosides are a family of glycolipids composed of lipid (ceramide) and carbohydrate moieties with sialic acid, which are found in abundance on the external surface of the neural membrane. They are thought to have a role in maintenance and repair of nervous tissues, stabilization of paranodal junctions, and clustering of ion channels [12]. GM1 is ubiquitously expressed, but probably more abundant in motor than in sensory nerves. IgG anti-GM-1 antibodies are associated with pure motor axonal forms of Guillain-Barré syndrome (GBS). High-level IgM anti-GM-1 antibody titers can be detected in approximately 50 % of patients with MMN. Low titers of IgM anti-GM1 antibodies have been detected in small number of patients with motor neuron disease (MND). High titers of IgM anti-GM1 antibodies may distinguish MMN from MND and other neuropathies, serving as a potential biomarker for this disorder [13].

The actual mechanism by which these antibodies might damage motor nerves or nerve terminals is unclear. Data from experimental models in GBS revealed effects of GM1 antibodies on the function of peripheral nerves that may be relevant for MMN pathogenesis. Binding of anti-GM1 antibodies to GM1-rich paranodal junctions may alter paranodal anatomy and cause mislocalization or disruption of sodium and potassium channel clusters. Antibodies may activate the classic complement pathway leading to deposition of complement factors, including the membrane attack complex, compromising axonal membrane integrity with sodium channel cluster disruption. These experimental findings may provide pathogenic mechanisms that lead to conduction block and ultimately axonal loss [12]. However, MMN patients with and without anti-GM1 IgM titers have similar clinical features. Seronegative patients could contain unidentified antibodies against molecules with similar function to GM1. IgM antibodies extracted from the sera of patients with MMN were found to bind to a mixture of lipids containing GM1, galactocerebroside, and cholesterol [14]. Disulfated heparin disaccharide has been identified as a potential antigen in patients with motor neuropathies [15]. Cases of MMN and other immune-mediated neurological disorders such as demyelinating neuropathies, myasthenia gravis, and multiple sclerosis have been reported following use of monoclonal antibody therapy [16], suggesting a role of systemic immune dysregulation in the pathogenesis of these disorders.

Clinical Presentation

The prevalence of MMN is not well known but is estimated at about 0.6 per 100,000 population [17]. The disease is more prevalent in males (male to female ratio = 2.7 to 1). The age of onset is usually in the third to fifth decades. Patients present with slowly progressive asymmetrical weakness, usually in the distal upper extremities, although proximal involvement may occur [5, 18]. Weakness usually starts in the hands or forearm, but the first symptoms may present in the distal leg (20–30 %) or occasionally in the upper arms (5 % of cases) [12]. Differential weakness in muscles supplied by the same motor nerve has been reported. This has been described with finger extensors, causing different degrees of finger drop on attempted extension [19]. Neurological examination reveals lower motor neuron involvement consisting of fasciculations and weakness, often prominent in the distribution of named peripheral nerves. During the early stages of the disease, weakness may be limited to the distribution of a single named nerve, often leading initially to a misdiagnosis of an entrapment neuropathy [3]. For example, it is not uncommon for a patient to present with a slowly progressive wrist drop or intrinsic hand muscle weakness, misdiagnosed initially as entrapment of the radial nerve at the spiral groove or ulnar neuropathy at the cubital tunnel, respectively. Muscle atrophy is not prominent in weak muscles, despite the degree and chronicity of weakness. However, over the long term, atrophy may occur [18]. Upper motor neuron signs are notably absent, and muscle stretch reflexes are usually diminished.

Respiratory and bulbar weakness is unusual [3–6, 9, 19–29]. Cranial nerve involvement is rare; however, external ophthalmoplegia and unilateral tongue weakness and atrophy have been described in association with MMN [30, 31]. Although mild sensory complaints may be present, the sensory examination usually remains normal [10].

Differential Diagnosis

The differential diagnosis includes any disorder that presents with slowly progressive primarily distal weakness, especially in the upper extremities, without accompanying upper motor neuron or sensory signs. These include the rare adult-onset forms of spinal muscular atrophy, monomelic amyotrophy (see below), brachial amyotrophic diplegia (see below), and some rare forms of inherited or sporadic distal myopathies. These disorders are distinguished by a careful family history, laboratory testing including creatine kinase (CK) level, and anti-GM1 antibody, as well as EDX testing to look for neurogenic versus myopathic changes. If EDX testing shows evidence of neurogenic changes, a careful search for conduction block or other signs of demyelination is warranted. Genetic testing can be performed if clinically indicated based on the clinical phenotype. In indeterminate cases, muscle biopsy may help distinguish between neurogenic and myopathic etiologies, looking for evidence of chronic denervation-reinnervation, inflammation, or findings suggestive of a metabolic or inherited myopathy.

Evaluation and Diagnosis

The typical clinical presentation of MMN allows differentiation from ALS. These features include an indolent time course and progression, asymmetric limb weakness, a non-myotomal pattern of weakness, and absence of significant muscle wasting, upper motor neuron signs, and bulbar weakness [4, 9]. In this clinical context, one should test for serum antibodies against gangliosides, especially GM1 [3, 4, 20]. It should be noted, however, that low titers of IgM anti-GM1 antibodies are nonspecific and can be found in normal subjects as well as in a variety of neurologic and autoimmune disorders including ALS, sensorimotor polyneuropathy, chronic inflammatory demyelinating polyneuropathy (CIDP), Guillain-Barré syndrome, myasthenia gravis, and systemic lupus erythematosus (SLE) [4, 32–34]. High titer anti-GM1 antibodies may predict a more severe clinical presentation in MMN patients (severe weakness, disability, and axonal loss) compared to antibody-negative patients [20]. However, the diagnostic significance of this observation is undetermined, as no differences were observed regarding response to intravenous immunoglobulin (IVIG) between these groups of MMN patients [19].

The EDX findings typically show focal conduction block along motor axons that spares sensory axons along the same peripheral nerve segment [7, 8]. The conduction block in MMN is often chronic and may remain unchanged for several years. Conduction blocks may go undetected unless multiple segments of several nerves are tested [8]. Definite conduction block has been defined as a greater than 50 % reduction of the compound motor action potential (CMAP) amplitude and area over a long nerve segment or a CMAP amplitude and area reduction of at least 30 % over a short distance (2.5 cm) detected by inching. Probable conduction block has been defined as a reduction in CMAP amplitude and area of at least 30 % over a long segment of an arm nerve. Both definitions require the distal CMAP amplitude to be at least 1 mV [7, 8, 12, 35] (Fig. 22.1). A careful interpretation of conduction block is required to differentiate conduction block from a decrease of CMAP amplitude and/or area due to temporal dispersion and phase cancellation [36]. Other electrophysiologic signs of demyelination such as temporal dispersion, slowed motor conduction velocities, prolonged distal motor latencies, and prolonged or absent F-waves may occur in association with the conduction blocks [7, 8]. The needle EMG exam shows typical neurogenic changes, including reduced recruitment of motor unit action potentials (MUAPs) in weak muscles. Secondary axonal changes may be seen, including fibrillation potentials and large, prolonged MUAPs.

Cerebrospinal fluid (CSF) is acellular, but protein levels may be elevated (usually <100 mg/dl). Serum immunofixation is normal in the majority of patients but an IgM monoclonal protein can be detected in some cases. Creatine kinase can be mildly elevated in up to two-thirds of patients [12]. MRI of the brachial plexus has been reported in MMN patients to show increased signal intensity and in some cases may co-localize with the conduction block seen on nerve conduction studies [37, 38]. Ultrasonography may also demonstrate abnormalities in the brachial plexus and nerves [39].

Treatment and Management

Human IVIG is considered standard treatment for MMN and its beneficial effects, demonstrated by improvement in strength, have been verified by several controlled [40–44] and uncontrolled clinical trials [21, 45–52] and retrospective studies [19, 20, 53]. The dose of IVIG is usually a total of 2 g/kg given in divided doses over 2–5 days. Pretreatment with 50 mg oral diphenhydramine (Benadryl®), 100 mg IV hydrocortisone, and 650 mg acetaminophen may be used to prevent side effects. Some degree of improvement occurs in up to 80 % of patients with MMN treated with IVIG, with 50–60 % of patients experiencing significant useful functional benefit. Despite improvement in strength, IVIG treatment usually does not reduce serum anti-GM1 antibody titers [21, 52, 54]. The onset of improvement in strength varies from 1 to 7 days after treatment, and maximal improvement is reached by an average of 2 weeks [54]. The duration of improvement varies from patient to patient but tends to be reproducible in each patient. Typically, the optimal benefit persists for 3–6 weeks. In approximately 10 % of patients, the effect may last longer, up to a year after a single treatment. The dose and frequency

of IVIG infusion should be based on the treatment response of the individual patient, and the period of maximal improvement after IVIG infusion should be monitored in each patient. The minimal dose that produces an optimal improvement is used for long-term maintenance treatment. Lack of improvement after two to three courses of IVIG infusion is considered a treatment failure. Over several years of treatment, effective IVIG dose requirements tend to increase by 30 % [17]. Subcutaneous immunoglobulin is an emerging alternative for IVIG. It can be self-administered and has been reported to be as effective for chronic MMN treatment [12].

The side effects of IVIG are usually minor and occur in less than 10 % of patients. Common side effects include mild headache, fatigue, and myalgias, but more severe side effects including anaphylactic reaction (seen in patients with IgA deficiency), thromboembolic events secondary to increased serum viscosity, aseptic meningitis, and acute renal tubular necrosis may occur [55–57]. Patients with more prominent muscle wasting often show reduced or shorter duration of improvement. With time, IVIG treatment may become less efficacious, with reduced recovery in weakness and shorter duration of remission [12, 52, 58].

Cyclophosphamide has been reported to produce sustained long-term benefit in 50–80 % of the patients with MMN. However, its side effect and toxicity profile, including an increased risk for neoplasms such as transitional cell cancer of the bladder with high cumulative lifetime doses (>75 g), has somewhat limited its utility in MMN. The use of monthly IV pulsed therapy for up to 6 months may limit the likelihood of serious side effects [7, 59]. Corticosteroid treatment is usually ineffective in the treatment of MMN. In fact, steroids may occasionally worsen weakness experienced by patients with MMN [3, 60, 61].

Rituximab, a monoclonal antibody directed against the B-cell surface membrane marker CD20, was reportedly beneficial in open-label studies and case series, but further studies could not establish its efficacy in MMN [12, 62, 63].

Course and Prognosis

The clinical course of MMN is usually benign, although the severity of weakness in some patients can be severe and debilitating [4, 5, 18, 21–23]. The response to various treatments is generally good. As noted above, the treatment response may lessen compared to the initial response, or the duration of the effect after each treatment may become shorter following long-term IVIG infusion therapy. In resistant or refractory cases, other immunosuppressive treatments may be considered. Weakness usually progresses slowly and can usually be stabilized or improved with immunosuppressive or immunomodulating treatment. Respiratory and bulbar weaknesses are exceedingly rare [28–30], and the disorder does not shorten the life span. Early diagnosis and initiation of IVIG treatment may help to delay the occurrence of axonal loss and irreversible neurological deficits [17].

Other Presumed Immune-Mediated Lower Motor Neuron Syndromes

Patients with a pure lower motor neuron disorder with localized regions of motor conduction blocks at non-entrapment sites that spares sensory axons are diagnosed as having MMN with conduction block. However, there are groups of patients with slowly progressive asymmetrical lower motor neuron weakness with a clinical presentation similar to those with MMN, in whom conduction block or other signs of demyelination are not detected [5]. These patients may be divided into those with either predominantly distal or proximal weakness. Patients presenting with distal weakness are more common and are difficult to clinically distinguish from patients with MMN with conduction block. The similar clinical characteristics between patients with MMN with and without conduction block suggest that conduction block may be undetected instead of absent or activity dependent [64, 65]. High titers of anti-GM1 antibodies were seen in 64 % of all such patients in one series [5]. Patients with predominantly proximal weakness are less common and have a later age of onset. This presentation occurs more commonly in men, who present with proximal lower motor neuron weakness that often remains confined to one or two extremities over the next 3–5 years [5].

EDX studies show evidence of motor axonal loss in a segmental distribution, without conduction block. Differentiating between a motor neuropathy and ALS, especially the progressive muscular atrophy variant of ALS (see below), is consequentially quite difficult. The diagnosis may depend on other investigations including laboratory tests to look for very high titers of antibodies to GM1 or a therapeutic trial of IVIG to look for a treatment response [4, 5, 54]. High-titer serum IgM anti-GM1 antibodies, when present, are a useful indicator that the lower motor neuron syndrome may be immune-mediated and potentially treatable [54, 66, 67]. In contrast, there has been no clear response to cyclophosphamide therapy in patients with predominantly proximal weakness or with low anti-GM1 antibody titers [64]. The decision whether to treat patients with a lower motor neuron syndrome without electrophysiologic evidence of conduction block is difficult.

Nonimmune-Mediated Lower Motor Neuron Syndromes

Spinal Muscular Atrophy

The spinal muscular atrophies (SMAs) consist of a complex heterogeneous group of genetic motor neuron disorders. A detailed discussion of the spinal muscular atrophies is provided in Chap. 21. The characteristic clinical presentation is that of progressive, symmetric, proximal muscle weakness, and atrophy, without upper motor neuron signs. In the three

major forms of this disorder, onset is in infancy or early childhood, with an autosomal recessive inheritance pattern linked to chromosome 5q. In the most severe form, Werdnig-Hoffman disease, death occurs by age two. However, other SMA variants exist with differences in their pattern of inheritance, gene linkage, age of onset, progression, distribution of weakness, and prognosis. Rare patients present in adulthood, with proximal or distal weakness. This chapter focuses on a specific form of adult-onset spinal muscular atrophy, X-linked recessive bulbospinal muscular atrophy.

X-Linked Recessive Bulbospinal Muscular Atrophy (Kennedy Disease)

In 1968, Kennedy and his colleagues described a clinical syndrome in 11 males from 2 families, with an X-linked recessive inheritance, characterized by adult-onset slowly progressive weakness, atrophy and fasciculations of bulbar and proximal muscles, and hyporeflexia or absent muscle stretch reflexes. Elevated serum CK (up to ten times normal) was common [68]. Some patients also had gynecomastia, impotence, and an essential tremor [68]. This clinical syndrome was named Kennedy-Stefanis disease in 1981 [69]. In 1991, LaSpada et al. identified a mutation in the androgen receptor gene as the cause of Kennedy disease [70–72]. The mutation is characterized by an increase in the size of a cytosine-adenosine-guanine (CAG) repeat within the first exon of the androgen receptor gene on chromosome Xq11-q12.

Etiology and Pathogenesis

Kennedy disease or bulbospinal muscular atrophy (BSMA) is an X-linked recessive disorder caused by a mutation within the first exon of the androgen receptor gene corresponding to an expansion of tandem CAG repeats on the X chromosome [70, 72]. The number of CAG repeats ranges from 40 to 62, which is only double the number seen in normal individuals. The phenotypic expression varies between and within affected families and does not usually correlate with the size of the mutation in most of the case series reported [73]. However, there is a correlation between the number of CAG repeats and age of onset, with a larger number of CAG repeats associated with earlier age of onset [74, 75].

While partial loss of androgen receptor function mediated by decreased receptor expression and activity occurs in Kennedy disease, this is unlikely to be the major cause of motor neuron degeneration. Experiments in a transgenic mouse model of bulbospinal muscular atrophy provided evidence to support the hypothesis that the polyglutamine expansion results in a *toxic gain of function* that leads to accumulation of abnormal proteins and degeneration of motor neurons [76, 77]. Furthermore, pathologic findings in patients with Kennedy disease reveal intranuclear aggregations containing androgen receptor protein in the brainstem and spinal cord motor neurons [78, 79]. However, the mechanism by which this intranuclear aggregation leads to neuronal degeneration is not well defined [79].

Point mutations in the dynactin-1 gene have been identified to cause BSMA with predominance of distal muscle weakness and wasting (distal BSMA). These patients commonly present with bilateral vocal fold paralysis and weakness and wasting of the face, hands, and distal legs [80, 81].

Clinical Presentation

Clinical features vary from asymptomatic hyperCKemia to severe muscle disease with bulbar involvement requiring artificial ventilation [80]. HyperCKemia may occur a decade in advance of symptom onset [82]. Kennedy disease typically presents in men in the third to fifth decade with gradually progressive weakness. Initial symptoms may include perioral or postural tremor, proximal or distal weakness, dysarthria, dysphagia, jaw drop, contraction fasciculations, or flexor muscle cramps. In most cases, weakness starts in the lower limbs, followed by the upper limbs, the bulbar muscles, and lastly the facial muscles. Muscle weakness and wasting usually have an asymmetric distribution and are more marked proximally. Distal weakness, if present, is often more prominent in the upper extremities, and muscle wasting of the intrinsic hand muscles is not uncommon. Fasciculations are often found in appendicular muscles. Muscle stretch reflexes are depressed or absent. Myalgia and muscle cramps may precede weakness for years. Some patients complain of exercise-induced muscle cramps and hand tremor several years before weakness develops. The hand tremor (found in up to 80 % of reported patients) has the characteristics of an essential tremor, is sometimes responsive to propranolol [68, 83–89]. Upper motor neuron signs are absent.

A classic and striking clinical feature of BSMA is the presence of facial fasciculations, most prominent around the mouth and chin. Fasciculations are present at rest but appear more prominent with contraction and are best elicited by having the patient whistle or blow out their cheeks. Facial fasciculations are reported in more than 90 % of case reports. Weakness and atrophy of the bulbar muscles, primarily of the facial muscles and muscles of mastication occur in variable degrees on neurological examination. Tongue wasting and fasciculations are also common and may predate the onset of bulbar symptoms. Despite weakness and fasciculations of the bulbar muscles on neurological examination, very few patients report dysarthria or dysphagia. The latter symptoms do not usually occur until very late in the disease course, usually more than 10 years after the initial presentation [68, 83, 85–92].

Sensory symptoms are unusual, but distally impaired vibration and pinprick perception have been described [92]. Despite the lack of sensory complaints or physical findings,

most patients studied have absent or low amplitude sensory nerve action potentials (SNAPs) on nerve conduction studies [73, 83, 89]. The underlying pathology responsible for sensory abnormalities in Kennedy disease is unclear. Kennedy found mild axonal loss in the peripheral nerves with intact dorsal roots in one autopsy case [68]. Sural nerve biopsies in other series have shown mixed features, including marked loss of myelinated nerve fibers, axonal atrophy, and segmental remyelination [73, 87, 93].

Female carriers may develop fasciculations, mild distal weakness, muscle cramps, or hyperCKemia later in life in about 50 % of cases. Tongue atrophy and fasciculations may occur in one fifth of these individuals by the seventh or eighth decade [80].

Systemic manifestations reported in most patients with Kennedy disease include gynecomastia and impotence. These are attributed to androgen insensitivity as a direct consequence of the expanded trinucleotide androgen receptor gene repeats. Diabetes mellitus may occur in a minority of patients with Kennedy disease, although its relationship with the gene defect is still uncertain.

Differential Diagnosis

The differential diagnosis of Kennedy disease includes disorders that present in the third to fifth decade with primarily proximal lower motor neuron weakness and bulbar signs. These include the progressive muscular atrophy variant of ALS, immune-mediated motor neuropathies, other late-onset SMAs, and myopathies including inflammatory, endocrine, and late-onset metabolic or inherited myopathies. These are usually distinguished by a careful family history, laboratory testing including CK level, serum anti-GM1 antibody titers, and TSH if indicated, as well as EDX testing to look for evidence of neurogenic versus myopathic changes. If EDX testing shows chronic neurogenic changes, a careful search for conduction block or other signs of demyelination is warranted. Genetic testing can be performed if clinically indicated to differentiate BSMA from late-onset SMA. In indeterminate cases, muscle biopsy may distinguish between neurogenic versus myopathic etiologies, excluding inflammatory, metabolic, or inherited myopathies.

Evaluation and Diagnosis

The diagnostic mainstay of Kennedy disease is primarily clinical: the classic clinical presentation and a supportive family history of X-linked inheritance. The diagnosis is confirmed by genetic testing. Serum CK levels are usually elevated, ranging from 900 to 8,000 IU/l, much higher than the CK elevation found in other anterior horn cell diseases, and sometimes implicating the diagnosis of myopathy [73]. Nerve conduction studies (NCS) often demonstrate low amplitude or absent SNAPs [68, 83, 85–89]. Motor NCS are normal except that CMAP amplitudes may be low if recorded from weak and wasted muscles. Needle electromyography (EMG) shows neurogenic changes, including increased insertional activity and reduced recruitment of large, prolonged duration, polyphasic motor unit action potentials (MUAPs) in affected muscles. Needle EMG examination of the facial muscles, such as the mentalis muscle, may show *grouped repetitive motor unit discharges* that occur with mild activation of the facial muscles. Such discharges are highly characteristic of Kennedy disease [85, 89]. Since these discharges occur with mild voluntary contraction rather than spontaneously, they are distinguished from myokymic or neuromyotonic discharges. Muscle biopsy reveals variability of fiber size with groups of angular atrophic fibers, grouped muscle atrophy, and pyknotic nuclear clumps. There is usually no fiber-type grouping [80]. Frequent atrophic groups containing mixed fiber types may be seen in Kennedy disease and other motor neuron syndromes or motor neuropathies [94, 95]. Nonspecific myopathic features, including increased central nuclei and necrotic fibers are also seen, which might also explain the abnormally high CK level. The diagnosis is confirmed by DNA analysis for the CAG mutation within the first exon of the androgen receptor gene on chromosome Xq11-q12.

Treatment and Prognosis

Currently, there is no specific treatment for Kennedy disease. The overall life expectancy is normal or only slightly shortened, as the nature of the disease is very slowly progressive. Bulbar weakness occurs relatively late in the course of the disease. Severe dysarthria or dysphagia that leads to aspiration pneumonia occurs rarely [68, 91].

Monomelic Amyotrophy (Hirayama Disease)

Monomelic amyotrophy is a rare form of motor neuron disease, first reported in the Japanese literature by Hirayama in 1959. He described the condition as a "juvenile muscular atrophy of a unilateral upper extremity" [96, 97]. Although most cases since the original report have been reported from Japan and India, the disease has been described in young adults from all parts of the world. Many different names have been used for this entity. These include Hirayama disease, monomelic atrophy, benign focal atrophy, benign focal amyotrophy, Sobue disease, and juvenile segmental muscular atrophy [97–104].

Etiology and Pathogenesis

The etiology of monomelic amyotrophy is unknown. Postulated mechanisms include subtle ischemia of the spinal cord, especially the anterior horn cells which lie in the watershed area, possibly precipitated by trauma to the arm or neck. Immobilization after trauma was associated with

monomelic amyotrophy in one small series [105]. Breig et al. proposed that forward bending of the neck could flatten the spinal cord from front to back and stretch the vessels sideways, possibly inducing a secondary vascular disorder [106]. Another proposed process involves an overstretch mechanism associated with compression of the dura and spinal cord against the vertebra during neck flexion [96]. It has been suggested that there is a short length of the cervical dural canal that cannot compensate for the flexion-related increased length of the vertebral canal. Thus, the dural canal becomes tight during neck flexion, resulting in anterior shift of the posterior dural wall as well as the spinal cord. The spinal cord also gets flattened against the C5–C6 vertebral body. There is forward movement of the posterior dura mater, obliterating the subarachnoid space and leaving a large posterior epidural space with prominent epidural venous plexus during neck flexion [107].

Hirayama reported a single patient with monomelic amyotrophy who died of lung cancer at the age 38, 23 years after the disease onset. The autopsy revealed shrinkage and necrosis of the anterior horn cells, with decrease number of large and small nerve cells and mild gliosis in the C5–T1 spinal segments, especially at C7–C8. The posterior horn was normal and the white matter was well preserved. The intra- and extramedullary vascular system of the spinal cord showed no abnormalities. The necropsy findings were suggestive of circulatory insufficiency of the lower cervical cord, although the true mechanism remained unknown [96].

Clinical Presentation

The true incidence and prevalence of monomelic amyotrophy is unknown. Most cases are sporadic, although a familial form has been reported. The male to female ratio is 5:1. The majority of patients are between 18 and 22 years old. Patients present with an insidious onset of unilateral weakness and atrophy of the hand muscles. In most cases, no particular precipitating infection or trauma is identified. The weakness tends to progress slowly over 1–3 years and then stabilizes. It is usually asymmetric and mainly affects the C7–T1 myotomes; however, proximal weakness in the arm can also be observed. Bilateral symmetric involvement has been reported in 10 % of cases, though in most the onset is unilateral [107]. Muscle atrophy is limited to the muscles of the hand and forearm, often sparing the brachioradialis muscle. This pattern of forearm involvement is referred to as *oblique amyotrophy.* In approximately one fourth of patients, the weakness is worse with cold exposure (cold paresis). Tremulousness of fingers in outstretched hands, or *mini-polymyoclonus*, has also been reported [107]. Muscle stretch reflexes are usually normal, and upper motor neuron signs are absent. Sensation in the affected extremity is preserved, except for rare and mild sensory abnormalities over the dorsum of the hand [96, 102, 104–106, 108–119].

Differential Diagnosis

The differential diagnosis of monomelic amyotrophy includes diseases that present with painless weakness and atrophy of a distal upper extremity, including syringomyelia, intramedullary spinal cord neoplasms, spinal cord infarction, inherited, or sporadic distal myopathies that affect the upper extremities before the lower extremities, rare adult-onset forms of spinal muscular atrophy, and the early stages of ALS. MMN is also worth considering in the differential diagnosis, although marked atrophy is notably absent early on in the disease. These disorders are differentiated by a careful family history, laboratory testing including CK level, and anti-GM1 antibody, as well as EDX testing to look for evidence of neurogenic versus myopathic changes. If EDX testing shows evidence of neurogenic changes affecting only motor axons or neurons or both, a careful search for conduction blocks or other signs of demyelination is warranted. The clinical course is also useful in differentiating these disorders, since stabilization of deficits usually occurs in monomelic amyotrophy, but not in the other disorders.

Evaluation and Diagnosis

The diagnosis is often made based on the classic clinical presentation of distal hand weakness and atrophy, usually in a young male. Laboratory investigations, including blood chemistries and cerebrospinal fluid (CSF) analysis, are normal, with the exception of the serum CK which may be slightly elevated. On EDX testing, motor NCS may be normal, or reveal asymmetrically low median or ulnar CMAP amplitudes. Slightly prolonged distal motor latencies or slightly slowed conduction velocities may occur, depending on the degree of axonal loss. The SNAPs are always preserved. On needle EMG, fibrillation potentials are not prominent and are found in slightly less than half of the patients. MUAPs are large and prolonged in duration, and recruitment is invariably reduced in muscles innervated mostly by the C7, C8, and T1 roots. Muscles innervated by the C5 and C6 roots are either normal or minimally affected. Low-amplitude, short-duration MUAPs, which represent early reinnervated motor units, occur in approximately 20 % of patients. Interestingly, similar EDX abnormalities are also detected, to a much lesser degree, in clinically unaffected limbs, particularly in the contralateral hand. Findings on muscle biopsy are often consistent with neurogenic atrophy without inflammatory infiltrates [96, 102, 103, 109, 112–115]. Features described on MRI performed in neck flexion include flattening of the spinal cord against C5–6 vertebral bodies, forward movement of the posterior cervical dura mater, obliteration or marked reduction in the size of posterior cervical subarachnoid space, and contrast-enhancing crescent-shaped posterior cervical epidural space. Segmental atrophy of the lower cervical and upper thoracic spinal cord has also been described [96, 107, 109, 120–123].

Course and Prognosis

The course in monomelic amyotrophy is generally benign. Distal weakness and atrophy usually progress slowly over 1–3 years, followed by relative stabilization. In one long-term series, disease progression subsided within 5 years in 75 % of 102 patients [111].

Brachial Amyotrophic Diplegia (Flail Arm Syndrome)

There are a few case reports of patients with sporadic adult-onset chronic progressive severe bilateral arm weakness and atrophy, without lower extremity involvement, presumably secondary to anterior horn cell loss. The clinical presentation is typically that of pure lower motor neuron weakness. The progression of the disorder is much slower than in typical ALS. EDX studies show denervation restricted to the proximal arm muscles.

The first case was reported by Mulder in 1957, describing a patient with weakness confined to the arms, and used the term "hanging arm syndrome" for the disorder [124]. In 1998, Hu et al. used the term *flail arm syndrome* to describe 39 patients who presented with severe bilateral arm weakness [125]. This presentation accounts for around 10 % of patients with motor neuron disease [126]. This subset of patients had a longer median survival of about 60–70 months compared to bulbar-onset and limb-onset ALS population with a median survival rate of 27–35 months [125, 126]. In 1999, Katz et al. described ten patients with sporadic slowly progressive proximal arm and shoulder girdle muscle weakness and atrophy, with variable degrees of distal arm involvement, which they termed *brachial amyotrophic diplegia*. Respiratory and bulbar muscles were spared. Eight of the ten patients had a pure lower motor neuron syndrome that was strictly confined to the upper extremities, both by clinical and EMG criteria. The other two patients had evidence of denervation on EMG in the upper and lower extremities, and one of them had upper motor neuron signs. More importantly, seven of the ten patients showed no signs of weakness in other regions after 67 months of follow-up, implying a slower progression than expected in typical ALS [127]. A case series by Sasaki et al. in 1999 described eight patients with a similar presentation of slowly progressive lower motor neuron weakness involving shoulder girdle and proximal arms. EDX studies revealed denervation in the upper extremities in all patients. In 2009, Wijesekera et al. reported on two ALS cohorts followed for over 12–14 years. The flail arm syndrome represented 11 % of a large cohort of ALS patients from London, England (1,188 patients), and 5 % of a smaller cohort from Melbourne, Australia (432 patients). In addition to better survival (60–70 months), the median time to spread to a second region of the neuraxis was 29 months in the flail arm syndrome. This was significantly longer when compared to limb-onset ALS (8 months), bulbar-onset ALS (12 months), and progressive muscular atrophy (14 months) [126]. Autopsy, performed in one patient, showed degeneration of the pyramidal tracts and loss of anterior horn cells in the cervical cord and brainstem motor neurons, similar to the pathologic findings in ALS [128].

The pathogenesis of this disorder is unknown. The clinical presentation is different from typical ALS given the slowly progressive course, restriction to the proximal arm and shoulder girdle muscles, and lack of upper motor neuron signs. It also differs from monomelic amyotrophy, which occurs in a younger age group, affects predominantly the hands, and is mostly asymmetrical in its presentation. The EDX studies in the flail arm syndrome show no evidence of conduction block or other features of demyelination, as noted in MMN with conduction block. It can be distinguished from the rare inherited cases of adult-onset proximal spinal muscular atrophy as well as various myopathic disorders by the lack of lower extremity involvement. Other disorders to be considered in the differential diagnosis include bilateral anterior cerebral artery (ACA)-middle cerebral artery (MCA) watershed infarcts, cervical spondylosis, anterior spinal artery infarction, and post-radiation amyotrophy, as well as early ALS [125, 127, 128].

Progressive Muscular Atrophy

A lower motor neuron syndrome is seen in patients with the progressive muscular atrophy variant of ALS (see Chap. 20). These patients present with slowly progressive, asymmetric weakness, wasting, and fasciculations, which may progress for years and ultimately lead to death. These patients have no evidence of upper motor neuron dysfunction, although corticospinal tract involvement has been observed in some autopsied cases. EDX studies reveal evidence for denervation and chronic reinnervation.

Progressive Bulbar Palsy

Another group of patients with ALS present with progressive bulbar dysfunction exhibiting both upper and lower motor neuron signs, such as tongue atrophy, weakness and fasciculations, and spastic speech (see Chap. 20). These patients eventually develop classic ALS.

Fazio-Londe Disease and Brown-Vialetto-Van Laere Syndrome

Fazio-Londe and Brown-Vialetto-Van Laere syndrome (BVVLS) are now considered to be the same disease entity with addition of deafness in the latter [129]. Recessive mutation

in the C20orf54 gene on chromosome 20p13 which encodes the human homolog of a rat riboflavin transporter has been implicated as being causative of this disorder [130]. BVVLS is characterized by progressive pontobulbar palsy (weakness of bulbofacial and extraocular muscles) and bilateral sensorineural hearing loss. The clinical course is progressive, with rate of progression variable between affected families. Long tract signs, lower motor neuron dysfunction, cerebellar ataxia, and respiratory muscles weakness may become apparent with disease evolution. The age of onset varies from infancy to adulthood. A recent report suggested abnormality of riboflavin transport and improvement with supplementation of riboflavin [129].

Hereditary Spastic Paraplegia

Hereditary spastic paraparesis (HSP) comprises a group of clinically and genetically heterogeneous neurological disorders that share the common feature of an insidiously spastic progressive gait disorder and associated weakness of the lower extremities. HSP is generally classified as *uncomplicated* or pure when motor symptoms are restricted to lower extremities, with variable mildly decreased vibration sense in toes and urinary urgency, and as *complicated* when there are associated symptoms like amyotrophy, ataxia, seizures, neuropathy, deafness, cataracts, mental retardation, thin corpus callosum, and ichthyosis in addition to the spastic paraparesis [131, 132].

Etiology and Pathogenesis

HSP mode of inheritance can be autosomal dominant, autosomal recessive, and X-linked. There are over 17 genes related to HSP and 52 loci, designated SPG, numbered in order of their discovery. Uncomplicated HSP (uHSP) on postmortem studies shows axonal degeneration limited to the CNS affecting primarily the caudal aspects of the descending cortical spinal tracts with maximal involvement in the thoracic spinal cord, and rostral aspects of the ascending fasciculus gracilis with maximal involvement in the cervicomedullary region. Decreased number of cortical pyramidal and anterior horn cells has been observed [95, 133].

The diversity of proteins involved in different forms of HSP suggests that axonal degeneration in HSP is caused by variable biochemical abnormalities. The molecular processes possibly involved in the pathogenesis of HSP include abnormalities in primary axonal transport, the Golgi apparatus, mitochondria, myelin synthesis, and corticospinal tract development [133, 134].

Clinical Presentation

The clinical presentation including age of onset, degree of deficit, and associated symptoms varies both within and between families. The different subtypes of uncomplicated HSP usually cannot be differentiated based on phenotype [131, 132].

Symptoms of HSP may begin at any age. When symptoms begin at early age (before 2 years of age), HSP may manifest as "toe walking" and look like spastic diplegic cerebral palsy without much functional worsening over decades. If onset is after infancy (after age 6) or during the teenage years or later, the gait disorder usually slowly progresses over many years, causing variable degrees of disability. Urinary urgency is common and may be an early symptom of HSP [133].

The neurological examination in uHSP consists of increased tone in lower extremities, weakness particularly in flexor muscles (iliopsoas, hamstrings, tibialis anterior), hyperreflexia, extensor plantar responses, and variable mildly decreased vibration sense in toes. High-arched feet are common, but not invariably present. Upper extremities reflexes may be brisk but dexterity, muscle strength, and tone remain normal in uHSP. A sudden onset and symptom progression over weeks or months is not typical for HSP and would suggest an alternative or coexisting disorder. Other features that suggest alternative diagnoses include marked asymmetry, spasticity and weakness in the upper extremities and bulbar muscles, and a cutaneous sensory level. Muscle atrophy and fasciculations are not typical for uHSP but can be seen in many types of complicated HSP (cHSP), including Troyer syndrome (SPG20) and Silver syndrome (SPG17) [132, 133].

Limited generalization can be made regarding cHSP, as each disorder represents a unique clinicopathological entity. It is useful for practical purposes to recognize three clinical phenotypes: (1) spastic paraplegia associated with peripheral motor neuropathy and/or distal wasting (e.g., Troyer and Silver syndromes); (2) spastic paraplegia associated with cognitive impairment (e.g., SPG11 which is often associated with a thin corpus callosum and considered to represent 50 % of recessively inherited HSP); and (3) spastic paraplegia associated with additional neurologic and systemic abnormalities [132, 133].

Differential Diagnosis and Evaluation

The diagnosis is usually straightforward if there is a known family history of pure progressive spastic paraparesis. If there is no known family history, other diagnoses to be considered in the appropriate clinical context include human T-cell lymphotropic virus type 1 (HTLV-1)-associated spastic paraparesis (see below), vitamin B12 deficiency, vitamin E deficiency, multiple sclerosis, primary lateral sclerosis, cervical spondylotic myelopathy, neurosyphilis, and spinal cord tumor.

In some cases, HSP can be confirmed by genetic testing. However, a family history may be absent with autosomal recessive or X-linked inheritance patterns, incomplete genetic penetrance, spontaneous (*de novo*) mutations, genetic anticipation (child affected before parents), and in cases of wrong paternity. These individuals with a clinical picture of HSP and no apparent family history are usually designated as having "apparently sporadic" spastic paraplegia. Genetic penetrance is age_dependent and high but typically incomplete [132, 133]. HSP should be considered a diagnosis of exclusion when there is no family history.

If there is a known family history, but other neurologic or systemic features are present, the differential diagnoses widen to include metachromatic leukodystrophy, globoid cell leukodystrophy, adrenoleukodystrophy, adrenomyeloneuropathy, spinocerebellar atrophy, hexosaminidase A deficiency, and familial ALS. In such cases, the diagnostic evaluation should include MRI of the brain and spinal cord; HTLV-1 and HIV antibodies; vitamin B12 and E levels; VDRL, FTA-ABS, or MHA-TP; plasma very long chain fatty acids; arylsulfatase A; and galactocerebrosidase, copper, and ceruloplasmin levels. CSF analysis for cell count, protein, glucose, VDRL, oligoclonal bands, and IgG synthesis rate/index may be considered, depending on the clinical presentation.

The evaluation of both complicated and uncomplicated HSP requires EMG study, neuroimaging, and laboratory tests to exclude alternate disorders. The most common MRI abnormality observed is thinning of the cervical and thoracic spinal cord. Other MRI abnormalities include loss of corpus callosum volume and higher incidence of cerebral white matter lesions. Nerve conduction studies and needle EMG are normal in most cases of uHSP, as is the CSF analysis. Lower limb somatosensory evoked potentials may show central conduction delay or low amplitudes. Central motor conduction times are delayed or non-recordable from the lower limbs [132, 134].

Genetic Subtypes of HSP

Autosomal Dominant (AD) HSP

SPAST-Associated HSP

SPAST gene encodes the *spastin* protein. This is the most common form of AD uHSP (40–45 % of cases). Its onset is variable from childhood to late adult life with a bimodal peak distribution in the first decade and above age 30. *SPAST* mutations are thought to mostly cause uHSP and an excess of males has been identified. Complex phenotypes with cerebellar ataxia, tremors, epilepsy, thinning of corpus callosum, mental retardation, and lower motor neuron dysfunction have been described. Progressive cognitive decline has also been reported [134–137].

SPG3A

This is the second most common AD HSP (10 % cases), and the gene encodes for the protein *atlasin*. Its onset is usually before age 10 and it manifests with an uncomplicated phenotype. An association with axonal peripheral neuropathy has been reported [134, 138].

Other AD HSP forms include *SPG6*, associated with NIPA1 gene, manifesting with an uHSP phenotype; *SPG 8* associated with the KIAA0196 gene, characterized by severe spasticity and reduced vibration sense; *SPG 13*, associated with the gene HSPD1, with a typically uHSP phenotype with late onset; and *SPG 17*, due to mutation in BSCL2 gene that manifests as a cHSP with associated amyotrophy of the small hand and feet muscles, onset in early teens to late 30s (Silver syndrome). Other AD HSP forms include SPG 9, 10, 12, 18, 19, 29, 33, 34, 36–38, 41 and 42 [95, 132–134].

Autosomal Recessive (AR) HSP

Examples of AR HSP include *SPG5A*, associated with the CYP7B1 gene, and an uHSP phenotype; *SPG 7*, associated with the *paraplegin* gene, accounting for about 5 % of AR HSP cases. This mutation is associated with uncomplicated and complicated phenotypes with ataxia, dysarthria, nystagmus, pale optic discs, and peripheral neuropathy; *SPG11*, associated with mutations in the gene that encodes *Spatacsin* and characterized by uHSP or cHSP variably with a thin corpus callosum, cognitive impairment, and lower motor neuron or sensorimotor axonal neuropathy; *SPG 15*, associated with mutations on ZFYVE26 gene, manifests as a cHSP accompanied by mental impairment, pigmentary retinopathy, cerebellar dysfunction, and distal amyotrophy; *SPG20*, associated with mutation in *spartin* gene causes Troyer syndrome, characterized by spastic tetraparesis, dysarthria, distal amyotrophy, short stature, and learning difficulties; *SPG 21*, associated with the gene encoding *maspardin*, produces Mast syndrome with associated dementia, cerebellar and extrapyramidal signs, and a thin corpus callosum . Other recessive forms are rare and include SPG 14, 23-28, 30, 32, 35, 39, 43-48, and 50-52 [95, 132–134, 139, 140].

X-Linked HSP

SPG1, associated with a mutation in L1CAM gene, is characterized by hydrocephalus, mental retardation, and adducted thumbs. The clinical spectrum also includes X-linked hydrocephalus with aqueduct of Sylvius stenosis, MASA syndrome (*m*ental retardation, *a*phasia, *s*pastic paraplegia, and *a*dducted thumbs), and X-linked agenesis of corpus callosum; *SPG2*, associated with a mutation in the proteolipoprotein gene (PLP1), manifests mainly as a cHSP, and may be associated with a peripheral neuropathy and white matter changes on MRI; *SPG 16* is another X-linked HSP that presents with aphasia, decreased vision, and mild mental retardation [95, 132, 134].

Treatment and Prognosis

Treatment of HSP aims to reduce muscle spasticity through medication (e.g., baclofen or tizanidine) and muscle stretching exercises to prevent contractures. Physical activity can be useful to improve endurance and lower extremity strength. Urinary urgency may respond to anti-cholinergic medications such as oxybutynin. Uncomplicated HSP gait spasticity and weakness may worsen insidiously over many years. Upper extremity, speech, swallowing, and respiration muscles remain unaffected. Life expectancy is not altered in uHSP. The prognosis of cHSP is quite variable and dependent on the clinical phenotype and associated medical comorbidities [132, 133].

Multiple System Disorders with Prominent Motor Signs

Adult-Onset Hexosaminidase A Deficiency (Late-Onset Tay-Sachs Disease)

The adult-onset form of hexosaminidase A deficiency (also known as late-onset Tay-Sachs disease) is a rare disorder, recognized only in the last three decades. The disorder is characterized by slowly progressive degeneration of the cerebellar and upper and lower motor neuron systems. Some patients have psychiatric disturbance, including psychosis and depression. The onset is usually during childhood, although symptoms are often not recognized until the second or third decade of life. The adult-onset form is quite different from the well-known rapidly progressive infantile form of hexosaminidase A deficiency, known as Tay-Sachs disease [141, 142].

Etiology and Pathogenesis

Hexosaminidase is a lysosomal enzyme that participates in the metabolism of GM2 ganglioside. Deficiency of the enzyme causes accumulation of lysosomal GM2 ganglioside, which leads to the neuronal degeneration. There are two major isoforms of hexosaminidase: hexosaminidase A, which consists of two different subunits (α [alpha] and β [beta]), and hexosaminidase B, consisting of only β [beta] subunits. The gene encoding for the α (alpha) and β (beta) subunits are located on chromosomes 15 and 5, respectively. A defect in the gene encoding for either the α (alpha) or β (beta) chains results in a deficiency of hexosaminidase A. An absolute deficiency of hexosaminidase A causes infantile Tay-Sachs disease, whereas a partial deficiency results in the late-onset form of Tay-Sachs [142].

The infantile form of the disease is characterized by progressive dementia, myoclonus, seizures, pyramidal signs, cerebellar involvement, and a macular cherry red spot. The disorder is inherited in an autosomal recessive manner and is more prevalent in the Ashkenazi Jewish population than in other ethnic groups. Late infantile and juvenile-onset forms of the disease with a slowly progressive clinical course also exist [142–145]. However, it was not until 1973 that Navon et al. first reported four adult siblings with hexosaminidase A deficiency with apparently no clinical symptoms [146]. Neurological symptoms became apparent with subsequent evaluation [147].

The study of enzyme activity in patients with the adult-onset form reveals significant residual enzyme activity, in contrast with patients with the infantile form in whom enzyme activity is totally absent or very low. Different types of mutations exist, leading to partial hexosaminidase A deficiency in different families and prominent clinical heterogeneity in the late-onset form. Some patients are homozygous for a single mutation, whereas others are compound heterozygotes, with two abnormal alleles on the homologous chromosome [148–153].

Clinical Presentation

The age of onset is usually in the second decade, although the age at time of diagnosis varies from 11 to 67 years [151]. The disorder is inherited through an autosomal recessive mode of transmission. Neurological manifestations result from degeneration of the pyramidal cells, lower motor neurons, cerebellum, and cerebellar connections. Sensory and cranial nerve involvement are unusual features, but early and severe sensory loss has been reported [154]. Twenty seven percent of patients were found to have evidence of an axonal polyneuropathy in one cohort with 30 patients [155]. A sensory neuropathy with internuclear ophthalmoplegia was reported in one patient [156]. Although the disorder affects multiple systems, the *cerebellum* is the most prominently affected in all reported cases. Dysarthria and truncal ataxia are usually the earliest manifestations and precede appendicular ataxia. In some patients, cerebellar signs are mild and of little functional significance. Nearly every patient reported also has *lower motor neuron* involvement. Weakness and atrophy initially involve the lower extremities and are more prominent in the proximal muscles. Indeed, it is not uncommon for patients to be misdiagnosed as Kugelberg-Welander disease (a variant of spinal muscular atrophy) early on in the disease course. In one case series, 9 of 14 patients also had upper motor neuron signs, but severe spasticity was rare [152]. The neurological picture may resemble spinal muscular atrophy when lower motor neuron signs predominate or ALS when prominent upper and lower motor neuron signs coexist [148, 151, 157–169].

Another important manifestation of adult-onset hexosaminidase A deficiency is *recurrent psychosis*. The psychosis may precede or follow the neurological manifestations [148, 157–161]. Rare patients present with psychosis as the sole manifestation [148, 152, 170, 171]. Depression is also

common. Patients with psychotic episodes may have more severe neurologic symptoms compared with those patients without psychosis. This may be secondary to treatment with various psychoactive drugs which have been shown to be toxic to lysosomes in vitro and may actually worsen the lipidosis or deplete hexosaminidase (see below) [152, 170–173]. Other clinical manifestations reported in some patients include dementia [174], extrapyramidal findings, and dystonia [152, 175, 176].

Differential Diagnosis

The differential diagnosis includes juvenile and adult-onset forms of spinal muscular atrophy, especially when lower motor neuron signs predominate, as well as the spinocerebellar ataxias (see below), myopathy, multiple sclerosis, and ALS. These disorders are differentiated by a careful family history, MRI of the brain to look for evidence of white matter disease or cerebellar degeneration, laboratory testing including creatine kinase (CK) level, as well as EDX testing to look for evidence of neurogenic versus myopathic changes. Genetic testing may be performed if clinically indicated.

Evaluation and Diagnosis

Adult-onset hexosaminidase A deficiency should be considered in the differential diagnosis of patients with lower motor neuron manifestations accompanied by spinocerebellar degeneration, especially those with a history of psychosis or psychiatric disorder such as depression. Laboratory investigations, including serum CK level, are usually normal. Neuroimaging studies of the brain usually show cerebellar atrophy. EDX studies may show abnormal sensory conduction studies. Motor nerve conduction studies are usually normal, unless recorded from weak muscles, in which case the CMAP amplitudes are low, with normal or slightly slowed conduction velocities. The needle EMG examination shows abnormal spontaneous activity including complex repetitive discharges, fasciculations, and fibrillation potentials. Long-duration, high-amplitude, and polyphasic MUAPs with reduced recruitment are seen in affected muscles [148, 152, 155, 174]. Muscle biopsy shows neurogenic changes including fiber-type grouping [148, 158–161, 174]. Pathologic findings on rectal biopsy and the appendix include swollen and abnormal neurons in the myenteric plexus on light microscopy [152].

A definitive diagnosis is made by measuring hexosaminidase A activity in leukocytes or fibroblasts. Hexosaminidase A activity is significantly reduced in serum, leukocytes, and skin fibroblasts in adult-onset patients, in contrast to the total or nearly total absence of the enzyme in the infantile type [148–152, 159, 166, 167, 174]. Once the diagnosis is established, DNA testing can be performed in specialized laboratories to determine the specific gene defect [177]. Prenatal diagnosis for this condition is possible [178].

Currently, the standard screening for Tay-Sachs carriers is performed by testing a blood sample for hexosaminidase A enzyme activity. This does not screen for the gene defect itself. While standard screening identifies abnormal individuals, it does not differentiate between the infantile and late-onset carrier states. When both parents are identified as carriers, DNA testing can be carried out to determine whether the defective gene is that of the infantile or the late-onset type. This testing is recommended for couples whose decision regarding the pregnancy would be altered by whether they were at risk for having a child with infantile or late-onset Tay-Sachs.

Treatment and Management

There is currently no known specific treatment for late-onset Tay-Sachs disease. Treatment consists primarily of symptom management. This includes physical therapy for gait and balance training, speech therapy for dysarthria, and occupational therapy as clinically indicated. Aggressive physical therapy is important to prevent complications from falls, which can result in life-threatening injuries. Because some of the medications used to treat psychosis and depression are known to be toxic to lysosomes and can worsen symptoms, these medicines are best avoided [152, 170–172, 179]. Such medications include neuroleptics such as phenothiazines as well as antiepileptic drugs used as mood stabilizers and antidepressants. In a retrospective and short-duration prospective review of medication adverse effects in late-onset Tay-Sachs patients, certain psychotropic medications, particularly haloperidol, chlorpromazine, and risperidone, worsened neurologic symptoms. Benzodiazepines such as lorazepam and clonazepam were relatively safe and carbamazepine was the mood stabilizer with the least frequent neurologic worsening [179]. Enzyme testing and prenatal diagnosis are available and genetic counseling for the patient and their families cannot be overemphasized [148, 152, 159, 161, 174].

Course and Prognosis

The clinical course in adult-onset hexosaminidase A deficiency is slowly progressive and varies widely between individuals. Some patients manifest with mild dysarthria and ataxia with slow progression over years, while others are wheelchair bound by the fourth or fifth decade of life from a combination of ataxia and weakness. Recurrent psychotic episodes can also be severely debilitating.

Spinocerebellar Degenerations

There are several multiple system disorders in addition to late-onset Tay-Sachs disease that present with ataxia as a prominent feature yet are accompanied by lower motor neuron signs. Other accompanying features include spasticity,

dementia, optic atrophy, ophthalmoplegia, peripheral neuropathy, or extrapyramidal signs. These features easily distinguish them from typical ALS. They are broadly classified as autosomal dominant or autosomal recessive cerebellar ataxias, and the genetic basis of many of these disorders is now known [180, 181].

Adult Polyglucosan Body Disease

Adult polyglucosan body disease (APBD) is an exceedingly rare neurological disorder. The clinical presentation is pathognomonic: progressive upper and lower motor neuron dysfunction, sensorimotor peripheral polyneuropathy, gait disturbance, urinary incontinence, and dementia. All components of the disorder may not be present initially. Some cases appear to be sporadic, and some familial, with a high proportion occurring in families of Ashkenazi Jewish descent. The pathological hallmark of the disease is the presence of a large number of polyglucosan bodies, which structurally resemble Lafora bodies or corpora amylacea, in central and peripheral neuronal processes and astrocytes [182]. The clinicopathological characteristics of the disease were first recognized in the late 1970s [183].

Etiology and Pathogenesis

The presumed cause of APBD is genetic, especially in patients of Ashkenazi Jewish descent. A Tyr329Ser mutation in the glycogen branching enzyme gene on chromosome 3, causing a glycogen branching enzyme deficiency, has been described in Ashkenazi Jewish patients with APBD [184, 185]. Ubogu et al. reported a single APBD patient with reduced glycogen brancher enzyme activity associated with a heterozygous point Tyr329Ser mutation [186]. Ziemssen et al. reported the first patient of non-Jewish descent with a novel missense mutation (Arg515His and Arg524Gln) in the glycogen branching enzyme gene [187].

The true pathogenic mechanism for the clinical manifestations of APBD remains unknown. Since a deficiency of the glycogen branching enzyme is found in only a subgroup of patients with APBD, primarily those of Ashkenazi Jewish descent, the disease may have more than one biochemical basis [184]. The accumulation of polyglucosan bodies in the nervous system is the pathologic hallmark of the disease [182, 183, 188, 189]. However, accumulation of polyglucosan bodies is also seen in other diseases such as Lafora's disease and type IV glycogenosis [190] and may occur as a nonspecific phenomenon in the aging nervous system (corpora amylacea). Structurally, polyglucosan bodies are composed primarily of glucose polymers, with a small variable component of phosphate and sulfate groups and a minimal protein component, the nature of which is unknown [182, 191]. Polyglucosan bodies in APBD are seen in the central nervous system, predominantly within astrocytic processes in the subpial and subependymal regions, cerebellum, and in myelinated axons in the peripheral nervous system (Fig. 22.2). There is severe loss of anterior horn cells. Deposition of polyglucosan bodies is also seen in myocardium, liver, smooth muscles, and to a lesser extent in skeletal muscles [170, 180]. The mechanisms responsible for tissue damage include impairment of astrocytic processes secondary to massive accumulation of polyglucosan bodies, or the underlying metabolic defect may damage the neuron directly, with the accumulation of polyglucosan bodies occurring as a secondary effect [192].

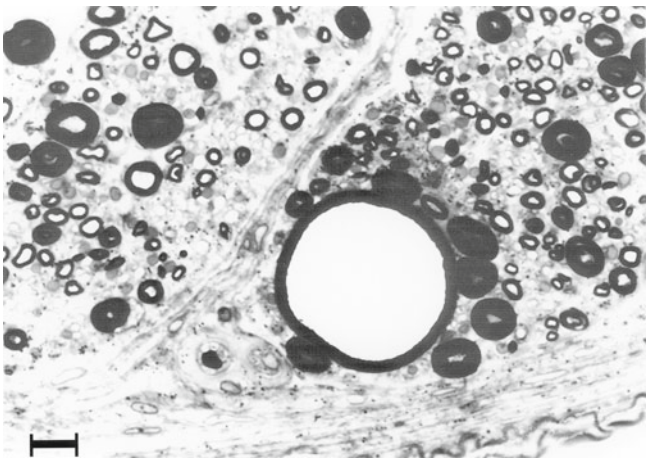

Fig. 22.2 Transverse section of the sural nerve from a 62-year-old man with adult polyglucosan body disease. Note intra-axonal location of polyglucosan body, measuring approximately 50 μm, and distending the axon. Polyglucosan bodies are composed primarily of glucose polymers, with a small variable component of phosphate and sulfate groups and a minimal protein component (Bar = 10 μm; magnification = ×1028)

Clinical Manifestations

As noted above, APBD can be sporadic or familial. The pattern of inheritance appears to be autosomal recessive in some case reports. Most patients present between the fourth and sixth decades, and there is no gender predisposition. The clinical manifestations include progressive upper and lower motor neuron dysfunction, peripheral neuropathy with prominent sensory loss in the lower extremities, gait disturbance, urinary incontinence, and dementia [188, 189, 193, 194]. However, all of the clinical manifestations may not be present, and the severity of clinical manifestations varies among patients [195]. Cognitive impairment tends to occur during the advanced stages of the disease. Of the 24 patients reported in a review series, 11 patients did not have dementia and four patients lacked urinary incontinence [189]. Some patients present with dementia, urinary incontinence, and gait disturbance, without upper or lower motor neuron signs [196, 197], while others present with only upper and lower motor neuron signs and resemble ALS, with only minimal non-motor CNS manifestations [195].

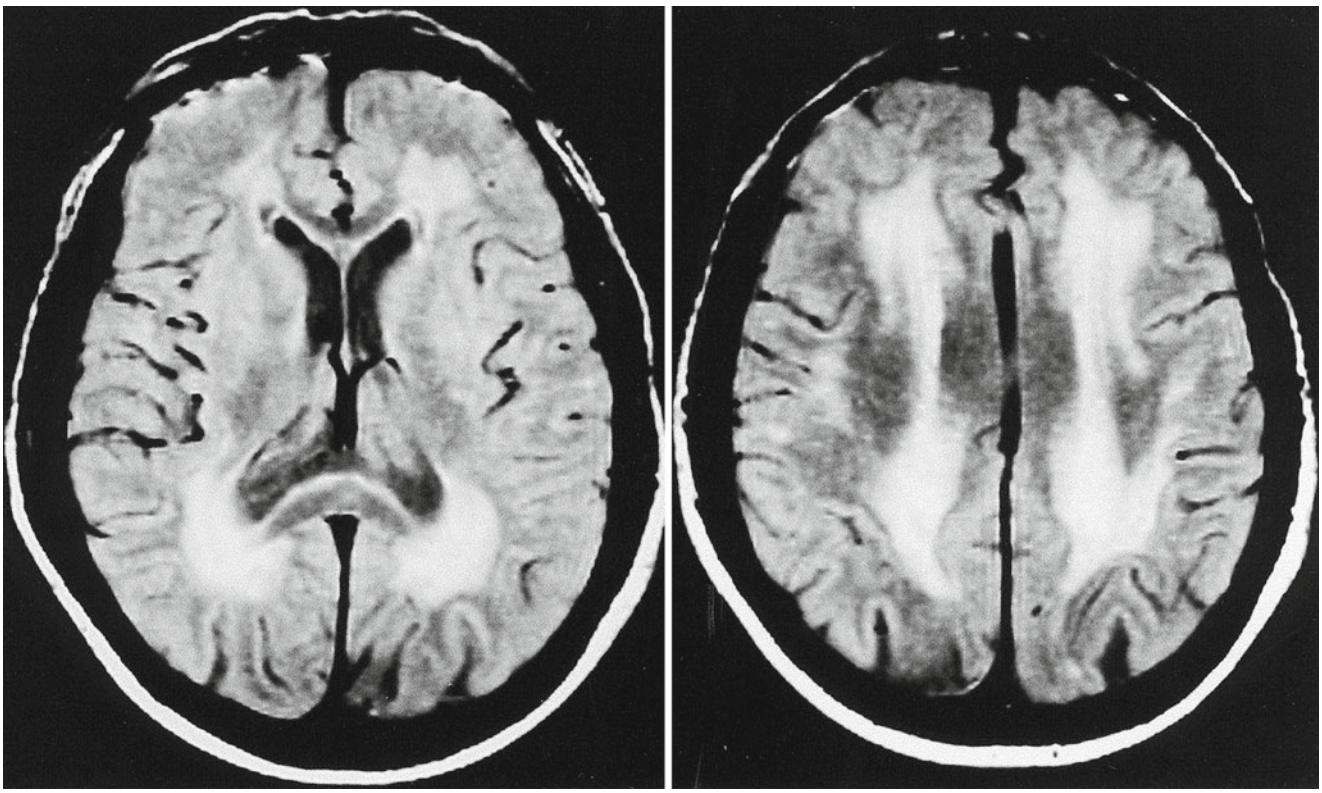

Fig. 22.3 Double echo non-contrasted axial brain MRI images of a 62-year-old man with adult polyglucosan body disease. Note diffuse bilateral white matter signal abnormalities in periventricular and subcortical white matter characteristic of adult polyglucosan body disease

Differential Diagnosis

Clinically APBD must be differentiated from other neurological disorders with progressive upper and lower motor neuron dysfunction, including ALS, primary lateral sclerosis, late-onset multiple sclerosis, and other multisystem disorders with upper and lower motor signs including vitamin B12 and E deficiencies, metachromatic leukodystrophy, globoid cell leukodystrophy, adrenomyeloneuropathy, and spinocerebellar atrophy.

Evaluation and Diagnosis

The clinical context that should prompt an evaluation for APBD is progressive upper and lower motor neuron dysfunction and gait instability that may resemble typical ALS but is accompanied by dementia and urinary incontinence. Distal sensory loss may be found on clinical exam. Extensive white matter abnormalities are seen on brain MRI (Fig. 22.3) [187, 188]. EDX studies reveal mild-to-moderate slowing of motor nerve conduction velocities and low amplitude or absent SNAPs [189]. Routine laboratory investigations are usually normal. A definitive diagnosis is based on pathological findings of widespread deposition of polyglucosan bodies in the central and peripheral nervous systems. Sural nerve biopsy shows multiple intra-axonal polyglucosan bodies (see Fig. 22.2), which in the appropriate clinical context, can confirm the diagnosis of APBD [188, 193]. Axillary skin biopsy may show polyglucosan bodies in the myoepithelial cells of apocrine glands, confirming the diagnosis as well [198]. Reduction of leukocyte glycogen branching enzyme activity is found mainly in Ashkenazi Jewish patients but may be demonstrated in non-Ashkenazi Jewish patients as well [184, 187].

Treatment, Course, and Prognosis

There is no specific treatment for APBD. Supportive therapy is the mainstay of treatment, geared toward symptom control. The disease usually progresses over a period of 1–21 years, eventually leading to death [188, 189, 192].

Other Multiple System Disorders

Other multiple system disorders that may have prominent lower and upper motor neuron signs include Hallervorden-Spatz disease (pantothenate kinase-associated neurodegeneration), Guamanian Parkinson-ALS, Creutzfeldt-Jakob disease, Huntington's disease, Pick's disease, and the Shy-Drager syndrome (multiple systems atrophy). Each, however, has distinctive clinical presentations that easily differentiate them from typical ALS.

Other Atypical Motor Neuron Syndromes

Motor Neuron Disease Associated with Electrical Injury

There are rare case reports of adults and children who develop a delayed upper and lower motor neuron syndrome after exposure to an electrical injury or lightning. Weakness begins in an upper extremity, usually at the site of trauma, and evolves into a diffuse motor neuron syndrome.

Etiology and Pathogenesis

The underlying mechanism of the electrical injury and its relationship to spinal cord damage, in particular damage to the anterior horn cells, is unclear. While pathologic changes in the central nervous system (CNS) of experimental animals, or individuals executed by electrocution, include petechial hemorrhages, swelling and dissolution of myelin sheaths and axons, neuronal ischemia, and death, similar findings are not seen in autopsies of patients with motor neuron disease associated with electrical injury [199]. Autopsy findings in one patient with motor neuron disease after an electrical injury revealed the classic changes found in ALS, including loss of anterior horn cells, cells in hypoglossal nuclei, and degeneration of the corticospinal tract. There was no evidence of vascular-mediated injury or mechanical distortion of the spinal cord [199].

Transient weakness and paraplegia that occur immediately or shortly after an electrical injury usually recover within a few hours to 4 days in most cases [199–203]. Permanent neurologic sequelae are usually seen when weakness develops days to years after the injury, as noted in one case series of 27 patients with spinal cord injury after an electrical accident [201]. This may reflect a group of patients with delayed anterior horn cell injury. The possible relationship of motor neuron disease to antecedent electrical injury is also described in various small case studies [204, 205]. One proposed mechanism for delayed spinal cord injury after an electrical injury includes vascular occlusion secondary to slow endothelial fibrosis and intimal thrombosis, which then leads to ischemia in the microvascular circulation. Another proposed mechanism involves injury to cellular DNA secondary to thermal, mechanical, or vascular insult leading to cell death [206]. To date, evidence supportive of a true causative relationship between electrical injury and the delayed development of motor neuron disease remains elusive. A systematic review of the literature supports a syndrome of nonprogressive spinal cord damage following electrical injury with lower and upper motor neuron components. The more severe the shock, the more likely affected individuals developed a nonprogressive motor syndrome. For the progressive and nonprogressive motor neuron syndromes, the median interval between electrical injury and disease onset was 2.25 years and 1 week, respectively. The relationship between electric injury and ALS was less certain, and the evidence reviewed did not support a causal relationship between ALS and electric shock [207].

Clinical Presentation

Electrical injuries usually occur from high voltage lines, household circuits, or lightning. Transient neurological deficits immediately after an electrical shock are well described, and recovery usually occurs within 4 days. If a persistent motor neuron syndrome occurs, it develops at variable time periods after the electrical injury. Weakness and atrophy usually begin in the extremity of the original site of injury, commonly the upper extremity. Weakness then progresses in an ALS-like fashion to the contralateral limb. Bulbar weakness and upper motor neuron signs develop later on [199, 201, 206–211]. Sensory symptoms can occur in the region of the electrical injury.

Treatment, Course, and Prognosis

The clinical course of the motor neuron disorder associated with electrical injury is similar to ALS, with death occurring within 30–36 months after initial disease presentation. There are no known specific treatments; care consists of supportive measures similar to those provided in ALS [199, 211].

Post-radiation Motor Neuron Syndrome

In 1948, Greenfield and Stark reported three patients who developed a progressive pure lower motor neuron syndrome in the lower extremities 3–5 months after receiving radiation therapy for testicular cancer, with a calculated tissue dose of 5,000–6,000 rad to the retroperitoneal and para-aortic region [212]. Since this report, there have been multiple case reports of a similar clinical syndrome occurring after ionizing radiation therapy for various tumors, including testicular tumors, pheochromocytomas, lymphoma, medulloblastomas, and papillary carcinomas of the kidney [213]. The term *post-radiation motor neuron syndrome* has been proposed. The syndrome consists of painless, flaccid weakness usually involving the lower extremities without sensory manifestations, pain, sphincter dysfunction, or long tract signs.

Etiology and Pathogenesis

The pathogenesis of delayed radiation injury to the spinal cord is not well defined. Furthermore, the primary site of pathology is debatable. Some evidence suggests that the disease process involves damage to the lumbosacral ventral nerve roots, while other evidence suggests anterior horn cell pathology. A single autopsy case demonstrated evidence of demyelination and axonal loss in sensory and motor roots, with chromatolytic changes in the lumbar anterior horn cells,

presumably due to nerve root involvement. No vascular changes were seen in the spinal cord [214].

The underlying process responsible for the motor nerve root or anterior horn cell damage is unclear. However, based on purported pathogenic mechanisms in delayed radiation myelopathy and encephalopathy, it is likely that a combination of factors is involved in post-radiation motor neuron syndrome. These include direct radiation-induced damage to glial cells and neurons and ischemic changes secondary to radiation-induced damage to vascular endothelial cells [214–216].

Clinical Presentation

The clinical syndrome is characterized by progressive weakness of the lower extremities, with marked atrophy and fasciculations that develops months to years after radiation therapy. Muscle stretch reflexes are depressed or absent in the lower extremities. Sphincter function and sensation are spared, and upper motor neuron signs are absent [217–227]. Interestingly, the lower extremities are preferentially involved, although radiation may have included the entire neuraxis. The weakness generally stabilizes after several months, although in some patients, weakness is progressive over several years. A delayed lower motor neuron bulbar palsy, consisting of dysarthria, dysphagia, and in some cases neck weakness, has also been reported following radiation therapy to the head and neck for various neoplasms [228].

Evaluation and Diagnosis

The diagnosis is based on a history of lower motor neuron weakness primarily involving the lower extremities, months to years following radiation exposure. The dose of radiation exposure in reported cases ranges from approximately 3,500 to 5,600 rad. CSF is usually normal, although there may be a mild elevation of CSF protein to approximately 50 mg/dl [216]. MRI and CT myelogram of the spine are normal. On EDX studies, nerve conduction studies show low amplitude CMAPs in the lower extremities, with intact SNAPs. On needle EMG, fibrillation potentials are often present in the lower extremities. Myokymic discharges may also be seen in lower extremity muscles. Long-duration, high-amplitude, and polyphasic MUAPs with reduced recruitment is present in both lower extremity muscles, sometimes asymmetrically. EDX testing of the upper extremities is normal in most cases, depending on the site of radiation [216–221]. It is important to exclude other causes of progressive lower extremity weakness, such as tumor recurrence (in cases of spinal cord tumor), ALS, and myopathies.

Treatment and Management

As is the case with most motor neuron disorders, there is no specific treatment for post-radiation motor neuron disease, other than supportive symptom management. Treatment with anticoagulation has been utilized in patients with delayed radiation-induced cerebral radionecrosis and myelopathy with some recovery of function. The presumed mechanism of action is anticoagulation-mediated arrest and reversal of small vessel endothelial injury; the fundamental pathology of radiation necrosis [229]. However, lack of vascular changes in previous autopsy reports of post-radiation-induced motor neuron disease suggests that its pathogenesis may differ from radiation-induced myelopathy or cerebral radiation necrosis [214, 216]. Therefore, treatment modalities used for cerebral radiation necrosis may not be as useful in radiation-induced motor neuron disease.

Course and Prognosis

The clinical course is slowly progressive, with symptoms usually confined to the region of the spinal cord exposed to the original radiation. Most patients stabilize after several months and usually survive for 15–20 years after the initial presentation, although the weakness can be quite severe and debilitating.

Paraneoplastic Motor Neuron Disease

Paraneoplastic disorders occur as a remote effect of cancer. Whether MND occurs as a paraneoplastic syndrome is controversial. The concept of paraneoplastic MND was introduced by Brain et al. in 1965, based on the description of 11 patients with cancer and MND [230]. They suggested that these patients differed from patients with classical ALS due to the prominence of lower motor neuron involvement and the relatively slow clinical course. Autopsy of two patients revealed loss of anterior horn cells, with upper motor neuron involvement observed in a single patient. Norris observed an unexpectedly high incidence of malignancy in a series of ALS patients (6 %) compared with the general population [231].

Since these original reports, many have questioned whether the association of cancer and MND is simply a coincidence of two relatively common diseases or if there is a true etiologic relationship between the two conditions. Several epidemiologic studies have failed to find an increased incidence of cancer in patients with ALS compared with the general population, although several small studies have reported a co-occurrence of cancer and MND, at frequencies higher than incidence expected in the general population [232–234].

Etiology and Pathogenesis

Evidence supportive of the existence of paraneoplastic MND includes the following: (1) the observation that MND may occur in association with cancer, (2) reports of neurologic symptom remission or stabilization following tumor treatment [235–237], (3) the detection of antibodies to neuronal

and tumor cell antigens in some patients with cancer and MND, and (4) reports of MND or lower motor neuron involvement in patients with other well-known paraneoplastic disorders associated with neuronal antigens [232, 238].

The proposed pathogenesis of paraneoplastic MND is an immune-mediated disease process, similar to the mechanism involved in other paraneoplastic syndromes. However, the particular antibody or antibodies responsible for lower motor neuron dysfunction has not been identified. The disorder appears to be associated with several autoantibodies, depending on the clinical manifestations and the type of cancer. Antibodies associated with a motor neuron syndrome in some patients with cancer include (1) anti-Hu antibodies with small cell lung cancer [239, 240], (2) anti-Yo antibodies reported in one patient with ovarian carcinoma [241], (3) increased M protein in patients with lymphoproliferative disorders [242], (4) antibodies to the ganglioside GD1b in patients with thyroid adenoma [243], and (5) anti-neuronal antibodies that react with the initial segment of axons and nodes of Ranvier in a patient with breast cancer [244].

Clinical Presentations

Paraneoplastic motor neuron syndromes can be roughly classified into the following:

1. Motor neuron syndrome as a component of paraneoplastic encephalomyelitis in association with anti-Hu antibodies. In 1992, Dalmau reported that 20 % of patients with anti-Hu antibody associated paraneoplastic encephalomyelitis and sensory neuronopathy also showed signs and symptoms of lower motor neuron involvement [239]. However, pure or predominant motor neuron involvement without encephalomyelitis is rarely reported. A predominant lower motor neuron syndrome with anti-Hu antibodies is described in one patient with small cell lung cancer and one patient with prostate cancer. The motor neuron syndrome can mimic typical ALS, and the onset of neurological symptoms often precedes the diagnosis of cancer by 4–10 months. The progression of neurological symptoms appears to be similar to typical ALS. Death occurs within 5–23 months after the onset of symptoms. The disorder responded poorly to any type of immune-modulatory therapy, and treatment of the associated cancer was non-beneficial to the neurological deficits [232, 239, 240].
2. Lower motor neuron syndrome associated with Hodgkin's and non-Hodgkin's lymphoma. A clinical syndrome characterized by subacute progressive, painless lower motor neuron weakness with minimal or absent sensory symptoms has been reported in association with lymphoma. The progression of neurological symptoms varies. In some patients, the clinical progression is slow and some demonstrate improvement or normalization of neurological deficits, independent of the underlying cancer course. In others, the disease is relentlessly progressive. Upper motor neuron signs eventually develop in most cases, with a clinical course similar to typical ALS [232, 241, 245–248].
3. Clinical syndrome resembling typical ALS with upper and lower motor neuron manifestations. This syndrome has been reported in association with a variety of tumors including non-small cell lung cancer, Hodgkin's lymphoma, ovarian cancer, uterine cancer, and breast cancer [230, 232, 235, 236, 241, 249]. The syndrome consists of progressive upper and lower motor neuron manifestations in a fashion resembling typical ALS, though progression tends to be slower than expected with ALS. Studies of patients with lymphoproliferative disorders and motor neuron disease demonstrate that the combination of upper and lower motor neuron signs occurs more often than the pure lower motor neuron syndrome alone, although a true etiologic relationship between the MND and cancer in this group of patients is difficult to prove [242, 246]. The onset of neurological deficits can follow or precede the diagnosis of cancer. Death from respiratory complications occurs within 18–30 months from the onset of neurological symptoms. The response to immune-modulatory treatments and to the treatment of the underlying cancer is poor.
4. A predominant upper motor neuron syndrome resembling primary lateral sclerosis in association with breast cancer. The clinical presentation is due to upper motor neuron dysfunction, with onset of the neurological syndrome preceding the diagnosis of breast cancer in most cases. The clinical course is often chronic progressive, but some patients also develop lower motor neuron signs and progress to typical ALS, following the expected clinical course [232, 250, 251]. Thus far, no associated antibodies have been identified with this syndrome.

Treatment, Course, and Prognosis

Despite several reports of improvement or stabilization of neurological symptoms following treatment of the underlying cancer, the long-term response of paraneoplastic MND to immune-modulatory therapy and treating the underlying cancer is generally poor based on large patient series [232]. The clinical course of paraneoplastic MND is variable and dependent on the particular clinical syndrome. In general, the clinical progression is slightly less rapid than in typical ALS.

Since the neurological features commonly precede the diagnosis of cancer in many patients, it may be reasonable to search for cancer in specific clinical settings. For example, Forsyth and Dalmau recommend that patients with pure upper motor neuron syndromes resembling primary lateral sclerosis undergo screening mammography to search for breast carcinoma [232]. Patients with motor neuron involvement and encephalopathy should be screened for anti-Hu antibodies and small cell lung cancer. Patients with an atypical motor neuron syndrome and monoclonal protein on serum immunofixation or immunoelectrophoresis, elevated

CSF protein, or other laboratory evidence suggestive of a lymphoproliferative disorder should undergo skeletal survey and bone marrow biopsy [232, 242, 245, 246, 252, 253].

Motor Neuron Disease Associated with Various Toxins and Drugs

A possible relationship between environmental toxins, in particular heavy metals, and MND has been a topic of interest for years [254]. However, definitive evidence of a causal relationship is scarce. A lead-induced motor neuron syndrome was described by Boothby et al. in 1974. They reported a 50-year-old male battery worker with progressive weakness, muscle wasting, fasciculations, and increased muscle stretch reflexes, especially in the distal upper extremities, with increased urine lead output. EDX studies showed normal NCSs, with needle EMG evidence of denervation and reinnervation in the hand muscles and thighs [255]. Systemic symptoms were present, including irritability and anemia, with basophilic stippling in the red blood cells, characteristic of lead intoxication. His neurological deficits gradually improved after treatment with penicillamine. However, there have been no subsequent reports that support the relationship between chronic lead exposure and typical MND with upper and lower motor neuron signs. Chronic lead exposure, as seen with battery workers and car radiator repairers, may result in a progressive lower motor neuron syndrome that most prominently affects the wrist and finger extensors and intrinsic hand muscles. Constitutional symptoms, such as weight loss, abdominal pain, constipation, fatigue, mood changes, and microcytic anemia with basophilic stippling, are common [255, 256]. The diagnosis is made by elevated lead levels in urine.

A possible relationship between heavy metals and Guamanian Parkinson-ALS syndrome has been postulated. There is one report of elevated aluminum levels in the CNS tissue of a patient with Guamanian neurodegenerative disease, but subsequent studies failed to demonstrate any significant elevation in serum and urine heavy metal levels in patients with Guamanian Parkinson-ALS compared with normal control groups [257].

Drugs including *dapsone* and *nitrofurantoin* may rarely result in a lower motor neuron syndrome that generally reverses following drug withdrawal.

Motor Neuron Syndrome Associated with Hyperparathyroidism

An association between hyperparathyroidism and muscle weakness was first reported over 50 years ago [258]. Primary hyperparathyroidism may be associated with neuromuscular symptoms including symmetric proximal weakness in the lower extremities, hyperactive reflexes, spasticity, hoarseness of voice, and dysphagia. These symptoms are usually accompanied by mild sensory symptoms and abnormal cognition which helps to distinguish it from typical ALS [258]. Although the neurological complications of primary hyperparathyroidism are common and relatively minor, in a few cases, these may be severe enough to imply an untreatable neurological disorder [259]. However, epidemiological studies have failed to support a definite causal relationship between hyperparathyroidism and MND, despite several case reports suggesting an association with primary hyperparathyroidism. A few patients reportedly showed improvement of neuromuscular symptoms after parathyroid adenoma resection [260–264].

In 1974, Patten et al. reported an ALS-like syndrome in five patients with primary hyperparathyroidism. Two of these patients had complete functional recovery of their clinical syndrome after undergoing parathyroid adenoma resection [265]. However on subsequent review, one of these patients had normal MUAP morphology on needle EMG, and the other had large MUAPs without abnormal spontaneous activity, making the diagnosis of MND unlikely in these patients [258, 265].

In 1998, Jackson et al. reported five patients with ALS and primary hyperparathyroidism, among approximately 600 ALS patients seen in their neuromuscular clinic over a period of 6 years [258]. Patients with a diagnosis of ALS were screened with a serum calcium and parathyroid hormone level and were also questioned if they had ever been treated for hypercalcemia or hyperparathyroidism. All patients had muscle weakness, atrophy, and fasciculations. In four patients, the symptoms began in the lower extremities. One patient presented with bulbar weakness. Upper motor neuron signs including spastic tone and hyperactive reflexes were noted in all five patients. In three patients, the hyperparathyroidism was discovered during their evaluation for ALS, and in two patients the diagnosis of hyperparathyroidism preceded the diagnosis of ALS. Needle EMG examination revealed widespread denervation in all patients. All of the patients died within 2–3 years of their parathyroid adenoma resection, secondary to MND progression. This study called into question the causal relationship between MND and hyperparathyroidism, since removal of the parathyroid adenoma did not alter the progression of the neurologic illness. Nonetheless, screening tests for hyperparathyroidism may be considered in patients with MND, as these are cost-effective and the potential for reversibility exists following tumor resection.

Retrovirus-Associated Motor Neuron Disorders

Infection with human immunodeficiency virus (HIV) is associated with a variety of neuromuscular disorders (see Chap. 38). HIV infection may cause a progressive vacuolar myelopathy associated with dementia and an axonal polyradiculopathy in

patients with AIDS. Experimental studies in mice show that retroviruses can induce a lower motor neuron syndrome, implying a causal relationship between retroviruses and MND pathogenesis [266–270]. There are rare reports of patients with HIV infection and classic ALS, or a clinical syndrome resembling primary lateral sclerosis or progressive spinal muscular atrophy, without other explainable causes [271–274]. Bibrachial amyotrophic diplegia or flail arm syndrome has been reported as a neuromuscular manifestation of HIV infection [275, 276].

The human T-cell lymphotropic virus type 1 (HTLV-1) is a well-known cause of spastic paraparesis in endemic areas, termed tropical spastic paraparesis or HTLV-1-associated myelopathy (HAM). Bladder dysfunction and mild sensory symptoms commonly accompany the lower extremity weakness. A motor neuron syndrome mimicking ALS has been described in a series of patients with HTLV-1 infection [277]. Spastic paraparesis or features of typical ALS associated with minor sensory findings or bladder dysfunction should prompt a screen for HTLV-1 antibodies, particularly in endemic areas.

Post-poliomyelitis Syndrome

Post-poliomyelitis syndrome is characterized by slowly progressive muscle weakness that occurs decades after recovery from acute paralytic poliomyelitis (see Chap. 19). The clinical presentation includes muscle pain, fatigue, and weakness and atrophy usually in previously affected limb(s), often accompanied by fasciculations [278]. Fatigue is usually the most prominent initial manifestation. Weakness of bulbar and respiratory muscles may also occur. Upper motor neurons signs are not seen [279, 280]. The clinical course is very slowly progressive.

The possible mechanisms responsible for the clinical manifestations of post-poliomyelitis syndrome include death of residual functional motor neurons as part of the normal aging process, premature aging of anterior horn cells previously infected by the polio virus, loss of the number of muscle fibers per motor unit with aging, and a delayed immune-mediated disease process [278]. The diagnosis is made after excluding other possible etiologies such as radiculopathy, neuromuscular junction disorders, and myopathy.

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Dorsal Root Ganglion Disorders

23

Ales Hlubocky and Benn E. Smith

Abbreviations

CANOMAD	Paraproteinemia chronic ataxic neuropathy ophthalmoplegia IgM paraprotein cold agglutinins disialosyl antibodies
CDDP	*cis*-Diamminedichloroplatinum
CISP	Chronic immune sensory polyradiculopathy
CSS	Central sensory syndrome
HSAN	Hereditary sensory and autonomic neuropathy
MISP	Malignant inflammatory sensory polyganglionopathy
NISP	Nonmalignant inflammatory sensory polyganglionopathy
POLG	Polymerase gamma
SCLC	Small cell lung carcinoma

Introduction

Historical Perspective

The term "tabes dorsalis" (translated as "wasting of the back") is said to have first used by Hippocrates to describe the unsteady walk of those give to venereal excess [1]. In the nineteenth century, it was Stanley [2] who made the correlation between incoordination and posterior column disease [2], although the distinction of cases of incoordination without paraplegia from those with paraplegia is ascribed to Todd [3], who used two postmortem studies to document the hypothesis that incoordination alone can arise from posterior column disease with two autopsy cases [3]. In 1858 Duchenne used the term l'ataxie locomotrice (locomotor ataxia) to describe patients with progressive incoordination and preserved muscular strength [4]. Some 30 years later, Gowers commented that in his day syphilitic tabes dorsalis was a common disorder resulting from disease of either the posterior columns or the peripheral sensory nerves or both [5, 6].

As Treponema pallidum infection and its late neurologic complications faded from common medical practice in the early twentieth century, so did patients with isolated sensory impairment. Although a case report of predominantly sensory neuropathy in a patient with carcinoma was made in 1934 [7], primary degeneration of dorsal root ganglion neurons in humans was first described by Denny-Brown in 1948 [8]. He reported two cases of "primary sensory neuropathy" associated with carcinoma of the lung, which were pathologically distinct from tabes dorsalis. In these cases there appeared to be a primary loss of dorsal root ganglion neurons with secondary loss of axons in the posterior roots, posterior columns, and peripheral nerves. This contrasted with the pathology of tabes where severe loss of myelinated fibers in the posterior columns was accompanied by relative preservation of dorsal root ganglion neuron cell bodies [8, 9]. The primary disease process in tabes is probably inflammatory and occurs at the level of the spinal root [9]. Diabetic and alcoholic pseudotabes or pure sensory neuropathies were also recognized by Denny-Brown who identified the primary pathologic process in these disorders to be in peripheral nerve sensory fibers [8].

Pure sensory neuronopathy associated with malignancy was subsequently reported by many authors [8, 10–19]. The syndrome was most commonly associated with lung cancer, although a variety of other malignancies were included in case reports. Wilkinson and colleagues were the first to report that this syndrome might be antibody-mediated [18, 20]. Non-paraneoplastic sensory neuronopathy was recognized

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by Wartenberg [21] who reviewed the reports of Martin [22] and Barré [23]. These cases resembled a pure sensory form of Guillain-Barré syndrome. Subsequently, there were a series of reports [24–27] describing an indolent progressive or subacute sensory syndrome which was not associated with malignancy but had many clinical features similar to the cases described by Denny-Brown [8]. Malinow and colleagues [28] first described an association between sensory neuronopathy and Sjögren syndrome which has subsequently been observed by others [29–31].

Metabolic causes for sensory neuronopathy were identified during the search for essential nutrients. Wintrobe and colleagues [32–34] found severe degeneration of dorsal root ganglion neurons in swine fed diets deficient in vitamin B6 and pantothenic acid. More recently, it has been demonstrated that excess vitamin B6 may produce a pure sensory syndrome in humans [35] and in rats [36]. In both cases this appears to involve degeneration of peripheral and central dorsal root ganglion axons with relative sparing of the cell bodies. Degeneration of dorsal roots and posterior columns in vitamin E-deficient rats was reported in the 1940s and 1950s [37–41]. The dorsal root ganglion cell bodies were almost completely spared. This was similar to vitamin E-deficient patients with chronic malabsorption [42] or a selective defect of vitamin E absorption [43, 44].

Although many toxins produce predominantly sensory symptoms, pure sensory ganglionopathy or ganglioneuropathy is rarely seen. Cisplatin causes a pure sensory syndrome which was first described 20 years ago [45, 46]. There is evidence to suggest that the dorsal root ganglion neuron is the primary target for the neurotoxicity of this drug [47, 48]. Other toxins which have a predilection for causing pure sensory neuropathy or ganglionopathy include alkyl mercury compounds and organophosphates [49].

Development of the Dorsal Root Ganglion

Dorsal root ganglia develop from the neural crest during early embryogenesis. Both neurons and satellite cells originate from the neural crest. Other cells derived from the neural crest include Schwann cells, some cranial sensory ganglion neurons, sympathetic and enteric autonomic neurons and glia, adrenal chromaffin cells, connective tissues of the head and neck, the facial skeleton, melanocytes, thyroid C cells, and carotid body type I cells [50]. The origin of the perineurial sheath cells of the ganglion is still controversial. They are probably derived from mesodermal fibroblasts [51, 52]. Soon after the neural crest separates from the neural tube, it organizes into segmental collections of cells. The work of Le Douarin and colleagues demonstrated that neural crest cells differentiate into specific lineages (neuron, satellite cell, melanocyte, etc.) at the time of ganglion formation [50]. The precursors of Schwann cells, melanocytes, and adrenal chromaffin cells migrate out of the ganglion. The remaining cells terminally differentiate into neurons and satellite cells. The final neuron cell division occurs shortly after the ganglion has formed.

Following terminal cell division, the neurons begin a complex process of differentiation. Initially the cells are bipolar. As axonal growth begins, one process enters the primordium of the root; the other enters the origin of the segmental nerve. As the newly formed axons extend, the cell body changes shape so that the axons coalesce into the final mature pseudounipolar configuration. The axons grow toward targets in the periphery or spinal cord as Schwann cells migrate along the growing axons. During axonal growth, the Schwann cells surround bundles of axons and segregate them into single axons that are destined to be myelinated or into small bundles destined to be nonmyelinated axons [53]. Within the ganglion, the neuron cell bodies are ensheathed by satellite cells which share many characteristics with Schwann cells.

Anatomy of the Dorsal Root Ganglion

The dorsal root ganglia lie in the intervertebral foramina at the point where the dorsal and ventral roots converge (Fig. 23.1a). The fascicles of sensory and motor fibers come together, but individual axons do not commingle until after they leave the ganglion in the segmental nerve. Most of the intermixing of motor and sensory axons to form mixed peripheral nerves occurs as the fibers pass through the plexus. Within the ganglion, cells are clustered around the fascicles of sensory fibers (Fig. 23.1b).

The ganglion appears grossly as a thickening of the perineurial sheath where the roots meet. The sheath of the ganglion is continuous with the sheath of the roots and segmental nerves. The perineurium and epineurium of the nerve are also continuous with the dura as the roots enter the spinal canal, forming a continuous sheath from the peripheral nerve, over the ganglion and roots to the dura. This tough sheath explains why traction of the peripheral nerve usually results in avulsion of the roots from the cord rather than a tear in the plexus or nerve. The perineurial sheath around the ganglion has the same cellular composition as the perineurium of nerve. It is composed of 10–20 layers of flat cells which are interleaved. Cells are attached to their neighbors with frequent tight junctions. The perineurium is one of the barriers to diffusion which constitutes the blood-nerve barrier. The blood supply to the ganglion comes from perineurial arterioles derived from segmental arteries. Although detailed studies of ganglion vascular supply have not been completed, blood flow has been found to be intermediate between that of peripheral nerve and brain [54, 55].

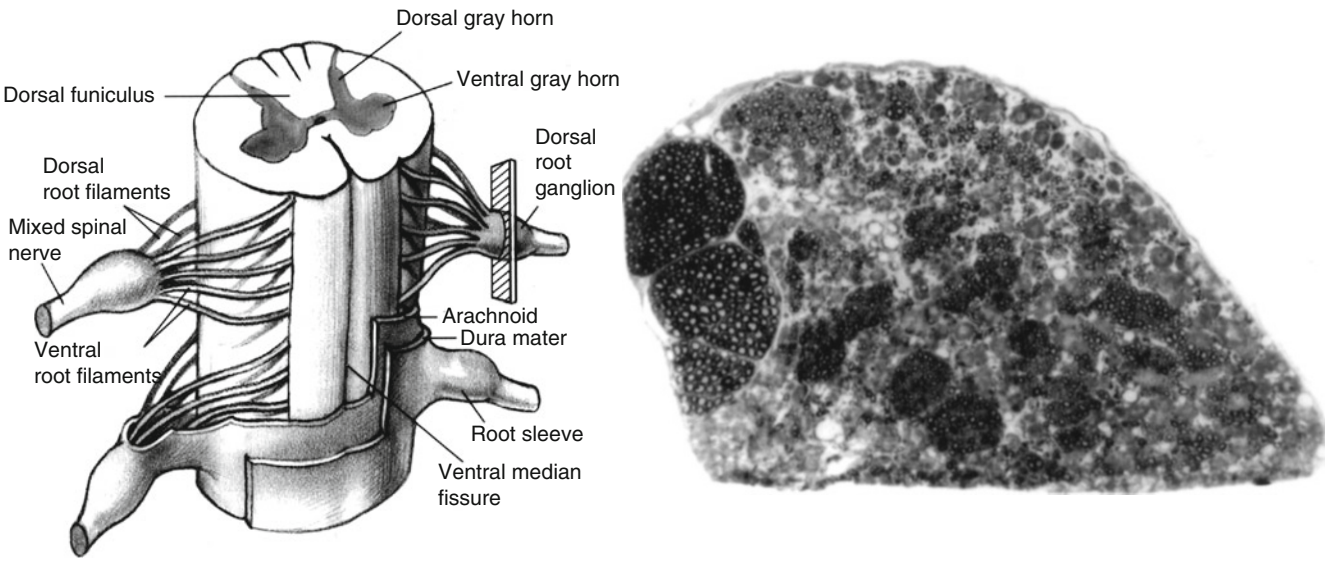

Fig 23.1 DRG anatomy

Perforating arterioles leave the epineurial vessels and pass through the perineurial sheath. The capillaries within the ganglion are fenestrated which result in a low barrier to diffusion between blood and endoneurium of the ganglion. This is different from the peripheral nerve trunk where the capillary endothelial cells form a significant diffusion barrier and are joined by tight junctions [56]. Dorsal root ganglion neurons are therefore exposed to toxins or drugs present in serum. This may be one of the factors that render sensory neurons prone to toxic injury.

The microanatomy of the ganglion is relatively simple. Clusters of ganglion cells are composed of neurons that vary from 10 to 100 μm in diameter. There is a direct relationship between neuron cell body size and size of nerve fibers leaving the cell [57]. The initial single axon leaving the cell is often coiled in a complex glomerulus-like shape immediately adjacent to the cell body. The central and distal axonal processes are formed immediately after the glomerulus [58]. The work of Coggeshall has shown that each ganglion cell may give rise to several peripheral and several central axons presumably due to branching soon after axons leave the ganglion [59, 60].

There is a continuous spectrum of dorsal root ganglion neuron diameters. There are, however, two distinct classes of cells by light and electron microscopy: large clear cells and small dark cells. Cells can now be classified into many different types depending on their surface growth factor receptors (e.g., Trk A, B, and C) or the class of neurotransmitter predominating in the cell (e.g., calcitonin gene-related peptide, substance P). Since these markers associate with cells of different sizes, they may reflect different functional specializations. The direct relationship between size, sensory modality, growth factor receptor, and neurotransmitter has, however, not been established.

A sheath of 4–6 flattened satellite cells (or satellite glial cells) encapsulates each neuron cell body. These cells are of the same lineage as Schwann cells. The satellite cell is, in turn, covered by a basal lamina which is continuous with the basal lamina of the Schwann cells that ensheath or myelinate the axon. Recent studies of neuron-satellite cell interactions have demonstrated that ATP released from the somata of dorsal root ganglion neurons activates satellite cells. These in turn exert complex excitatory and inhibitory modulation of neuronal activity under normal and injurious conditions [61].

Neurochemistry of the Dorsal Root Ganglion

With the exception of some cranial nerves, all somatic and visceral input makes its way to the central nervous system by way of primary afferents that initially synapse in discrete regions of the dorsal gray horn of the spinal cord. Several lines of evidence suggest that these afferents communicate with the central nervous system by excitatory neurotransmitters; morphologic studies of first-order synapses demonstrate synaptic vesicles, end plate thickening, and synaptic clefts, while microneurophysiologic techniques provide evidence of monosynaptic EPSPs (but not monosynaptic IPSPs) and synaptic delay [62]. Painstaking pharmacologic studies have demonstrated a number of substances that fulfill strict criteria for candidate neurotransmitters in dorsal root ganglion cells. These molecules must be (1) identified in the afferent terminals of the primary afferent, (2) present in the fraction collected with depolarization of the afferents in question, (3) able to mimic the physiologic effects of depolarization when applied exogenously, and (4) responsible for the same

physiologic response in the postsynaptic neuron whether released by physiologic stimuli or with exogenous application [62].

The ever-expanding list of substances found in dorsal root ganglion cells which appear to meet the above criteria began with the excitatory amino acids glutamate and aspartame [63] and has come to include a host of neuropeptides such as substance P [64], somatostatin [65], VIP [65], cholecystokinin [66], angiotensin II [67], bombesin [68], CGRP [68, 69], NGF [70], and multiple neurotrophins [71–73].

Neurophysiology of the Dorsal Root Ganglion

Basic Neurophysiology

Sensory information is conveyed from the peripheral sensory receptor via the dorsal root ganglion cell, through the peripheral and then the central axon, to the dorsal gray matter of the spinal cord or to higher second-order sensory neurons in the cuneate and gracile nuclei. The observation that some dorsal root ganglion cell bodies have low thresholds to electrical excitation suggests that this property may be required to insure the reliable propagation of impulses past the pseudounipolar axon junction and into the spinal cord [74]. The primary afferents that synapse segmentally in the dorsal gray relay single impulses and trains of spikes from their respective receptive fields when particular stimuli occur that mediate their excitation. Although the second-order sensory relay neurons may be driven by dorsal root ganglion inputs from a variety of different sensory modalities, the primary sensory nerve cells are thought to be activated most effectively by a single modality [75]. These include *cutaneous mechanoreceptors* [76] which distribute their large Aβ axons to Rexed laminae III, IV, V, and the dorsal portion of VI; *cutaneous nociceptors* [77] which relay information via small-diameter Aδ fibers to laminae I, II, and V; *cutaneous thermoreceptors* [78] which extend processes to the dorsal horn via small-diameter Aδ and C fibers but whose specific patterns of termination have not been well established; *muscle receptors* [79] which convey proprioceptive data to the cord from primary muscle spindle endings (Aα afferent fibers) to laminae VI and VII, secondary muscle spindle endings (Aβ afferent fibers) to laminae IV, V, VI, VII, and IX, and Golgi tendon organs (Aα afferent fibers) to laminae V, VI, and VII; and *visceral receptors* [80] which terminate in laminae I and V.

Given the complexities of neural circuitry and the wide array of dorsal root ganglion afferents which impinge on second-order sensory relay neurons in the dorsal horn, it comes as no surprise that sensory coding mechanisms involve a large range of variables, including modality specificity, spatial factors, and a range of temporal factors including frequency coding, temporal transformation, impulse interval patterning, and intrinsic as well as extrinsic modulatory influences [81].

Clinical Neurophysiology

While the intricacies of recording individual dorsal root ganglion cell responses to a variety of stimuli are largely the focus of bench physiologists, the tools of clinical neurophysiology provide the clinician with a useful arsenal of methods to study the dorsal root ganglion cell with both its peripheral sensory axon and its central sensory axon. Sensory nerve conduction studies assess the integrity of the peripheral sensory axon and the dorsal root ganglion cell body but often are unaffected by disease proximal to the dorsal root ganglion cell body level [82]. Lesions at or distal to the dorsal root ganglion cell body characteristically result in reduction or loss of amplitude in the sensory nerve action potential [83].

Quantitative sensory testing, on the other hand, is a set of psychophysiologic methods which assess the entire sensory system from the peripheral receptor to the postcentral gyrus [84]. Disease at any level can result in elevation of sensory detection thresholds and, if sufficiently severe, insensitivity. Reliable methods for determining vibratory, cold, and heat pain/visual analog pain scale threshold values have been described and used extensively in both research [85–87] and clinical applications [71, 88]. It must be remembered that while sensory nerve conduction studies can be performed without the cooperation of the patient, and in practiced hands are not liable to surreptitious falsification by the test subject, because quantitative sensory testing depends on subjective responses of what the individual perceives, this type of testing cannot overcome a bias toward abnormality in test subjects.

The central axon which projects from the dorsal root ganglion cell body to relay nuclei in the medulla oblongata can also be assessed by electrophysiologic means. In addition to quantitative sensory testing (see above), somatosensory evoked potentials (SEPs) can interrogate the whole of the sensory pathway from periphery to cerebral cortex. SEPs are the electrical responses of the nervous system, from the peripheral nerve trunk to the parietal cortex, to specific, and typically electrical, stimuli. The commonly used SEP techniques involve stimulation of a mixed or cutaneous peripheral nerve with recording over the nerve, plexus, spine, and scalp, most reliably with signal averaging of several hundred responses so as to extract reproducible recordings of well-defined responses between 1 and 50 uV in amplitude from an electrically noisy background [89]. The combination of an abnormal SEP suggesting a spinal cord localization combined and a normal peripheral sensory nerve action potential raises the possibility of disease affecting the central sensory axon of the dorsal root ganglion cell (central sensory syndrome, see below).

Disorders

Malignant Inflammatory Sensory Polyganglionopathy

Introduction

The 1948 report of Denny-Brown is now widely acknowledged to the first recognized account of two patients with profound sensory deficits and, albeit only by postmortem examination, small cell carcinoma of the lung; the postulated mechanism for the neurologic syndrome was a metabolic abnormality produced by the malignant cells [8]. A survey of the literature shows that there have been many clearly described such cases of malignant inflammatory sensory polyganglionopathy (MISP) [7, 8, 10–17, 19, 90–116]. The terms "malignant" and "nonmalignant inflammatory sensory polyganglionopathy" are used because they are descriptive and parallel the terms in place for disease of roots (polyradiculoneuropathy) and nerves (polyneuropathy) [117]. Other synonyms used in the literature include subacute sensory neuronopathy (SSN) or paraneoplastic SSN [118–130].

Etiology and Pathogenesis

A variety of neoplasms have been associated with MISP, the most common being small cell ("oat cell") lung carcinoma (SCLC) (see Table 23.1). Virtually every patient with MISP and primary lung carcinoma smoked cigarettes or used other tobacco products. In the majority of cases (123/165 patients), neurological symptoms preceded discovery of carcinoma by several months (median 8, range 0.5–62 months) [7, 8, 11, 13, 14, 16, 17, 19, 90–110, 116, 131], although in some cases (35/165 patients) the reverse was true (median 6, range 0.5–36 months) [13, 19, 90–93, 97, 99, 111, 113, 115]. In 6/165 patients neurological symptoms and diagnosis of cancer were simultaneous [15].

Lucchinetti and colleagues found that SCLC was the most common cancer associated with ANNA-1 (anti-Hu) positivity in their series of 162 patients with paraneoplastic neurologic disease [132]. Among their 162 patients, SCLC was not found in at initial evaluation in 56 %. After discovery of the ANNA-1 seropositivity, more aggressive evaluation sometimes led to discovery of a previously occult neoplasm. MRI of the chest demonstrated a definite mass in 10 of 45 individuals with equivocal findings by conventional radiography or CT scanning. In seven subjects for whom imaging failed to disclose a tumor, SCLC was discovered by bronchoscopy, mediastinoscopy, or thoracotomy. Among 21 individuals with a nondiagnostic bronchoscopy, SCLC was documented by either mediastinoscopy or thoracotomy. Seven ANNA-1-positive patients with no direct evidence of SCLC in life were found to have the malignancy at autopsy, while another three individuals lacked evidence of the tumor even at autopsy [132]. Importantly, these workers at Mayo Clinic found an unrelated primary malignancy coexisting with SCLC in 13 % of patients with ANNA-1 seropositivity (Table 23.2), six of which proved to be renal cell carcinoma and in another four a second primary lung neoplasm [132].

Although pathogenic antibodies have been described in a number of paraneoplastic neuromuscular disorders including Lambert-Eaton myasthenic syndrome (voltage-gated calcium channel antibodies) and myasthenia gravis (acetylcholine receptor antibodies), a clear pathogenic role for antibodies in MISP (antineuronal nuclear or anti-Hu antibodies) has not been established; rather, these antibodies can be thought of as helpful markers for MISP and the tumor which is most often associated with it (small cell carcinoma of the lung) [133]. There is increasing evidence that cytotoxic T lymphocytes are involved in MISP, both in dorsal root ganglia as well as affected central nervous system structures [134–136].

Table 23.1 Tumor type or location in 159 MISP patients

	Number (% of total)
Lung	136 (85.5)
Small cell/"oat cell" carcinoma	128 (80.5)
Anaplastic	3 (1.9)
Bronchial	3 (1.9)
Squamous cell carcinoma	2 (1.3)
Hodgkin disease	5 (3.1)
Prostate carcinoma	3 (1.9)
Breast	2 (1.3)
Ovary	1 (0.6)
Uterus	1 (0.6)
Adrenal carcinoma	1 (0.6)
Chondromyxosarcoma	1 (0.6)
Colon (adenocarcinoma)	1 (0.6)
Epidermoid carcinoma	1 (0.6)
Esophagus (squamous cell carcinoma)	1 (0.6)
Gastric carcinoma	1 (0.6)
Mediastinal carcinoma	1 (0.6)
Neuroblastoma	1 (0.6)
Reticulum cell sarcoma	1 (0.6)
Synovioma	1 (0.6)
Testicular seminoma	1 (0.6)
Total	159 (100)

Table 23.2 Tumors coexisting with SCLC in ANNA-1-positive patients (After Lucchinetti et al. [132])

Renal cell carcinoma	6
Non-SCLC lung carcinoma	4
Prostate carcinoma	3
Breast carcinoma	3
Bladder carcinoma	1
Ovarian carcinoma	1
Choroid papilloma	1
Cervical carcinoma	1
Total patients with coexisting tumor(s)[a]	17 (13 %)

[a]Three patients had more than one coexisting tumor

Clinical Presentation

There are three major presentations of MISP – an ataxic syndrome, a hyperalgesic-ataxic syndrome, and an ataxic or hyperalgesic-ataxic syndrome with prominent gastrointestinal dysmotility, the latter not thought to occur often as part of nonmalignant inflammatory sensory polyganglionopathy (NISP). Although the hyperalgesic-ataxic syndrome appears to be the most frequently encountered presentation of MISP to neurologists, the ataxic or hyperalgesic-ataxic variety with gastrointestinal manifestations may be more common than realized. Because the syndrome can present as isolated intestinal pseudo-obstruction with subclinical neurologic deficits in the limbs, these individuals may present to non-neurologist physicians such as internists and gastroenterologists who elect not to pursue neurologic consultation. In addition to sensory ataxia with or without hyperalgesia or gastrointestinal dysmotility, MISP patients on occasion present with variable degrees of flaccid weakness and atrophy, generalized dysautonomia (including tonic pupils, orthostatic hypotension, and sudomotor dysfunction), cerebellar ataxia, brainstem signs (including nystagmus, dysphagia, and cranial nerve palsies), myelopathy, and limbic encephalomyelopathy [90].

The primary clinical manifestations of MISP appear to reflect the subpopulations of neurons involved, whether large-diameter dorsal root ganglion neurons (resulting in ataxia as well as vibratory and proprioceptive sensory loss), small-diameter dorsal root ganglion cells (neurons which convey pain and temperature sensation), or gastrointestinal myenteric plexus neurons (giving rise to severe constipation and other manifestations of alimentary dysmotility). Denny-Brown described MISP patients presenting with ataxia [8], as did Dodgson [10], Heathfield [11], Henson [12, 98], and others [13, 16, 18, 19, 90, 92, 93, 101, 137]. MISP patients with a combination of hyperalgesia and ataxia were reported by Weber [7], Denny-Brown [8], Henson [12], Smith [14], and others [15, 17, 19, 113, 114, 131, 90, 93, 103]. MISP patients with the ataxic or hyperalgesic-ataxic syndrome and gastrointestinal dysmotility were discussed by Lhermitte et al. [111], Chalk et al. [93], and Dalmau et al. [90].

Diagnosis

Symptoms

In the literature reports of the ataxic variety, so-called positive sensory symptoms such as "numbness" and a "pins and needles" sensation were among the most common presenting symptoms. Other presenting symptoms included gait unsteadiness and diminished fine motor control; pain was never a prominent initial symptom. In patients with the ataxic-hyperalgesic-type aching in the limbs, shooting limb pains, "burning" sensations, and painful paresthesia were frequent initial symptoms, usually followed later in the course of disease by gait unsteadiness, incoordination, and loss of manual dexterity. Patients with ataxic or ataxic-hyperalgesic MISP with gastrointestinal dysmotility typically sought medical attention with abdominal complaints, including belly pain, nausea, vomiting, and severe constipation; limb symptoms such as pain, paresthesia, and incoordination were often absent and seldom prominent. The patient reported by Lhermitte et al. reported at first of nausea, dysphagia, and rectal pain, followed shortly thereafter by acute intestinal obstruction (no cause being discovered at laparotomy) and pain in all four limbs; on physical examination he was noted to have generalized wasting of muscles, loss of deep tendon reflexes, and distal sensory loss [111]. Some individuals with this third type of MISP complained only of gastrointestinal symptoms, although subclinical sensory loss and hyporeflexia were detected on examination.

Signs

On neurologic examination, the majority of MISP patients demonstrated normal strength or perhaps mild weakness, as well as greater or lesser degrees of both distal and proximal diminished sensation (particularly vibration and joint position sense) which was not uncommonly asymmetric, and deep tendon hypo- or areflexia – frequently most pronounced in the lower extremities. In profoundly affected individuals the posterior column modality sensory loss was often so marked as to lead to pseudoathetosis. Other deficits, which were noted most often in the ataxic and ataxic-hyperalgesic groups, suggested disease beyond the primary sensory neuron. In the series of Horwich et al. 1/5 of patients had relatively isolated sensory loss and ataxia, while 3/5 demonstrated eye movement abnormalities (including nystagmus in 3/5 and gaze palsy 1/5), 3/5 showed some level of weakness (1/5 moderate proximal weakness and 2/5 mild either proximal or diffuse weakness), and dementia and confusion were each reported in 1/5 [19]. Among the patients of Anderson et al. 8/12 patients were brought to medical attention with sensory polyganglionopathy as their "main clinical syndrome," although other examination abnormalities in these seven included mild, diffuse, or patchy weakness, sensorineural deafness, cerebellar ataxia, urinary retention, and a unilateral extensor plantar response [138]. In the other 4/12 patients, the "main clinical syndromes" included MISP with either autonomic failure (not further specified) or lower motor neuron weakness; one of these patients presented with MISP, autonomic failure, encephalopathy, cerebellar ataxia, and diffuse weakness [138]. Chalk et al. reported cerebellar dysfunction in 4/26, encephalopathy in 2/26, and other CNS abnormalities in 7/26 of their patients with MISP [93]. Patients in the series of Dalmau et al. [90] were identified by presence of the antineuronal nuclear antibody (anti-Hu); they observed asymmetric sensory deficits as well as common involvement of the face and trunk. Although brainstem signs were recorded in 32 % of the patients of Dalmau et al. all patients who came to autopsy were found to have brainstem abnormalities [90].

Laboratory Tests

Normal to moderately elevated CSF protein values were seen in most MISP patients. Of the five patients reported by Horwich et al. the mean CSF protein level was 63 mg/dl (range 12–120) [19]. In Anderson's series the mean concentration in 11 patients was 127 mg/dl (range 36–315) [138]. CSF pleocytosis was not a typical finding in this population. In the series of Horwich et al. [19], the CSF nucleated cell count was "usually normal," while in Anderson's patients only 2/10 had abnormal nucleated cell counts at 62 and 105 cells/mm^3 [138]. In the 26 patients in the series of Chalk et al. 18 had CSF examinations; of these, 13 had elevated protein levels (mean 104 mg/dl, range 48–230); one subject has an increased protein value accompanied by mild lymphocytic pleocytosis (protein 90 mg/dl; 8.0 lymphocytes/uL) [93]. Among these 26 patients, no individual had malignant cells by cytologic examination [93].

As early as 1965, Croft et al. reported four patients with MISP associated with small cell carcinoma of the lung ("oat cell" carcinoma) with complement-fixing antineuronal antibodies which reacted against whole brain [18]. Using a fluorescent antibody technique later that year, Wilkinson and Zeromski confirmed antineuronal antibodies in these same four patients [20]. It has more recently been determined that these antineuronal antibodies in MISP patients react specifically with the nuclei of neurons in the central and peripheral nervous systems but not with non-neuronal nuclei [131, 138, 139]. Antineuronal nuclear antibodies type 1 (also called anti-Hu antibodies) demonstrate specificity for a number of neuronal nucleoprotein antigens between 35 and 40 kD in molecular weight [131]. In reviewing the case records of 162 sequential ANNA-1 positive adult patients with symptoms and signs suggestive of a paraneoplastic disorder without any other plausible explanation (such a metastasis, metabolic, vascular, or iatrogenic process), Lucchinetti and co-workers found 103 with a pure or predominant sensory syndrome and/or gastrointestinal dysmotility [132]; interestingly, most of these patients were not known to have cancer at the time of the serologic testing, and in one-fifth of the cases, the seropositivity for ANNA-1 was an incidental finding. Lennon et al. using an indirect immunofluorescence assay, described immunoglobulin G antibodies reactive with neurons of the myenteric and submucosal plexuses in the gastrointestinal tracts of 4/5 patients with severe gastrointestinal dysmotility and small cell lung carcinoma, some of whom had evidence of peripheral neuropathy [140]; in all four patients symptoms of intestinal pseudo-obstruction preceded diagnosis of small cell carcinoma by months or years (mean 13, range 4–28 months).

Other serologic markers sometimes seen in specific connective tissue disorders, such as antinuclear antibodies (directed toward non-neuronal nuclei), antibodies to extractable nuclear antigens, rheumatoid factor, and antineutrophil cytoplasmic antibodies, are not typically found in MISP patients. Neither antisulfatide antibodies – reported to occur in some cases of idiopathic axonal sensory neuropathy – nor antibodies against myelin-associated glycoprotein (MAG) sometimes found in patients with an immunoglobulin M monoclonal protein and progressive demyelinating sensorimotor neuropathy, were found by Pestronk et al. in 12 patients with MISP or NISP [141].

Electrophysiologic Tests

Nerve conduction studies in patients with MISP frequently showed low-amplitude or absent sensory nerve action potentials. Motor (compound muscle action potential) amplitudes were normal or relatively preserved. Needle electromyography (EMG), although typically normal, sometimes demonstrated mild abnormalities such as enlarged motor unit potentials or usually low-grade fibrillation potentials, pointing to some degree of involvement of motor neurons.

Of the four patients in the Horwich series which were studied, no sensory evoked responses were obtained (2/2), and motor nerve conduction studies were normal in 3/4; of the three patients who had EMG, one was normal, one had enlarged motor unit potentials but no increased insertional activity, and one showed both abnormal motor unit potentials and fibrillation potentials [19]. Similarly, in Anderson's patients, sensory nerve action potentials were absent or low in amplitude, motor nerve conduction velocities were either normal or mildly slowed, and except in the few patients with clinical evidence suggesting lower motor neuron involvement, EMG did not demonstrate evidence of denervation [138]. Among Chalk's patients, sensory nerve action potentials were absent in all but four individuals, each of whom had one or more preserved sensory response. Of the 65 sensory nerve conduction studies performed in this group, there were only two within the normal amplitude range. Sensory nerve conduction velocities could not be determined in that no individual had recordable responses with proximal stimulation of sensory nerves. By contrast, mean compound motor action potential amplitudes and motor nerve conduction velocities did not differ significantly from established normal values. Eleven of Chalk's subjects had no abnormal resting electromyographic activity, while eight others had occasional fibrillation potentials in intrinsic foot, head, or paraspinal muscles. Mild motor unit potential enlargement was found distally in all but three patients [93]. Auger et al. found that the trigeminal "blink" reflex was normal in 17/17 patients with MISP, while 20/43 subjects with NISP has abnormal "blink" reflexes [142].

Imaging Studies

Dalmau and coworkers obtained head CT scans in 21 patients, none of whom were thought to have abnormalities related to their paraneoplastic disease; cranial MRI studies were obtained in 32 individuals, 23 of which were said to be normal. Of the remaining scans, three had changes not related

to their paraneoplastic disease, two had changes possibly related to paraneoplastic processes (one with periventricular hypodensities and bifrontal atrophy thought to be related to limbic encephalopathy, the other with cerebellar atrophy related to paraneoplastic cerebellar degeneration), and four had MRI changes clearly related to their paraneoplastic disorders (all four had limbic encephalopathy and high intensity lesions on T2-weighted sequences in temporal and/or frontal lobes) [90]. Lauria and colleagues studied two subjects with MISP associated with ANNA-1 positivity who found to have T2-weighted magnetic resonance imaging high signal intensity in the posterior columns of the cervical spinal cord [143]. When screening for a tumor and conventional radiological methods (CT, MRI) are negative, whole-body [18F] fluorodeoxyglucose positron emission tomography (18FDG-PET) can be considered [144–146]. In 15 patients with a paraneoplastic neurological syndrome and ANNA-1 (anti-Hu) antibodies, radiological methods led to the diagnosis of cancer in 12 patients but not in the other 3, whereas 18FDG-PET showed abnormal uptake in the mediastinum in all 15 patients, in accordance with the expected location of the malignancy [144].

Pathology Studies

The primary locus of disease in MISP appears to be the dorsal root ganglion. Horwich et al. reported the principal neuropathologic features as: (1) degeneration of the dorsal root ganglion cells with inflammation and phagocytosis in the acute phase and decreased numbers of neurons accompanied by fibrosis in the chronic phase; (2) degeneration of the posterior roots and peripheral sensory nerves, with loss of myelinated fibers followed by Schwann cell proliferation and fibrosis; and (3) degeneration of the posterior columns of the spinal cord, in early stages with nerve fiber degeneration and infiltration by macrophages and reactive astrocytes and in the long-term with myelinated fiber loss and gliosis [19]. Twenty-seven MISP patients have been described in the literature with detailed neuropathologic accounts. In essentially every case the dorsal root ganglia, posterior roots, and dorsal columns of the spinal cord were affected [19]. Findings included neuronal loss in the dorsal root ganglia in 26/26 patients, residual nodules of Nageotte in 25/26, and inflammatory cell infiltrates in 13/26 [19, 137, 138]. Horwich et al. came to the conclusion that patients with ganglionopathy lasting less than 7 months tended to have dorsal root ganglia inflammatory infiltrates, while those with clinical symptoms of ganglionopathy more than 11 months had no marked inflammation; there was, however, a single exception of a patient who had such changes in only one dorsal root ganglion [19].

Although detailed pathologic studies of MISP patients are not reported frequently, a few descriptions have found their way into the neurologic literature. Ohnishi and Ogawa demonstrated selective loss of large-diameter neurons in the L5 dorsal root ganglion, marked decrease in the density of large myelinated fibers in the dorsal root and sural nerve, and almost total loss of myelinated fibers in the posterior column fasciculus gracilis in an MISP patient who succumbed to small cell carcinoma of the lung 29 months after symptoms of ataxic sensory neuronopathy began [137]. These investigators performed postmortem studies of the sural nerve, L5 dorsal root ganglion, L5 dorsal and ventral roots, and fasciculus gracilis, reporting quantitative morphometric data at each of the four levels examined. The sural nerve showed decreased large (diameter >5.62 μm) and small (diameter <5.62 μm) myelinated fibers (number of myelinated fibers per square mm of fascicular area), the densities measuring 50 (3,086 ± 461, mean ± SD, in controls) and 2,031 (5,422 ± 344 in controls) for large and small myelinated fibers, respectively. The total number of neurons in the L5 dorsal root ganglion was 35,632 (52,815 ± 2,881 in controls); the numbers of large (diameter >45 μm) and small (diameter <45 μm) nerve cell bodies were 2,494 (18,050 ± 2,283 in controls) and 33,138 (33,872 ± 2,279 in controls), respectively. The total number of myelinated nerve fibers in the L5 dorsal root was 17,533 (42,026 ± 2,066 in controls), with numbers of large and small myelinated fibers measuring 877 (14,332 ± 923 in controls) and 16,656 (27,694 ± 1,743 in controls), respectively. In the L5 ventral root, myelinated fiber total number approximated normal limits at 7,380 (8,179 ± 466 in controls). In the corresponding fasciculus gracilis, the myelinated nerve fiber densities (number per square mm of fascicular area) were 2,785 (21,819 ± 714 in controls) and 932 (22,058 ± 512 in controls) at the T5 and C3 spinal cord levels, respectively (122). Wanschitz and coworkers presented detailed autopsy findings in a case of a 69-year-old woman with MISP and autonomic dysfunction associated with ANNA-1 antibodies and SCLC [107]. They described inflammatory infiltrates in dorsal root and autonomic ganglia consisting of endoneurial T cells, B cells, and plasma cells. Some of these ganglion cells demonstrated cytoplasmic and nuclear staining for IgG. CD8+ T cells were found to be adherent to the surface of both IgG positive and IgG negative neurons, which these workers interpreted as providing evidence that both T-cell-mediated destruction and humoral mechanisms are involved in MISP [107]. A broad overview of the neuropathologic findings in paraneoplastic syndromes including MISP is provided by Scaravelli and associates [147].

Similar pathologic alterations (including neuronal loss, gliosis, perivascular inflammation, and fibrosis) have also been described as occurring variably at other sites in the nervous system including the cerebral hemispheres, basal ganglia, brainstem, cerebellum, and spinal cord (posterior and anterior horns) of some MISP patients. Some of these had clinical evidence of disease beyond the primary sensory

neuron, while in others the pathologic findings were subclinical [18, 19, 95, 99].

In patients with MISP and severe gastrointestinal dysmotility as well as in those who presented with isolated paraneoplastic intestinal pseudo-obstruction – sometimes with subclinical evidence of neuropathy, the main pathologic abnormality was in the myenteric plexus innervating the gastrointestinal wall. Lhermitte et al. [111] described marked neuronal loss, nodules of Nageotte, and Schwann cell proliferation in the small bowel myenteric plexus, with infiltration lymphocytes and macrophages strictly confined to the region of the myenteric plexus in the esophagus, stomach, colon, and rectum. They also documented chronic inflammatory lesions in the posterior and anterior spinal roots as well as in the Gasserian ganglion [111]. Schuffler et al. presented abnormalities in the myenteric plexus throughout the gastrointestinal tract, with infiltration with plasma cells and lymphocytes and, in addition, large areas of plexus devoid of neurons; dorsal root ganglia findings included neuronal loss and lymphocytic infiltrates. Others have described similar neuropathologic alterations [140, 148, 149]. Written accounts of one of the first documented MISP cases, originally reported by Denny-Brown in 1948 [8] and subsequently by Wyburn-Mason [94], noted that the patient was said to have died "after severe and intractable vomiting, with abdominal pain and distension." JG Greenfield performed the autopsy, noting that the "liver was normal but pushed to the right by great enlargement of the colon and stomach" and that "the colon was enormous throughout, being about 4 in. in diameter. Even the rectum was considerably larger than normal" [94]. Although descriptions of histological findings in the intestines were not provided in these reports [8, 94], this may have been an early demonstration of paraneoplastic pseudo-obstruction in a patient with ataxic MISP.

Treatment and Management

There are no controlled clinical trials in MISP. Even so, treatment of patients on a case-by-case basis – and particularly those with SCLC – has been largely disappointing. Horwich et al. reported that a variety of treatments, including steroids, azathioprine, nitrogen mustard, and radiation therapy, were universally unsuccessful in reversing the neurologic syndrome, although treatment of the underlying neoplasms in three patients (one each with synovioma, breast carcinoma, and Hodgkin lymphoma) appeared to have prolonged survival (mean survival 43 months, range 10–96 months [19], compared with a mean survival of 11 months in 119 MISP patients, range 0–96 months) [7, 8, 10–20, 90, 92, 95, 96, 98–103, 111–115, 131, 138–140]. Anderson et al. observed that treatment with corticosteroids coincided with remission of limbic encephalopathy in one of their patients but noted that symptoms and signs of MISP appeared during the steroid therapy which did not respond to an increased dose of prednisone [138]. Sagar and Read reported a patient with MISP associated with Hodgkin disease, whose tumor (stage 3b, mixed cellularity) and neurologic deficits (including limb clumsiness and inability to walk due to profound sensory ataxia) responded to treatment with prednisolone, procarbazine, nitrogen mustard, and vinblastine, the patient noting only slightly impaired manual dexterity and minor dysesthesia 23 months after treatment was begun [114]. Brunet et al. described two similar patients with MISP in Hodgkin disease whose clinical neurological deficits improved significantly following treatment, in one case with 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), vincristine, and procarbazine and in the other case with CCNU, vincristine, prednisone, and procarbazine after a trial of nitrogen mustard, vincristine, prednisone, and procarbazine had failed; the authors noted that some symptoms persisted despite treatment, including paresthesia (both patients), impaired sensation (one patient), and gait ataxia requiring a cane to walk (one patient) [113]. Chalk and colleagues had adequate follow-up data on 14/26 patients; the mean duration of follow-up was 18 months (range 1–60 months). Among these 14, 12 received antineoplastic treatment (7 with SCLC, 3 breast cancer, 1 lymphoma, and 1 adenocarcinoma of unknown primary site); 9 of the 12 had clear-cut improvement in their cancer, but none had neurologic improvement. The MISP worsened relentlessly in seven patients, while in five others, progression appeared to halt after the cancer was treated [93]. Hughes and coworkers note that seldom do neurologic deficits improve significantly following treatment of underlying lymphoma in patients with MISP [150]. Uchuya and coworkers studied responses of patients with a variety of paraneoplastic neurologic syndromes to high-dose intravenous immunoglobulin; of 13 patients with MISP, one refused treatment, one improved (from not being able to walk unassisted to being able to walk easily, ride a bicycle, and go hunting, remaining improved 15 months later), and five remained stable – although some were already stable prior to institution of the treatment [151]. Oh and associates reported two cases of MISP as well as six others from the literature with some degree of response to various forms of immunotherapy early in the course of neurologic disease [106]. Keime-Guibert and associates reported an open treatment trial of intravenous immunoglobulin, cyclophosphamide, and methylprednisolone on ten patients with MISP associated with encephalomyelitis and seven patients with paraneoplastic cerebellar degeneration; of the seven patients (initial Rankin scores greater than or equal to 4), none improved, while among nine patients who were initially still ambulatory (Rankin scores less than or equal to 3), none improved but two stabilized (two with MISP) [152]. In a retrospective study of 200 patients with paraneoplastic encephalomyelitis (PEM)/MISP (SSN), treatment of the tumor was an independent predictor of improvement and stabilization

of the neurological disorder suggesting that an early diagnosis of the cancer may provide a better chance of stabilizing the neurological disorder [153].

Prognosis

While one of the most common patterns of onset of neurological symptoms in MISP is subacute (over days to weeks); occasional patients have more abrupt presentations (over hours), while others report gradual symptom onset over weeks to months. In its most severe form, many patients become bedridden and succumb from complications of bed rest or inactivity rather than from direct cancer progression [153]. Of five MISP patients reported by Horwich et al. the mean time from onset of neurologic symptoms to death was 28 months (range 6–96 months), with one survivor (greater than 24 months at last follow-up) among 5 patients [19]. In the 12 patients described by Anderson et al. with MISP and small cell lung carcinoma, the mean time from neurologic symptom onset to death was 10 months (range 1.5–37 months), with 3 survivors (2–37 months since last follow-up) among 12 patients [138]. According to accounts in the peer-reviewed medical literature, at least three patients with MISP associated with Hodgkin disease had significant neurologic improvement following successful treatment of the underlying lymphoma, with a mean follow-up of more than 29 months (range 15 to greater than 36 months) [113, 114].

Nonmalignant Inflammatory Sensory Polyganglionopathy

Introduction

In 1968, Dyck et al. [24] described the clinical and pathological features of two cases of acute pure sensory neuropathy without malignancy, similar to those in the entity discussed by Wartenberg [21], concluding that multifocal radicular sensory loss with selective loss of large-diameter sural nerve fibers suggested dorsal root ganglia as the primary site of disease. Sterman et al. later reported an additional three patients in whom no neoplasm was identified, who presented with subacute widespread sensory symptoms (paresthesia and dysesthesia), ataxia, and severe sensory loss, none of whom recovered; these clinicians postulated a disease process confined to the dorsal root and Gasserian ganglia, noting the similarity to the pattern of deficits between their patients and animals with experimental pyridoxine and doxorubicin intoxications [25]. Dalakas published a longitudinal study of 15 patients with usually slowly progressive distal paresthesia and sensory ataxia who were found to have profound loss of large-diameter fiber sensation, areflexia, and normal strength, but neither malignancy nor antineuronal antibodies [154]. With four of these patients having monoclonal paraproteinemia, the authors suggested that immune mechanisms might have played a role. More recently Windebank et al. presented the clinical, laboratory, neurophysiologic, and pathologic findings in 42 patients with acute or subacute sensory neuropathy, discussing the natural history and response to treatment in individual cases [31]. They concluded that the acute or subacute, often focal or asymmetric, onset of symptoms in the absence of inflammation in distal peripheral nerve suggested an immune-mediated or vascular process at a proximal level, either at the posterior root or dorsal root ganglion. In another series, Griffin et al. described 13 patients with acute, subacute, or chronic ataxic sensory neuropathy, often with autonomic features, associated with Sjögren syndrome [30]. These investigators reported clinical, laboratory, and electrodiagnostic data and in addition presented detailed sural nerve, posterior root, and dorsal root ganglion pathology, emphasizing the differences between their patients and those with either idiopathic or malignant sensory polyganglionopathy. They advocated that Sjögren syndrome be considered in patients with severe sensory and autonomic neuropathy with ataxia and proprioceptive sensory loss. Additional series and individual case reports describe more than 100 patients with acute or subacute sensory neuropathy without malignancy [26, 28, 155–161].

This section discusses disorders of the dorsal root and spinal ganglia which are thought to be immune, excluding cases associated with malignancy or toxins affecting primary sensory neurons, that is, nonmalignant inflammatory sensory polyganglionopathy (NISP). With these exclusions the remaining conditions affecting proximal peripheral divisions of the dorsal root ganglion cell appear to be inflammatory. In the few cases in which biopsy material has been obtained, inflammation was often striking, implying immune mechanisms. At least some of these conditions previously described as of unknown localization were convincingly shown to specifically target dorsal roots proximal to the dorsal root ganglion. Sinnreich et al. described these patients presenting with gait ataxia, large fiber sensory loss, and paresthesias with frequent falls characterized by normal nerve conduction and EMG studies, characteristic somatosensory evoked potential (SEP) abnormalities with delayed central responses, elevated CSF protein levels, thickened lumbar nerve roots on MRI scans, inflammatory demyelinating changes on lumbar rootlet biopsies, and favorable response to immune-modulating treatment. The authors named the condition "chronic immune sensory polyradiculopathy (CISP)" reflecting the immune pathophysiology as well as the localization the disorder [162].

Etiology and Pathogenesis

Although nonmalignant inflammatory sensory polyganglionopathy (NISP) has been associated with Sjögren syndrome [28, 30, 31, 154, 156, 157, 160], paraproteinemia [31, 154],

celiac disease [155], and a rare complication of Epstein-Barr virus infection [163], with others having been reported as the sensory form of Guillain-Barre syndrome [164, 165], or predominantly sensory neuropathies associated with serum antibodies to chondroitin sulfate C [166] or sulfatide [141], many NISP patients are not found to have an underlying etiology and therefore fall into the unsatisfying category of "idiopathic."

Hainfellner and colleagues described a case of NISP presenting with acute painful sensory loss, areflexia, ataxia, urinary retention, and constipation who died 5 weeks into his illness [167]; autopsy demonstrated widespread inflammatory infiltration of dorsal root and autonomic ganglia with evidence of a prominent CD8+− mediated attack on these ganglion cells. Gherardi and coworkers found clonal populations of T cells in 80 % of patients with NISP as opposed to 20 % of elderly controls [168]. These reports suggest that cell-mediated immune mechanisms are at work in NISP as well as in sensory ganglionopathies associated with malignancy (see above).

Clinical Presentation

Although there is considerable clinical heterogeneity, three syndromes tend to predominate among patients with NISP – an ataxic presentation, a hyperalgesic presentation, and a mixture of the two. The extent to that a patient falls into one or another type appears to depend on the subset of neurons affected, the rapidity of involvement, and perhaps other factors. In the ataxic presentation predominantly large-diameter neurons are impaired or destroyed, giving rise to proprioceptive deficits and sensory ataxia. In the hyperalgesic syndrome dysfunction of small-diameter neurons which convey pain and temperature sensation is postulated. In the latter presentation there may also be a variable degree of autonomic involvement. The majority of NISP patients, however, have combinations of ataxia and pain or dysesthesia. NISP patients presenting with ataxia have been described by Sterman et al. [25], Kaufman et al. [26], Dalakas [31], Griffin et al. [30], and others [28, 156, 158, 159, 161]. NISP patients with prominent hyperalgesia were reported by Dyck et al. [24], Mitsumoto et al. [157], Laloux et al. [160], and Windebank et al. [31].

Diagnosis

Symptoms and Signs

In the ataxic syndrome presenting symptoms were numbness and tingling, unsteadiness of gait, diminished fine motor control, and occasionally pain, although this latter symptom was rarely prominent. In patients with the hyperalgesic syndrome, shooting limb pains, burning numbness, and painful paresthesia sometimes were among the presenting symptoms. Patients with ataxic and hyperalgesic NISP develop difficulty walking, poor coordination, and loss of manual dexterity. In hyperalgesic NISP pain, burning sensations, lancinating pains, and dysesthesia were sometimes prominent. Neurologic examination characteristically demonstrated normal strength, varying degrees of both distal and proximal diminished sensation (particularly vibration and joint position sense), and deep tendon hypo- or areflexia. In severely affected individuals the deafferentation was often so profound that limbs drifted off into space without the patient knowing (pseudoathetosis); in certain cases nocturnal eye protection was needed to prevent inadvertent ocular injury from a wandering finger. Autonomic manifestations such as Adie pupils, loss of sinus arrhythmia, or abnormal valsalva ratio values were sometimes apparent [30].

Laboratory Testing

Most NISP patients were found to have normal to slightly elevated CSF protein values. Of the 15 patients reported by Dalakas, the mean CSF protein value was 42 mg/dl (range 19–128) [154]. In Windebank's series of 30 patients, the mean value was 48.5 mg/dl (range 17–146), although two patients who presented acutely were found to have readings of 300 and 290 mg/dl [31]. On repeat CSF analysis later in the course of disease, both of these individuals had normal CSF protein determinations. CSF pleocytosis is not considered a typical feature of inflammatory demyelination and when present suggests infiltrative or infectious conditions (e.g., HIV infection) [169]. One of Windebank's patients who presented acutely, however, initially had a CSF nucleated cell count of 115 lymphocytes/mm^3; a subsequent lumbar puncture showed normal cells [31]. What is the significance of these cerebrospinal fluid (CSF) abnormalities? An elevated protein level in the absence of pleocytosis, as seen in both Guillain-Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), is thought to be associated with spinal or meningeal inflammation [170, 171]. In the majority of NISP cases, the CSF protein was normal or slightly elevated, most often without pleocytosis, while in subacute monophasic cases, abnormal spinal fluid findings were restricted to the initial phase.

Serologic markers (antinuclear antibodies, extractable nuclear antigens, rheumatoid factor, and antineutrophil cytoplasmic antibodies) raise the possibility of specific connective tissue disorders. Many patients with Sjögren syndrome and NISP demonstrated seropositivity for extractable nuclear antigens such as ro (SS-A) and la (SS-B) [30]. Dalakas described four individuals with ataxic sensory findings suggesting NISP and paraproteinemia, three with IgM kappa and one with IgA kappa monoclonal proteins [154]. Windebank et al. reported one case each of IgM kappa and IgG kappa monoclonal paraproteinemia in their NISP cohort [31]. Patients with sensory polyganglionopathy and antineuronal nuclear antibodies type 1 either had previously known

malignancy or subsequently were found to have cancer [18, 103]. A few case reports have appeared which document antineuronal antibodies in patients with sensory ganglionopathies in whom no malignancy could be found in life and in some cases at autopsy [172, 173], although the guiding principle of prudent diagnosis is that ANNA-1 (anti-Hu) seropositivity in a patient with sensory polyganglionopathy is a compelling evidence for an underlying small cell carcinoma of the lung [93]. These occult cancers may elude diagnosis for a number of years.

Electrophysiologic Testing

The most common nerve conduction abnormality in NISP was absent or low-amplitude sensory nerve action potentials (SNAP) with normal or relatively preserved motor (compound muscle action potential) amplitudes. Needle electromyography (EMG) was typically normal, although occasionally demonstrated mild abnormalities, indicating minimal involvement of motor units. Auger et al. observed that the trigeminal "blink" reflex was abnormal in 20/43 subjects with NISP while being normal in 17/17 patients with MISP [142].

Of 41 patients in Windebank's series, all but one showed a decrease in the amplitude of SNAPs with only mild slowing of conduction velocity [31]. From the majority of nerves tested, no SNAP could be elicited. Only eight of these patients had sensory conduction velocities below the range of normal, five from the distal median nerve. Motor nerve conduction studies were abnormal much less often than sensory studies. Ten of the 41 patients had abnormal compound muscle action potential amplitudes or conduction velocities, most commonly in the median and peroneal (fibular) nerves. EMG was usually normal. Eleven of the patients had fibrillation potentials in intrinsic foot muscles, while an occasional patient demonstrated fibrillation potentials in a leg or intrinsic hand muscle. Motor unit potential changes were more prominent, with abnormalities in 18 patients.

In Griffin's series 13 patients showed absent SNAP in most of the clinically involved limbs; seven of the patients had absent SNAP in all nerves tested [30]. Motor conduction abnormalities were limited to mild alterations in compound muscle action potential amplitudes and motor conduction velocities. EMG showed only minimal evidence of denervation in isolated muscles.

Knazan et al. performed extensive electrophysiologic testing on a 19-year-old man who after a "flu-like" illness developed sudden onset of severe sensory ataxia with marked disturbances of proprioception and vibration sense, minimal involvement of cutaneous sensation, areflexia, and normal strength [161]. These workers found normal motor conductions in the median, ulnar, and posterior tibial nerves; absent SNAP stimulating the median, ulnar, or sural nerves; and normal EMG of upper and lower limb muscles. No H reflex could be elicited. Median and tibial somatosensory evoked potentials could be recorded, although the median N20 scalp response was prolonged and the tibial P40 waveform was either absent or markedly prolonged [161].

In a series of patients with gluten sensitivity Hadjivassiliou et al. noted that all had either absent or attenuated sensory potentials at the time of diagnosis. Ten of the seventeen individuals showed asymmetric sensory fiber involvement either in a non-length-dependent fashion or patchy nerve involvement. Three of the seventeen had unrecordable potentials from nerves in both upper and lower limbs. Four patients showed length-dependent sensory fiber involvement but had no motor fiber involvement, in support of the diagnosis of sensory ganglionopathy [174].

The absence of SNAPs argues for involvement at or distal to the level of the dorsal root ganglion. In isolated disease of spinal roots, such as in traumatic root avulsion or CISP, SNAP amplitudes remain normal [154, 162, 175].

Imaging Studies

Magnetic resonance imaging studies of the cervical spinal cord of patients with NISP have sometimes demonstrated regions of increased signal intensity on T2-weighted sequences [143, 163, 176].

Pathologic Studies

Morphologic study of the dorsal root ganglion cell has focused on the peripheral (sural) nerve with only a few reports of spinal ganglia or dorsal root alterations. Inflammatory infiltrates have been demonstrated in biopsy and autopsy material from a number of patients with clinical features of NISP. In the sural nerves of two patients, Dyck et al. found decreased myelinated fiber (MF) density (mean 4,247/mm^2, range 2,286–6,209) primarily affecting large MF, a low rate of axonal degeneration, and no interstitial or endoneurial inflammation [24]. These abnormal findings are consistent with but do not directly demonstrate disease of the spinal ganglia. Windebank et al. described pathologic studies of 22 sural nerves in NISP [31]. Although the mean MF density was significantly decreased at 4,327 MF/mm^2 (range 52–9,968) compared with the mean value from 58 controls at 8,451 MF/mm^2 (range 5,101–12,995), no significant difference was found in the median MF diameter (5.32 μm in patients vs. 5.20 μm in controls). When the area of axons and myelin was assessed separately, however, striking differences were found. The median axon area was 4.24 μm^2 (range 2.19–7.71) compared with 7.09 μm^2 (range 3.15–12.63) in controls. The median myelin area was 17.79 μm^2 (range 6.81–24.22) compared with 14.20 μm^2 (range 7.78–29.55) in controls. Teased fiber analysis showed that the average percent of normal fibers (condition A) was lower (58.6 %, range 0–92 vs. 89.4 %, range 62–100), the percent of fibers with de- and remyelination (conditions C, D, F, or G) was higher (11.1 %, range 0–54 vs. 1.6 %, range 0–11),

and the percent of teased fibers undergoing axonal degeneration (conditions E or H) was higher (29.2 %, range 0–98 vs. 8.5 %, range 0–27) than in normal controls. A small mononuclear cell perivascular infiltrate was found in only 1/22 sural biopsy specimens. When taken with clinical and electrophysiologic findings, Windebank's studies demonstrating axonal atrophy suggest a more proximal site of disease (e.g., the spinal ganglia).

Twelve of Griffin's thirteen patients underwent sural nerve biopsy [30]. Five of these were reported as having reduced or severely reduced MF density. The mean MF density of the other six was 3,263 MF/mm^2 (range 688–7,598). They found inflammatory cells around epineurial blood vessels in six sural nerve specimens. Griffin et al. documented the thoracic dorsal root and spinal ganglion biopsy findings in three individuals [30]. All three demonstrated fiber loss in the dorsal roots. Inflammation was present in all three cases, with perivascular infiltrates in two cases and scattered inflammatory cells in small numbers throughout the endoneurium. Prominent mononuclear inflammatory cell infiltrates were noted in the three dorsal root ganglia specimens, typically situated around individual somas. In one patient immunohistochemical staining showed most of the inflammatory cells to be T lymphocytes, with only occasional macrophages. Neuronal loss varied from case to case and appeared to relate to the presence of these two types of inflammatory cells. In another case of NISP associated with Sjögren syndrome, we observed similar findings in lumbar dorsal root ganglion biopsy (see Fig. 23.2); in addition the posterior root appeared to be relatively unaffected, but the sural nerve showed marked reduction in the density of myelinated fibers.

Spinal nerve root histology in one patient in the series of Hadjivassiliou showed patchy loss of myelin staining and inflammatory infiltrates of lymphocytes and macrophages. Dorsal root ganglia also showed a less pronounced, diffuse lymphocytic infiltrate with loss of occasional neurons. Sensory ganglioneuropathy in this case was therefore thought to be inflammatory in nature and in the context of more widespread inflammatory changes affecting central and peripheral nervous system [174].

Because of the potential complications involved and for technical reasons, perhaps spinal ganglion biopsy should be restricted to only a very select group of patients with severe disease in whom malignant involvement must be excluded [177]. This procedure should be done only in highly specialized medical institutions.

Treatment and Management

Although various forms of immunotherapy have been given to patients with NISP, trials of treatment have not been sufficiently rigorous to establish whether any of these therapies are effective. A number of patients have received corticosteroids or other immunosuppressant therapy, and some have undergone plasma exchange or IVIG treatment [30, 31, 154, 178, 179]. To date no convincing results demonstrate that any treatment is more efficacious than no treatment. In individual anecdotal cases or case series, however, stabilization in clinical course or improvement has been associated with corticosteroid treatment, plasma exchange, IVIG treatment, or infliximab, a TNF blocker [180]. In addition, some patients appear to improve spontaneously, and some success has been shown with a strict gluten-free diet in patients with celiac disease [174].

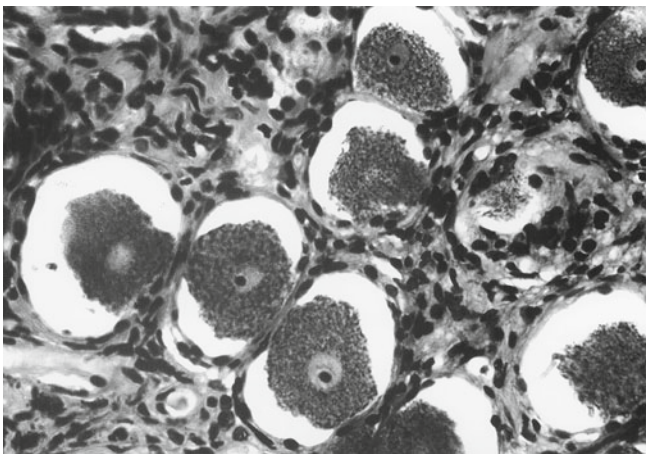

Fig 23.2 DRG pathology in NISP

Prognosis

Considering the two largest series of cases, the onset and pace of worsening are quite heterogeneous. Some patients present with a subacute or chronic progressive course, others have an explosive onset over hours. The disease course is most often chronic and progressive as reported in 20/38 patients by Windebank et al. [31] and in 8/13 patients by Griffin et al. [30]. In others the deficits remains unchanged – 10/38 [31] and 4/8 [30]. Still others had a chronic monophasic illness – 8/38 [31]. One of Griffin's patients followed a chronic relapsing course. Mean follow-up periods for these series were 98 months (range 12–324 months, Windebank's patients) and 41 months (range 5–190 months, Griffin's patients).

Toxic Polyganglionopathy

Many agents cause predominantly sensory symptoms and findings. These include drugs which alter microtubule structure such as vincristine and other vinca alkaloids; taxanes such as docetaxel, paclitaxel, thalidomide, lenalidomide, bortezomib, and ixabepilone [181, 182]; agents that interfere with axonal transport such as the hexacarbon solvents; and agents that disrupt axonal structure such as acrylamide and

ethylene oxide. In all these cases, the brunt of the injury appears to fall on the axon, with relative preservation of the neuron cell body. Without significant disease affecting the soma, there is the potential for recovery of function when the toxic source is removed.

For other agents, the major site of cellular damage is the neuronal perikaryon. This produces a distinctive clinical pattern with early proximal and distal sensory involvement, widespread hyporeflexia, and slow recovery after cessation of exposure. Cisplatin and vitamin B6 overuse fall in this category.

Cisplatin

Introduction

For *cis*-Diamminedichloroplatinum (II) (CDDP) which is a first-line agent for treating ovarian, testicular, and other neoplasms, neurotoxicity is dose limiting. The primary target is the dorsal root ganglion (DRG) neuron or its axon. Marrow depression and nephrotoxicity are significant adverse effects of CDDP therapy. Myelosuppression, which is common with prolonged usage, responds to erythropoietin. Nephrotoxicity has been reduced by saline diuresis [183]. The current primary dose-limiting side effects of CDDP are ototoxicity and neurotoxicity. Ototoxicity is common and thought to be due to a direct toxic effect on cochlear hair cells. Clinically apparent central neurotoxicity is rare [184, 185], although present if carefully sought with electrophysiological testing [186]. Significant peripheral neuropathy was reported soon after the drug was introduced [45, 46].

Etiology and Pathogenesis

Human studies have been limited. The reason for predominant sensory neuron toxicity may relate to drug access rather than selective neuronal vulnerability. CDDP does not cross the blood–brain barrier, and therefore, motor neurons and other central nervous system neurons are not directly exposed to toxic levels of drug. Because fenestrated capillaries supply the DRG, sensory neurons are exposed to serum levels of drug. This has been confirmed in human autopsy studies. Tissue platinum assays revealed the highest platinum concentration in tumor tissue (mean 3.3 μg/g), but similarly high concentrations were found in peripheral nervous tissue (3.5 μg/g in sural nerve and 3.8 μg/g in spinal ganglia). This compared with much lower concentrations in brain (0.17 μg/g) [187, 188]. Electrophysiological studies in cancer patients treated with CDDP confirm that large-diameter sensory axons are involved [189, 190]. Most studies have been interpreted as suggesting that the DRG neuron is the primary target [186, 191] which is compatible with findings in animals. It is not clear whether autonomic neurons, which are not protected by the blood–brain or blood-nerve barrier, are injured by cisplatin [192, 193]. Neuropathologic studies have shown loss of large myelinated fibers, most severe distally, and evidence of axonal degeneration [187, 194]. A single autopsy case in a child who had been treated with high-dose CDDP revealed severe loss of axons in both peripheral nerve and in the dorsal columns of the spinal cord [46].

Development of animal models for the study of CDDP neurotoxicity has been difficult because of the development of severe nephrotoxicity before neurotoxicity can be detected. In surviving animals, the possibility that neuropathy is due to renal failure rather than to CDDP has been difficult to ascertain. Behavioral studies which stress balance function have demonstrated a deficit in CDDP-treated mice [195] associated with biochemical abnormalities in DRG and slowing of tail nerve conduction. Several groups have demonstrated similar slowing of nerve conduction in rats [196–199]. Using similar doses, changes in DRG neurons of rats have been identified. These include neuronal shrinkage, nuclear abnormalities, and both decrease and increase of neurotransmitters [195, 199–202]. Examination of distal nerve segments has not generally provided additional information. Animal model studies have suggested that CDDP and related compounds have either facilitated access or preferential storage in the peripheral nervous system, particularly in DRG [203]. DNA-platinum adduct formation in rat DRG has been demonstrated in vivo [204].

Mechanistic studies of CDDP-induced neurotoxicity have been limited. CDDP binds to DNA of cancer cells and induces apoptosis. We have demonstrated that CDDP binds to neuronal DNA and induces apoptosis of DRG neurons in vitro and in vivo (Fig. 23.2). This is accompanied by upregulation of cellular markers associated with entry into the cell cycle. Apoptosis and entry into the cell cycle can be prevented by inhibitors of cyclin D1 and by agents such as nerve growth factor or insulin-like growth factor-1 that promote neuronal differentiation [205].

Clinical Presentation

The neuropathy is dose limiting and closely related to total cumulative drug dose [186, 188, 206, 207]. Neurotoxicity is apparent in the majority of adult patients who receive more than 400–500 mg/m^2 of CDDP [46, 187, 208]. The neuropathy is predominantly sensory with initial complaints of paresthesia in the distal extremities [187]. In some cases, symptoms begin proximally and may progress to severe sensory ataxia. Progression of neuropathy may continue for several months after cessation of CDDP [209], a phenomenon referred to as coasting. There have also been reports of symptoms developing 3–8 weeks after the last dose of chemotherapy [210]. Other platinum compounds produce similar toxicity. The experimental platinum analogs, ormaplatin [211] and oxaliplatin, cause similar neurotoxicity [212, 213]. Carboplatin is less neurotoxic [180]. In high doses, however, carboplatin does produce the same type of neuropathy as cisplatin [181, 214, 215].

Diagnosis

The diagnosis should be suspected in patients who develop sensory symptoms after two or more cycles of cisplatin treatment. Both *positive* (pain and paresthesia) and *negative* (numbness and ataxia) sensory symptoms may be present. The symptoms are usually symmetric and predominant in the lower limbs. This contrasts with malignant and nonmalignant sensory polyganglionopathies. In both of these disorders, symptoms often begin asymmetrically in the face and upper limbs [31, 93]. Nerve conduction studies typically show reduced or absent sensory nerve action potential amplitudes. In severe cases, somatosensory evoked potential amplitudes may also be reduced [186]. Other studies including examination of the cerebrospinal fluid are normal.

Treatment and Management

In 1992, Apfel demonstrated that cisplatin neurotoxicity might be prevented by nerve growth factor [195]. Nerve growth factor prevented cisplatin-induced alterations in behavior, electrophysiology, and DRG neuropeptides. This type of neuroprotection has been demonstrated for DRG [216, 217], sympathetic neurons [218, 219], PC12 cells [220], and in vitro [205]. In parallel studies, NT3 and NT4/5 have been shown to have neuroprotective effects for auditory system cells [221, 222] and DRG neurons [223]. All of the studies cited here have been empirical observations. In spite of this evidence, clinical trials have not been initiated. There is a fear that growth factors should not be used in patients with cancer because of the possibility of stimulating tumor growth. Better understanding of the mechanism of cell injury and protection will allow therapeutic trials to proceed.

Several other agents have been shown to have a protective effect against CDDP neurotoxicity in vitro and in vivo. Albers et al. [224] searched and selected quasi-randomized or randomized controlled trials in which participants received cisplatin (or related compounds) chemotherapy with or without a potential chemoprotectant (acetylcysteine, amifostine, ACTH, BNP7787, calcium and magnesium, diethyldithiocarbamate, glutathione, Org 2766, oxcarbazepine, or vitamin E) and were evaluated 0–6 months after completing chemotherapy using quantitative sensory testing (primary) or other measures including nerve conduction studies or neurological impairment rating using validated scales (secondary). One of four eligible amifostine trials [225–228] used quantitative sensory testing and demonstrated a favorable outcome in terms of amifostine neuroprotection, but the vibration perception threshold result was based on data from only 14 participants receiving amifostine who completed the posttreatment evaluation and should be regarded with caution. Of the six eligible glutathione trials [229–234], one used quantitative sensory testing but reported only qualitative analyses. Four eligible Org 2766 trials [235–238] employed quantitative sensory testing and reported disparate results; meta-analyses of three trials using comparable measures showed no significant vibration perception threshold neuroprotection. The remaining trial reported only descriptive analyses. The single eligible trials involving acetylcysteine [239], diethyldithiocarbamate [240], calcium and magnesium [241], and oxcarbazepine [242] and the two eligible trials involving vitamin E [243, 244] did not perform quantitative sensory testing. In all, data from 1,537 participants were included. The author concluded that at present, the data are insufficient to conclude that any of the purported chemoprotective agents (acetylcysteine, amifostine, calcium and magnesium, diethyldithiocarbamate, glutathione, Org 2766, oxcarbazepine, or vitamin E) prevent or limit the neurotoxicity of platin drugs among human patients.

Pyridoxine Abuse

Introduction

Vitamin B6 was recognized as an essential nutrient in the 1930s. The closely related compounds pyridoxal, pyridoxamine, and pyridoxine all function as active vitamins [245]. Neuropathy from vitamin B6 deficiency was initially described in swine fed with a pyridoxine-deficient diet [34, 246]. Neuropathy from vitamin B6 overuse was first described in a series of patients in 1983 [35]. The findings suggested a primary sensory ganglionopathy. It was caused by large doses of vitamin B6 which were being used as alternative therapy for premenstrual syndrome, schizophrenia, and carpal tunnel syndrome.

Etiology and Pathogenesis

Krinke and colleagues first demonstrated in dogs that high doses of pyridoxine in the diet caused progressive sensory ataxia associated with loss of DRG neurons and axons in peripheral nerve and dorsal columns [247]. This was subsequently confirmed in rats [36].

In two human studies, somatosensory evoked potential amplitudes were reduced suggesting involvement of central sensory pathways [35, 248]. A tissue culture study demonstrated that compounds which could be converted into active coenzyme were toxic to DRG, whereas inactive analogs were not [249]. This strongly suggested that the neurotoxicity was related to interference with the cellular action of the vitamin.

Clinical Presentation

Patients who developed sensory ataxia were taking 2–6 g of pyridoxine each day by mouth [35]. This compares to the minimum daily requirement of 2 mg/day. Progressive ataxia developed within weeks to months of starting the vitamin. In another report, two patients were accidentally given 132 and 183 g of pyridoxine intravenously over 3 days. They developed global sensory loss within several days which progressed to complete and permanent deafferentation

[250, 251]. At the other end of the spectrum, patients taking doses between 250 mg and 2 g developed numbness and paresthesia which subsided after discontinuing megavitamin use. Taken together with the animal studies, this strongly suggests that the polyganglionopathy is dose related. Clinical findings depend on severity. They include gait ataxia, loss of joint and position sense, and hyporeflexia with preserved muscle strength. Except in severe cases, recovery was the rule following discontinuation of the vitamin supplement.

Diagnosis

The diagnosis should be suspected in a patient with progressive, symmetric, large fiber predominant sensory loss. Patients need to be questioned carefully about holistic and alternative medicine treatments because this information may not be spontaneously volunteered. Nerve conduction studies show reduced or absent sensory nerve action potentials and reduced or delayed central sensory conduction [35, 248]. Other laboratory findings including cerebrospinal fluid examination are normal.

Treatment and Management

The molecular mechanisms responsible for the axonal degeneration are not fully understood, but pyridoxine-induced neuropathy in animals may be reversed by systemic administration of trophic factors, such as neurotrophin-3 or other compounds with NGF-like properties [252, 253]. Discontinuing pyridoxine supplementation resulted in resolution of symptoms and signs over weeks to months except in very severe cases [251]. In some subjects with good functional recovery, there were residual electrophysiological abnormalities. This suggests that part of the recovery resulted from peripheral sprouting or central adaptation, which would be compatible with a primary polyganglionopathy.

Central Sensory Syndrome

Introduction

The central sensory syndrome (CSS) is a group of rare disorders characterized by clinical abnormalities thought to be predominantly or purely limited to the central (posterior column) axon segment of the dorsal root ganglion cells involved.

Etiology and Pathogenesis

The disorders that have been linked to CSS to date include compressive posterior column myelopathy, myelopathy in HIV infection (gracile tract degeneration) [254], Holmes-Adie syndrome [255], subacute myelo-optic neuropathy (clioquinol intoxication) [256], tabes dorsalis [5, 6, 9], and, at least in experimental animals, vitamin E deficiency [43]. We could also include immune conditions such as CISP in this group [162] or even inherited disorders like spinocerebellar ataxia type 4 (Biemond ataxia) [257–262].

Clinical Presentation

Patients with the central sensory syndrome present with sensory loss, ataxia, and hyporeflexia. This may be present from birth in the case of Biemond ataxia, can be acquired by infection with HIV and subsequent myelopathy, or may occur late in life as a consequence of cervical spondylosis.

Diagnosis

The clinical and laboratory hallmarks of CSS, all three of which must be present for conclusive diagnosis, are: (1) abnormal sensation, typically involving dorsal column modalities such as vibration and joint position sense, often resulting in significant ataxia; (2) normal sensory and motor nerve conduction studies (as the lesion is proximal to the dorsal root ganglion cell body); and (3) either central abnormalities on somatosensory evoked potential testing and/or abnormal quantitative sensory testing.

Treatment and Management

The treatment of the central sensory syndrome depends on its etiology. Some cases of compressive CSS (for instance, due to a midline C3, 4 disks impinging on the posterior columns) may be entirely reversed with decompressive surgery. Other causes are not nearly as amenable to therapeutic intervention.

Prognosis

A detailed discussion of the prognosis of each of the varied causes of CSS is beyond the scope of this chapter.

Differential Diagnosis

The differential diagnosis involves separating MISP, NISP, and toxic polyganglionopathies from other sensory neuropathies. A variety of sensory polyneuropathies must first be considered. They include (1) metabolic, inflammatory demyelinating, toxic, deficiency, and other syndromes, beginning with sensory manifestations but at more advanced stages affecting other classes of neurons (axons), for example, motor and autonomic; (2) inherited neuropathies; (3) other cancer-related sensory neuropathies; (4) toxic syndromes; (5) deficiency states; and (6) infections.

Many polyneuropathies begin with sensory symptoms and findings, giving the sometimes false impression that there is no motor fiber involvement, only to be followed by motor symptoms and signs later. This is the pattern for the majority of polyneuropathies. The tendency for early distal sensory involvement occurs in polyneuropathies associated with metabolic conditions including diabetes mellitus [263],

hypothyroidism [264], primary biliary cirrhosis [265], and uremia [266]; in infectious polyneuropathies such as those described with diphtheria [6], human immunodeficiency virus (HIV) [169], leprosy [267], and Lyme disease [268]; in inflammatory-dysimmune diseases including dysproteinemias [30, 269], nonsystemic vasculitis [270], and Sjögren syndrome [29]; in inherited neuropathies such as Fabry disease [271], hereditary sensory and autonomic neuropathies (HSAN) type I [272], II [273], IV [274], and V [275], inherited amyloidosis [276], spinocerebellar degenerations [171, 260–262], and polymerase gamma (POLG)-related ataxic neuropathy [277–279]; and in toxic polyneuropathies such as those seen with exposure to arsenic [280], dichlorophenoxyacetic acid [281], dimethylaminopropionitrile [282], ethylene oxide [283], gold [284], hexacarbons [285], isoniazid [286], misonidazole [287], phenytoin [288], platinum [186], polychlorinated biphenyls [289], *N*-3-pyridylmethyl *N*′-*p*-nitrophenyl urea (PNU) [290], thallium [291], tainted L-tryptophan [292], and vincristine [293]. The reasons for early distal sensory predilection are usually explained by length-dependent dysfunction of peripheral nerve axons and the greater length of afferent versus efferent axons.

In evaluating a patient with symmetrical sensory symptoms and findings, perhaps the first matter that might be decided is whether the process seems likely to be inherited or not. If familial neuropathy can be excluded, the list of possibilities can be reduced substantially. The features which support the contention that a sensory neuropathy may be inherited might be summarized as age at onset, course, nature of symptoms, population of neurons (fibers) affected, type of pathologic alteration, pedigree information, and related laboratory findings. Indications of inherited sensory neuropathy may be present in the perinatal period (HSAN II-V) or develop during the second or later decades. Perhaps more typical than age of onset is the slowly insidious development of symptoms over many years which characterize HSAN I, spinocerebellar degeneration, POLG-related ataxic neuropathy, Fabry disease, and perhaps Tangier disease. In general, patients with inherited sensory neuropathies do not experience paresthesia as part of their neuropathies. The presence of prominent paresthesia (a "positive" sensory symptom) therefore favors an acquired sensory neuropathy. Sometimes in inherited neuropathy one class of neurons (fibers) is particularly vulnerable to being affected, whereas acquired sensory neuropathies tend to involve most classes. A history of a similar disorder among blood relatives or observing boney abnormalities or other physical findings (e.g., yellow-orange discoloration of the pharyngeal tonsils in Tangier disease or angiokeratosis of the buttock, scrotum, and perineum in Fabry disease) or laboratory abnormalities (e.g., hypocholesterolemia and abnormal serum lipoprotein electrophoresis in abeta- and hypobetalipoproteinemia, abnormal liver function tests in POLG ataxic neuropathy, or low leukocyte alpha galactosidase in Fabry disease) suggesting a specific variety of inherited neuropathy, though uncommonly encountered, obviously helps in identifying inherited neuropathy.

Having concluded that the patient's sensory symptoms are not likely to be inherited, the next step might be to decide whether the sensory symptoms are the onset of a more generalized polyneuropathy. Broad medical information about a patient often provides telltale clues. When sensory symptoms are associated with diabetes mellitus, uremia, hypothyroidism, acromegaly, hepatic failure, or severe hypoglycemic attacks, the correct diagnosis should come to mind. The course and pattern of the symptoms may suggest heavy metal intoxications, acute intermittent porphyria, vitamin B12 or copper deficiency, and a variety of other disorders. Clinical signs might also prove helpful, including microvascular or proliferative retinopathy (diabetes mellitus), macroglossia (amyloidosis, hypothyroidism), or sluggish deep tendon reflexes (hypothyroidism). Useful laboratory investigations include elevated fasting blood glucose and glycosylated hemoglobin (diabetes mellitus), increased thyroid stimulating hormone (hypothyroidism), elevated serum creatinine (uremia), or serum or urine monoclonal gammopathy (paraproteinemia, chronic ataxic neuropathy ophthalmoplegia IgM paraprotein cold agglutinins disialosyl antibodies (CANOMAD) [294], amyloidosis, or other blood dyscrasia).

The paraneoplastic or malignant inflammatory sensory polyganglionopathies (MISP), particularly the ones associated with small cell carcinoma of the lung, are not so readily distinguished from nonmalignant inflammatory sensory polyganglionopathy (NISP) on clinical ground alone. A history of smoking, constitutional symptoms (e.g., weight loss, fever, lymphadenopathy), or findings of malignancy suggest the paraneoplastic disorders. Particularly in persons 50 years and older, one may wish to obtain a chest radiograph, an X-ray metastatic bone survey; assess for monoclonal proteins in plasma and urine; and, if appropriate, obtain bone marrow, nerve, or other tissue to make a diagnosis of myeloma (multiple of osteosclerotic), amyloidosis (familial or acquired), or monoclonal gammopathy of undetermined significance.

Toxic syndromes may be suggested by their occurrence in clusters, exposure to putative toxins, distinctive physical findings (e.g., myokymia in gold intoxication, brawny induration of the limbs in eosinophilia-myalgia syndrome, palmoplantar cutaneous exfoliation in arsenic poisoning, or striate leukonychia (Mees lines) in metal intoxication), and suggestive laboratory abnormalities (e.g., peripheral eosinophilia in eosinophilia-myalgia syndrome associated with tainted L-tryptophan, peripheral basophilic stippling of erythrocytes in arsenical intoxication, or abnormal urine heavy metals in arsenic and thallium poisoning).

Deficiency syndromes such as vitamin B12 or copper deficiency can also present with combinations of characteristic

symptoms (unsteady gait, especially on uneven terrain and in the dark), physical findings (cognitive impairment, canities, limb and truncal ataxia, pseudoathetosis, and extensor plantar responses), and laboratory abnormalities (decreased cyanocobalamin or copper levels with megaloblastic anemia).

Infections such as tabes dorsalis, leprosy, and HIV infection might also be distinguished on the basis of symptoms and signs (e.g., tabetic "foot flapping" gait and Argyll-Robertson pupils, leonine facies with hypesthetic ears in Hansen disease, or anorexia, lymphadenopathy, and cutaneous findings in AIDS) and laboratory testing (positive syphilis serology, demonstration of mycobacteria on tissue biopsy, or positive HIV serology).

Other useful considerations include the size category of neurons (fibers) affected and the clinical pattern of neurological deficits. The specific sensory modalities involved may also prove helpful in establishing the diagnosis. Sensory neuropathies with prominent dysfunction or loss of large-diameter fiber modalities with examination findings such as kinesthesia and ataxia include hypothyroid polyneuropathy, uremic neuropathy, tabes dorsalis, vitamin B12 or copper deficiency, IgM paraproteinemic neuropathy, CANOMAD, spinocerebellar degenerations such as Friedreich ataxia, POLG ataxic neuropathy, toxic exposure to platinum or nitrous oxide, paraneoplastic sensory polyganglionopathies [17], toxic polyganglionopathies such as those associated with pyridoxine [35] and doxorubicin [295], infiltrative disease such as hematogenous metastasis to dorsal root ganglia sparing roots and nerves [296] and Sjögren syndrome [30], and idiopathic nonmalignant inflammatory sensory polyganglionopathies [31, 154]. Conditions with sensory neuropathies in which small-diameter fiber modalities may be prominently affected include amyloidosis, diabetes mellitus, Fabry disease, hereditary sensory and autonomic neuropathies, immune dysautonomias, Hansen disease, Tangier disease, and toxin exposures including gold, misonidazole, and tainted L-tryptophan. Other sensory neuropathies may involve both large- and small-diameter fiber modalities.

What is the differential diagnosis of diseases of the proximal sensory segments, the so-called polyganglioradiculoneuropathies? Even when armed with discriminating neurological history taking and examination skills as well as modern laboratory and electrophysiologic investigations, it is often difficult to sort out this group. The differential diagnosis of sensory polyganglioradiculoneuropathy rests on the exclusion of underlying malignancy. There is a female preponderance in NISP, while malignant inflammatory sensory polyganglionopathy affects the sexes similarly. In NISP clinical manifestations of Sjögren syndrome (e.g., dry eyes and mouth) may be present, while signs of severe systemic disease such as cachexia and weight loss (sometimes associated with cancers) are unusual. Magnetic resonance imaging can help to exclude structural intraspinal diseases. CSF for malignant cells can be useful. Although serologic testing such as for antinuclear and extractable nuclear antigens may be positive in NISP, antineuronal nuclear type 1 or anti-Purkinje cell antibodies have only rarely been described in these conditions. In MISP extractable nuclear antigen serologies are normal, and antineuronal nuclear 1 [103] or anti-Purkinje cell antibodies (personal communication, VA Lennon) are sometimes, though not invariably, demonstrated. As in the polyneuropathies, disorders which most commonly might be associated with both sensory and motor dysfunction on occasion may primarily affect the posterior roots, resulting in pure or relatively pure sensory polyradiculopathy. These include a pure sensory form of the Guillain-Barré syndrome [21], CISP [162], lympho- or plasmaproliferative disease [297], meningeal lymphomatosis [298], and meningeal carcinomatosis [299]. The pattern of deficits on neurologic examination may help distinguish polyganglioradiculoneuropathies from sensory polyneuropathies, but does not assist in dissecting out the specific causes of proximal sensory disease. Patients with sensory polyneuropathies have distal symmetric, "stocking-glove distribution" hypesthesia, absence or reduction of distal deep tendon reflexes, and normal muscle strength. Those with sensory polyradiculopathies and polyganglionopathies can demonstrate distal and proximal, symmetric or asymmetric sensory loss, widespread deep tendon hypo- to areflexia, and normal strength.

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Part V

Neuromuscular Disorders: Peripheral Neuropathies

Approach to Peripheral Nerve Disorders

24

David N. Herrmann and Eric L. Logigian

Introduction

There are numerous causes of peripheral neuropathy. Advances in the understanding of the immune and genetic basis of a number of peripheral neuropathies have permitted more precise characterization and effective therapy for many of them. This has led to an array of investigative options, with variable specificity, making the diagnostic evaluation more complex. A structured approach is necessary to make an etiologic and cost-effective diagnosis of peripheral neuropathy (Table 24.1). The clinician identifies the presence of neuropathy by documenting symptoms and signs of a peripheral nervous system disorder. Characterization of the spatial and functional (motor, sensory, autonomic) pattern of nerve fiber involvement as well as the pathophysiology and temporal profile are essential to categorize neuropathies and limit the differential diagnosis. Consideration of medical comorbidity, medication and neurotoxin exposure, and the family history further narrows the list of possible etiologies. These steps are accomplished with a focused history and examination (often including family members), electrodiagnostic testing (nerve conduction studies and electromyography), and judicious laboratory testing. Cutaneous nerve or skin biopsy and specialized electrophysiological testing may be required in some instances. This approach allows an etiological diagnosis to be established in at least 76 % of cases [1, 2].

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Does the Patient Have a Peripheral Nervous System Disorder?

The presence of a peripheral nervous system disorder is usually evident from the presenting signs and symptoms. No single clinical finding is definitive; rather, a combination of motor or sensory findings and their distribution permits the distinction between a central and a peripheral nervous system disorder. Reduced or absent deep tendon reflexes coupled with weakness, wasting, and fasciculations suggests dysfunction of lower motor neurons, nerve roots, or motor axons. Knowledge of the patterns of central sensory dysfunction (e.g., a "level" in spinal cord lesions) and peripheral sensory dysfunction (e.g., "stocking-glove," dermatomal, individual, or multiple sensory nerves) is also important in making this distinction. Central nervous system pathology may mimic a peripheral pattern of sensory dysfunction. Focal sensory symptoms, for example, hand numbness, may be seen with thalamic or parietal lesions; an apparent "stocking-glove distribution" of sensory loss may occur with cervical cord lesions, and posterior column dysfunction produces abnormalities in distal lower extremity proprioception and vibration sense and a positive Romberg test. Particular difficulty may arise with acute generalized weakness (e.g., Guillain–Barre syndrome (GBS) versus spinal shock), when there is peripheral and central nervous system involvement (e.g., vitamin B12 deficiency) or when symptoms predominate over signs (e.g., small fiber sensory neuropathies). The history, motor examination, sensory testing, and reflex abnormalities thus need to be considered collectively. Electrophysiologic testing or neuroimaging studies may occasionally be required to document or exclude involvement of the peripheral or central nervous system.

How Are the Findings Distributed in Space?

Peripheral nerve disorders should be characterized as being focal, multifocal, (asymmetric), or diffuse (symmetric) (Table 24.2). Focal disorders include radiculopathies (ventral

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Table 24.1 Stepwise approach to the diagnosis of peripheral nervous system disorders

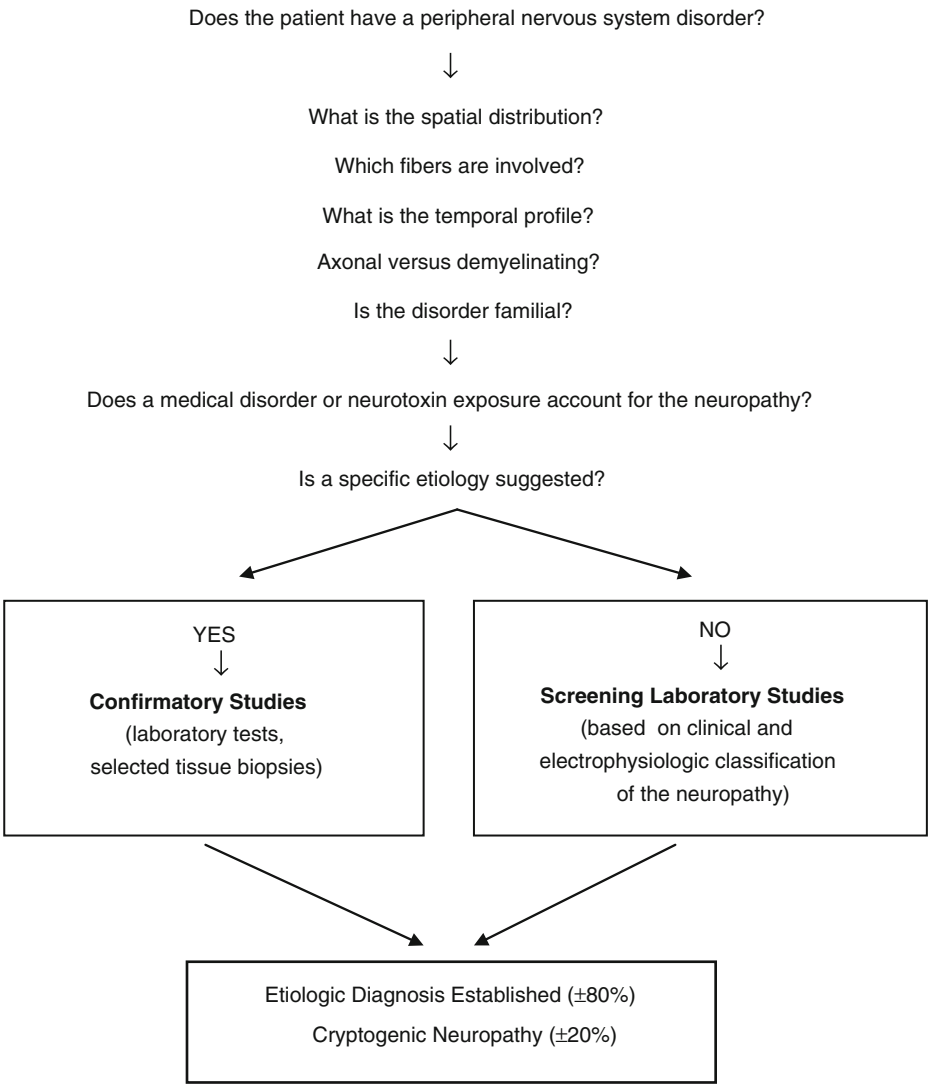

Table 24.2 Peripheral nervous system disorders: spatial patterns

Focal	Multifocal (asymmetric)	Diffuse (symmetric)
Mononeuropathy	Multiple mononeuropathies	Polyneuropathy
Monoradiculopathy	Polyradiculopathy	Dorsal root ganglionopathy
Brachial plexopathy	Motor neuropathy	Motor neuronopathy
Lumbosacral plexopathy	Motor neuronopathy	
Motor neuronopathy		
Dorsal root ganglionopathy		

or dorsal), plexopathies (brachial or lumbosacral), mononeuropathies (including cranial neuropathies), and rarely segmental neuronopathies. Multifocal patterns include polyradiculopathy and multiple mononeuropathies. This chapter will focus on the diagnostic approach to multifocal and diffuse disorders. Most acquired polyneuropathies evolve symmetrically, initially with a sensory disturbance in the feet which "ascends" to the knees, prior to involving the fingertips, forearms, anterior chest wall, and vertex. This is referred to as a length-dependent or "dying-back" neuropathy. Patients with symmetrical polyneuropathies may recall that sensory symptoms in one foot briefly preceded onset of identical symptoms on the other side, with subsequent symmetrical progression. This history should not dissuade the clinician from designating the neuropathy as symmetric [3]. Some symmetrical polyneuropathies are not length dependent. Patients with Guillain–Barre syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP) [4–6], or porphyric neuropathy, for example, may have proximally accentuated weakness.

Neuropathy that begins in one leg or in the hands, for instance, usually indicates an asymmetric disorder. The history is vital in making this distinction since cumulative multifocal deficits may become confluent over time and appear on physical examination to be symmetrically or diffusely

Table 24.3a Differential diagnosis of neuropathy based on clinical and electrophysiologic classification: axonal and symmetric

Sensorimotor, axonal	**Predominantly motor axonal**
Acute	Acute
AMSAN syndrome	AMAN syndrome
Vasculitis	Porphyria
Alcohol/nutritional/toxic	Dapsone toxicity
Arsenic toxicity (rarely demyelinating)	Vincristine toxicity
Subacute/chronic	Critical illness polyneuropathy
Vitamin B12, B1 deficiency	Acute alcohol-related neuropathy
Gastric surgery	Subacute/chronic
Celiac sprue, Whipple's disease	Subacute motor neuronopathy (paraneoplastic)
Alcohol toxicity	CMTX, CMT2
Arsenic, thallium toxicity	Lead poisoning
N-Hexane toxicity	Vincristine
Acylamide,CS2 toxicity	Hypoglycemia (insulinoma)
Organophosphate toxicity	**Sensory only, axonal**
Ethylene oxide toxicity	Acute
Colchicine, chloroquine toxicity	Idiopathic sensory neuronopathy (onset often focal)
Disulfiram toxicity	Paraneoplastic
Metronidazole toxicity	Acute pyridoxine toxicity
Nitrofurantoin toxicity	Cis-platinum Paclitaxel
Phenytoin toxicity	Miller Fisher syndrome (often demyelinating)
HIV DSP	HIV infection
Lyme disease	Subacute/chronic
HTLV1	Paraneoplastic (Anti HU+ or Anti HU−) (onset may be asymmetric)
Paraneoplasia (solid organ tumors)	Paraprotein-associated Sjogren's syndrome (may be asymmetric)
MGUS-associated (IgA/IgG)	Mitochondrial cytopathy Thalidomide toxicity
Multiple myeloma	Dideoxycytidine toxicity
Amyloidosis	Didanosine toxicity
Diabetes	Pyridoxine toxicity
Hypothyroidism	Chronic inflammatory sensory neuropathy
Acromegaly	Primary biliary cirrhosis
COPD	Vitamin E deficiency
CTD (SLE, Sjogren's, MCTD)	Friedreich's ataxia
PNS vasculitis	Hereditary sensory neuropathy (type 1)
Sarcoidosis	
Benign, elderly	

Adapted from Donofrio and Albers [32], Tables 2–7
AMSAN acute motor and sensory axonal neuropathy, *CS2* carbon disulfide, *HIV DSP* human immunodeficiency virus distal symmetrical polyneuropathy, *HTLV1* human T lymphotropic virus 1, *MGUS* monoclonal gammopathy of unknown significance, *COPD* chronic obstructive pulmonary disease, *CMT* Charcot-Marie-Tooth disease, *CTD* connective tissue disease, *SLE* systemic lupus erythematosus, *MCTD* mixed connective tissue disease, *PNS* peripheral nervous system, *AMAN* acute motor axonal neuropathy, *CMT* charcot marie tooth disease

Table 24.3b Differential diagnosis of neuropathy based on clinical and electrophysiologic classification: demyelinative (clinically symmetric)

Motor > sensory demyelinating (acquired)	**Motor > sensory inherited (uniform demyelination)**
Acute	CMT1A,B
AIDP	CMTX (may have intermediate electrophysiology)
SLE	CMT3
HIV-associated AIDP	CMT4 Metachromatic leukodystrophy
N-Hexane-associated neuropathy (initially)	Globoid leukodystrophy
Diphtheria	Cockayne syndrome Tangier's disease (some cases)
Gold toxicity	**Sensory and motor polyneuropathy with indeterminate electrophysiology**
Subacute/chronic (acquired)	
CIDP (idiopathic or with associated condition)	Diabetes mellitus
POEMS/Castleman syndrome	End-stage renal disease
MGUS-associated neuropathy (e.g., IgM)	CIDP (some cases)
Hypothyroidism	CMT1B
Amiodarone	CMTX
Perhexiline	
Chloroquine	
Cytosine arabinoside	
Tacrolimus	
GVHD, organ rejection	

Adapted from Logigian [30], Tables 2–7
AIDP acute inflammatory demyelinating polyneuropathy, *GVHD* graft versus host disease

distributed when in fact they accrued asymmetrically. Nonetheless, clinical examination may be helpful in confirming inter or intra limb asymmetries in the degree of nerve involvement.

The syndrome of mononeuropathy multiplex is important to recognize as it has a limited differential diagnosis which includes several treatable forms of neuropathy [e.g., vasculitic neuropathy, leprosy, CIDP variants, and multifocal motor neuropathy with conduction block (MMN)] [7] (Tables 24.3a, 24.3b, and 24.3c).

Multifocal neuropathies may have characteristic distributions. The neuropathy of lepromatous leprosy, for example, has a temperature-dependent distribution affecting superficial, often unnamed, nerves from the coldest regions of the body (preferentially the earlobes, the nose, and the dorsal extremities) [8].

Nerve conduction testing and needle electromyography (EMG) can be used to confirm the spatial distribution of neuropathy and may identify asymmetry (particularly in sensory nerves) that is not apparent on clinical grounds, thus suggesting the presence of mononeuropathy multiplex.

Table 24.3c Differential diagnosis of neuropathy based on clinical and electrophysiologic classification: clinically asymmetric

Sensorimotor axonal	Demyelinating mixed motor and sensory
Acute	Acute
Vasculitis	AIDP (rarely asymmetrical)
Endocarditis	Subacute/chronic
Perineuritis	MADSAM
Lyme disease	Focal upper limb CIDP
Subacute/chronic	HNPP
Vasculitis, isolated PNS	Leprosy
Vasculitis, systemic	**Demyelinating, motor only**
vasculitis with connective tissue disease	Subacute/chronic
Vasculitis, paraneoplastic (rare)	Multifocal motor neuropathy
Vasculitis with infection (HIV, hepatitis B and C)	
Cryoglobulinemia	
Diabetes mellitus	
Sarcoidosis	
Perineuritis	

MADSAM multifocal acquired demyelinating sensory and motor neuropathy, *CIDP* chronic inflammatory demyelinating polyneuropathy, *HNPP* hereditary neuropathy with liability to pressure palsies

What Is the Pattern of Nerve Fiber Type Involvement?

The signs and symptoms of a peripheral neuropathy are determined by which fiber types (sensory, motor, and autonomic) are affected. A sensory greater than motor neuropathy is the commonest pattern; however, motor dysfunction may predominate (e.g., CIDP, GBS, Charcot–Marie–Tooth disease (CMT)). Pure sensory syndromes suggest a dorsal root ganglionopathy particularly when abnormalities are not length dependent. Similarly pure motor involvement raises the possibility of a motor neuron disorder. Autonomic dysfunction may go unrecognized when mild. Autonomic dysfunction can be seen in conjunction with sensory and motor involvement (e.g., diabetes mellitus) or may be the dominant feature (e.g., acute pandysautonomia). The pattern of nerve fiber involvement should also be considered from the point of view of whether large– or small-caliber nerve fibers are involved. From a practical standpoint, large-caliber nerve fibers include motor fibers and type A-α and A-β sensory afferents that subserve tendon reflexes, position, and vibration sense, while small-caliber A-δ and C fibers subserve autonomic function and mediate pain and temperature sensation [9]. Mixed large and small fiber neuropathies with sensory and motor involvement are the rule; however, at the onset, the only symptom of polyneuropathy may be positive sensory phenomena (pain, falling asleep sensation, pins and needles, prickling). Significant motor and autonomic fiber involvement may occur over time.

Table 24.4 Predominantly small fiber neuropathies

Acute	Chronic
Diabetes mellitus (e.g., insulin initiation)	Diabetes
Idiopathic small fiber sensory neuropathy	Marked hypertriglyceridemia
Acute pandysautonomia	
Dimethylaminopropionitrile toxicity	Sjögren's syndrome
	Primary amyloidosis
	Familial amyloidosis
	Fabry's disease
	Tangier's disease
	Hereditary sensory and autonomic neuropathies: (type I (some), III, IV, V)
	Chronic idiopathic small fiber sensory neuropathy

Preferential involvement of small-caliber nerve fibers on the other hand is only seen in a few conditions (Table 24.4). While the occurrence of neuropathic pain (burning, aching, stabbing, contact hyperalgesia) suggests involvement of sensory fibers, its presence is not specific for any pattern (small, large, or mixed caliber) of sensory fiber involvement [10]. Small fiber neuropathies, however, present with neuropathic pain and allodynia as the dominant feature or as dysautonomia or a combination of neuropathic pain and dysautonomia. Examination findings are often limited to contact hyperalgesia and a mild distal disturbance in sharp–dull discrimination with normal deep tendon reflexes (e.g., chronic distal idiopathic small fiber sensory neuropathy (ISFSN) or small fiber diabetic neuropathy). Bedside evaluation of the autonomic nervous system is usually limited to assessments of orthostatic hypotension, pupillary responses, and sudomotor abnormalities (e.g., anhidrotic skin).

By contrast, large fiber dysfunction is suggested by the finding of a lower motor neuron pattern of weakness, loss of deep tendon reflexes, impaired proprioception, an abnormal Romberg test, and impairments of gait and balance ("ataxic neuropathy"). Predominantly large fiber neuropathies suggest a differential diagnosis that includes dorsal root ganglionopathies (idiopathic, Sjogren's syndrome, paraneoplastic, or toxic), vitamin B12 deficiency, and predominantly sensory ataxic variants of CIDP and IgM MGUS-related neuropathies [11, 12] (Tables 24.3a, 24.3b, and 24.3c).

The pattern of nerve fiber involvement should be confirmed with ancillary testing. Standard nerve conduction studies and needle EMG are sensitive to large fiber sensory and motor dysfunction. Electrodiagnostic (EDX) testing may demonstrate both motor and sensory involvement, when the pattern appears to be one of a purely sensory or motor neuropathy clinically. Conversely it is diagnostically important to verify the pure sensory or motor nature of a disorder, when a neuronopathy (e.g., motor neuron disease or paraneoplastic sensory neuronopathy) is suspected.

Routine EDX studies are insensitive in the evaluation of small fiber sensory neuropathies. If cardiac dysautonomia is suggested clinically, this should be quantified with baroreceptor reflex testing (blood pressure response to the Valsalva maneuver), cardiovagal testing (heart rate variability with respiration), and heart rate and blood pressure responses to upright posture (tilt table evaluation) [13]. Commonly, as in chronic ISFSN ("burning feet syndrome"), cardiac autonomic dysfunction is not prominent, and such studies are less helpful. Rather, skin biopsy with quantitation of epidermal nerve fiber density, quantitative sudomotor axon reflex testing (QSART), and quantitative sensory testing (QST) are more sensitive [14–18].

What Is the Temporal Profile of the Disorder?

The temporal evolution of the neuropathy is diagnostically helpful and also directs the acuity of investigations and management. The history is most important in characterizing the tempo of the neuropathy, although the physical and electrophysiologic examinations do give some information about disease chronicity. The clinician should define the time from onset to nadir or from onset to the current state if the nadir has not been reached as being acute (days to weeks), subacute (6 weeks to 6 months), or chronic (6 months to years). The course should also be described as being (1) monophasic, (2) progressive (uniform or stepwise), or (3) relapsing, remitting. Acute sensorimotor neuropathy with a time to nadir of less than 6 weeks is caused by a limited number of disorders (Tables 24.3a and 24.3b). This temporal course is most commonly due to GBS; other considerations include porphyric neuropathy, rapidly progressive vasculitic neuropathies, some acute toxic neuropathies (e.g., large ingestion of thallium or arsenic), and critical illness polyneuropathy (CIP). Severe, subacute progressive or stepwise sensorimotor polyneuropathy with a time to nadir of 2–6 months has a broader differential diagnosis. The main treatable neuropathies in this category are CIDP, vasculitic neuropathy, and less commonly vitamin deficiencies (vitamins B1 and B12) and metabolic disturbances (e.g., hypothyroidism and renal failure) (Tables 24.3a, 24.3b, and 24.3c).

Chronic polyneuropathies may be either on an acquired or hereditary basis; however, very slow progression that occurs over decades strongly suggests an inherited disorder.

Is the Neuropathy Primarily Axonal or Demyelinating?

In reality, many neuropathies have overlapping pathological features; however, it is almost always possible to define the predominant pathophysiologic mechanism.

The causes of axonal neuropathies are abundant, while demyelinating polyneuropathy suggests just a few etiologies. Neuropathies should be characterized as being either primarily axonal or demyelinating and if demyelinating as either segmental (multifocal) or uniformly so. Multifocal or segmental demyelination is usually acquired, while uniform demyelination is typically on a hereditary basis [19]. An exception to this is hereditary predisposition to pressure palsies (HNNP), where nerve conduction studies show a nonuniform pattern of multifocal, distally predominant slowing of conduction velocities and conduction block at entrapment sites.

A limitation of the clinical examination is its inability to discriminate with any degree of certainty whether a neuropathy is primarily axonal or demyelinating. Weakness and loss of deep tendon reflexes out of proportion to muscle atrophy as well as palpably enlarged nerves suggest a demyelinating neuropathy, while prominent muscle atrophy along with weakness, fasciculations, and a distally dominant pattern suggests axonal loss.

Nerve conduction studies and needle EMG are required to clarify the pathophysiology in most instances. Exceptions include patients with typical presentations of diabetic neuropathy, HIV distal symmetrical polyneuropathy, and alcohol-related polyneuropathies where EDX studies may not be necessary [20].

Although pathophysiology is inferred rather than directly assessed with nerve conduction studies and needle EMG, the correlation with sural nerve biopsy is reasonably good, and currently employed electrophysiologic criteria for demyelination have good specificity but limited sensitivity [21, 22]. EDX studies evaluate the peripheral nervous system broadly at proximal and distal sites, which is important as sural nerve biopsy demonstrates only distal pathology. Sural biopsy commonly shows only axonal changes in patients with CIDP, for instance; more proximal nerve segments showing demyelination are not sampled.

Family History

Hereditary neuropathies account for about 40 % of patients with undiagnosed neuropathies who are intensively evaluated in a specialized setting [1]. The underrecognition of hereditary neuropathies can be attributed to several factors including a failure to elicit an adequate family history, the occurrence of de novo mutations (e.g., peripheral myelin protein-22 (PMP-22) gene duplication) as well as recessive and x-linked inheritance patterns, and the fact that the neuropathy may remain asymptomatic for decades. Such patients typically have signs of neuropathy on examination but are unaware of their neuropathy (or those of family members) because of its slow progression. Three features allow one to distinguish inherited from acquired cases in most instances. First, long-standing inherited neuropathies may produce characteristic deformities of the foot

(pes cavus) and of the spine (kyphoscoliosis). Second, in comparison to most acquired neuropathies, typical hereditary motor sensory neuropathy has little in the way of positive sensory symptoms. Third, clinical and EDX examination (nerve conduction studies) of family members even when asymptomatic may reveal polyneuropathy. Genetic tests are available for most demyelinating hereditary neuropathies (the most common types being Charcot–Marie–Tooth type 1A (CMTIA), CMT1B, CMTX, HNPP, and CMT4C) and approximately 30 % of axonal form of Charcot–Marie–Tooth disease [23, 24]. Genetic testing should be focused and guided by the clinical and electrophysiologic findings and inheritance pattern of the neuropathy (autosomal dominant, recessive, or X-linked) [23, 24]. Such testing can also be helpful to confirm a hereditary neuropathy among patients with an inherited neuropathy phenotype when a family history is lacking or when one is unable to examine family members, for atypical presentations raising the question of a treatable neuropathy such as CIDP and genetic counseling [23, 24].

Medical Comorbidity, Medications, and Toxins

Once the peripheral nerve disorder has been characterized as above, the clinician considers whether any medical disorder suggested by the review of systems and general examination accounts for the neurological picture. The review of systems should include inquiry about diabetes mellitus, connective tissue disease, underlying malignancy, infection, malnutrition, megavitaminosis (pyridoxine), and exposure to drugs, alcohol, or toxins at the workplace. Clues to a systemic disorder or toxic exposure associated with neuropathy are summarized in Table 24.5. The use of over-the-counter preparations (e.g., pyridoxine) is not often reported by patients unless specifically inquired about. Possible toxic exposures should coincide with the onset of the neuropathic symptoms. A peripheral neuropathy with a remote onset from the reported exposure or that progresses well years after termination of exposure is likely unrelated.

Putting It All Together

At this point, having characterized the neuropathy, one of three scenarios may exist: First, in a proportion of cases, a tentative etiologic diagnosis can been made (e.g., diabetic sensory polyneuropathy, GBS). Second, a number of clues from the medical and family history may direct specific investigations. Third, there may be no specific findings to direct further work-up. This latter scenario is common in the setting of chronic sensorimotor axonal polyneuropathies. Here laboratory testing is performed based on knowledge of

Table 24.5 Clues to a neuropathy associated with a systemic disorder or toxin exposure

Skin and appendages
Hyperpigmentation – POEMS syndrome, adrenomyeloneuropathy
Hypopigmentation – POEMS syndrome, leprosy
Vitiligo – vitamin B12 deficiency
Ichthyosis – Refsum's disease
Photosensitivity – SLE, porphyria
Angiokeratoma – Fabry's disease
Dupuytren's contracture – alcoholic liver disease, diabetes mellitus
Mees' lines – arsenic, thallium
Hair loss – thallium, hypothyroidism, SLE
Cheilosis/glossitis – vitamin B1–3, B6, B12, and folate deficiency
Macroglossia – amyloidosis
Erythema migrans – Lyme disease-associated peripheral neuropathy
Erythema nodosum – leprosy, sarcoidosis, inflammatory bowel disease
Purpura – vasculitis, cryoglobulinemia, amyloidosis
Pruritis – primary biliary cirrhosis
Hypertrichosis – POEMS syndrome
Renal
Fabry's disease
Systemic vasculitis
HIV infection
Diabetes mellitus
Connective tissue disorders
Gastrointestinal
Acute abdomen – porphyria, lead poisoning
Chronic diarrhea – malabsorption neuropathies, Whipple's disease, celiac disease
Rheumatologic
Raynaud's syndrome – cryoglobulinemia, connective tissue disease
Arthritis – Lyme neuropathy, SLE, rheumatoid arthritis, Sjogren's syndrome
Lymphoreticular
Lymphadenopathy – POEMS syndrome, Castleman syndrome, Waldenstrom's macroglobulinemia, lymphoma, HIV infection, paraneoplasia
Hepatosplenomegaly – POEMS syndrome, amyloidosis, plasma-cell dyscrasia
Orange tonsils – Tangier's disease
Pulmonary
Asthma – Churg–Strauss syndrome
Ophthalmologic
Cataracts – diabetes, Cockayne syndrome, myotonic dystrophy
Corneal Clouding – Fabry's disease
Retinitis pigmentosa – Refsum's disease, Cockayne syndrome, Bassen–Kornzweig disease
Microaneurysms – diabetes mellitus
"Beaded retinal vasculature" – vasculitis
Xerophthalmia – Sjogren's syndrome, sicca syndrome, sarcoidosis
Optic disc edema – POEMS syndrome, CIDP, AIDP
Auditory
Hearing loss – Refsum's disease, Cockayne syndrome, mitochondrial disorders, vasculitis

Table 24.6a Laboratory evaluation of undiagnosed neuropathies (axonal)*

Sensorimotor, axonal polyneuropathy	**Predominantly motor axonal**
Acute	Acute
Occasionally helpful	Essential
Lumbar puncture	Lumbar puncture (cytoalbuminemic dissociation)
24-h urine for heavy metals (arsenic, thallium)	Occasionally helpful
Urine/fecal porphyrins	Urine/stool for porphyrins
Red cell transketolase activity (thiamine deficiency)	Urine for toxins (e.g., acute arsenic intoxication)
Lyme serology (endemic areas)	Subacute/chronic
Subacute/chronic	Essential
Essential	SIEP/IFIX
Fasting glucose, HgA1c	Occasionally helpful
SIEP/IFIX	*GM1* ganglioside antibodies
HIV serology (if risk factors present)	Genetic testing (e.g., axonal CMT/distal hereditary motor neuropathy, if hereditary neuropathy phenotype)
Vitamin B12 level	Androgen receptor gene mutations (Kennedy's syndrome) SMN gene mutations (spinal muscular atrophy)
Occasionally helpful Oral glucose tolerance test	**Sensory only, axonal**
MMA levels	Acute
Thyroid function tests	Essential
Serum triglycerides, HDL (if pain is prominent)	ANA, anti Ro, anti La
ANA, anti Ro, anti La	Screening for occult malignancy
Genetic testing (axonal CMT if hereditary neuropathy phenotype)	Paraneoplastic antibodies
Rarely helpful	HIV serology (if risk factors present)
Peripheral nerve antibodies (e.g., antisulfatide antibodies)	Occasionally helpful
Predominantly small fiber neuropathy	GQ1B antibodies
Acute	Salivary gland biopsy (in some instances)
Essential	Subacute/chronic
Fasting blood glucose/HaA1c	Essential
Subacute/chronic	ANA, anti Ro, anti La Salivary gland biopsy (in some instances)
Essential	Screening for occult malignancy Paraneoplastic antibodies
Fasting blood glucose/HaA1c	HIV serology (if risk factors present)
Fasting triglycerides	Vitamin B12/
ANA, anti Ro, anti La	
Occasionally helpful Oral glucose tolerance test	Thyroid function studies
SIEP/IFIX (primary amyloidosis)	Occasionally helpful
Transthyretin mutations (familial amyloidosis)	Oral glucose tolerance test
Cholesterol, HDL (Tangier's disease)	Vitamin E levels
Leukocyte alpha-galactosidase (Fabry's disease)	MMA levels

*Laboratory testing should be selective and based on the clinical and electrophysiologic context

the differential diagnoses associated with the particular neuropathy syndrome (Tables 24.6a and 24.6b).

Role of Laboratory Testing

Laboratory studies may be helpful in documenting the presence of a systemic disease associated with neuropathy. In general, when the history and physical examination do not provide a clue to the presence of these diseases, the screening tests designed to detect their presence are usually negative. Most patients with peripheral neuropathy, whether acute or chronic, should have a complete blood count, serum electrolytes, renal and liver function studies, a serum B12 level, and screening for diabetes mellitus (fasting blood glucose (FBG) and HgA1c). A 75-g oral glucose tolerance test should be considered as an additional screening study for occult diabetes mellitus, in the setting of predominantly sensory or small fiber neuropathies, when a FBG and HgA1c are normal. Patients with chronic sensorimotor polyneuropathies should also be screened for paraproteinemia with serum immunofixation and immunoelectrophoresis as standard serum protein electrophoresis may not identify clinically important yet small monoclonal spikes.

Use of batteries of laboratory tests and "antibody panels" without regard for the characteristics of the neuropathy is discouraged and not cost-effective. The sensitivity, specificity, and impact upon care of a number of

Table 24.6b Laboratory evaluation of undiagnosed neuropathies (demyelinating)*

Demyelinating polyneuropathy (multifocal)	**Sensory and motor polyneuropathy with indeterminate electrophysiology**
Acute	Acute
Essential studies	Essential studies
Lumbar puncture (cytoalbuminemic dissociation)	Lumbar puncture (cytoalbuminemic dissociation)
HIV serology (if pleocytosis or risk factors)	Subacute/chronic
Lyme serology (if pleocytosis or risk factors)	Essential
Occasionally helpful	Fasting blood glucose/HgA1c
Urine for arsenic and porphyrins	Occasionally helpful
Viral hepatitis panel (B and C)	Lumbar puncture (cytoalbuminemic dissociation with CSF protein >150 mg/dl favors CIDP)
ANA, anti-dsDNA	**Demyelinating polyneuropathy (uniform)**
Subacute/chronic	Occasionally helpful
Essential	CMT1A, CMT1B, CMTX, CMT4C DNA studies
Lumbar puncture for cytoalbuminemic dissociation (CIDP)	Rarely helpful
HIV serology (if pleocytosis or risk factors)	(depends on clinical setting)
Lyme serology (if pleocytosis or risk factors)	Serum phytanic acid
Fasting blood glucose, HgA1c	Leukocyte arylsulfatase A
SIEP/IFIX/urine Bence-Jones protein	B-galactosidase, sphingomyelinase
Skeletal survey (if paraprotein present)	
Occasionally helpful	
CMT1B, CMTX DNA studies (if distinction between CMT and CIDP unclear)	
HNPP DNA studies	
GM1 ganglioside antibodies (if purely motor)	
MAG antibodies (if distal and predominantly sensory)	

SIEP/IFIX serum immunoelectrophoresis and immunofixation, *HgAlc* hemoglobin Alc, *ANA* antinuclear antibodies, *SMN* survival motor neuron, *MAG* myelin-associated glycoprotein, *MMA* methylmalonic acid, *CIDP* chronic inflammatory demyelinating polyneuropathy, *HNPP* hereditary neuropathy with predisposition to pressure palsies
*Laboratory testing should be selective and based on the clinical and electrophysiologic context

commercially available peripheral nerve antibody assays (e.g., antisulfatide antibodies in undiagnosed sensory neuropathies) are uncertain [18, 20, 25]. When no clinical clues to the etiology of a neuropathy are found, selective use of laboratory tests based on the neuropathy syndrome is preferred (see Tables 24.6a and 24.6b).

Role of Nerve and Skin Biopsy

Tissue biopsy is only required in a minority of patients with peripheral neuropathy [26–28]. Studies have indicated that sural *nerve biopsy* yields a diagnosis in about 27 % of cases and provides useful information in a further 37 % of instances [21, 26]. The nerves biopsied include the sural (most frequently), superficial peroneal, and radial sensory nerves (see Chap. 12). Selection of a moderately involved nerve (based on sensory nerve conduction studies) is preferable.

The primary indication for cutaneous nerve biopsy is to identify potentially treatable causes of neuropathy in undiagnosed progressive acute or subacute asymmetric and less commonly symmetrical sensorimotor polyneuropathies. In practice, this is usually to confirm a suspected diagnosis of peripheral nervous system vasculitis prior to initiation of therapy. Performance of a simultaneous muscle and nerve biopsy is advocated in the evaluation of PNS vasculitis and increases sensitivity by at least 25 % [27]. Nerve biopsy in this setting less commonly identifies carcinomatous or lymphomatous infiltration or granulomatous disease (e.g., sarcoidosis). A pattern of focal perineurial inflammation (perineuritis) may also be seen in this group of patients and, while often idiopathic, may be associated with underlying sarcoidosis, cryoglobulinemia, or occult malignancy.

Nerve biopsy may also be used to confirm a diagnosis of leprosy, if skin biopsy is not diagnostic. Nerve biopsy can be helpful in identifying amyloidosis (acquired or familial); however, skin and abdominal fat pad sampling is less invasive and can be biopsied initially. Nerve biopsy will occasionally reveal evidence of a demyelinating polyneuropathy (CIDP), in patients with indeterminate progressive sensorimotor polyneuropathies that do not meet electrodiagnostic criteria for acquired demyelination. A biopsy may also be of value in distinguishing hereditary from acquired demyelinating neuropathies, when the clinical, electrophysiologic, and genetic evaluation is inconclusive.

Assessment of epidermal innervation with *punch skin biopsy* using immunohistochemical techniques (antibodies to the axonal marker, protein gene product 9.5) is helpful in

documenting the presence of small fiber neuropathy in patients with burning feet syndrome, when nerve conduction studies are normal or equivocal (see Chap. 13). This method may have greater sensitivity than sural nerve biopsy and is minimally invasive but does not offer an etiological diagnosis [17, 18, 28, 29]. However, cutaneous nerve biopsies are of low diagnostic yield and questionable value in patients with indolent chronic sensorimotor or predominantly sensory axonal polyneuropathies [3].

Pitfalls in the Evaluation of Peripheral Neuropathy

Errors in the diagnosis of neuropathy are common if the approach is not systematic or if electrodiagnostic studies are of poor quality and performed without consideration of the clinical picture.

"False-Positive" Diagnosis of Peripheral Neuropathy: Lumbosacral Polyradiculopathy

Lumbosacral polyradiculopathy from spinal stenosis may be difficult to distinguish from polyneuropathy. Distal sensory loss, weakness, and ankle areflexia may be seen in both instances. The two disorders can be distinguished by the presence of pseudo-claudication or radicular back pain in spinal stenosis and distal "burning" pain in neuropathy [30]. Electrophysiologically, the finding of normal sensory nerve action potentials with needle EMG abnormalities in proximal leg and paraspinal muscles in lumbosacral polyradiculopathy contrasts with the low-amplitude sensory nerve action potentials and upper extremity abnormalities seen in polyneuropathies.

Not All Distal Weakness Is Due to Peripheral Neuropathy

Distal muscle wasting and weakness are seen in rare cases of distal myopathy (e.g., inclusion body myopathy, Welander syndrome) or spinal muscular atrophy [30].

Amyotrophic Lateral Sclerosis (ALS) May Be Misdiagnosed as Peripheral Neuropathy

There are occasional patients with a distal sensory disturbance in the feet who have in addition severe, progressive muscle wasting and weakness. Initially, such patients may be assumed to have a severe, predominantly motor polyneuropathy. Over time, the correct diagnosis of ALS with a coincidental minor sensory neuropathy becomes obvious [30].

Failure to Consider Age

Reduced vibration sense in the feet and ankle areflexia may be seen among the normal elderly population. Similarly lower extremity sensory nerve action potentials and to a lesser extent compound muscle action potentials are of significantly lower amplitudes or absent in patients over the age of 60 as compared to young adults [31]. Peripheral neuropathy may be erroneously diagnosed if the patients' symptoms are not carefully considered and if age-based normal values for nerve conduction studies are not applied.

Distinction Between Acute Central and Peripheral Nervous System Disorders

Acute mononeuropathies of the radial, proximal median, and peroneal nerves may initially be misdiagnosed as a stroke. Careful attention to the distribution of weakness (confined to a single nerve territory) resolves the uncertainty since small cortical infarcts do not usually exactly mimic mononeuropathies.

Erroneous Diagnosis of CIDP

It is not uncommon for the diagnosis of demyelinating neuropathy to be made based on a report of slowed nerve conduction velocities, despite a history and examination which are inconsistent with this electrodiagnosis. The discrepancy is clarified when repeat nerve conduction studies are normal and the patient indicates that the extremities were not warmed during the initial study. Overemphasis on slowing of nerve conduction velocities at common sites of entrapment, misdiagnosis of conduction block due to overstimulation of motor nerves at distal sites, or failure to appreciate the presence of normal anatomical variants (Martin–Gruber anastomosis) may erroneously be taken as evidence of a demyelinating neuropathy [32].

The Diagnosis of Peripheral Neuropathy Is Correct but the Cause Is Falsely Attributed

If a risk factor for peripheral neuropathy exists (e.g., diabetes mellitus), an association is often presumed. In general, this assumption will be correct. However, errors arise when care is not taken to ensure that the clinical and EDX features are consistent with this assumption. An example of this is the diabetic patient who presents with painless acute or subacute weakness on a background of chronic distal sensory findings. In this instance, EDX studies may show a chronic polyneuropathy with demyelinating features. While

Table 24.7 Neuropathies for which there is disease-modifying therapy

Plasmapheresis	**IVIG**	**Corticosteroids**
GBS/variants	GBS/variants	CIDP
HIV-associated GBS	HIV-associated GBS	Systemic vasculitis
CIDP	CIDP	MADSAM syndrome
MGUS neuropathy (some IGA/IGG)	MMN	Isolated PNS vasculitis
Refsum's disease	MGUS neuropathy	Sarcoidosis
	MADSAM syndrome	PNS vasculitis (CTD-associated)
Cytotoxics (e.g., cyclophosphamide)	**Endocrine treatment**	**Vitamin replacement**
Isolated PNS vasculitis	Hypothyroid neuropathy	B1
Systemic vasculitis	Acute diabetic small fiber neuropathy	B12
MMN	Acromegaly	E
CIDP		Copper
Rituximab	**Antimicrobials**	**Radiation/surgery**
Anti-MAG neuropathy?	Lyme disease	Osteosclerotic myeloma
IgM-associated demyelinating neuropathies?	Leprosy HIV DSP?	POEMS syndrome
	CMV	**Liver Transplantation**
		Familial amyloidosis

the EDX studies may be consistent with the patients known diabetic neuropathy, the prominent subacute painless weakness is atypical and suggests the possibility of superimposed CIDP.

False-Negative Diagnosis of Peripheral Neuropathy

This occurs most frequently in the setting of very mild sensory polyneuropathies or predominantly small fiber painful sensory neuropathies, as on examination findings are often minimal and routine nerve conduction studies normal or equivocal.

Approaches to the Management and Follow-Up of Patients with Peripheral Neuropathy

Therapeutic approaches consist of those that alter the natural history of the disease (Table 24.7) versus symptomatic pharmacotherapies and rehabilitative strategies to limit disability. The specific management approaches and algorithms for individual subtypes of neuropathy are described in subsequent chapters. Disease-modifying agents are variable in their degree of efficacy, cost, and side-effect profile. In only a few instances have therapies been subjected to prospective and randomized evaluation. These factors bear heavily on the decision to initiate or continue therapy. Multifocal motor neuropathy and peripheral nervous system vasculitis are cases in point. While intravenous immunoglobulin and cyclophosphamide in the case of multifocal motor neuropathy and corticosteroids and cyclophosphamide for PNS vasculitis have demonstrated efficacy, the optimal regimens and duration of therapy are less certain. In multifocal motor neuropathy, some patients may require periodic intravenous immunoglobulin indefinitely in order to avoid relapse. The modest efficacy of immunotherapy in some disorders is reflected in stabilization or slowing of progression over a period of years. The conventional period of follow-up over 1 to several months in order to guide management decisions may be too short to appreciate only slowing of progression, and therefore, serial follow-up over a longer period of time is often required.

The optimal outcome measures to assess progress or response to therapy are uncertain. Traditional approaches in the clinic rely on a combination of the patient's report of their progress, assessment of symptoms, and serial assessment of the degree of neurological impairment (neurological examination and a grading scale of strength). Nerve conduction studies and electromyography are commonly used as a marker to judge response to therapy. This approach has significant limitations. Neurological symptom scores (e.g., the neuropathy symptom score (NSS)) are weak indicators of severity and progression in, for instance, diabetic neuropathy [33, 34]. The Medical Research Council (MRC) grading scale for strength has good inter-rater reliability in a clinical trial setting but is nonlinear with the upper 50 % of strength represented by grades 4–5. It performs less well in assessing mild degrees of weakness and detecting mild changes in strength from one office visit to the next. Neurological impairment scores such as the MRC scale and the neurological disability scale correlate weakly with functional outcome measures such as the Rankin scale [34]. Nerve conduction studies often do not correlate well with clinical improvement, at least in part, because they assess a limited number of distal nerve segments that may or may not correspond to clinical symptoms and signs.

The clinician is best served by combining a focused and serial neurological examination of selected muscle or nerve distributions, with inquiry about a defined but individualized set of activities of daily living at each visit and serial functional assessments. In terms of the latter, we find it helpful to identify one or more simple bedside measurements or activities (e.g., grip dynamometry, arising from a chair, heel walking, Rombergism) that can be followed in the clinic.

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Approach to Small Fiber Neuropathy

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Introduction

The term "small fiber neuropathy" (SFN) commonly refers to a condition characterized by damage of small-caliber nerve fibers (thinly myelinated Aδ and unmyelinated C) with somatic functions, namely, peripheral axons carrying thermal and nociceptive sensation, and with autonomic functions. When there is an isolated or predominant impairment of the subgroup of these small fibers with autonomic function, the term "autonomic neuropathy" is used. In addition to symptoms and signs reflecting peripheral deafferentation (e.g., thermal and pinprick hypoesthesia), SFN includes neuropathic pain symptoms and signs (e.g., burning pain, allodynia, hyperalgesia) which often dominate the clinical picture and have contributed to inclusion of SFN within the more general class of painful neuropathies. Autonomic disturbances can occur but are usually limited and often underdiagnosed. In patients with pure SFN, clinical and neurophysiologic investigations do not show involvement of large myelinated nerve fiber, thus making the diagnosis of SFN challenging in clinical practice. However, patients complaining of symptoms suggesting SFN must be diagnosed for at least three main reasons. First, the definition of the diagnosis can lead to a focused screening of potential etiologies. Second, early disease-modifying or symptomatic treatments can be initiated. Third, awareness of the disease can increase patients' compliance, which is particularly important in the treatment of neuropathic pain.

Over the last 15 years, SFN has been the subject of intensive investigations prompted by the availability of skin biopsy, a novel tool that readily permits morphometric and qualitative evaluation of somatic unmyelinated C fibers innervating the epidermis. Skin biopsy has overcome the limitations of routine neurophysiologic tests to detect the damage of small nerve fibers. This approach has extended to the study of autonomic neuropathies and, through the analysis of dermal myelinated nerve fibers, of inherited and immune-mediated neuropathies.

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Small Nerve Fibers

Thermosensory and Nociceptive Functions

Small-caliber nerve fibers encompass several functions which underlie both our ability to distinguish among different non-noxious and noxious thermal stimuli and the multiplicity and variability of symptoms in SFN. Aδ and C fibers include multiple groups of thermosensitive skin afferents, most of which have distinct response functions enabling them to encode the stimulus intensity. The identification of dedicated afferents to the transduction of warmth and cold sensation provides a basis for their classification as "cold" and "warm" fibers [1]. Moreover, skin nerve endings and resident cells express several members of the transient receptor potential (TRP) ion channel family, which operate over specific temperature ranges, providing a molecular basis for thermosensation [2, 3]. Based on their activity which depends

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on the temperature of their environment, human TRP have been grouped into six families, three of which (vanilloid channels [TRPV], melastatin channels [TRPM], ankyrin transmembrane protein channels [TRPA]) deserve particular interest as thermoreceptors [4].

Aδ fibers have a primary role in conveying cold sensation, as demonstrated by differential nerve block experiments [5]. They are activated by static innocuous cold stimuli in the range between 20 and 30 °C, and by menthol, which induces sensitization and increase of their discharge rate. Microneurographic studies have also identified subclasses of C fibers which respond to cold stimuli [6]. This observation was prompted by the evidence that menthol induces spontaneous burning pain, cold hyperalgesia, and flare reaction during A-fiber block that abolishes cold sensation [7]. This subclass of C fibers, known as "type 2," were found to have a distinct bimodal response to heating and cooling, with discharge rate at skin temperatures down to 0 °C and above 45 °C associated with a "hot burning" quality the perception. It has been suggested that their function is not to detect cold objects but rather to provide information about skin temperature for the purposes of unconscious thermoregulation, for which their high sensitivity would be appropriate. Their primarily role in innocuous cold nociception would provide a warning about potentially dangerous temperatures. Cold hyperalgesia and burning sensation to cold stimuli, in association with cold hypoesthesia, have been described in patients with neuropathy. These phenomena have been attributed to the disinhibition or the sensitization of this class of C fibers [6, 8]. Finally, some large myelinated fibers innervating Merkel and Ruffini pressure mechanoceptors also respond to cold stimuli down to 14.5 °C [9], likely explaining the illusionary perception that an object may appear heavier when it is cold rather than warm. The sensation of cold becomes painful when hairy and glabrous skin is exposed, respectively, to temperatures between 10 and 15 °C and 18 °C. Noxious cold stimuli induce different sensations such as pricking, burning, aching, and heat. Experimental studies demonstrated that both Aδ and C fibers are activated by these stimuli, explaining this pattern of sensation. Indeed, if Aδ fibers are blocked and C fibers remain active, a noxious cold stimulus is perceived as burning or heat. Recent studies showed that the Nav1.8, the sodium channel expressed in dorsal root ganglion (DRG) neurons and small-caliber nerve fibers, plays a critical role in the detection of noxious cold stimuli [10].

Cutaneous warm fibers are activated by static temperatures above 30 °C, with a maximal discharge rate at 40–43 °C. Like cold fibers, they adapt after repetitive stimuli. Differential fiber block studies have demonstrated that warm sensation is conveyed by C fibers [5]. Noxious heat stimuli induce an almost instantaneous sharp and pricking pain followed by a later dull and burning sensation. This phenomenon disappears if the stimulus is applied in the proximal sites of the body and is experienced in the hairy skin only [11]. This dual type of pain indicates that different fibers are activated. Studies with differential blocks have demonstrated that the fast pain is conveyed by Aδ fibers, whereas the long latency pain is mediated by C fibers. Aδ nociceptors involved in heat pain sensation have been classified into two groups. Type I fibers are present in glabrous and hairy skin and respond to short-lasting high temperatures (>53 °C), whereas they show a delayed activation upon long-lasting stimuli (30 s). After a burn injury, these fibers become sensitized to heat stimuli and mediate thermal hyperalgesia [12, 13]. Type II fibers have a lower threshold (47 °C) and are activated by long-lasting stimulation (53 °C for 30 s) with an adaptation during the response. They are not present in the glabrous skin, explaining the lack of first sharp pain after heat stimuli in the palm of the hand. Heat-responsive C fibers are estimated to be located at a depth between 20 and 600 μm in the epidermis and dermis [14]. Their range of activation is between 37 and 49 °C and is similar in glabrous and hairy skin. However, only those innervating the hairy skin sensitize after a burn injury.

Temperature perception depends on the balance between the input from skin thinly myelinated Aδ and unmyelinated C fibers, and the sensory experience is the result of the integration of their activity in the central nervous system. One demonstration came from studies comparing patients with complete or partial damage of non-noxious warm or cold pathways [15]. These experiments showed that when thermal sensations are disrupted, a noxious stimulus elicits a sensation of pricking pain with a higher threshold compared to healthy subjects. Conversely, when one thermal modality is preserved, both noxious and non-noxious stimuli acquire the characteristic of the intact modality, resulting in a paradoxical sensation. Therefore, innocuous cold stimuli are perceived as non-painful warm in the skin areas in which only warm sensation is intact, and vice versa. Moreover, in these areas, noxious cold and heat stimuli induce a sensation of heat pain. Therefore, lesions or diseases throughout these pathways are responsible for some of the neuropathic pain symptoms.

A further important role is that played by voltage-gated ion channels expressed in DRG neurons, sympathetic neurons, and small-caliber axons. Among them, sodium channels merit particular interest due to their critical role in the generation and conduction of action potentials in the nociceptive pathway. Indeed, ectopic spontaneous activity in primary afferent neurons and axons following nerve injury is matched by the increased expression of different sodium channel subunits, contributing to peripheral and central sensitization that reflects in the typical symptoms of neuropathic pain (e.g., burning, paroxysmal, and evoked pain). The Nav1.7, Nav1.8, and Nav1.9 are preferentially expressed within peripheral nervous system neurons and, along with Nav1.6, have been detected in intraepidermal nerve fibers (IENF) of rat paw [16]. Nav1.7, a tetrodotoxin-sensitive

subunit, acts as a threshold channel that amplifies subtle depolarizations such as generator potentials, bringing neurons to voltages that stimulate Nav1.8, a tetrodotoxin-resistant subunit, which contributes most the inward current responsible for the depolarizing phase of action potentials. Thus, Nav1.7 is poised as a molecular gatekeeper of pain detection at peripheral nociceptors [17]. Changes in the functional properties of Nav1.7 due to single amino acid substitutions have been linked to multiple pain syndromes, including inherited erythromelalgia (IEM), paroxysmal extreme pain disorder (PEPD), and, more recently, SFN [17, 18]. Studies in experimental models of neuropathic pain have also shown changes in levels of expression in multiple sodium channel subunits. Nav1.3 channels are overexpressed in nociceptors soon after nerve damage, such as within neuromas, contributing to the typical ectopic discharges [19, 20]. Nav1.8 is first downregulated then upregulated in uninjured adjacent axons hours after the damage, contributing to changes in excitability [21]. Nav1.8 is also essential to the excitability of cold sensing terminal axons, and its overexpression was recently found to be determinant to the cold hypersensitivity induced by oxaliplatin in an animal model, a feature typical of human neuropathy [22]. Nav1.9 channels are preferentially expressed in small-caliber non-peptidergic DRG, trigeminal, and myenteric neurons and have been found in nerve endings of skin and cornea [21]. Its expression is thought to contribute to the functional specialization of peptidergic (IB4+) and non-peptidergic (IB4−) neurons [23], though the role in neuropathic pain remains uncertain at the light of experimental studies showing either upregulation or downregulation in different pain states, and unchanged nociceptive behavior in null mice [24]. IENF express also the isoform type 2 of the sodium-calcium exchanger (NCX2) that under normal conditions contributes to calcium extrusion. Changes in persistent sodium influx following axon damage might reverse the sodium-calcium exchange and induce degeneration [16].

Features of Skin Nerve Fibers

Skin separates internal tissues from the external environment, creating a protective barrier that contributes to maintenance of body homeostasis and immunological defenses and provides a structural substrate for peripheral aspects of the transduction and transmission of sensory stimuli. The epidermis is the topmost living layer and is composed of four different layers of keratinocytes that differentiate as they progress from the basal layer to the stratum corneum, with a turnover of about 30 days. The other resident cells include Langerhans cells, melanocytes, and Merkel cells. The basement membrane (dermal-epidermal junction) separates the epidermis from the subpapillar dermis which is organized in papillae in which vascular plexus and periodic capillary loops reside. In the glabrous skin, the apexes of the papillae contain Meissner's mechanoreceptors. Their density in the fingertip is 33.0 ± 13.2 (standard deviation [SD]) *per* square millimeter [25, 26]. Pacini's and Ruffini's corpuscles reside deeply in the dermis and are commonly excluded from routine skin biopsy examination. The matrix of the superficial dermis also includes fibroblasts, hair follicles, arrector pilorum muscles, blood vessel, and sebaceous and sweat glands.

IENF are the endings of dorsal DRG small-diameter neurons and have exclusive somatic function as demonstrated by the degeneration only after axotomy or DRG destruction, but not after sympathectomy [27]. Intriguingly, IENF lose their Schwann cell ensheathment while crossing the dermal-epidermal junction, similar to large myelinated fibers when reaching the inner core of mechanoreceptors where the sensory stimulus is transduced [28]. No synaptic contact between IENF and epidermal cells has been described, and the presence of naked axons is likely to favor communication through paracrine pathways. IENF widely express TRPV1 [29], a channel crucial for thermal hyperalgesia induced by tissue inflammation [30]. Also keratinocytes and other nonneuronal cells (e.g., vascular smooth muscles, endothelium) express members of the TRP family which participate in the homeostasis of temperature sensations and play a role in the pathogenesis of mechanical hyperalgesia and inflammatory pain [26, 31, 32]. Moreover, keratinocytes secrete chemical substances (e.g., neurotrophins, ATP, β-endorphin, interleukins) which may influence DRG neuron excitability. Is has been also shown that mechanical stimulation of keratinocytes can affect DRG neurons through ATP and purinergic receptor signalling. On the other hand, peptidergic nerves (i.e., expressing CGPR and SP) influence keratinocyte maturation and the ability of Langerhans cells to present antigens to lymphocytes [33, 34]. Therefore, one current view is to consider the whole skin, and in particular the epidermis, as a huge polymodal receptor which functions are based on the relationship between resident cells and nerves [35].

Small Fiber Neuropathy

Definition

The criteria to diagnose SFN have been based for more than a decade on the different methods used to assess the selective damage of small fibers, including clinical examination, routine and nonconventional neurophysiological studies such as the cutaneous silent period examination [36], laser-evoked potentials (LEPs) [37], contact heat-evoked potentials (CHEPs) [38], quantitative sensory testing (QST) of thermal and pain thresholds [39], and morphometric assessment of IENF using skin biopsy [40]. This led to a nonhomogenous approach to the

diagnosis in clinical practice and research. Most recently, the NEURODIAB expert panel [41] has proposed a graded definition of SFN as follows: (1) *possible* – presence of length-dependent symptoms and/or clinical signs of small fiber damage; (2) *probable* – presence of length-dependent symptoms, clinical signs of small fiber damage, and normal sural nerve conduction study; and (3) *definite* – presence of length-dependent symptoms, clinical signs of small fiber damage, normal sural nerve conduction study, and altered IENF density at the ankle and/or abnormal QST thermal thresholds at the foot.

Epidemiology

There are no focused studies that provide definite epidemiological data on SFN. Before the availability of the current tools, the diagnostic criteria were not narrow enough to permit a retrospective analysis. On the other hand, the prevalence of SFN in more recent case series of sensory neuropathies is biased by the selection criteria of patients. Therefore, although supposed to be common, especially among patients with diabetes or metabolic syndrome and connective tissue diseases, the precise frequency of SFN is not known.

Symptom Presentation and Clinical Examination

SFN has been considered prototypical of painful neuropathy. This is not completely correct because mixed (large and small fiber) and even predominantly large fiber neuropathies can also present with severe neuropathic pain symptoms, at least over some periods of their course. However, the most common complaint of SFN is that of burning feet, although patients can show dysautonomic disturbances (e.g., abnormal sweating of leg and/or feet, xerostomia and/or xerophthalmia, dizziness, genitourinary disturbances), and about 15 % of them have calf cramps [42].

The quality of neuropathic pain can differ in different patients, though about 60 % of patients describe it as spontaneous, such as burning or like a sunburn, paroxysmal, pruritic, or deep. It is frequently worse at rest, particularly at night, interfering with sleep. Evoked pain more commonly presents with thermal (cold or warm) allodynia or dynamic mechanic (i.e., tactile) allodynia. Patients may complain that the feet are cold although they are warm at touch or feel as if their feet and legs are constricted, like in a skin that is too tight. Allodynia may make bedsheets intolerable or induce pain while wearing certain footwear or walking. Symptoms of restless legs syndrome can also coexist.

Neurological examination focused to feet and soles can detect thermal and/or pinprick hypoesthesia in up to 40 % of patients and disclose hyperalgesia or aftersensation in 10–20 % of patients [43]. Vibratory sensation, examined by the 64 Hz tuning fork and assessed referring to available normative values [44], should be normal at the toe. In pure SFN, there should be no muscle atrophy or weakness. Deep tendon reflexes should be normal. Various forms of autonomic dysfunction may be reported by the patients, though it is important to ask focused questions (e.g., reduced or excessive sweating, constipation or diarrhea, impotence, micturition disturbances, dry eyes and/or mouth, dizziness at postural variation). It has been reported that, in SFN patients, functions mediated by cholinergic and skin vasomotor fibers are more impaired than those mediated by systemic adrenergic fibers, reflecting in more frequent vascular deregulation in the lower limbs than cardiovascular autonomic impairment [45]. This observation was confirmed in a large group of pure SFN patients [43]. In most patients, SFN starts distally and shows a length-dependent course with proximal involvement of the legs and, later, of the hands. Some patients can present with diffuse symptoms involving feet, hands, low abdomen, and perioral region, such as in SFN caused by oxaliplatin neurotoxicity. In a small number of patients with SFN, discomfort may first be felt in the face or scalp [46]. In these cases, as well as in patients complaining of patchy or asymmetric sensory symptoms, sensory neuronopathy (i.e., ganglionopathy) should be considered and appropriate diagnostic work-up started in order to rule out paraneoplastic or immune-mediated diseases [47] even in patients with pure SFN [48].

Table 25.1 SFN symptom inventory questionnaire (atleast 2 are required)

Sensory	Autonomic
Peripheral pain (burning)	Sicca syndrome (dry mouth/eyes)
Paresthesia	Accommodation disturbances
Allodynia	Hyperhydrosis/hypohydrosis
Diminished temperature sensation	Micturation disturbances
Diminished pain sensation	Impotence/diminished lubrication
	Gastroparesis
	Diarrhea/constipation
	Facial flushing
	Orthostatic complaints
	Palpitations

Questionnaires and Scales

The only validated tool available is the SFN Symptom Inventory Questionnaire (SIQ) [49]. It includes 13 questions, each having 4 response options: 0 = never, 1 = sometimes, 2 = often, 3 = always (Table 25.1). It has been proposed to define the diagnosis of SFN in patients with at least 2 positive answers and evidence of IENF and/or thermal threshold QST abnormalities, after large fiber impairment is ruled out by clinical and nerve conduction examinations.

Table 25.2 Acquired and genetic diseases associated with pure and predominantly somatic SFN

Metabolic	Diabetes	Immune-mediated	Celiac disease
	Impaired glucose tolerance		Sarcoidosis
	Hypothyroidism		Sjögren syndrome
			Paraneoplastic syndrome
Drugs and toxics	Antiretroviral drugs		
	Metronidazole	Genetic	Fabry's disease
	Bortezomib		Sodium channel mutations (SCN9A)
	Chronic alcohol abuse		Familial burning feet syndrome
			Hemochromatosis

The clinical picture of SFN is dominated by neuropathic pain symptoms. Therefore, it is important to grade both spontaneous and evoked (allodynia and hyperalgesia) pain intensity in all the patients; this can be especially helpful in the evaluation of the efficacy of treatments at follow-up visits. The Neuropathic Pain Scale (NPS) or the Visual Analogue Pain Scale (VAS) can be used to score pain from 0 (no pain) to 10 (most intense pain imaginable).

Natural Course

In a cohort of pure SFN [43], a potential etiology was determined in 25 % of patients. In particular, diabetes or impaired glucose tolerance (IGT) accounted for about 35 % of cases, Sjögren syndrome for 7 %, and hypothyroidism for 5 %, whereas SFN remained idiopathic in about 40 % of patients. At 2 years follow-up, in 20 % of patients formerly diagnosed with idiopathic SFN, diabetes or IGT was found. About 10 % of patients diagnosed with SFN showed a progression to a mixed (large and small fiber) neuropathy. In most patients with SFN, the clinical picture did not change over time, though about 30 % of them experienced a worsening of neuropathic pain intensity. Some patients with SFN may complain of disproportionate generalized pain and fatigue [50]. Whether this is part of an underlying disorder or a problem of coping with the disease remains frequently unanswered.

Recovery from SFN has been described [51] as well as courses with continuous symptoms and with intermittent symptoms [52, 53]. It has been also reported that the improvement of the metabolic status in patients with IGT can be associated with the recovery of SFN and with a decrease of pain intensity [54].

Etiology and Pathogenesis

There are a number of conditions clearly associated with pure and predominantly somatic SFN (Table 25.2). Conversely, small nerve fibers are frequently impaired in a large number of mixed neuropathies. Two examples are amyloid and chemotherapy-associated neuropathy. Both conditions can present with early symptoms reflecting the damage of small fibers, but neurophysiologic tests almost invariably show, with the exception of bortezomib in a small percentage of patients, the involvement of large sensory fibers [55, 56].

SFN has been described in association with several acquired conditions and systemic diseases, including diabetes and prediabetes, hypothyroidism, hyperlipidemia, statin, antiretroviral, and metronidazole therapy [43, 57–64], immune-mediated and connective tissue disorders [48, 65–70], infectious diseases [71, 72], chemotherapy [73, 74], chronic alcohol abuse [75], and paraneoplastic syndromes [76]. Fabry and Tangier diseases are rare genetic syndromes in which early neurological manifestations can include SFN [77]. Patients with SFN have been described also in hereditary hemochromatosis [78]. The frequency of SFN in each of these conditions varies in different series and is not precisely known. Moreover, many reports are anecdotal, making a causal correlation rather doubtful. However, a thorough screening should be always performed. Finally, in a substantial proportion of patients, ranging from 25 to 90 % in the different case series, the etiology may remain unknown [43, 79–82].

About one decade after the first description of familial SFN cases [83, 84], screening of the gene SCN9A encoding for the Nav1.7 the sodium channel demonstrated single amino acid substitutions (mutations and polymorphisms) in this peripheral sodium channel in 30 % of patients with a diagnosis of idiopathic painful SFN [18]. This observation supports definition of a new syndrome of channelopathy-associated SFN. A further family with acromesomelia (small hands and small feet) and SFN carrying another missense mutation of Nav1.7 has been also described [85]. All these novel Nav1.7 variants produced hyperexcitability of DRG neurons, on the basis of different changes in channel function compared to those typically found in IEM and PEPD. However, it has not been possible thus far to define a correlation between phenotype, genotype, and cell electrophysiological changes for the SFN variants. Indeed, the same amino acid substitution has been found to be associated with three different phenotypes such as severe facial pain, hands and feet pain, and scalp discomfort in three patients, two of which are from a single family, demonstrating intra– and interfamily phenotypic diversity in pain syndromes produced by a

single gain-of-function variant of Nav1.7 [86]. The bases for this phenotypic diversity are not yet clear. They may include modifier loci and environmental or epigenetic factors.

Despite the association of SFN with multiple acquired and genetic conditions, the pathogenesis underlying the degeneration of small fibers remains unknown. For example, it has been shown that diabetes reduces the ability of small epidermal nerve fibers to regenerate after chemical denervation with topical capsaicin even in patients without neuropathy [87]. It may be therefore hypothesized that hyperglycemia affects the machinery of axonal transport, though there is no strong evidence in support of this view. Immune-mediated mechanisms have been advocated for SFN associated with sarcoidosis and Sjögren syndrome based on the response to immune-modulating or immune-suppressant treatments in single patients or small case series [88–90], but this mechanism has not been shown by serum transfection experiments in animal models. Even the evidence that mutations of Nav1.7 causes unequivocal functional changes of small DRG neurons, from which small nerve fibers arise, does not directly explain their degeneration. It is possible that sodium overload in neurons and small axons induces an increase of intracellular calcium due to the reverse (calcium-importing) sodium-calcium exchange since the sodium-calcium exchanger is colocalized with Nav1.7 in small-caliber peripheral axons [16], but this has not been proven yet. Moreover, voltage-gated channels have complex interactions, suggesting that changes can affect each other [91].

Investigations in Small Fiber Neuropathy

Laboratory Tests

SFN should be first considered as potential complication of a possible underlying systemic disease, and diagnostic work-up should be directed at discovering it. Since diabetes mellitus is one of the most common causes of SFN, fasting glucose, glycosylated hemoglobin, and an oral glucose tolerance test should be performed. In addition to routine blood chemistry, screening of serum and urine protein electrophoresis and immune electrophoresis, thyroid hormones, vitamin B12, folate, cuprum, and antinuclear antibodies (including SS-A and SS-B) should be performed. Celiac disease should be considered and ruled out when suspected. Among immune-mediated disorders, Sjögren syndrome and sarcoidosis should be always taken into account. Amyloidosis should be also suspected, though at the diagnosis, patients commonly present a mixed neuropathy with dysautonomia and cardiac and/or liver involvement. A panel of onconeural antibodies, especially anti-Hu, anti-CV2/CRMP-5, and antiganglionic acetylcholine receptor antibodies, should be screened to rule out a paraneoplastic form [92].

Genetic conditions, such as Fabry's disease, are rare and present with a syndromic picture. When suspected, protein assay and mutations in alpha-galactosidase gene should be searched. The recent definition of channelopathy-associated SFN suggests that it may be helpful to screen SCN9A for gain-of-function mutations in patients with idiopathic SFN, especially if they have an early onset and positive familial history.

Neurophysiologic Studies

Since large fibers are not affected in SFN by definition, nerve conduction studies should not show abnormalities in sural nerve action potential amplitude (SNAP) or conduction velocity. However, in some patients, plantar sensory nerves can be abnormal [93, 94] suggesting that the involvement of most distal large myelinated fibers may be demonstrable at least in some.

A painful electrical cutaneous stimulus can elicit a phase of electrical silence in the muscle during a maximal voluntary contraction by the inhibition of motoneurons. This nociceptive reflex, known as cutaneous silent period (CSP), is mediated by Aδ fibers and has been used in patients to detect small fiber damage [36, 95–98]. Further studies demonstrated that it is also partly mediated by Aβ fibers [99]. The CSP can be analyzed in terms of latency and duration, but its diagnostic value in SFN is questionable in the light of a poor specificity [100].

Microneurography is a minimally invasive method that allows single Aδ and C fiber activity recording [101]. It has been used to demonstrate C fiber dysfunction in erythromelalgia after capsaicin denervation and in painful neuropathies [102–105]. This technique has significantly contributed to knowledge on the physiology of nociceptors and mechanisms underlying their sensitization [6, 8, 106–108]. Nevertheless, it is time consuming and requires both an expert investigator and a collaborative patient, being unsuitable for the assessment of small fibers in routine clinical settings.

Laser-generated radiant heat pulses selectively excite free nerve endings in the superficial skin layers and are recorded from the scalp as late and ultralate laser-evoked potentials (LEPs) which are generated by Aδ and C fibers, respectively [109]. LEPs provide an accepted method of investigating nociceptive pathways and have been used to detect the damage of small fibers in painful neuropathies [37, 110–113]. However, LEPS are frequently absent both in SFN and mixed neuropathies [43, 114], making this technique nonspecific for diagnosis in individual patients.

Contact heat-evoked potential stimulators (CHEPs) provide a technique, more recently developed [115], that exploits an extremely rapid heat rising time to evoke Aδ– and C-fiber-related scalp components. Only a few studies on SFN

have been performed using this technique, mainly demonstrating a correlation with Aδ fiber damage and skin denervation [38, 114, 116–118].

Quantitative Sensory Testing

The most popular technique used to investigate the function of small fibers has been the determination of perception thresholds to warm, cold, and by pain quantitative sensory testing (QST) devices [39, 119, 120]. This is discussed in details in Chap. 11. Several reports demonstrated thermal threshold abnormalities in patients with SFN and neuropathic pain [43, 121, 122]. However, despite its widespread use, QST has some drawbacks that limit the reliability of results in clinical practice. Indeed, this approach has proved to be more useful in population studies than in individual patients [123, 124]. The expected correlation between cold and/or warm threshold, conveyed by Aδ and C fibers, respectively, and IENF density was found in some [125–129], but not all the studies [130–132].

QST was also used to investigate whether the individual pattern of signs and symptoms reflecting specific alteration in nociceptive processing allows stratification of patients based on their somatosensory profile rather than the underlying etiology, thus providing a mechanism-based classification of neuropathic pain. The analysis of 13 QST parameters including measurements of negative (e.g., hypoesthesia) and positive (e.g., hyperesthesia) sensory thresholds performed in a cohort of 1,236 patients of neuropathic pain patients did not confirm this hypothesis [133]. Indeed, there was a remarkable phenotypic heterogeneity across the major neuropathic pain syndromes that included an overlap between central and peripheral nervous system diseases. For example, polyneuropathy and central pain were both reported to have low rates of positive and high rates of negative sensory signs, with similar frequencies of paradoxical heat sensation.

A recent study investigated two groups of patient with nerve injury with and without neuropathic pain and did not find any difference in the thermal thresholds, with a higher frequency of evoked pain (light touch allodynia and reduced mechanical pain thresholds) in the pain group only [134]. Overall, the analysis of sensory thresholds by QST may provide information on the nociceptive pathway functions and be a valid complement to the bedside examination. However, it should be used in relation to the clinical context and in conjunction with other tests [123].

Skin Biopsy

This valuable diagnostic procedure is most commonly performed using a 3-mm disposable circular punch under sterile technique, after topical anesthesia with lidocaine. No suture is required. The specimen contains both the epidermis and the dermis. A skin specimen is commonly taken at the leg, 10 cm above the lateral malleolus, within the territory of the sural nerve. Healing occurs within 7–10 days. The procedure, including the immunohistochemical assay and the procedure for quantification of IENF, has been detailed in guidelines and is discussed comprehensively in Chap. 13 [135]. Skin biopsy is a safe technique, with an estimated frequency of side effects of 1.9:1,000, most commonly mild infection due to improper wound management, which recovers with topical antibiotic therapy, or excessive bleeding which does not require suturing. Normative reference values adjusted per age decade and gender (using bright-field immunohistochemistry) are available and provided the lower cutoff to define the quantification of IENF as normal or reduced in individual patients [136]. A novel method to measure dermal nerve length is also available [137]. It proved to correlate with IENF density and demonstrated a high performance in distinguishing SFN from healthy individuals. Further studies are warranted to establish age- and gender-matched normative reference values and the impact of dermal nerve quantification in symptomatic patients with normal IENF density, in asymptomatic patients at risk to develop neuropathy, and in patients with mixed (large and small) neuropathies.

Skin biopsy represent the most reliable technique to diagnose SFN [138]. It demonstrated the correlations between the loss of IENF and the clinical presentation in patients with diabetes, HIV, connective tissue disorders, and other conditions at risk for SFN [139]. The density of IENF correlates with the loss of pinprick sensation in patients with idiopathic SFN [140]. It correlates also with the number of symptoms of SFN and, inversely, with the quality of life of patients with SFN associated with sarcoidosis [49]. In patients with diabetic neuropathy, IENF density progressively declines over time and was not correlated with the degree of metabolic control, indirectly supporting the hypothesis that hyperglycemia may trigger mechanisms maintaining axonal damage. In HIV neuropathy, a baseline reduction of IENF density predicted the risk of developing neuropathy symptoms over a 2.9-year period, which was 14-fold higher in patients with a density lower than 10 IENF/mm [141]. This is in keeping with studies showing that morphological changes of IENF, mainly large axonal swellings, may predict the development of an overt neuropathy at 2 years follow-up [139, 142].

An even less invasive sampling method is the suction of the epidermis alone using the “blister technique” [143]. It does not cause bleeding and local anesthesia is not needed. A comparative analysis of IENF density between this technique and the punch biopsy did not show differences [144].

Treatments for Small Fiber Neuropathy

Causative therapies should be given whenever possible. However, there is no evidence of efficacy of disease-modifying treatments in SFN. Response to intravenous immunoglobulin or immune-suppressant drugs has been reported in single patients or small cases of patients with SFN associated with sarcoidosis and Sjögren syndrome [88–90]. In Fabry's disease, enzyme replacement therapy failed to induce the regeneration of IENF [145].

Most patients with SFN need treatments for neuropathic pain for which guidelines are available; outlined also in detail in Chap. 80 [146]. The available evidence is based on studies of painful neuropathies of different etiology, whereas no clinical trial has been focused on SFN.

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Charcot-Marie-Tooth Diseases

26

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Introduction

Charcot-Marie-Tooth (CMT) disease (also called hereditary motor and sensory neuropathy; HMSN) is a heterogeneous group of hereditary diseases of peripheral nerve (Table 26.1). CMT disease is a common disorder affecting children and adults, which may lead to significant impairment. Modes of inheritance include autosomal dominant, autosomal recessive, and X linked.

Historical Perspective and Classification

The earliest identification of hereditary peripheral neuropathies dates back to clinical and clinicopathological reports by Virchow, Aran, Eichorst, Friedreich, Osler, and others [1]. The definitive descriptions by Tooth [2] and Charcot and Marie [3, 4] in 1886 led to the recognition of the condition as Charcot-Marie-Tooth disease (CMT). In 1889, a family with X-linked CMT was reported [5]. An early-onset, severe form was contributed by Dejerine and Sottas in Charcot's group at the Salpetrière Hospital in Paris, France [6]. The association with tremor was noted by Roussy in 1926 [7]. Different forms of inheritance were later categorized by Allan [8].

The advent of modern electroneuromyography (ENMG) in the 1960s permitted further classification of CMT into one with relatively normal nerve conduction velocities (NCV), axonal and preservation of the myelin sheath (CMT2 or HMSNII), and another with slow NCVs and histological features of hypertrophic demyelinating neuropathy with Schwann cell abnormalities and prominent onion bulb formation (CMT1 or HMSNI) [9–11]. The features of CMT1 and CMT2 were outlined in two landmark publications detailing the genetic and clinical characteristics of over 200 patients [12, 13]. CMT1 patients have median motor NCVs below 38 m/s. Slowing is uniform along individual nerves and between nerves; this distinguishes CMT1 from acute or chronic inflammatory demyelinating polyneuropathy [14, 15]. CMT2 patients have NCVs above 38 m/s. A separate intermediate NCV CMT subtype (DI-CMT) was also recognized [16–18]. The Dejerine-Sottas syndrome (DSS or CMT3 or HMSNIII) features NCVs of <10 m/s. Classification systems based on inheritance and clinical, electrophysiological, and histological features are being complemented by mutation analysis, since major phenotypic variations appear to be best explained by the impact of specific mutations on myelin and axonal functions and interactions. Furthermore, pedigrees in which young members have fairly normal NCVs, whereas older relatives have severe slowing, have been described [19]. In general, clinical deficits correlate better with progressive axonal degeneration than with slowed NCVs.

In the 1980s, genetic linkage studies demonstrated the first CMT loci on chromosome 1 [20] and chromosome 17 [21–23]. In 1991 CMT1A, the most common form of CMT, was associated

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Table 26.1 CMT subtypes

Subtype	Gene	Chromosome	Distinctive features
CMT1A	*PMP22*	17p12	Most common subtype, onion bulbs nerve biopsy
CMT1B	*MPZ*	1q23.3	Often identical to CMT1A, late-onset axonal variant
CMT1C	*LITAF/SIMPLE*	16p13.13	No distinctive features
CMT1D	*EGR2*	10q21.3	Rare subtype, no distinctive features
CMT1E	*PMP22, MPZ, Cx32*, others		Association of CMT with deafness
CMT1F	*NEFL*	8p21.2	NEFL mutations also associated with CMT2E
HNPP	*PMP22*	17p12	Asymmetric recurrent neuropathy, tomacula
HNA	*SEPT9*	17q25	Recurrent painful brachial plexopathies, dysmorphic features
CMTX1	*Cx32*	Xq13.1	Common subtype, CNS involvement, variable NCVs
CMTX2	Unknown	Xp22.2	Infantile onset, mental retardation
CMTX3	Unknown	Xq26	Prominent paresthetic pain, women with high arches
CMTX4	Unknown	Xq24-q26.1	Severe, deafness and mental retardation in males
CMTX5	*PRPS1*	Xq22.3	Axonal neuropathy, deafness, optic neuropathy
CMTX6	*PDK2*	Xp22.11	Axonal polyneuropathy
DI-CMTA	Unknown	10q24.1-q25.1	Second decade onset
DI-CMTB	*DNM2*	19p13.2	Mild–moderate, neutropenia, cataract, onion bulbs
DI-CMTC	*YARS*	1p35.1	Variable onset
DI-CMTD	*MPZ*	1q23.3	Variable distal wasting, weakness and sensory loss
DI-CMTE	*INF2*	14q32.33	Second decade onset, legs > arms, kidney disease, hearing loss
CMT2A1	*KIF1B*	1p36.2	Rare
CMT2A2	*MFN2*	1p36.2	Common subtype, variable onset and severity
CMT2B	*RAB7*	3q21.3	Most sensory, foot ulcerations, occasional onion bulbs
CMT2B1	*LMNA*	1q22	Second decade onset
CMT2B2	*MED25*	19q13.33	Minimally reduced NCVs
CMT2C	*TRPV4*	12q24.11	First decade onset, vocal fold dysfunction
CMT2D	*GARS*	7p14.3	Worse hand than leg weakness, slow progression
CMT2E	*NEFL*	8p21.2	Variable onset age and severity
CMT2F	*HSPB1*	7q11.23	Slow progression
CMT2G	Unknown	12q12-q13.3	Slow progression of foot deformity, conduction velocities may be normal
CMT2H/K	*GDAP1*	8q21.11	Variable onset and severity, some with pyramidal signs
CMT2I	*MPZ*	1q23.3	Asymptomatic or cramps with foot deformities
CMT2J	*MPZ*	1q23.3	Fourth to sixth decade onset, deafness, sensory and autonomic dysfunction
CMT2L	*HSPB8*	12q24.23	Also linked to dHMN2A
CMT2M	*DNM2*	19p13.2	Prominent gait ataxia
CMT2N	*AARS*	16q22.1	Onset first to sixth decade, asymptomatic or distal weakness/sensory loss/deafness
CMT2O	*DYNC1H1*	14q32.31	Early onset and delayed milestones
CMT2P/AR-CMT2	*LRSAM1*	9q33	Second or third decade onset, distal weakness, mild sensory changes
DSS	*PMP22, EGR2, MPZ, PRX*		Onset in infancy or early childhood, hypertrophic nerves
CHN	*PMP22, EGR2, MPZ*		Neonatal hypotonia, areflexia and arthrogryposis
CMT4A	*GDAP1*	8q21.11	Infancy onset, severe, vocal cord paralysis, onion bulbs
CMT4B1	*MTMR2*	11q21	Infancy onset, severe, focally folded myelin sheaths
CMT4B2	*SBF2*	11p15.4	First to second decade onset, glaucoma, myelin outfoldings
CMT4C	*SH3TC2*	5q32	Prominent scoliosis; early loss of ambulation; heterozygotes: mildly affected
CMT4D Lom	*NDRG1*	8q24.22	First decade onset, gait difficulty, skeletal deformities, hearing loss
CMT4E	*EGR2*	10q21.3	Cranial nerve involvement, arthrogryposis, and respiratory failure
CMT4F	*PRX*	19q13.2	First decade onset, gait ataxia, onion bulbs
CMT4G Russe	*HK1*	10q22.1	Severe disability, prominent sensory loss, intermediate motor NCVs
CMT4H	*FGD4*	12p11.21	Early onset, scoliosis, hypomyelination, redundant myelin sheaths
CMT4J	*FIG 4*	6q21	Severe phenotype, childhood onset, motor dominant
CMT RIA	*GDAP1*	8q21.11	Variable severity
CMT RIB	*KARS*	16q23.1	Self-abusive behavior and dysmorphic features
GAN	*Gigaxonin*	16q23.2	Early onset, mental retardation, tightly curled hair

with a 1.5-Mb duplication within chromosome 17p11.2, which contains the myelin gene *PMP22* [24, 25]. Mutations in *PMP22* were linked also to demyelinating neuropathies in Trembler and Trembler-J mice [26, 27] and to CMT1A and DSS [28–30]. Transgenic mice and rats that overexpress *PMP22* were found to develop neuropathies resembling CMT1 [31–33]. CMT1A also occurs with partial or complete trisomy of the short arm of chromosome 17, as part of a phenotype with developmental and growth delay, craniofacial and skeletal anomalies, and heart defects [34, 35].

The second most common subtype, X-linked recessive CMTX1, was found to result from mutations in the gap junction protein beta 1/connexin-32 (*GJB1/Cx32*) on chromosome Xq13.1 [36]. Other loci and two more genes have been identified for subtypes CMTX2, CMTX3, CMTX4, CMTX5, and CMTX6 (see below) [37].

The 1990s also saw the identification of other CMT genes. CMT1B and some cases of DSS were found to be associated with mutations in the myelin protein zero gene (*MPZ*), located on chromosome 1q23.3 [38–40]. Mutations in the zinc-finger-domain-containing transcription factor early growth response two gene (*EGR2* or *Krox20*) on chromosome 10q21.3 were linked to congenital DSS, hypomyelinating neuropathy (CHN), and CMT1D [41]. Deletion of *PMP22* was associated with hereditary neuropathy with liability to pressure palsies (HNPP) and several other phenotypes [42]. Recent studies identified numerous nonrecurrent genomic rearrangements of atypical size on the 17p12 chromosome, encompassing the *PMP22* gene, in patients with either CMT1A or HNPP, further underscoring the fact that either altered dosage or dysregulation of this gene is the major cause for the CMT1A and HNPP phenotypes [43]. An HNPP-like condition, hereditary neuralgic amyotrophy (HNA), was mapped to chromosome 17q25 [44, 45]. Mutations of all of these genes have been associated with several overlapping clinical phenotypes. For instance, DSS occurs with *PMP22*, *Cx32*, *MPZ,* and other mutations [19, 41, 46–48]. Some 50 genes have been associated with different CMT subtypes, and their number continues to increase [49].

CMT disease genes can be categorized by cell biological criteria. Some play a role in signal transduction or the cell cycle (*GDAP1, MTMR2, SBF2, SPTLC1, NDRG1*), others are associated with the cytoskeleton (*NEFL, DYNC1H1, INF2, gigaxonin, LMNA, MFN2, RAB7, PRX, KIF1Bβ), and* some with Schwann cell membranes (*MPZ, Cx32, PMP22*), yet others are transcription factors (*EGR2, SOX10*) or are involved in protein degradation (*LITAF/SIMPLE, LRSAM1*). Mutations in aminoacyl tRNA synthetases which catalyze the esterification of an amino acid to its cognate tRNA have been identified (*AARS, GARS, KARS*, and *YARS*) in several subtypes; they may be pathogenic by way of other cellular roles than protein synthesis. The various CMT genes do not act in isolation; for instance, *PMP22* and *MPZ* co-localize and may interact in the myelin sheath [50]. In the Trembler mouse, Schwann cells are deficient in neural growth factors; this could lead to impaired axonal and myelin maintenance [51]. In rodents, *PMP22* overexpression upregulates the *CXCL14* gene which modulates expression of myelin genes and alters cell proliferation, and is expressed exclusively by sciatic nerve Schwann cells [52]. And *EGR2* regulates the transcription of several myelin genes.

This chapter gives greater emphasis to the more common CMT subtypes such as CMT1A, CMTX, CMT1B, CMT2, and HNPP than others. Rare mutations are discussed in some detail when they are associated with unique phenotypes or specifically contribute to understanding of normal and abnormal nerve physiology. Hereditary motor (HMN), sensory and autonomic (HSAN), and sensory (HSN) neuropathies; neuropathies with multiorgan disturbance or prominent central nervous system (CNS) involvement are reviewed briefly.

Epidemiology

CMT is found worldwide in people of all races and ethnic groups. It is among the most common heritable neurologic disorders, but estimates of its frequency vary. An exhaustive study from Norway indicated a prevalence of 3.6 per 10,000 people [53], whereas a worldwide meta-analysis estimated a prevalence of 1 in 10,000 people [54]. A Japanese epidemiologic study demonstrated a prevalence of 10.8 per 100,000 people [55]. In the USA, CMT affects approximately 150,000 people. It may be less common among African Americans; this may represent a lower frequency of specific mutations or protection from disease manifestation through unknown disease-modifying mechanisms.

Estimates of the frequency of CMT subtypes vary [54]. CMT1 accounts for about 50 % of CMT, CMT2, and CMTX for 10–15 % each. DI-CMT forms are rare. CMT1A accounts for 70–80 % of CMT1, CMT1B for about 10 %. CMT2A2 accounts for about 20 % of CMT2. CMTX1 accounts for 90 % of all CMTX. A Finnish study of 435,000 individuals found a prevalence of 16/100,000 people for HNPP and 20/100,000 people for CMT in general [56].

The autosomal-recessive forms are rare (less than 10 % of CMT in general) in the Western societies. Given the small size of sibships, many may remain unrecognized and be considered sporadic. Several have been described only in a small number of families with some being restricted to specific ethnic groups, for example, CMT4D Lom and CMT4G Russe. However, in populations with a high degree of consanguinity, for example, in North Africa, the Middle East, or in European Gypsies, autosomal-recessive forms likely account for 30–50 % of all CMT [57].

Clinical Presentation

Symptom Onset

Subjective and objective age of onset may vary with subtype, penetrance, familial phenotype, perceptiveness, and ascertainment bias. One of the authors' (FPT) patients reported symptom onset in his 50s; however, his family had been aware of his steppage gait 30 years prior. Asymptomatic individuals may be detected during mutation screening of families after a relative has been diagnosed. As a noteworthy caveat, a family history may be unrecognized due to oligo- or asymptomatic relatives, lack of perceptiveness of symptoms, nonpaternity, and late onset or early death of relatives; furthermore, de novo mutations with a truly negative family history must be considered, as well as autosomal-recessive inheritance. CMT1A has one of the highest de novo mutation rates, similar to neurofibromatosis type 1. Some families notice delayed walking in affected offspring. One of the authors' (FPT) patients was able to accurately diagnose CMT in children of her family by watching their feet point down when sitting on the ground. Other complaints include thin lower legs, clumsiness, and difficulty running. Onset in the first decade is common, but some patients date disease onset into young or mid or even late adulthood. Exceptions are more severe phenotypes such as DSS and CHN. Most CMT1A patients develop clinical evidence of disease before age 20 [58].

Fig. 26.1 Severe limb weakness and gait impairment in CMT4D Lom

Patient Complaints

Motor symptoms typically predominate over sensory. Often patients experience weakness and muscle wasting, foot deformities, loss of balance, and tripping over objects due to foot drop. Manipulating small objects such as forks, zippers, or pencils may be difficult. Parents or teachers of a child may notice a delay in motor milestones, clumsiness, frequent falls, or toe walking. Ankle sprains and fractures are frequent. Paresthesias, in contrast to acquired neuropathies, are typically less severe and rarely a presenting symptom; however, they may be acknowledged upon questioning. On the other hand, patients may deny sensory symptoms despite marked loss of sensation on examination. In CMT1 radicular pain may result from enlarged nerve roots (sometimes visible by MRI) because of ongoing demyelination and remyelination with connective tissue proliferation. Complaints of cold feet often associated with hair loss or leg edema occur. Non-neuropathic pain can be caused by pressure or strain of various structures associated with bones, joints, and tendons and abnormal posture at the knees, hips, and back, which results from foot weakness and fixed-foot deformities such as Achilles tendon shortening. Because of hammertoes and high arches, patients experience painful calluses and have difficulty finding shoes. Kyphoscoliosis and abnormal gait can lead to back pain. Patients complain of lower and upper limb cramps, often worse with fatigue.

Physical Findings

In some forms of CMT (e.g., HNPP and HNA), focal asymmetric features predominate; in others (e.g., certain *PMP22* mutations, HMSNP, HNA, and others), proximal weakness predominates. But typically, a predilection exists for distal limbs as the site of disease onset and for more severe symptoms and signs, and weakness and muscle atrophy affect the legs more and earlier than the arms (Fig. 26.1). Distal limb muscles atrophy over time and may produce the classic "inverted champagne bottle" or "champagne glass" appearance (Fig. 26.2). In young children, the exam may be entirely normal or limited to impaired heel gait. Proximal weakness is rare except in the most severely affected, in certain subtypes, and in hereditary focal neuropathies. Therefore, most patients with marked distal weakness are

Fig. 26.2 Distal leg atrophy in DI-CMTC. Inverted champagne bottle appearance of distal leg atrophy in a family with DI-CMTC. *Left* to *right*: the first, fourth, fifth, sixth, and tenth individuals have CMT; the second, third, seventh, eighth, and nineth are unaffected blood relatives

able to walk, albeit often with ankle foot orthoses. Severely affected patients may lose their ability to walk without assistance (Fig. 26.2). Sensation may be normal until adulthood, but distal, mild, and pansensory loss is common. Reflexes are absent or depressed. Foot deformities (including high arches or flat feet, hammer toes, and shortened Achilles tendons with fixed foot drop), while stigmata of CMT are nonspecific, as they can occur in chronic acquired neuropathies (Fig. 26.3). They become more prevalent with age and contribute to unequal wearing of shoes. Gait is compromised by poor proprioception, distal weakness, and foot drop due to weakness and later due to Achilles tendon shortening resulting in steppage gait. Enlarged and excessively firm nerves may be present in CMT1, sometimes visible in the superficial cervical nerves and palpable along peripheral nerves of the arms. Postural tremor occurs in up to 25 % of patients. Whether it is incidental or part of the syndrome remains controversial [7, 59, 60]. CMT may have a more severe phenotype in men, possibly because of environmental (nerve trauma) or X-linked modifying factors; evidence for CMT gene regulation by androgens and progesterone derivatives suggests a genetic influence for this gender difference [61, 62]. Gender differences may be superseded by the great phenotypic variability among and within families. Some CMT subtypes are notable for relatively isolated motor, sensory, and autonomic dysfunction. Discrete and subtle CNS involvement has been described occasionally [63–65]. Cranial neuropathies are rare, but various pupillary abnormalities [66–75] and laryngeal dysfunction with aspiration and dysarthria [76] occur, and sensorineural deafness has been described with multiple specific mutations [67–85].

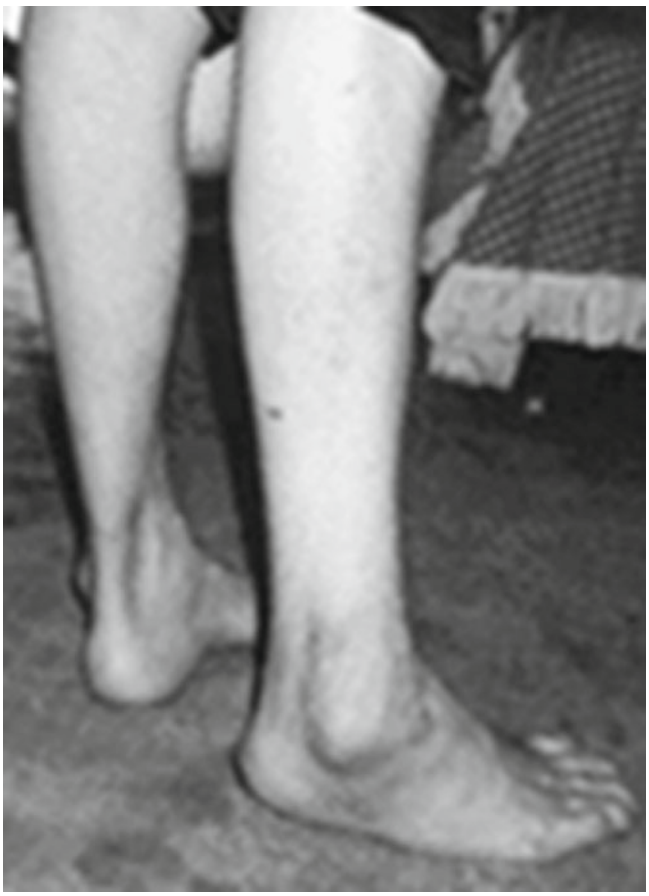

Fig. 26.3 Achilles tendon shortening with fixed foot drop and high arches in DI-CMTC. Achilles tendon shortening is often preventable if addressed early on with daily stretch exercises and foot bracing. Given the advanced stage shown here, this individual underwent surgery to improve gait and discomfort and to reduce likelihood of secondary damage to more proximal joints

Clinical Course

Slow progression of disability is typical. Therefore, any sudden deterioration requires consideration of superimposed acquired, for example, diabetic, autoimmune, or possibly independently inherited forms of neuromuscular diseases [86–90]. Severity varies widely between genetic subtypes, but also between families in a mutation-dependent fashion, and also within families [91]. Some adults require ankle foot orthoses only in the sixth decade, while children may already have foot drop, proximal leg weakness, and clawing of the fingers. A study of 43 CMT2 patients documented slow progression of weakness and disability, but most patients remained ambulatory [92]. During pregnancy, some patients experience more rapid deterioration from which they usually, but not always, recover [93, 94]. During medical procedures, prolonged immobilization of the body and limbs in fixed positions can result in nerve compression. Patients must inform their physicians of their CMT and request extra padding during procedures. Achilles tendon shortening is often preventable if addressed early on with daily stretch exercises and foot bracing. Different AFOs are appropriate for daytime versus nighttime use. Sometimes surgery is indicated for severe skeletal deformities to improve gait and discomfort and to reduce likelihood of ensuing damage to the knees, hips, and spine. Some patients find wider shoes a more comfortable fit for their high arches and hammertoes; wider shoes may also lessen local nerve compression. Sleep, upper airway, and pulmonary disorders result from pharyngeal, laryngeal, and phrenic nerve involvement with obstructive sleep apnea and vocal cord and diaphragmatic dysfunction and from restless leg syndrome (RLS) and periodic leg movement of sleep; some are more common in certain subtypes [70, 76, 82, 95]. Individuals with CMT1 suffer emotional stress that is similar to patients with comparable disability due to a stroke [96], with 44 % endorsing significant disability and 18 % depression; in this study, high disability predicted attitude about procreation, and 36 % of individuals opted against childbearing.

Diagnostic Evaluation

The purpose of investigative assessment in patients with a possible inherited neuropathy is to confirm or refute the working diagnosis and to determine whether a treatable neuropathy might exist as the sole condition or be superimposed on an inherited condition. The evaluation should include tests that address causes of neuropathies such as endocrinological, infectious, and immunological abnormalities, vitamin and nutritional deficiencies, and nerve compression.

Cerebrospinal fluid (CSF) analysis is rarely necessary but may be helpful in confusing clinical situations in which an acquired immune neuropathy is being considered. In CMT, CSF protein is usually normal but may be elevated above 100 mg/dl, in contrast, CSF protein is elevated in nearly all patients with DSS [97]. Elevated protein occurs in HNPP with recurrent polyradiculoneuropathy [98]. In a comparison of CMT1A, CMT1B, and CMTX, CSF protein (and CK) elevations were more common with *MPZ* mutations [99].

Establishing inheritance patterns can narrow the differential diagnosis and eliminate the need for some genetic tests. For practical purposes, CMTX forms need not be considered with well documented male-to-male disease transmission. On the other hand, the absence of a family history cannot be used to rule out a hereditary disorder because of the possibility of difficulties in ascertainment, variable penetrance and expressivity, nonpaternity, and de novo or recessive mutations.

Molecular genetic testing should be discussed as an option, when the clinical phenotype, family history, and ENMG suggest an inherited neuropathy. Clinical exam and ENMG often cannot definitively establish a diagnosis due to the overlap among clinical syndromes and the significant variability among family members with an identical genotype. Genetic verification permits sound family and prognostic counseling and advances the scientific understanding of phenotypes and pathomechanisms. In the current clinical practice, genetic testing often does not happen due to its cost. The importance of genetic evaluation is exemplified by a report of two sisters with severe CMT1 and healthy parents, for whom autosomal-recessive inheritance had been presumed until a low-level somatic and germline mosaicism of an *MPZ* mutation was identified in the unaffected mother with transmission to her affected daughters [100]. Patients may be difficult to persuade to undergo testing, because for many subtypes, genetic tests are not available yet, and thus, even with an extensive testing panel, all tests may return normal. With advancements in sequencing technologies, screening for all known CMT genes in a single assessment is an attractive opportunity that will significantly facilitate molecular diagnosis in the very near future. Although routinely fresh blood is required for DNA analysis, alternative sources of biological material are also applicable. For example, *PMP22* mutations have been diagnosed in 12-year-old, highly degraded DNA from sural nerve biopsies [101].

Genotyping does not exclude mutations with 100 % certainty. Laboratory errors such as mislabeling occur. DNA can degrade in transit. If results are counterintuitive, the test should be repeated. Point mutation analysis is largely limited to the protein-coding sequences but does not include the promoter, enhancer, silencer, deep intronic, or other non-translated sequences. Search for copy number variants, apart from *PMP22* duplication/deletion, is not performed on a routine basis. Mutations in more than one CMT gene in a patient (digenic inheritance) cannot be currently excluded. And genetic tests are not commercially available for many CMT genes.

Early ENMG studies showed slowed NCVs in patients with peroneal muscular atrophy [9–18]. Median motor NCVs are below 38 m/s in CMT1 and above 38 m/s in CMT2, though some studies have proposed a cutoff of 42 m/s. The distinction is not always clear: Relatively normal NCVs were found in younger members of a family with a particular *MPZ* mutation, whereas older relatives had severely slowed NCVs [67]. Conduction values are symmetric, and differences between proximal and distal nerve segments are rare. While exceptions exist, the concept of uniform slowing suggests that in CMT1, all myelinated fibers are affected along the entire nerve, in contrast to disorders such as CIDP, characterized by patchy involvement of different nerve segments, conduction block, and temporal dispersion [14]. Nerves often are refractory to stimulation or require higher intensity and prolonged stimulation. CMAP amplitudes may be reduced or absent (especially in the distal lower limbs due to complete denervation of small foot muscles), as may be sural nerve sensory action potential (SNAP) amplitudes. EMG may be normal in proximal muscles but show distal changes with increased duration CMAPs. Signs of active denervation such as increased insertional activity and fibrillation potentials are not prominent in muscles unaffected by weakness. Phrenic nerve CMAP also shows reduced amplitudes.

Although demyelination is the histopathological hallmark of CMT1, the clinical hallmarks, weakness and sensory loss, are probably produced by axonal degeneration and not demyelination. Children with CMT1A, for example, have conduction slowing prior to the onset of symptoms, and the NCVs do not change appreciably as the disease progresses, suggesting that demyelination is not sufficient to cause neurologic manifestations. In addition, CMAP amplitudes, not NCVs, correlate best with weakness in CMT1A [102]: In a study of 42 patients with CMT1A, weakness correlated with axonal loss measured by reduced CMAP amplitudes, but not with NCV slowing, suggesting that disability results from loss or damage to large-caliber motor and sensory axons.

In CMT1A, NCVs range from 10 to 42 m/s, again illustrating that the distinction of CMT1 and CMT2 cannot rest on NCVs alone [58]. Sensory NCVs are similarly reduced, when obtainable, but are often absent. Sensory loss correlates with median sensory NCVs and CMAP amplitudes [103]. In a study of 80 children, ENMG changes were documented as young as age two, and motor NCV slowing progressed throughout the first 6 years of life; CMAP amplitudes were decreased early in the disease, and the normal CMAP increase with age was attenuated [104]. In addition, axonal excitability is altered in CMT1A [105]: Stimulation thresholds were above normal, and the threshold electrotonus was markedly abnormal, suggesting altered cable properties consistent with demyelination and exposure or spread of K^+ channels normally sequestered under the myelin. In a *Pmp22* transgenic mouse model, the degree of weakness correlated with the number of functional motoneurons, but not the number of myelinated fibers or myelin thickness [106]. Anatomical evidence exists of progressive length-dependent axonal loss in CMT1A [82, 107] and in mice overexpressing *PMP22*.

Depending on the specific genetic defect and (in some families) age-related changes, neuropathies associated with MPZ mutations can present as demyelinating (CMT1B), pure axonal (CMT2), or intermediate (DI-CMTD) forms [67, 99, 108].

In HNPP diffuse sensory conduction slowing independent of nerve entrapment was reported consistent with a background demyelinative distal polyneuropathy; slowed motor NCVs were less common, although DMLs and F-wave latencies were frequently prolonged consistent with a distal motor polyneuropathy, similar to that seen in IgM monoclonal gammopathy against myelin-associated glycoprotein or sulfated glucuronyl paragloboside [109]. Others found that slowing correlated with the exposure to entrapment [110]. EMG is normal in proximal muscles but may show distal changes with increased CMAP duration. Signs of active denervation such as increased insertional activity and fibrillation potentials are not prominent in muscles unaffected by weakness. ENMG can lead to a HNPP diagnosis, even when the clinical features do not suggest it. On the other hand, bilaterally normal median DMLs and sensory NCVs at the wrist appear to exclude HNPP. ENMGs were similar in oligosymptomatic and asymptomatic patients and became characteristic as early as the second decade [111]. The variability within families may be considerable. Diagnostic criteria for the disorder have been proposed including slowed median sensory NCVs at the wrist, bilaterally delayed median DMLs, prolonged DMLs, and motor NCV slowing in the peroneal nerves [112, 113].

In DSS, the original description found absent electrical responses in the legs only in some cases and complete absence in the most severe cases [6]; NCVs are below 12 m/s in the arms with uniform slowing and marked dispersion [9].

Neuroimaging

Imaging studies may show enlarged spinal roots, limb, and cranial nerves [97, 114–119]. Homozygosity for *PMP22* mutations enhances root hypertrophy [97]. Areas of demyelination may be identified in the CNS, which should be imaged in the presence of symptoms or signs not attributable to the PNS [63, 64, 72–75, 119]. In CMT1A, MRI may reveal early restricted involvement of intrinsic foot muscles with atrophy, fatty infiltration, edema, and contrast enhancement; with advanced disease, proximal leg distal muscles may be affected [115]. In a comparison study, CMT1A was characterized by peroneal nerve innervated muscle involvement, whereas CMT2A MRI showed fatty infiltration of superficial posterior

compartment muscles [116]. MRI in CMT2M showed calf muscle infiltration, often in a length-dependent fashion [117]. In CMT1B, ultrasound showed median and vagus nerve enlargement; cranial nerve size did not differ between patients with and without cranial neuropathies [118].

Clinical and Genetic Subtypes

CMT1

PMP22 Duplication and Mutations (CMT1A)

A1.5-Mb duplication on chromosome 17p12 that includes the *PMP22* gene is the cause of most cases of CMT1A with the remainder resulting from point mutations in this gene (www.molgen.ua.ac.be/CMTMutations/). The *PMP22* genomic region is flanked by homologous repetitive palindromic sequences, which serve as substrates for a non-equal crossover resulting in a duplication in the case of CMT1A or a deletion in the case of HNPP. The duplication has been detected in many ethnic groups and accounts for 70–80 % of CMT1 cases [46]. Ninety percent of patients with sporadic CMT1 have a de novo 17p11.2-12 duplication. Duplications of paternal origin comprise nearly 90 % and are caused by unequal meiotic crossover between both chromosome 17 homologues, whereas the much rarer maternal duplications (and deletions) result from an intrachromosomal process [120].

Phenotypic Variations and Genotype-Phenotype Correlations

While most patients with *PMP22* duplication have a typical course, unusual phenotypes occur, in particular with point mutations. Tremor (Roussy-Levy syndrome) can be associated with CMT1A [59]. Occasional patients will present with radiculopathies due to enlarged nerve roots. Early hand involvement, which is frequently unrecognized, was documented by dynamometry, 9-hole peg test, and disease-related manifestations in a study of 84 children with CMT1A [121]. A Guillain-Barré-like presentation with rapid progression over 1 day and 17p11.2-12 duplication has been described [122]. A family with *PMP22* duplication presented with slow progression and predominantly proximal upper limb weakness and wasting [123]. In a family with *PMP22* duplication the severity of sleep apnea and neuropathy were correlated, possibly due to pharyngeal involvement [95]. Two sisters with neuropathy due to *PMP22* duplication had prominent sensory complaints, tremor, and episodes of acute paralysis [124]. CMT1A with deafness has been associated with several specific mutations [77–80]; this sometimes referred to as CMT1E. A *PMP22* mutation in the fourth transmembrane domain leading to a premature stop codon (Cys109stop) causes a phenotype ranging from asymptomatic to severely affected [125]. A father with adult-onset CMT1A and a 3-year-old child with congenital pes cavus, both with *PMP22* duplication, illustrate the diversity of the phenotype and the appearance of anticipation [126]. Atypical phenotypes can also result from the coexistence of CMT with inflammatory neuropathy, which may reflect a greater propensity of peripheral nerves in CMT to suffer inflammatory injury [127–129]. CMT1A has also been associated with prolonged QT syndrome [130].

Pathogenesis

PMP22 is a 160 amino acid protein with four membrane-spanning domains that are highly conserved in evolution. The protein is most highly expressed in Schwann cells, where it localizes to compact myelin but also is found in the brainstem and spinal motor neurons. Structural analysis indicates both a pore and a cell adhesion function.

Analysis of sural nerve RNA from patients with CMT1A due to duplication suggests that *PMP22* mRNA and protein overexpression causes the dysmyelination [131]. The exact pathogenetic mechanism is unknown; however, in vitro, *PMP22* overexpression disturbs the Schwann-cell cell cycle and causes apoptosis, whereas downregulation accelerates cell proliferation [132]. In Schwann cells of CMT1A patients, the overexpression of ErbB2 and B3, the Schwann cell receptors for neuregulins, an axonal growth factor family, might inhibit myelination and cause recurrent demyelination and axonal damage [133].

PMP22 point mutations likely cause neuropathy by a mechanism other than gene dosage. *PMP22* mutations in Trembler and Trembler J mice, also found in some CMT1A patients [29], inhibit transport of normal and mutant proteins from the endoplasmic reticulum and Golgi complex to the cell surface and cause *PMP22* accumulation in the Schwann cell bodies [134]. This results in a reduction in the amount of *PMP22* protein available for myelination, implying at least in part a loss of function disease mechanism. Trembler mice are much more severely affected than mice carrying a single copy of *Pmp22* [135]. Trembler mice have less myelin than *Pmp22+/−* animals, and the steady-state levels of their myelin-specific mRNAs are dramatically reduced [136]. This additional effect of mutated *PMP22* is probably caused by the interactions of the mutated *PMP22* with other cellular constituents (a toxic gain of function mechanism).

Neuropathology

Most nerve biopsies from CMT1 demonstrate a hypertrophic demyelinating neuropathy with onion bulbs indicating chronic remyelination and loss of myelinated fibers, preferentially those with large diameter. Biopsies from CMT1A patients with *PMP22* duplication reveal normal epi- and perineurium; increased fascicular area, endoneurial collagen, and numbers of Schwann cell nuclei; and loss of large myelinated fibers that correlates with age and clinical severity. *PMP22* expression in nerve biopsies is increased [137]. Most teased fibers are abnormal with widespread segmental demyelination and frequent paranodal loss of myelin. Internode

length is decreased and variable with numerous short internodes. In contrast to *PMP22* duplication, cases of *PMP22* missense mutations presenting as CMT1A or DSS show hypomyelination and resemble Trembler mice. A family with a mutation affecting the splice acceptor site of intron two presented with a typical clinical CMT1A phenotype; the nerve biopsy revealed a demyelinating neuropathy without classical onion bulbs or tomacula [138]. Skin biopsy, a less invasive alternative, showed myelin abnormalities; *PMP22* mRNA and protein levels are increased in CMT1A and decreased in HNPP [139].

PMP22 Deletion and Mutations (HNPP)

Onset of neuropathies associated with *PMP22* deletions typically occurs between age 30 and 40 but ranges from the first to the eighth decade; nerve palsy may be present at birth [140]. Presentations vary remarkably. For example, a 2-year-old child presented with toe-walking, pain, stiffness, asymmetric weakness, and bilateral upper motor neuron findings, and by age seven episodic numbness and weakness in the arms and borderline NCV were identified, and HNPP was then diagnosed [141]. Due to its insidious onset, many patients are unaware of the disability or seek medical attention only late in life. Some are asymptomatic. Of about 1,000 individuals with CMT at single US center, 6 % were found to have HNPP [142]. The condition may occasionally be identified when individuals develop an acquired neuropathy and seek evaluation.

In typical HNPP, motor symptoms predominate over sensory. After resting a limb in an awkward position, patients may report dysesthesias and weakness lasting weeks to months, rather than seconds to minutes. Slight nerve compression and repeated local exercise leads to episodes of weakness with decreased perception to touch and pain. Most attacks are sudden and initially followed by recovery. Most present with a single nerve involvement, sometimes upon awakening. Precipitating trauma, such as carrying heavy loads or playing musical instruments, may be minimal and unavoidable. One of the authors (FPT) evaluated a 15-year-old girl who would develop numb fingers when holding a pen, and once, after sitting on her cousin's shoulders, both legs became weak for some 20 min. In another personally evaluated family, an affected father and son develop recurrent symptoms of a greater occipital neuropathy when lying supine on the floor during yoga exercises. The father's cousin developed brachial plexus neuropathy during deer hunting season due the recoil of the rifle and greater occipital neuropathy when working on pipes lying on his back in the crawlspace under his house [143]. Between episodes of palsy, the exam may be normal or mildly abnormal. There may be distal and mild pansensory loss. Reflexes are normal in over 60 %. In one study, ankle jerks were absent in close to 40 % of patients, and areflexia occurred in slightly more than 10 % [113]. There is typically no neuropathic pain. In a series of 17 patients, most had transient focal weakness or sensory loss related to activities that may compress nerves [144]. HNPP can present as familial carpal tunnel syndrome without nerve palsy [145].

Sites of compression are often those of anatomic vulnerability: the fibular neck for the peroneal nerve, the cubital tunnel for the ulnar nerve, the spiral groove of the humerus for the radial nerve, and the carpal tunnel for the median nerve. Rare sites of involvement include the surgical head of the humerus for the anterior branch of the axillary nerve [146]. In a study of 70 patients, the average number of nerve palsies over a lifetime was about two [111]; the most commonly affected structure was the peroneal nerve, followed by the ulnar, the brachial plexus, and the radial and median nerves; and weakness persisted for more than 3 months in 15 % of patients. In three members of one family, brachial plexus palsies were the only manifestation [147]. Brachial plexopathy in HNPP may be recurrent, isolated, or part of other multiple mononeuropathies and is painless, in contrast to HNA [148–150]. While typically the disability is mild, progressive polyneuropathy with recurrent episodes of palsy may result in significant disability.

Phenotypic Variation

While HNPP is the most common manifestation of *PMP22* deletions, other phenotypes have been identified [111, 140, 151–153]. In one study, 41 % of participants with HNPP were unaware of their condition, and a quarter were essentially without symptoms [152]. In oligo- or asymptomatic individuals, the exam may reveal subtle abnormalities such as distal hyporeflexia or Tinel signs: In one report, a girl had a steroid responsive peroneal neuropathy; significantly slowed motor and sensory NCVs were recorded in the clinically unaffected monozygotic twin and their father [154]. The second most frequent presentation may be largely symmetric, slowly progressive polyneuropathy with high arches and hammertoes [111, 151, 152]. Some patients have recurrent, sensory symptoms lasting minutes to hours triggered by limb position or nerve compression. Others present with a chronic sensory polyneuropathy. Not surprisingly, patients may evolve from one phenotype to another, and different phenotypes may coexist in a family. Rarely, patients present with subacute recurrent or confluent demyelinating multiple mononeuropathies and are misdiagnosed as acute (AIDP) or chronic inflammatory demyelinating polyneuropathy (CIDP) [98, 151, 155]. Cranial neuropathies, including deafness [81], are infrequent and may sometimes represent chance events. Other rare associations include CNS manifestations [63–65], moving toes and myoclonus [65], fulminant 4-limb weakness possibly related to nerve compression [156], and sciatic neuropathy as the initial presentation [157]. Subclinical CNS involvement may manifest as abnormal blink and jaw-opening reflexes and acoustic evoked potentials [64]. The co-occurrence of schwannomas in the median and medial plantar nerves and HNPP has led to speculations about a possible common genetic basis [158].

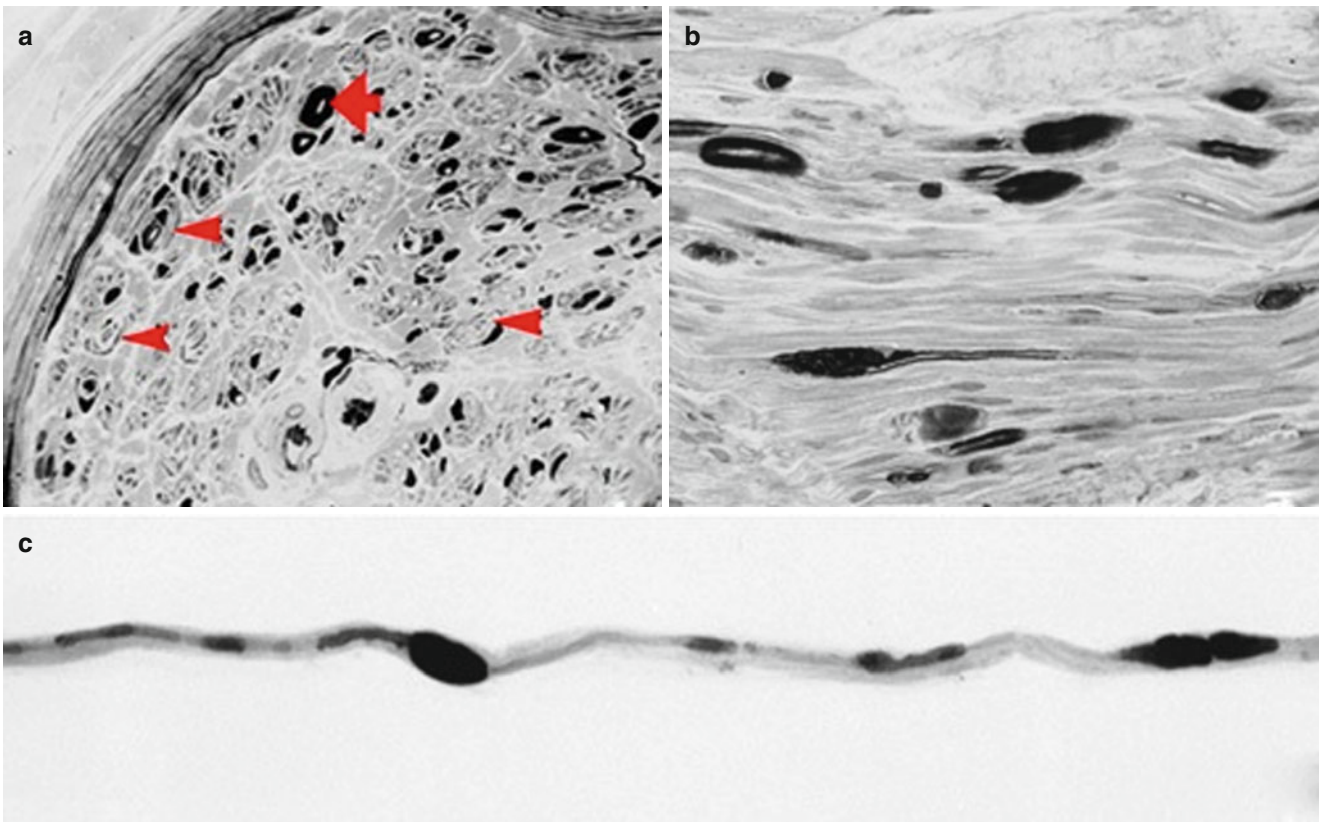

Fig. 26.4 Sural nerve biopsy in CMT1B showing tomacula. (**a**) Semithin cross section shows a marked depletion of myelinated nerve fibers. Scattered onion bulbs consist of concentrically arranged Schwann cell processes (*arrow heads*), some without a central myelinated fiber. Several myelinated fibers have a thick myelin sheath and an irregular contour, suggesting that they are tomacula (*large arrow*). (**b**) Semithin longitudinal section demonstrating tomacula in continuity with myelinated fibers. The myelin sheath is inappropriately thin, probably as a result of segmental remyelination or hypomyelination. (**c**) Teased myelinated nerve fiber containing tomacula that consists of globular expansions of myelin measuring 30–50 μm in length. Segments of the myelin sheaths between tomacula vary in thickness, and many of them are abnormally thin

Besides by *PMP22* deletion, HNPP can result from other *PMP22* mutations. Several HNPP patients with frameshift, nonsense, or splice-site mutations had typical phenotypes, likely because the mutations resulted in a functional deletion [159–161]. A mild phenotype resulted from a 3' splice-site mutation, preceding coding exon 3 [162]. Atypical phenotypes may also result from a combination of mutations in different CMT-causing genes. In one family, *PMP22* and *LMNA* mutations co-segregated, leading to a severe phenotype with unusual axonal involvement in addition to a typical myelinopathy [88].

Undiagnosed HNPP in an oligosymptomatic patient may complicate the treatment and diagnosis of an acquired neuromuscular disease later in life. For instance, a person with the disorder might develop diabetic amyotrophy or CIDP, and the ensuing clinical and electrical presentation and treatment responses might difficult to understand. HNPP has been diagnosed associated with ALS [89] and oculopharyngeal muscular dystrophy [90].

Pathogenesis

The fact that both *PMP22* deletions and frameshift or nonsense mutations are associated with HNPP suggests a loss of function mechanism. This notion is supported by the finding of *PMP22* underexpression in HNPP patient and transgenic mouse nerve tissue and of a similar clinical and histological phenotype in humans and animal models [135, 163, 164]. Homozygous *PMP22*-deficient animals have delayed myelination and weakness at 2 weeks, frequent tomacula at 3 weeks, severe nerve conduction slowing, onion bulbs and other signs of demyelination or remyelination when older than 2 months, and axonal atrophy at 12 months [164].

Neuropathology

Both motor and sensory fibers in most nerves show segmental demyelination and remyelination; variable, secondary, and axonal loss; and focal thickening of the myelin sheath or tomacula (Figs. 26.4 and 26.5) [165–168]. Outside of the tomacula the ratio of axon and fiber diameter (g ratio) is normal.

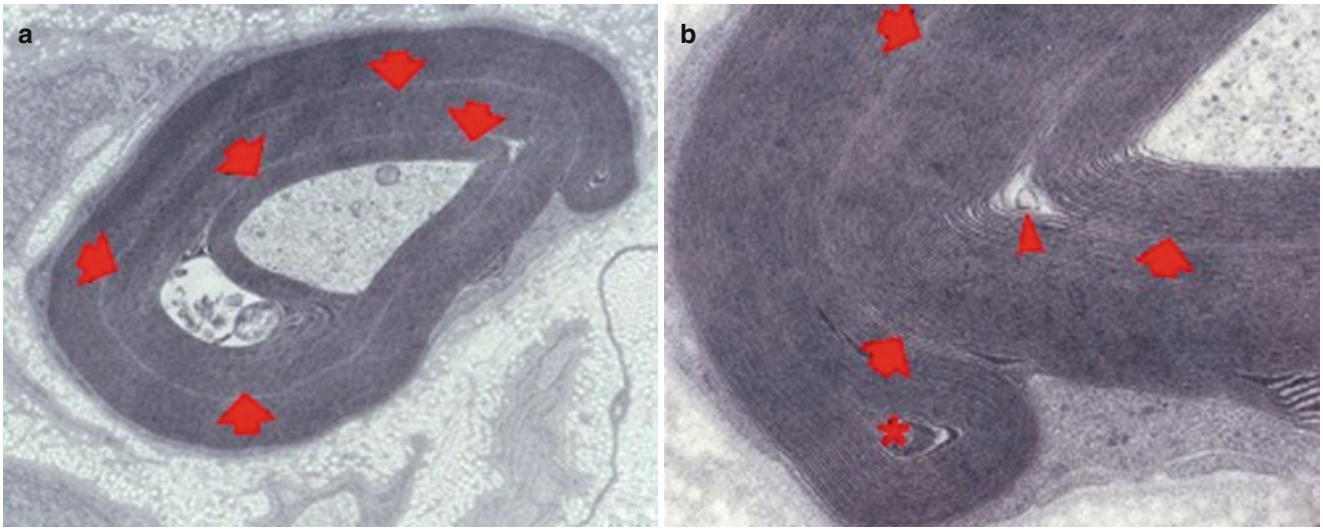

Fig. 26.5 Ultrastructure of a representative tomaculum. A redundant fold of myelin is wrapped nearly twice around the axon. The membranes of this fold are compacted about the original myelin sheath (19 lamellae) to form a hypermyelinated structure that is 97 lamellae thick along most of its circumference. The radial periodicity of these myelin lamellae is normal (14–15 nm). Where the extracellular surfaces of the original myelin sheath and the redundant fold fuse, a thin zone of reduced staining is formed (*large arrows*), which is about three myelin lamellae thick. The altered staining is mostly accounted for by the seam and the two adjacent intraperiod lines that are more lucent than elsewhere. The seam follows each turn of the redundant loop to form a giant spiral that ends in the ab-axonal Schwann cell cytoplasm. The paired membranes of these intermediate lines become indistinct within the cytoplasm, obscuring their connection with the surface membrane of the cell. Compaction of the internal surfaces of the redundant fold forms a second seam that is less distinct than the first one. It is formed by the line of fusion of the cytoplasmic surfaces of the Schwann cell membrane, thus producing an additional major dense line for each turn of the myelin fold. At the terminus of this seam, a small pocket of cytoplasm marks the site where the membrane of the fold loops back on itself (*asterisk* and *arrow head*). This remnant of cytoplasm is derived from the ad-axonal Schwann cell cytoplasm **A** × 13,000; **B** × 39,000

Onion bulb formation and increase in endoneurial connective tissue are limited. Tomacula are more often perinodal than internodal. Nodes of Ranvier are often obscured, probably by the transnodal myelin. There may be branching and duplication of the mesaxons, and more than one Schwann cell may participate in myelination [166]. In HNPP, the genetic defect disturbs adhesion of the myelin lamellae and may make them susceptible to displacement [167]. Ultrastructurally, the tomacula appear as redundant myelin loops, both external and internal, with intramyelinic folds. In a large teased-fiber study, a quarter of fibers were normal; half showed evidence of demyelination or remyelination, and half of fibers had tomacula [168]. Tomacula are not unique to HNPP but occur to various degrees with CMT1B and other CMT disorders, immune mediated, and other neuropathies [168–174].

CMT1B

This form of CMT results from mutations in the *MPZ* gene on chromosome 1q23.3 which codes for a membrane protein exclusively expressed by Schwann cells and constituting over 50 % of compact myelin. *MPZ* is a member of the immunoglobulin supergene family. The mature protein contains three major domains: an extracellular domain (amino acids [aa] 1–124), a transmembrane domain (aa 125–150), and a cytoplasmic domain (aa 151–219) [175].

Phenotypic Variations and Genotype-Phenotype Correlation

Typical clinical presentations are identical to CMT1A. Whether disability is greater in CMT1B or CMT1A is not clear [176]. CNS expression of mutated protein may be responsible for rare features such as dysphagia and deafness. Some 100 *MPZ* mutations have been identified. Over half are missense; the rest are nonsense, frameshift, deletion, or insertion mutations. They cluster in exons 2 and 3 encoding the extracellular domain, and in this way, they can disturb myelin compaction. Others are in the transmembrane (exon 4) or cytoplasmic (exons 5 and 6) domains or its margins. In rare cases, increased *MPZ* gene dosage is associated with CMT neuropathy [177].

Based on the age of onset and clinical and pathological features, most *MPZ* mutations are separable into two groups: one causing a severe, early-onset, demyelinating neuropathy and a second, causing a late-onset neuropathy with prominent axonal loss [178]. Patients with early onset usually have severe neuropathies with very slow NCVs. Many patients with late onset developed symptoms around or after age 40 and have relatively normal or only slightly slowed NCVs; nerve biopsies show prominent axonal loss with mild

demyelination. Insertion of a charged amino acid, altering a cysteine residue in the extracellular domain, and truncation of the cytoplasmic domain cause severe early-onset neuropathy, possibly due to disruption of the tertiary structure of MPZ and the MPZ-mediated adhesion and myelin compaction. Late-onset forms are usually caused by mutations that more subtly alter myelin structure but disrupt Schwann cell-axonal interactions and thereby lead to axonal degeneration.

Unusual phenotypes reflect the impact of specific mutations: Mild phenotypes with recurrent symptoms due to acute nerve compression in patients with demyelinating neuropathy have been associated with heterozygous nonsense mutation (Tyr145Stop) which leads to formation of an extracellularly truncated protein [179]. A combination of distal sensorimotor symptoms, cramps, restless legs syndrome, neuropathic pain, and carpal tunnel syndrome has been reported in a family with a missense Asp234Tyr mutation [180]. Chronic cough is described with the Thr124Met mutation [181]. A phenotype with tonic pupils and conduction block was described [182]. A mild late-onset phenotype with NCVs of 32 m/s resulted from an Asp122Glu substitution, which eliminates a crucial N-glycosylation site [68]. Tremor (Roussy-Levy syndrome) is associated with a heterozygous Asn131Lys substitution in the extracellular domain [60]. CMT1B responsive to immune modulation has been reported with some mutations [180, 183]. Mild recurrent CMT1B with an exon 3 Glu71stop mutation that may reduce MPZ expression was associated with sensitivity to intense manual work, demyelination and remyelination, myelin uncompaction, and axonal loss [184]. A double mutation with a de novo extracellular Val42 deletion and an intracellular Ala221Thr substitution was found in a 25-year-old woman with a progressive neuropathy since age 2. Her father had two normal alleles, and her mother had the Ala221Thr substitution [185]. A mixed demyelinating and axonal neuropathy, pes cavus, and pupillary light-near dissociation were associated with mutations His81Arg and Val113Phe lying on the same allele [69]; the phenotype was less severe than in two instances of isolated His81Arg mutations [186, 187]. A His39Pro extracellular domain mutation was linked to hearing loss and restless leg syndrome [82]. Significant intrafamilial variation was found in several families with a Thr124Met mutation initially classified as CMT2 with late-onset weakness and marked sensory abnormalities which also displayed deafness and pupillary abnormalities: Most patients had at least 1 NCV >38 m/s, and while demyelinating features were found in biopsies, axonal degeneration was also prominent, as were tomacula [67]. In another family, the same mutation was associated with respiratory and autonomic involvement including bladder, sudomotor, papillary manifestations, and neuropathic pain [70].

Pathogenesis

As a homophilic tetrameric adhesion molecule, the extracellular domains of four MPZ molecules form a doughnut-like structure which in turn interacts with the MPZ tetramer of the adjacent myelin membrane [188]. Co-localization studies of MPZ and *PMP22* suggest that they may interact. MPZ is also involved in cell-signaling processes and functions in intracellular and extracellular myelin compaction. Whether MPZ mutations cause predominantly axonal or demyelinating phenotypes may reflect their location in domains involved in myelin-axon or intra-myelin interactions [99]. In part, the effect of a heterozygous *MPZ* mutation may result from a 50 % reduction in functional gene dosage. The clinical, electrophysiological, and histological consequences of different mutations may also reflect the interaction of abnormal with normal MPZ units and with other cellular proteins. Abnormal MPZ can exert a dominant negative effect, thus reducing the amount of functional protein to less than 50 % and causing a more severe phenotype. Without this dominant negative effect, a milder form of CMT1B would result. In experimental system co-expression of wild-type and mutated MPZ confirms that some mutations inactivate wild-type protein, whereas others do not. In Schwann cell cultures, glucocorticoids stimulate the expression of MPZ and *PMP22*; this may explain the benefit of steroids in some cases of CMT1 [183, 189]. Schwann cells from *Mpz* knockout mice downregulate *PMP22* and upregulate myelin associated glycoprotein and proteolipid protein; mistargeting of these and other proteins to inappropriate cellular compartments and dysregulation of other adhesion molecules also occur [190].

Neuropathology

Nerve biopsy usually reveals hypertrophic demyelinating features with onion bulbs and loss of myelinated fibers. An autopsy study described hypertrophy and endoneurial fibrosis in peripheral and spinal nerves [191], while autopsy of another patient with His10Pro mutation showed prominent axonal pathology including focal axonal enlargements and thin myelin but no segmental demyelination [192]. Two biopsies from a family with a Lys96Glu mutation demonstrated prominent tomacula [172] (Figs. 26.4 and 26.5). Tomacula, focally folded myelin, and other specific myelin abnormalities have been reported in extracellular domain mutations such as Ser49Leu, Lys96Glu, Lys101Arg, Lys130Arg, lle135Leu, Ile106Leu, Asp109Asn, Ser34 deletion, Arg69Cys, Arg69His, and Arg69Cys; uncompacted myelin is found in a quarter to two-thirds of nerve fibers with mutations that include Thr4Ile, Arg69Cys, Arg69His, Asn131Lys, and Ser34 deletion [193–199]. Patients with mutations in the intracellular domain (exons 5 and 6) and in the exon 4 transmembrane domain (Gln186stop) or its margins showed

severe myelin uncompaction and hypomyelination. Not only typical demyelination and remyelination but also intracellular myelin uncompaction at the major dense line was associated with the Arg98Cys mutation in the extracellular domain in a patient with delayed motor development, typical CMT as an adult, and NCVs <10 m/s [200]; the same mutation was detected in a severely affected infant who died at 22 months [193]. Mutational introduction of cysteine residues is likely to compromise the correct disulfide bond and thus protein structure.

CMT1C

This subtype has no distinguishing clinical features versus other forms of CMT. Onset age is variable. ENMG and biopsies are indicative of chronic demyelination. Several mutations in the *LITAF* (*SIMPLE*) gene on chromosome 16p13.13 have been identified. This gene appears to have a role in protein degradation [201]; it is highly expressed in Schwann cells. Mutated, it may be pathogenic through both loss and toxic gain-of-function mechanisms [202].

CMT1D

This rare subtype presents with little phenotypic differences compared with CMT1A or B. It results from dominant specific mutations in the zinc-finger binding domain of the early growth response gene 2 (*EGR2* or *Krox20*) on chromosome 10q21.3. Other *EGR2* mutations have been associated with DSS and both recessive and dominant CHN [203]. EGR2 regulates transcription of *PMP22*, *MPZ,* and other myelin genes and plays a role in cellular proliferation and myelin maintenance. Homozygous Egr2 knockout mice show peripheral hypomyelination [41].

CMT1E

CMT1E denotes the association of *PMP22* or *MPZ* mutations with deafness [77–80, 82].

CMT1F

While mutations in the *NEFL* gene more often cause an axonal phenotype (CMT2E, see below), a demyelinating subtype has been described [204, 205].

CMTX

CMTX is an X-linked dominant neuropathy, where milder clinical manifestations are found in heterozygous woman compared to hemizygous men.

CMTX1 accounts for up to 20 % of all instances of CMT, making it the second most common CMT1 subtype after CMT1A. CMTX1 is associated with mutations in the gene encoding the gap junction protein connexin32 (*Cx32* or *GJB1*) on chromosome Xq13.1 [36]. The protein is expressed in Schwann cells and forms tunnel-forming gap junctions between the myelin lamellae. Over 160 different mutations have been described, scattered along the entire coding and cis-regulatory regions of *Cx32*. These include point mutations, deletions and insertions, and rarely deletions of the entire coding region. Some mutations may not affect the open reading frame but the promoter, splice sites, or untranslated portions of the mRNA. In distinction from the significant mutation-dependent variations in CMT1A and B phenotypes, patients harboring different *Cx32* mutations are similarly affected, consistent with a loss-of-function effect.

Phenotypic Variation

Symptoms commonly develop in the first decade but may appear before the age five or in the third decade [206]. Compared to CMT1A and B, paresthesias, sensory loss, and atrophy, especially of hand muscles, may be more prominent [207, 208]. Onset is later in women, in whom the condition is usually milder. In some cases, the severity in women may approach that observed in men [209], likely due to unequal inactivation of the X chromosome (lyonization) resulting in predominant expression of the abnormal *Cx32* allele in nerves. In men, CMTX1 tends to be more severe than CMT1A. Variable pes cavus deformity is present in those affected [210–212]. Median motor NCVs in men are usually <38 m/s, whereas in women they range from the demyelinating range to normal [213]. Women may be asymptomatic but have an abnormal ENMG. The CNS may be affected in CMTX1 and present with extensor plantar responses [71], dystonia [72], paresis, aphasia, dysarthria, cranial nerve palsies [73], sensorineural deafness and delayed brainstem auditory evoked potentials [83], and cerebellar pathology [74]. CNS manifestations may be precipitated by febrile illness, hyperventilation, or moving to higher altitudes. CNS signs and symptoms are usually transient, but persistent abnormalities have also been reported [75]. In some cases MRI shows reversible white matter lesions [73].

Pathogenesis

Cx32 localizes to regions of non-compact myelin, that is, Schmidt-Lanterman incisures and the paranodes of myelinating Schwann cells, where it forms gap junctions between adjacent myelin lamellae. The resulting cytoplasmic continuity accelerates the transport of metabolites, ions, and second messenger molecules between the ad-axonal and perinuclear regions of Schwann cells compared to the circumferential path along the Schwann cell cytoplasm [214]. *Cx32* mutations may interrupt this pathway or have other toxic effects, thereby injuring myelinating Schwann cells and their axons.

Different *Cx32* mutations have different effects on the ability of the mutant protein to form functional gap junctions; some mutant proteins cannot be detected within the cell; some accumulate within the cell but do not reach the cell membrane, while other mutants do reach the cell membrane and some of these form functional gap junctions.

Other CMTX neuropathies have broader nervous system manifestations. CMTX2 maps to chromosome Xp22.2 and is characterized by infantile onset, neuropathy, and mental retardation [215]. CMTX3 maps to chromosome Xq26 and presents with prominent paresthetic pain [216]; women may be asymptomatic but have high arches and weak foot dorsiflexion. CMTX4 maps to chromosome Xq24-q26.1. Men have a severe axonal neuropathy with muscle weakness from infancy, and most have associated deafness or mental retardation or both, while women are asymptomatic [84, 217]. CMTX5 with mostly axonal neuropathy, deafness, and optic neuropathy is due to mutations in the phosphoribosylpyro-phosphate synthetase (*PRPS1*) gene on chromosome Xq22.3 [85].

CMT2

As with other forms of CMT disease, phenotypic variation is common among and within CMT2 families. Some reports suggest that CMT2 has a later onset. One family with 50-year anticipation between generations has been reported [218]. Patients may have greater atrophy and distal leg weakness with relatively less hand weakness. Areflexia, pes cavus, and hammer toes may be less common than in CMT1. Nerve hypertrophy is absent, but it is variable in CMT1 as well. CMT2 often presents a diagnostic dilemma because characteristic features such as enlarged nerves and near-pathognomonic neurophysiologic findings are absent. With later onset, the condition may be difficult to differentiate from a late-life-acquired neuropathy when the family history is unclear. Thus, prevalence assessments are of uncertain validity, though estimates suggest that there is one case of CMT2 for every two cases of CMT1. CMT2 and CMT1 can rarely be differentiated by history and examination findings alone. Sural nerve pathology usually reveals reduced numbers of myelinated axons, especially of larger diameter. Rare myelin defects can be observed.

CMT2A1 and CMT2A2

The clinical onset of CMT2A can vary from childhood to old age. Affected members of a large southern Italian pedigree had distal weakness, wasting, hyporeflexia, and mild panmodal sensory loss [219]. Biopsies revealed loss of myelinated fibers, rare onion bulb formations, and mitochondrial abnormalities [219–221]. Mutations in the *MFN2* gene cause CMT2A2 [222, 223]. MFN2 protein (mitochondrial GTPase mitofusin 2) is a large dynamin-like GTPase located on the outer mitochondrial membrane. CMT2A was also linked to a loss-of-function mutation in the *KIF1Bβ* gene on chromosome 1p36.2; this subtype has been categorized as CMT2A1 [224]. KIF1B beta is a motor protein involved in the anterograde transport of mitochondria. *MFN2* mutations are far more common than *KIF1B* in CMT2A. CMT2A2 is clinically indistinguishable from CMT2A1, CMT2E, and CMT2F. *MFN2* mutations account for 20–33 % of CMT2; thus, CMT2A is the most common form of CMT2 and second in frequency only to CMT1A [221]. Some patients have optic atrophy or sensorineural hearing loss; this also referred to as HMSNVI [222]. There are two major forms of CMT2A: severe with early onset and mild with late onset [119, 221]. Some patients develop minor CNS changes; foot deformities occurred in all patients in a large Korean series [119]. Some patients have low-penetrance *MFN2* mutations with normal nerve conduction and minor neuromuscular changes on examination, but most CMT2A patients have an early-onset and severe phenotype; CMT2A accounts for 91 % of the severe phenotypes of CMT2 [225]. Of note, *MFN2* genetic defects have predominantly dominant inheritance; however, homozygous or compound heterozygous mutations are also reported in early-onset CMT2. Twenty MFN2 gene missense mutations were identified among 150 individuals with clinically diverse HSMN, dominant and recessive inheritance, and motor NCVs of 25 m/s or greater [226].

CMT2B

CMT2B is a predominantly sensory neuropathy, which has lead to a debate to its classification with hereditary motor and sensory neuropathy versus hereditary sensory and autonomic neuropathy. Patients may have foot ulcerations and even amputations, but no clinical weakness. High arches, hammertoes, and hyporeflexia are also present. Although neurophysiologic abnormalities are established early in life, clinical onset may be much later. Decreased CMAP amplitudes and denervation are characteristic. CMT2B biopsies reveal evidence of degeneration and regeneration, with the presence of occasional onion bulbs. CMT2B maps to chromosome 3q21.3 and is caused by mutations in the small guanosine triphosphatase (GTPase) late endosomal protein RAB7, a member of the RAS-associated GTP-binding proteins [227, 228]. RAB7 is ubiquitously expressed in sensory and motor neurons and serves to regulate linkage of vesicles and other membranes to the cytoskeleton and plays a role in lysosomal degradation.

CMT2B1

Onset of CMT2B1, an autosomal-recessive condition, in a Moroccan family is in the second decade. Features include distal and (less often) proximal weakness and pes cavus. Motor NCV are near normal. Linkage was found to chromosome 1q22 [229]; in a similar family a homozygous mutation in the

LMNA gene, which encodes the intermediate filaments lamin A and C, a component of the nuclear envelope, was detected [230]. In *LMNA* knockout mice, the authors found reduced axon density, axonal enlargement, and non-myelinated axons. This same gene is mutated in limb-girdle muscular dystrophy type 1B, autosomal-dominant Emery-Dreifuss muscular dystrophy, dilated cardiomyopathy type 1A, mandibuloacral dysplasia, and autosomal-dominant partial lipodystrophy. Co-occurrence of *LMNA* and *PMP22* mutations causes an unusual phenotype [88].

CMT2B2

A second form of autosomal-recessive axonal CMT has been mapped to chromosome 19q13.33 in a Costa Rican family. Patients have a sensorimotor polyneuropathy with distal arm and leg weakness and wasting, hyporeflexia, and sensory loss with normal or minimally reduced NCVs [231]. A missense mutation in the *MED25* gene, a transcriptional regulator, was identified in affected family members, which likely causes a loss of protein function [232].

CMT2C

CMT2C onset varies from congenital to late adulthood. Mild sensory loss is combined with weakness especially in the hands but also in the proximal legs, diaphragm, and intercostal muscles. Worsening hand weakness in the cold, neurogenic bladder and hearing loss are common. Vocal fold dysfunction can lead to early death. Other patients have scapuloperoneal spinal muscular atrophy or congenital distal spinal muscular atrophy. Mutations in the transient receptor potential vanilloid four (*TRPV4*) gene on chromosome 12q24.11 were found in several families [233–235]. TRPV4 is a nonselective cation channel. Gain of function mutations in *TRPV4* cause also various skeletal dysplasia syndromes including spondylometaphyseal dysplasia, brachyolmia, and metatropic dysplasia. Patients with both neuropathy and skeletal abnormalities have been described, underscoring that TRPV4-associated channelopathies are spectrum disorders. All neuropathy-causing mutations cluster around the ankyrin-repeat domain of the protein [235].

CMT2D

CMT2D patients often have worse hand than leg weakness and slow progression [236, 237]. Onset is typically in the second to third decades but rarely in infancy [238]. Tendon reflexes are usually absent in the arms and decreased in the legs. CMT2D is allelic disorder with distal spinal muscular atrophy type V [239], and both phenotypes can occur in the same family. They are caused by mutations of the *GARS* gene-encoding glycyl-tRNA synthetase on chromosome 7p14.3 [237]. Studies in *Gars* mice models suggest that the neuropathy is caused by a gain of toxic function of the mutant protein, rather than loss of aminoacylation properties; however, the exact pathomechanism is unknown [240].

CMT2E

CMT2E can be difficult to distinguish from CMT1A, CMT1B, or CMT2A, though more severe clinical phenotypes occur [205]. Onset age ranges from the first to third decades [205, 241, 242]. Multiple dominantly inherited mutations in different protein domains are reported in the neurofilament light chain gene (*NEFL*) on chromosome 8p21.2. NEFL is a major component of neurofilaments, the neuron-specific intermediate filaments maintaining neuronal cytoskeleton and determining axonal caliber [243]. *NEFL* mutations disrupt both self-assembly and co-assembly with medium and heavy chain neurofilaments. This impacts axonal transport of neurofilament building blocks and affects the anterograde and retrograde transport of other cell components, particularly of mitochondria, resulting in progressive degeneration and loss of neuronal viability. In contrast, the only recessive Glu210X mutation reported to date causes loss of NEFL protein. In affected persons homozygous for this mutation, this leads to lack of neurofilaments and progressive axonal loss [244]. ENMG indicates axonal involvement with demyelinating features and prolonged DMLs disproportionate to the conduction slowing, similar to findings in anti-MAG-associated neuropathy [245]. In some cases, NCVs are severely slowed, and for these a classification as CMT1F (see above) has been proposed [204, 205]. One nerve biopsy revealed axonal degenerative and regenerative features as well as onion bulbs [205]. This highlights the marked variability of clinical patterns with specific CMT gene mutations. Thus, strict genotype-phenotype correlations are difficult to establish.

CMT2F

CMT2F patients exhibit slow progression and primarily distal weakness. In a six-generation Russian family with autosomal-dominant inheritance, onset ranged from age 15 to 25 [246]. Patients had early hyporeflexia and symmetric, slowly progressive weakness and leg atrophy with foot drop, whereas upper limb weakness and wasting ensued years later. Sensory impairment was mild to moderate. Mutations in the small heat-shock 27-kDa protein 1 (*HSPB1*) gene on chromosome 7q11.23 were detected in the Russian [247] and subsequently in multiple families. This gene is also mutated in distal hereditary motor neuropathy type 2B (dHMN2B). *HSPB1* mutations may act by disrupting the intermediate filament or tubular networks, enhanced binding of client proteins, aggregate formation, or other mechanisms.

CMT2G

CMT2G was first described in ten relatives from a three-generational Spanish family [248]. The mean age at onset was 29 but with a broad range of 9–76 years. Patients had slowly progressive foot deformity, difficulty walking, hypo- or areflexia, and mild stocking hypesthesia. NCVs were normal

in some and mildly slowed in others. Biopsy showed regenerating fibers, fiber loss, and atrophy. A disease-associated locus on chromosome 12q12-q13.3 has been identified; however, the causal mutation is unknown [249].

CMT2H/K

This subtype denotes CMT linked to a locus at chromosome 8q21.11 [250] where dominant mutations in the ganglioside-induced differentiation-associated protein 1 (*GDAP1*) gene have been found. GDAP1, located in the outer mitochondrial membrane of neurons and Schwann cells, appears to function in mitochondrial fission pathways. Both autosomal-recessive and dominant forms are associated with defects in *GDAP1* [251]; the latter are often milder. Patient with dominant GDAP1 mutations present with axonal ENMG findings (i.e., moderately slowed NCVs >38 m/s and decreased CMAP amplitudes), onset age ranging from childhood to late adulthood, and generally slow progression without loss of ambulation [251]. Severity ranges from asymptomatic to wheelchair dependency at age 60. GDAP1 mutations are also associated with CMT4A (see below).

CMT2I

Several MPZ mutations have been associated with an autosomal-dominant, adult onset axonal CMT phenotype. Carriers may be asymptomatic or present with cramps, foot numbness, and deformities [77, 252–254]. One patient had normal NCVs at age 15, while older relatives had variable slowing into the CMT1 range, suggesting progressive NCV slowing with age [255].

CMT2J

Several families and isolated patients with CMT2 and onset in the fourth to sixth decade with marked sensory abnormalities, weakness, deafness, chronic cough, and autonomic dysfunction including pupillary abnormalities have been reported. NCVs ranged from below 38 m/s to normal. Biopsies showed axonal changes. Several MPZ mutations were identified [67, 181, 256, 257].

CMT2L

CMT2L denotes an axonal, autosomal-dominant subtype with linkage to chromosome 12q24.23 and mutations in the heat shock 22-KD protein 8 (*HSPB8*) gene. The encoded protein has chaperone and transport functions and is also implicated in distal hereditary motor neuropathy type 2A (dHMN2A) [258].

CMT2M

CMT2M is linked to mutations in the dynamin 2 (*DNM2*) gene on chromosome 19p13.2 [259–261]. Patients present with a sensorimotor neuropathy, prominent gait ataxia. NCVs are near normal and nerve biopsy reveals loss of large diameter fibers and rare onion bulb formation. *DNM2* mutations are also associated with autosomal-dominant centronuclear myopathy I and dominant DI-CMT B [261] (see below). Dynamins contain a GTPase domain and scaffolding proteins with a role in membrane trafficking.

CMT2N

CMT2N has a variable phenotype with onset ranging from the first to the sixth decade and from absence of symptoms to distal weakness and sensory loss, and deafness; NCVs range from 32 m/s to normal [262, 263]. It has been associated with Asn71Tyr and Arg329His mutations in the alanyl-tRNA synthetase (*AARS*) gene on chromosome 16q22.1. The mutation reduces aminoacylation activity of the protein [262].

CMT2O

A 4-generation 23-member family with early-onset sensorimotor neuropathy and delayed milestones has been described. NCVs were normal and nerve biopsies showed evidence of axonal degeneration. A missense mutation in the cytoplasmic dynein heavy chain 1 (*DYNC1H1*) gene on chromosome 14q32.31 [264] was identified. The protein is involved in cargo binding and axonal transport along microtubules.

CMT2P

This subtype with autosomal-dominant or autosomal-recessive inheritance is linked to homozygous or heterozygous mutations in an ubiquitin ligase encoded by the leucine-rich repeat-and-sterile alpha motif-containing one gene (*LRSAM1*) on chromosome 9q33 [265, 266]. Like the LITAF/SIMPLE implicated in CMT1C, LRSAM1 plays a role in protein degradation pathways. Affected individuals with a heterozygous frameshift mutation present in the second or third decade with progressive distal muscle weakness and mild distal sensory disturbances. ENMG revealed severe axonal changes confirmed by biopsy in one individual [265], whereas a mild axonal distal neuropathy with onset in early adulthood and NCVs >38 m/s was associated with a homozygous splice acceptor mutation [266].

DSS (HMSN3 or CMT3)

Originally described in 1893 as a hypertrophic polyneuropathy with onset in infancy or early childhood in patients born from unaffected parents, DSS is characterized by distal sensory loss with ataxia, pes cavus, distal weakness with proximal progression, palpable hypertrophied nerves, and Argyll-Robertson pupils [4, 6]. Lightning pain, described in the original two cases, is uncommon. In 1906 Marie reported a variant of DSS with distal atrophy, nerve hypertrophy, areflexia, intention tremor, and dysarthria but without sensory ataxia or Argyll-Robertson pupils [4]. Common features include early

onset, delayed motor milestones, severe gait disturbance, ataxia, variable nerve hypertrophy and thickened spinal roots, increased CSF protein, and very slow NCVs [9, 267]. Although a slowly progressive length-dependent sensorimotor deficit is typical, a relapsing-remitting course occurs [267].

Neuropathology

Hallmarks include extensive nerve and root hypertrophy due to demyelination-remyelination, decreased fiber density, segmental demyelination, onion bulbs, and sometimes giant whorls of cell processes [9]. In young patients, teased fibers reveal thinly myelinated internodes, irregularity of myelin sheath thickness, and segmental demyelination [267].

Pathogenesis

Mutations in *MPZ*, *PMP22*, *EGR2*, and *PRX* [28, 38, 47, 267, 268], and linkage to chromosomes 8q23-24 [269] have been described. The possible existence of milder and unrecognized hereditary neuropathies in one or both parents must be considered. Autosomal-recessive forms are discussed in the CMT4 subgroup below.

Congenital Hypomyelination Neuropathy (CHN)

Patients present with neonatal hypotonia, areflexia, distal weakness, slow NCVs, and at times, contractures or arthrogryposis [91, 270]. It may result from dominant *MPZ*, *PMP22*, or *EGR2* mutations, as well as from homozygous states when parents are heterozygous for the same or different mutations or when one mutation inherited from one parent is combined with a de novo mutation in the same or another gene [47, 203, 271].

Neuropathology

There is severe hypomyelination, demyelination, and axonal loss. Absence of active myelin breakdown and rare onion bulbs points to CHN, whereas demyelination or remyelination and abundant organized onion bulbs are common in DSS. CHN results from a congenital impairment in myelin formation, whereas DSS results from aberrant demyelination and subsequent remyelination of the peripheral nerve.

Hereditary Neuralgic Amyotrophy (HNA)

HNA has also been referred to as neuritis with brachial predilection, hereditary brachial plexus neuropathy, hereditary neuralgic amyotrophy with predilection for the brachial plexus, and idiopathic brachial plexus neuropathy. HNA is an autosomal-dominant form of recurrent focal painful neuropathy with predilection for arm involvement. An early report described a woman with three episodes of painful arm weakness, whose sister had experienced seven such attacks [272]. Some 200 families worldwide have been identified [273, 274].

Patients experience episodic weakness, atrophy, and sensory disturbances, usually preceded by severe pain in the affected arm. Onset is between 10 and 30 years of age, though rarely earlier. Near complete recovery begins within weeks to months after onset. Recurrences may affect either arm. Right arm involvement has been described most frequently. The lower cranial nerves; the lumbosacral plexus; the phrenic, long thoracic, and recurrent laryngeal nerves; and the sympathetic nervous system may be affected. As in the sporadic forms, attacks may follow infections or immunization [273]. Some patients follow a relapsing-remitting course and others a chronic undulating course [275]. While the frequency of attacks diminishes with age, patients accumulate deficits. ENMG reveals signs of denervation and reinnervation in weak muscles. Biopsies show decreased myelinated fiber density in individual nerve fascicles. Treatment focuses on pain control and rehabilitation; there is limited support for the use of corticosteroids and IVIG [276]. Common dysmorphic features include hypotelorism, short stature, cleft palate, partial syndactylism, unusual skin folds, and creases in the neck or scalp referred to as cutis verticis gyrata [45, 277]. Linkage to chromosome 17q25 was found in some families [45, 275, 278], and mutations in the *SEPT9* gene which plays a role in the cytoskeleton, cell division, and tumorigenesis have been identified [278].

CMT4

CMT4 describes autosomal-recessive forms of demyelinating CMT. In its most severe forms, there is overlap with DSS/CMT3. The classification represents distinct clinical and histological subtypes, of which several occur only among specific ethnic groups. Axonal autosomal-recessive subtypes include CMT2B.

CMT4A

CMT4A manifests in early infancy with delayed motor development, muscle atrophy, weakness, and occasionally, scoliosis. Vocal fold paralysis may develop. The disease may progress to severe motor weakness [279–281]. NCVs are in the demyelinating range, CMAP and SNAP amplitudes are reduced or absent. Pathologic hallmarks include hypomyelination with onion bulbs, though mixed features of demyelination and axonopathy histologically and by ENMG can exist and are referred to as CMT-RIA [280, 282, 283]. The axonal form is associated with vocal cord and diaphragmatic paralysis with midlife onset [283, 284]. Linkage to mutations in the ganglioside-induced differentiation-associated protein-1 (*GDAP1*) gene on chromosome 8q21.11 has been established [280, 281, 285, 286] (see also under CMT2H/K [250, 251]).

CMT4B1

CMT4B1 is a nonhypertrophic, severe, sensorimotor neuropathy with onset in infancy [174, 287]. As weakness progresses, some patients become wheelchair bound. A histological hallmark is the presence of focally folded myelin sheaths [288]. Linkage to chromosome 11q21 was established, where several homozygous or compound heterozygous mutations in a myotubularin-related protein 2 (*MTMR2*) result in premature translation termination or frameshift [289]. Such loss of function mutations could result in constitutive phosphorylation of an unknown substrate, with Schwann cell proliferation and myelin overgrowth.

CMT4B2

The CMT4B2 subtype is characterized by sensorimotor neuropathy, with onset in the first or second decade, and early-onset glaucoma. It has been identified in consanguineous families from Tunisia, Morocco, Brazil, and Japan. Motor NCVs are severely reduced, and nerve biopsies showed myelin outfoldings. Early visual deficiencies and later blindness result from congenital glaucoma with buphthalmos, megalocornea, and increased intraocular pressure [290]. Mutations were found in the gene for SET-binding factor 2 (*SBF2*) on chromosome 11p15.4, a pseudophosphatase- and myotubularin-related protein that may be involved in phosphoinositide-mediated signaling events controlling myelination [290, 291].

CMT4C

CMT4C manifestations are variable but include prominent scoliosis, early loss of ambulation, and respiratory problems; onset varies from infancy to age 12. Hearing loss and facial paresis may occur. NCVs are typically in the demyelinating range but may be intermediate [292, 293]. Nerve biopsies revealed axonal loss and abnormal Schwann cell processes with increased basal lamina production [294]. Linkage to chromosome 5q32 was found [292, 295], where multiple truncating and missense mutations in the *SH3TC2* gene (also known as *KIAA1985*) which codes for the SH3 domain and tetratricopeptide repeats-containing protein 2 have been found [292, 293]. The protein, localized to plasma membranes of Schwann and other neural cells, appears to play a role in myelin maintenance and axon-myelin interactions. Certain heterozygous mutations are associated with mild axonal polyneuropathy and/or carpal tunnel syndrome [296].

CMT4D or HMSN-Lom

CMT4D was first described in gypsies living in Bulgaria and later on in affected individuals from this ethnic group across Europe [297]. This variant is characterized by gait difficulties in the first decade, skeletal deformities, hearing loss, and severe sensorimotor deficits (Fig. 26.1). NCVs are less than 15 m/s, with unobtainable sensory responses. Biopsies reveal demyelination or remyelination and severe progressive axonal loss [298]. Onion bulb formations were more conspicuous in younger than older individuals. Hypomyelination and uncompacted myelin were observed together with intraaxonal accumulation of irregular curvilinear material. A private nonsense mutation in the N-myc downstream-regulated gene 1 (*NDRG1*) on chromosome 8q24.22 was reported [297]. A splice-site mutation in a non-Gypsy patient is also reported [299]. Ubiquitously expressed, but particularly in Schwann cells, NDRG1 may play a role in growth arrest and cell differentiation, possibly as a signaling protein shuttling between the cytoplasm and the nucleus. The protein may mediate Schwann cell signaling necessary for axonal maintenance.

CMT4E

CMT4E has a severe phenotype with cranial nerve involvement, arthrogryposis, and respiratory failure; some patients may walk with aid of a walker [300]. NCVs are below 10 m/s. Biopsies reveal near absence of myelin, occasional onion bulbs, and axonal loss. This CMT form is caused by autosomal-recessive mutations in the *EGR2* gene on chromosome 10q21.3 Less-severe EGR2 mutations with autosomal-dominant inheritance are classified as CMT1D and DSS [41] (see above).

CMT4F

CMT4F was first identified in a Lebanese family. Patients present with a disabling ataxic neuropathy with onset before age 10 with delayed developmental milestones, distal atrophy and weakness, pain, and prominent large fiber involvement resembling DSS. Motor and sensory responses are difficult to evoke in most individuals [268, 301]. Onion bulbs, loss of axons, and hypertrophied myelin sheaths are seen in biopsies. Several mutations in the periaxin (*PRX*) gene on chromosome 19q13.2 have been identified [268, 301–303]. PRX codes for L and S periaxin, which interact both with plasma membrane and cytoskeletal proteins and play a role in the assembly of signaling complexes at sites of cell-cell contact.

CMT4G Russe

CMT4G Russe is described in Gypsies residing in Bulgaria, Spain, Romania, and France [304, 305]. Patients have severe disability with prominent sensory loss, intermediate motor NCVs, and a high threshold for electrical nerve stimulation. It results from a mutation in an alternative untranslated exon of hexokinase 1 (*HK1*) on chromosome 10q22.1 [306].

CMT4H

CMT4H is an early-onset neuropathy with delayed milestones, distal weakness and atrophy, sensory impairment, and scoliosis described in two Lebanese and Algerian

families [307]. NCVS are below 15 m/s, and biopsies reveal axonal loss, hypomyelination, and eccentric folding of redundant myelin sheaths. Mutations in the *Frabin/FGD4* gene on chromosome 12p11.21 were found in the original and several other families of different ethnicities [308]. The protein is involved in Schwann cell shape, possibly by affecting Rho GTPase signaling pathways [309]. There is considerable clinical heterogeneity and variable functional impairment [309]. A less severe phenotype with slowly progressive polyneuropathy is also described where patients remain ambulatory to middle age [310].

CMT4J

CMT4J denotes a severe phenotype with variable but often childhood onset resulting from compound heterozygous mutations on chromosome 6q21 in the *FIG 4* gene which encodes the $PI(3,5)P_2$ 5 lipid phosphatase [311]. Patients have proximal and distal and asymmetric muscle weakness with rapid progression and only mild sensory loss. The phenotype resembles motor neuron disease, and indeed, some mutations in the same gene are associated with motor neuron disease subtype 11 with normal NCVs. ENMG reveals denervation in proximal and distal muscles and variable NCVs [312]. Neuropathologic findings include large fiber loss, thinly myelinated fibers, and small onion bulbs.

GAN

Autosomal-recessive giant axonal neuropathy presents in childhood and is associated with short stature, tightly curled hair, prominent CNS involvement including mental retardation and optic atrophy, severe disability, and MRI white matter hyperintensities. Missense, nonsense, and frameshift mutations in the gigaxonin gene on chromosome 16q23.2 lead to neurofilament accumulation and segmental axonal swelling [313].

Dominant Intermediate CMT (DI-CMT)

Individuals and families with NCVs atypical for both CMT1 and CMT2 have long been recognized. Before the advent of genetic testing, Bradley, Davis, and Madrid proposed a CMT classification that included an intermediate group, characterized by median motor nerve NCVs of 25–45 m/s and intermediate pathological changes compared to the hypertrophic neuropathy group [16–18]. The growing number of genetically and phenotypically characterized CMT families indicated that based on ENMG and pathological criteria, specific mutations in several genes indeed lead to intermediate phenotypes. These genes encode for MPZ [67, 108, 178], Cx32 [77, 212, 213, 314], NEFL [242, 315, 316], and GDAP1 [280, 282, 283]. Supporting the genetic heterogeneity of the intermediate CMT category, additional loci have been identified segregating in large families with dominant inheritance: DI-CMTA, DI-CMTB, DI-CMTC, and DI-CMTE.

DI-CMTA

DI-CMTA, originally reported in 1985 [317], is clinically characterized by second-decade onset, when patients develop leg weakness, difficulty running, and muscle cramps. Motor difficulties with exposure to cold occur. By the fifth decade, patients have severe weakness and distal limb atrophy, steppage gait, pes cavus, areflexia, and mild distal sensory loss. Later, the course stabilizes and elderly patients are typically not wheelchair bound. NCVs are 25–45 m/s. By biopsy, features of demyelination and remyelination (onion bulb formation and uncompacted enlarged myelin lamellae) and chronic axonopathy (large fiber loss and clusters of regenerated axons) coexist [317–320]. Linkage has been assigned to chromosome 10q24.1-q25.1 [320]; however, the causal gene is still unknown.

DI-CMTB

Patients with DI-CMTB are mildly to moderately affected; some have neutropenia or cataracts. NCVs range from 26 m/s to normal and CMAP amplitudes from severely reduced to normal. Nerve biopsies reveal predominantly axonal degeneration and loss of large diameter fibers; segmental demyelination and remyelination with onion bulb formation are rare [321, 322]. DI-CMTB is associated with mutations in the dynamin 2 (*DNM2)* gene on chromosome 19p13.2 [260, 261, 321–323], which is also implicated in CMT2M [259] (see above) and centronuclear myopathy.

DI-CMTC

The DI-CMTC subtype presents with typical moderate severity sensorimotor features (Figs. 26.2 and 26.3) and was first described in one US and one Bulgarian family with onset in childhood in the former and in young adulthood in the latter. Median motor NCVs were in the range of 24–58 m/s. Sural nerve biopsies revealed age-dependent morphological changes of axonal degeneration, absence of onion bulbs, and <10 % fibers with segmental remyelination [324] (Fig. 26.6). DI-CMTC is linked to chromosome 1p35.3 and is caused by mutations in the *YARS* gene encoding tyrosyl-tRNA synthetase (TyrRS) [325, 326]. So far, only three disease-causing *YARS* mutations have been described. The Bulgarian DI-CMTC patients carry an E196K mutation, while the US patients are heterozygous for a G41R substitution. A de novo in-frame deletion (153-158delVKQV) was identified in a single Belgian patient. In vitro and transgenic Drosophila studies suggest a gain-of-toxic-function neurodegenerative effect of the mutations [326, 327].

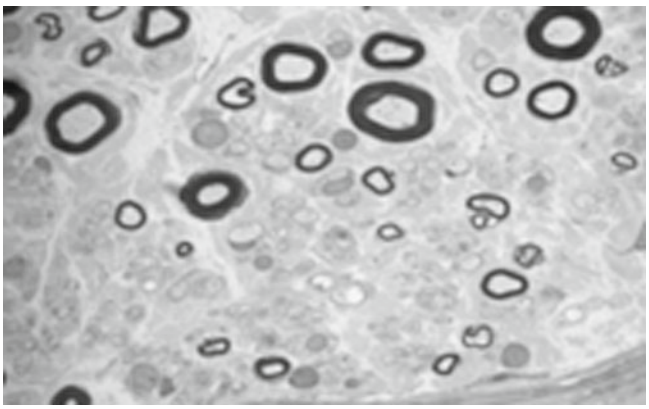

Fig. 26.6 Sural nerve biopsy in DI-CMTC. Semithin toluidine blue-stained cross section shows marked depletion of myelinated nerve fibers. Many remaining fibers have thin myelin sheaths

DI-CMTD

A four-generation family with autosomal-dominant CMT, variable distal wasting, weakness, and sensory loss (worse in the legs) was reported [108]. Motor NCVs range from 24 to 41 m/s. Biopsies revealed axonal changes, segmental demyelination and remyelination, but no onion bulbs. An Asp6Tyr mutation in the extracellular domain of MPZ was found.

DI-CMTE represents a sensorimotor neuropathy with onset in the second decade affecting the legs more than the arms, of variable severity associated with a kidney disorder ranging in severity from proteinuria to end-stage renal disease. Some patients have hearing loss. NCVs were in the intermediate range, and nerve biopsies revealed axonal loss and onion bulb formation. Renal biopsies showed focal segmental glomerulosclerosis. The condition results from a mutation in exons 2 or 3 of the inverted Formin 2 (*INF2*) gene on chromosome 14q32 [328]. Mutations of INF2 are also known to cause autosomal-dominant kidney disease without neuropathy. INF2 is involved in actin and microtubule maintenance in both Schwann cell myelin and glomerular podocytes, two cell types with a large surface area.

RI-CMTB

Recessive intermediate CMT (CMT RIB) has been described in a patient who also had developmental delay, self-abusive behavior, dysmorphic features and vestibular Schwannoma, and NCVs 39.5 and 30.6 m/s in the median and ulnar nerves. RI-CMTB results from mutations in the *KARS* gene encoding lysyl-tRNA synthetase on chromosome 16q23.1 [329].

Management

With the exception of CHN, a person's lifespan is not altered in most instances of CMT. Disability is highly variable and difficult to predict in young individuals, even among siblings [72, 96], but quality of life is generally lowered [330]. In the majority, CMT is slowly progressive. If progression accelerates, other causes, such as acquired neuropathies or other inherited neuromuscular conditions, should be sought [86–89, 331]. For children, a disability measure, CMT Pediatric Scale, has been validated [332]. Dealing with a life of initially mild but progressive disability can increase the risk of depression and lead to further disability. Referrals to mental health professionals may be indicated. Genetic counseling is indicated, in particular when affected or unaffected individuals with an affected child contemplate procreation. When both parents have symptomatic or asymptomatic CMT, they may have homozygous or compound heterozygous offspring with DSS or CHN.

Education can help patients and their families cope with the progression of disability and reduce the likelihood of avoidable nerve damage, for example, exposure to drugs and neurotoxins, such as alcohol. Internet resources are available from the Charcot-Marie-Tooth Association (www.CMTAUSA.org), the National Organization for Rare Diseases (www.RareDiseases.org), and many others. Patients should be familiar with disability rights regulations and entitlements to "reasonable accommodations" at work and in school.

Primary prevention is not a practical option at present. As CMT rarely affects life span, intellect, or independent living, most patients have children. Prenatal screening raises ethical issues; it is available in Bulgaria for high-risk Gypsy communities [333–335].

As no medical therapy can slow the progression of CMT, secondary prevention focuses on awareness and avoidance of intercurrent conditions or interventions that can exacerbate physical disability or lead to systemic or focal neuropathies, such as diabetes mellitus, vitamin deficiencies, hypothyroidism, neurotoxic agents, and prolonged immobilization during surgery. Awareness of the CMT diagnosis on the part of the patient and health care providers is essential: For example, malignancies may present indications for neurotoxic drugs such as platinum compounds or vincristine [336, 337]. At times alternative treatments with less neurotoxicity may be equally effective.

Patients should maintain a well-balanced diet and avoid obesity and impaired glucose tolerance which can foster back pain, acquired systemic and focal neuropathies including meralgia paresthetica, and spinal root disease. Limiting alcohol use is important given the lack of evidence re safe amounts. Nerves in HNPP in particular are sensitive to prolonged compression for which intoxication in general is a risk factor. Avoiding a sedentary lifestyle within the confines of any functional needs is important. Exhaustion of weak muscles may be undesirable, given the evidence for overuse weakness in CMT [338]. Individuals with HNPP should minimize work and recreational activities that can compress or injure nerves. Sleep disorders and laryngeal and

pulmonary involvement require evaluation and consideration of therapeutic options [76].

Pain may result from joint deformities or compensatory overuse of certain muscle groups. Abnormal gait and scoliosis can lead to back pain. Some types of pain may respond to nonsteroidal anti-inflammatory drugs. Dysesthetic pain may occur but is typically mild except in certain subtypes. It responds to the same drugs as in acquired neuropathies. Sometimes muscle cramps require treatment.

Depending on the degree of foot deformities, patients may benefit from Achilles tendon lengthening, tendon transfers, hammertoe correction, and release of the plantar fascia. However, such surgeries can often be prevented by conservative measures and lifelong follow-up with physical therapists.

Referrals to physical therapists and prosthetics or orthotics specialists are often required to prevent and treat joint deformities. AFOs can facilitate ambulation, prevent falls and injuries, and prevent Achilles tendon shortening, but if weakness spreads to proximal limbs, ambulation can be impaired even with AFOs. Special AFOs can be worn at night. With mild foot drop, boots can delay the need for AFOs. For moderate foot drop, lighter AFOs may be more appropriate. Thick-handle tools and cutlery can render certain activities of daily living easier.

While no adverse reactions to anesthetics including succinylcholine were identified in one study; succinylcholine may still be inadvisable [339]. As nitrous oxide (N_2O) may contribute to B12 deficiency, B12 levels should be assayed and deficiency be treated prior to N_2O anesthesia. Prolonged body and limb positions can result in nerve compression, especially in HNPP. Regional anesthesia is relatively contraindicated in CMT.

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Inherited Metabolic Neuropathies

27

Perry K. Richardson and Scott T. Demarest

Inherited Metabolic Neuropathies

The inherited metabolic neuropathies are a complex, heterogeneous group of disorders. In some, peripheral nerve dysfunction is one feature of a multisystem disease; in others neuropathy is the predominant manifestation of an underlying genetic mutation. These diseases were originally described based on clinical and pathologic characteristics and carry the names of their discoverer. With time, biochemical and later molecular genetic discoveries prompted classification by enzyme deficiency or genotyping. These major disorders are listed in their traditional classification in Table 27.1.

As understanding of the pathogenesis and molecular causes of the inherited disorders has improved, so have treatments. While many of these diseases remain ultimately fatal, some have improved life expectancy resulting from better supportive care and in some cases correction of a metabolic defect. A key development resulting from progress in genotyping is the recognition that some diseases have a wider phenotypic spectrum than initially thought. Mild or atypical presentations are increasingly identified, thus changing the expected course and outcome. The last decade has seen tremendous advances in gene therapies, enzyme replacement, and transplantation, including hematopoietic stem cell transplantation. While these treatments are still in their infancy, they are likely the future of treatment of some inherited metabolic neuropathies.

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Several online resources are updated frequently, providing information on the most recent research, testing, gene discoveries, and genotype-phenotype correlations. Gene Reviews and OMIM (Online Mendelian Inheritance in Man), accessed at www.genetests.org, are two of the best and most user-friendly resources for this rapidly evolving science.

Familial Amyloid Polyneuropathy

Familial amyloid polyneuropathy (FAP) is an autosomal dominant potentially fatal disorder of variable penetrance manifested by multiorgan dysfunction. The principal targets for symptomatic amyloid deposition are the peripheral nerves, the heart, the eye, and sometimes the kidneys, leptomeninges, and brain. The characteristic neuropathy is a progressive length-dependent painful sensorimotor polyneuropathy with autonomic dysfunction, although focal neuropathies, especially carpal tunnel syndrome, may occur. The characteristic pathogenic feature is transformation of the constituent mutated protein into β-pleated sheets of amyloid that are deposited in the target organs. The best described subtype is transthyretin (TTR) amyloid neuropathy, wherein mutated TTR monomers are produced in the liver. Recent data from long-term follow-up studies show that if performed early, liver transplantation can significantly prolong life expectancy. Therapy aimed at stabilizing TTR tetramers to reduce amyloid fibril formation has shown promise in early trials.

Classification

Before the emergence of molecular genetics, hereditary amyloidoses were classified by phenotype and ethnic origin, but currently FAP is classified by the amyloid fibril protein and genotype. A variety of phenotypes are described. Those with relevance to neuromuscular disease are included in

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Table 27.1 Inherited metabolic neuropathies

I. Inherited amyloidoses
(a) Transthyretin-related
(b) Apolipoprotein A1-related
(c) Gelsolin-related
II. Porphyrias
(a) Acute intermittent
(b) Variegate
(c) Hereditary coproporphyria
(d) ALA dehydrase deficiency
III. Disturbances of lipid metabolism
(a) Leukodystrophies
(i) Metachromatic
(ii) Globoid cell (Krabbe's disease)
(iii) Adrenoleukodystrophy/adrenomyeloneuropathy
(b) Lipoprotein deficiencies
(i) Tangier disease (alphalipoprotein deficiency)
(ii) Bassen-Kornzweig disease (abetalipoproteinemia)
(c) Fabry's disease (α-galactosidase deficiency)
(d) Phytanic acid storage diseases
(i) Classical Refsum disease
(ii) Infantile Refsum disease
(iii) Methylacyl-CoA racemase deficiency
(e) Cerebrotendinous xanthomatosis (cholestanolosis)
(f) Niemann-Pick disease (sphingomyelin lipidosis)
IV. Disorders with defective DNA repair
(a) Xeroderma pigmentosum
(b) Ataxia-telangiectasia
(c) Cockayne syndrome

Table 27.2 with their phenotypes and representative genotype. Apolipoprotein-A1 and gelsolin amyloidosis, named for their precursor proteins, are less common and present differently.

Epidemiology

Andrade first described FAP in 1952 in northern Portugal, where the gene carrier frequency is 1/538 and the disease prevalence is 1/1,000 [1]. The disease was later reported in Japan (1968), Sweden (1976), France, Brazil, and elsewhere. Penetrance varies by country of origin. Symptoms begin in the mid-30s in northern Portuguese patients, more often men, but the onset ranges from 17 to 78. Genetic anticipation is described. In endemic areas of Japan, men and women are equally affected with a high penetrance. In northern Sweden, the disease has a late onset (55–60 years) with lower penetrance [2, 3]. The Ile84Ser mutation in an Indiana/Swiss kindred shows essentially 100 % penetrance by age 50. About 1/100,000 US Caucasians carry the disease, although about 3 % of African Americans and 5 % of West Africans have a non-neuropathic familial amyloid cardiomyopathy associated with the Val122Ile mutation.

Transthyretin-Related Amyloidosis

Costa et al. discovered TTR (formerly prealbumin) to be the constituent protein of this most common cause of FAP [4]. The Val30Met mutation accounts for the majority of cases [5]. Clinical features can be divided into neurological and non-neurological manifestations. The earliest symptoms are burning pain, paresthesias, and sometimes painless ulcers and injuries to the feet and legs that spread to the arms in a relatively short time. Autonomic involvement in this subtype is early and includes GI dysfunction (constipation alternating with diarrhea, recurrent vomiting, weight loss), erectile dysfunction, orthostatic intolerance, and blurred vision. Clinical signs include loss of thermal and pinprick sensation in the feet that may extend above the ankles in as little as a few months after onset. Dissociated sensory loss with sparing of large fiber modalities (vibration, proprioception) is the hallmark of this neuropathy [6]. Neurogenic orthostatic hypotension manifested by marked drop in blood pressure on standing with a fixed pulse is often found along with scalloped pupils. Motor weakness begins later in the legs with a steppage gait and may spread to the hands with generalized hyporeflexia on exam. There may be upper limb involvement with median nerve compression from amyloid deposition in the carpal tunnel in many TTR amyloidosis subtypes. The Indiana/Swiss and Maryland/German subtypes present with early-onset carpal tunnel syndrome followed by lower limb neuropathy. Patients may develop Charcot joints and are ultimately wheelchair-bound or bedridden, with death from infection, malnutrition, or fatal cardiac arrhythmia.

Electromyography (EMG) is consistent with an axonal neuropathy, although it may be normal early on if pathology is limited to small fibers. Needle EMG shows evidence of acute and chronic denervation with distal limb predominance [7].

The heart is a major target organ for amyloid deposition in TTR amyloidosis. ECG shows arrhythmia or various types of heart block, leading to pacemaker insertion in as many as 31 % of patients [8]. The characteristic echocardiographic abnormality is one of refractile echoes giving a "granular sparkling appearance" [9]. TTR is also produced in the vitreous and the choroid plexus. Ocular involvement includes vitreous opacities and open-angle glaucoma that may be the presenting sign as described in Swedish patients. Less commonly, CNS involvement is heralded by dementia and lobar and subarachnoid hemorrhages from brain amyloidosis and amyloid angiopathy. Brain MRI may show meningeal enhancement in the oculoleptomeningeal subtype of amyloidosis (OLMA) associated with rare TTR mutations [10]. Other organs variably affected include the kidneys (especially in apolipoprotein-A1 amyloidosis), gastrointestinal tract, the skin, and the lungs.

Table 27.2 Phenotypes associated with familial transthyretin amyloidosis

Phenotype		
Type	Features	Representative genotype
TTR amyloid neuropathy (formerly familial amyloid polyneuropathy type I [Portuguese-Swedish-Japanese type])	*Early* Sensorimotor polyneuropathy of the legs Carpal tunnel syndrome Autonomic dysfunction Constipation/diarrhea Impotence *Late* Cardiomyopathy Vitreous opacities Nephropathy	Val30Met
TTR amyloid neuropathy (formerly familial amyloid polyneuropathy type II [Indiana/Swiss; Maryland/German type])	*Early* Carpal tunnel syndrome *Late* Sensorimotor polyneuropathy of extremities Autonomic dysfunction Constipation/diarrhea Impotence Cardiomyopathy Vitreous opacities Nephropathy	Ile84Ser
TTR cardiac amyloidosis (familial amyloid cardiomyopathy)	Cardiomegaly Conduction block Arrhythmia Anginal pain Congestive heart failure Sudden death	Val122Ile
TTR leptomeningeal/CNS amyloidosis	Dementia Ataxia Spasticity Seizures Hemorrhage (intracerebral and/or subarachnoid) Psychosis Hydrocephalus	Asp18Gly

From genereviews.org

Pathogenesis

The characteristic neuropathy of FAP affects nerve fibers in a sequential manner histologically and clinically. There is loss of unmyelinated sensory fibers accounting for the pain, temperature loss, and dysautonomia. This is followed by small and then larger myelinated fiber loss. Amyloid is demonstrated typically by Congo red staining and visualization of an apple-green birefringence with polarized light microscopy. These deposits are widespread, affecting nerve trunks, spinal roots, and sensory ganglia, characteristically found in the endoneurium and around vasa nervorum but also in the epineurium and perineurium [11, 12]. On teased fiber preparations, segmental demyelination may be found along with evidence of Wallerian degeneration. On electron microscopy, Schwann cell degeneration is seen in association with amyloid (Fig. 27.1). At high resolution the fibrillar amyloid is seen to be comprised of unbranched fibrils measuring 10 mm with parallel dense borders (Fig. 27.2). Amyloid deposits are found in almost every organ, and abdominal fat, sural nerve, rectal mucosa, or peritendinous fat specimens obtained at carpal tunnel surgery are the common accessible sites for diagnostic biopsy. The sensitivity of GI mucosal biopsy is 85 %, but sural nerve pathology may be more patchy and therefore less sensitive for diagnosis [13].

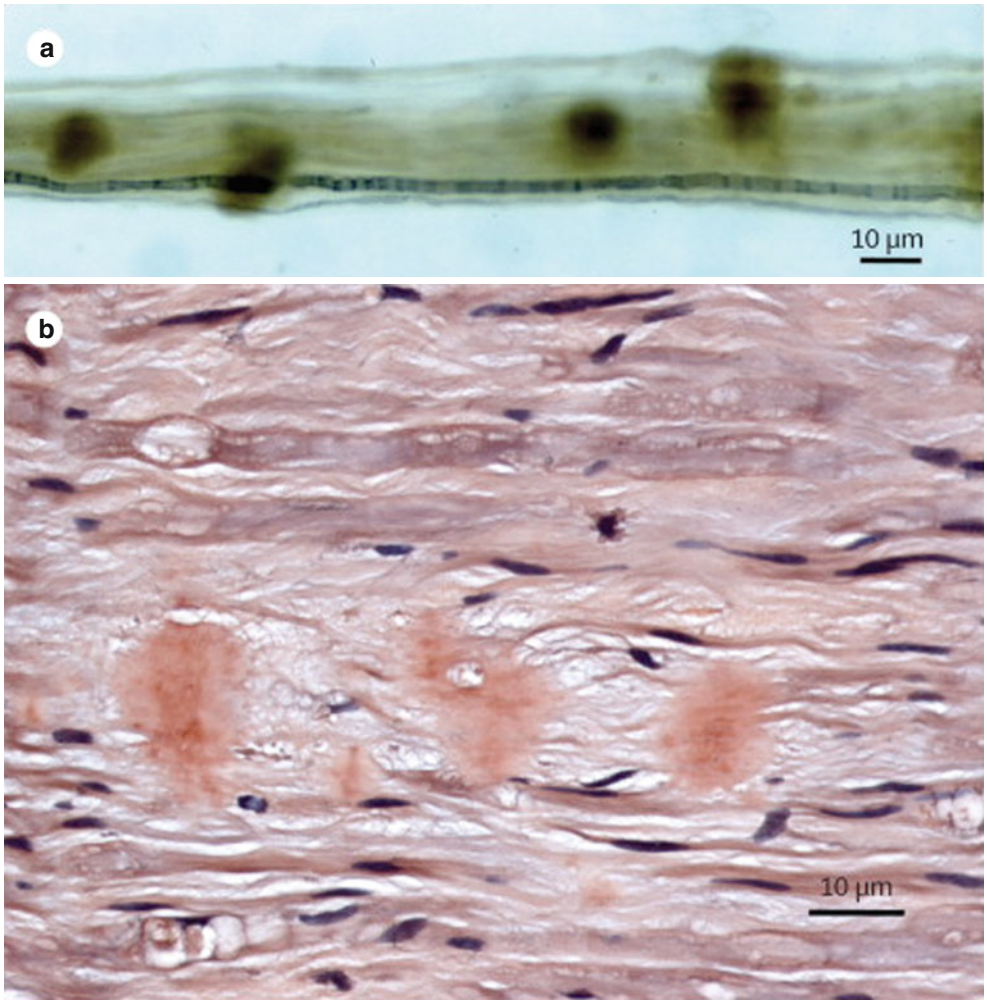

Fig. 27.1 Amyloid deposits in the endoneurium in transthyretin familial amyloid polyneuropathy. (**a**) Teased preparation of the endoneurial content of a nerve biopsy specimen from a 30-year-old man carrying the transthyretin Val30Met mutation. Balls of amyloid deposits can be seen scattered in the endoneurium. Osmium tetroxide stain was used. (**b**) Longitudinal section of a paraffin-embedded nerve biopsy specimen from a different 30-year-old man carrying the Val30Met mutation. Congo red-stained amyloid deposits can be seen (From Plante-Bordeneuve and Said [195]. Used by permission)

The TTR gene resides on chromosome 18 (18q11.2-q12.1) and contains four exons. There have been over 100 point mutations identified and one trinucleotide deletion. The soluble protein is a 55 kD tetramer composed of four identical monomers, each having an extensive β-pleated structure with eight β-pleated sheets arranged in two parallel plates. Under normal conditions, TTR transports thyroxine (T4) and retinol. Mutations cause the tetramer to dissociate into monomers that aggregate and form insoluble amyloid fibrils in the extracellular tissue [14]. In the heart, amyloid deposits have been shown to consist of both mutated and wild-type TTR [15]. The majority of patients are heterozygous for the TTR mutation, but compound heterozygotes and homozygosity have been described. Homozygous mutations do not appear to cause anticipation or a worse course, and some mutations are associated with a relatively more benign course, suggesting there is variable resistance to tetramer dissociation [16].

The ultimate cause of the neuropathy remains unknown. Nerve ischemia and nerve compression theories are postulated but lack evidence and justification. TTR fibrils may bind to the receptor for advanced glycation end products (RAGE) on specific cell targets and induce endoplasmic reticulum (ER) stress via MAP kinase signaling that may result in nerve dysfunction [14]. Based on accumulating biochemical studies, the hypothesized mechanisms of TTR neurotoxicity are summarized in Fig. 27.3. Since the variant TTR circulates from birth, amyloid deposition may also depend on unknown age-related mechanisms that promote amyloid fibrillogenesis. A transgenic mouse model exists but does not demonstrate nerve pathology [17].

Diagnosis

The diagnosis of FAP should be suspected in any patient with symptoms and signs of small fiber peripheral neuropathy, especially with a family history of FAP. Because of the variable penetrance of this disease, patients without a family history but with the phenotype should also be considered for evaluation. If the familial mutation is known, targeted mutation analysis will suffice. If the age of onset is later and a family

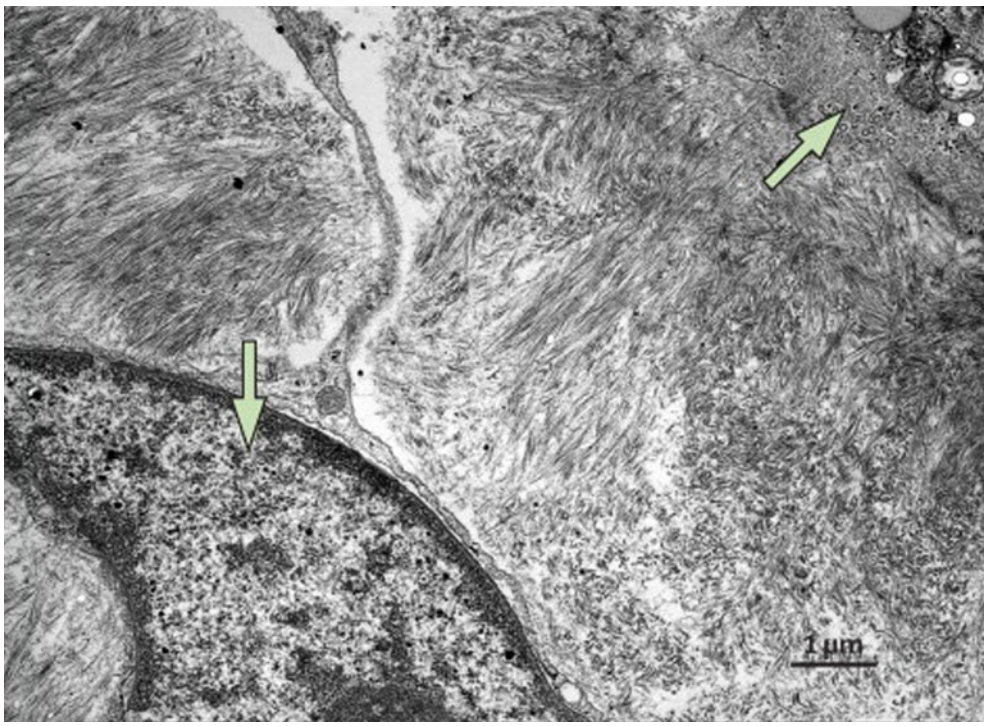

Fig. 27.2 Schwann cell degeneration in contact with endoneurial amyloid deposit in transthyretin familial amyloid polyneuropathy. Electron micrograph of a sural nerve biopsy specimen from a 34-year-old man carrying the transthyretin Val30Met mutation. The fibrillary structure of amyloid and the destruction of endoneurial cells can be seen. At the right upper corner of the photograph, a Schwann cell is degenerating (*arrow*), while at the left lower corner, a fibroblast can still be identified (*arrow*). Sample was stained with uranyl acetate and lead citrate (From Plante-Bordeneuve and Said [195]. Used by permission)

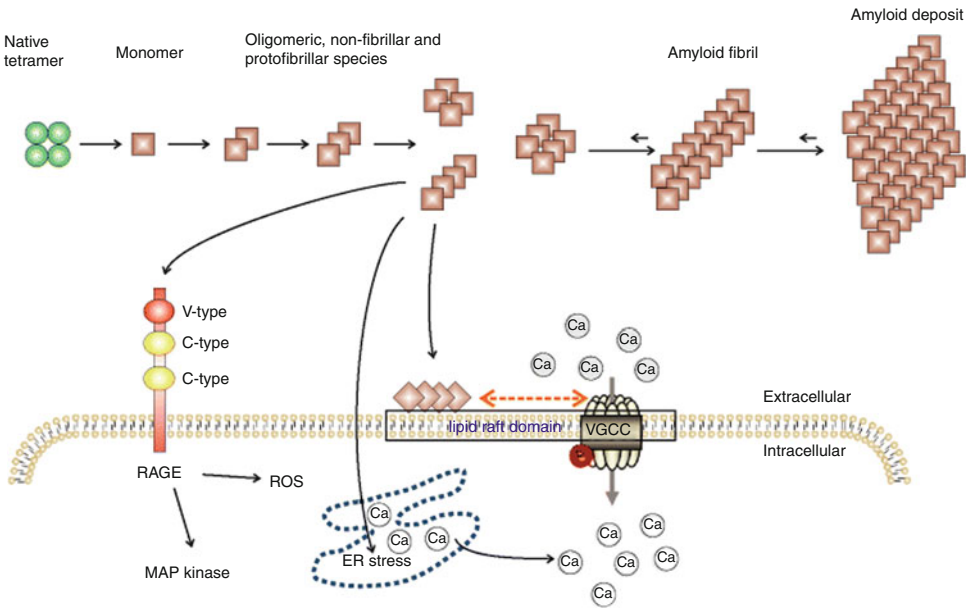

Fig. 27.3 Hypothetical mechanism illustrating how TTR may cause neuronal dysfunction. In this model, mutations in TTR destabilize the native tetramer leading to dissociation into a monomer, which can aggregate. Monomers, low-molecular-mass nuclei, oligomers or protofibrils are the major toxic species. Studies show that these low-molecular-mass diffusible species can bind to lipid membranes. In the model, binding to the lipid membrane disrupts the structure of the lipid rafts, thereby inducing changes in the membrane, which lead to activation and calcium entry through voltage-gated calcium channels (*VGCC*). Alternatively, TTR may bind to a receptor for advanced glycation endproducts (*RAGE*) to affect MAP kinase signaling and induce ER stress, with release of calcium from intracellular stores. ER stress is potentially cytodestructive, and RAGE receptors are known to regulate cascades that are involved in mitogenesis, cellular injury, death, and apoptosis. In contrast with the low-molecular-mass diffusible aggregates, larger amyloid deposits are less toxic than the low-molecular-mass diffusible species but may provide a local pool of TTR which can dissociate into toxic species. ROS, reactive oxygen species; V-type, V-type binding domain on RAGE; C-type, C-type binding domain on RAGE (From Hou et al. [14]. Used by permission)

history is negative, then diagnosis depends on clinical features, biopsy material, and DNA analysis. Blood tests may show an increased concentration of variant TTR in plasma. Confirmation of FAP requires immunolabeling of the amyloid type (TTR, apolipoprotein-A1, or gelsolin), differentiation from AL amyloidosis (serum light chain testing), and DNA testing to identify the specific mutation. Assessment should also include staging of the disease through tests of cardiac, ocular, renal, and brain disease. Autonomic evaluation should be considered, especially if liver transplantation surgery is planned. Prenatal and preimplantation genetic diagnosis is available to families undergoing genetic counseling.

Treatment and Prognosis

Treatment of TTR amyloidosis can be divided into symptomatic therapy and attempts to reduce the formation or pathogenicity of amyloid. Neuropathic pain may respond to appropriate anticonvulsants (gabapentin) or antidepressants that are serotonin-norepinephrine reuptake inhibitors (SNRI) such as duloxetine. Opioids and tramadol are other options [18]. Tricyclic antidepressants should be used with caution as they can worsen orthostatic hypotension and cardiac arrhythmias. Orthostatic hypotension can be particularly dangerous and contributes to mortality in the perioperative period. Strategies include correcting dehydration, liberalizing salt intake, fludrocortisone, midodrine, and elastic stockings. Gastroparesis and vomiting can be treated with small meals, hypomotility agents, and ondansetron. Diarrhea may respond to opioids or subcutaneous octreotide. Urinary catheterization may be necessary to reduce UTI and numerous drugs can reduce incontinence. Carpal tunnel syndrome tends to be more severe in FAP patients, and surgical carpal tunnel release should therefore be considered. Cardiac disease is treated with the appropriate drugs or insertion of a cardiac pacemaker or defibrillator. Vitreous disease is treated with vitrectomy or trabeculectomy if needed. Renal failure may require dialysis or transplantation.

Approximately 90 % of TTR is produced in the liver; thus, orthotopic liver transplantation has been used to treat TTR amyloidosis. First reported in Sweden, follow-up evaluation demonstrated reduced amyloid load by scintigraphy, diminished variant TTR in plasma, and purported clinical improvement, albeit with little effect on the neuropathy [19]. As experience with transplantation has grown, long-term natural history data is accumulating, with some reports of prolonged survival and stabilization or improvement of peripheral neuropathy. Evidence suggests that cardiac and eye disease generally persists and may be even accelerated after liver transplantation [15, 20]. This concern has led to combined liver and heart or liver and kidney transplantation. Since penetrance is variable, orthotopic liver transplantation is not recommended for asymptomatic carriers. Although the liver is the main source of TTR production, it does not develop significant amyloid deposition and therefore can be used for transplantation into patients without TTR amyloidosis, but reports of the development of amyloidosis after domino liver transplant have surfaced [21].

The FAP World Transplant Registry (www.fapwtr.org) in Sweden monitors the results of reported transplant patients. As of 2011, over 1,500 liver transplants have been included, over 80 % of which carry the Val30Met mutation. The postoperative 5-year survival rate was 77 %. Factors associated with improved survival were (1) symptoms less than 7 years (79 % vs. 60 %), (2) modified body mass index 600 or greater (82 % vs. 57 %), and (3) patients with the Val30Met mutation (79 % vs. 56 %). About a third of patients reported clinical improvement, especially gastrointestinal manifestations [22]. The 16-year experience at the Karolinska Institute indicated a 5-year survival of 92 %. Most symptoms stabilized though few improved with the polyneuropathy disability score being stable or improved in 78 %. Age at onset over 40, duration over 7 years and mBMI less than 600 were found to be negative prognostic factors by multivariate analysis [23]. In a Japanese cohort, the estimated probability of survival at 10 years in the subgroup of patients with FAP onset before the age of 50 who underwent liver transplant was 100 %, compared to 73 % in nontransplanted patients [24]. Other reports show progression of the neuropathy after transplantation [25]. This may be due to continued deposition of amyloid derived from wild-type TTR into the amyloid nidus present in peripheral nerve tissue similar to that found in patients with cardiomyopathy after liver transplant [26]. It is also hypothesized that continued deposition of mutated TTR into peripheral nerve can occur by transmission through CSF pathways from the choroid plexus to the nerve by via the subarachnoid space [27].

A number of reports show progression of cardiac arrhythmias necessitating pacemaker insertion [28] and cardiomyopathy [29], sometimes rapidly, after liver transplantation. A long-term follow-up study of 34 transplanted patients focusing on ocular, cardiac, and renal outcomes noted progression of ocular symptoms in 50 %, cardiac amyloidosis in 29 %, and reduced estimated glomerular filtration rate [20].

Other treatment strategies with varying success in TTR amyloidosis include (1) reducing the concentration of variant TTR, (2) inhibiting its synthesis, (3) stabilizing the tetramer, (4) inhibiting aggregation of amyloidogenic intermediates, (5) disrupting amyloid fibril formation, and (6) gene replacement with the normal TTR gene [30]. Plasmapheresis and immunoadsorption are ineffective. Tafamidis meglumine and diflunisal are two drugs that were found to stabilize TTR tetramers with the aim of reducing amyloid fibril formation. A phase II/III clinical trial of tafamidis showed favorable effect on neuropathy progression, quality of life, and mBMI [31]. NSAIDS can inhibit amyloid fibril formation. A phase

III study of diflunisal is underway, with excellent tolerability thus far. Gene therapy using ribozymes [32], small interfering RNAs [33], and antisense oligonucleotides [34] to degrade variant TTR RNA shows promise in vitro, but there are no clinical data.

Survival in those with FAP without liver transplant is approximately 9–13 years, with cardiac death in up to 30 % and infection, malnutrition, and severe autonomic failure contributing to mortality [35]. There is ethnic and mutation-related variation in survival [22]. It seems clear that orthotopic liver transplantation in appropriate patients can significantly prolong survival to over 20 years. Subgroup analysis indicates that patients under 50 with a shorter course of symptoms restricted to the peripheral nervous system have better outcomes [36]. Combined liver and heart or liver and kidney transplants should be considered in the presence of combined organ involvement, as cardiac complications are not halted otherwise.

Apolipoprotein-A1 Amyloidosis

Van Allen first described a family with onset in their fourth decade of progressive renal failure, gastric ulcers, and peripheral neuropathy similar to that found in TTR amyloidosis, although with less prominent autonomic neuropathy [37]. The amyloidogenic protein, apolipoprotein-A1, is a 28 kD plasma protein synthesized in the liver and small intestine. The Gly26Arg mutation is more prominently associated with peripheral neuropathy [38]. Pathology shows amyloid deposition in multiple areas of the peripheral nervous system.

Treatment is similar to that for TTR amyloidosis, with attention to renal function, eventual dialysis, antacids, or surgery for GI ulcers. Experience with liver or combined liver and kidney transplantation is sparse. Success in reducing plasma variant apoA1 levels by 50 % and improvement in neuropathy was reported after hepatorenal transplantation in one case [39].

Gelsolin Amyloidosis

Meretoja first reported patients with slowly progressive neurological and ocular dysfunction in Finland in 1969 [40]. The genetic defect is a mutation of nucleotide 654A on chromosome 9. The responsible protein was found to be gelsolin, a calcium-dependent regulatory protein, which regulates actin filament dynamics in the cytoplasm and binds and clears actin from plasma. Gelsolin is present in the skin, cornea, and nerve tissue. The characteristic clinical features include corneal lattice dystrophy, various cranial neuropathies, and abnormal skin laxity. The cranial nerves most affected are the upper branch of CN VII, CN XII, IX, XI, or V. A relatively mild mixed axonal and demyelinating sensory polyneuropathy is found. Cardiac conduction defects may necessitate pacemaker insertion and renal failure may ensue. Central nervous system complications include cerebral hemorrhage from amyloid angiopathy.

Treatment includes proper eye care and surgery for facial laxity. Gelsolin is not produced in the liver; therefore, transplantation is not indicated. The prognosis is more favorable than TTR amyloidosis with advances in renal transplantation and relatively little dysautonomia; however, chronic immunosuppression after renal transplant increases the risk of infection.

Porphyria

The porphyrias are a heterogeneous group of disorders resulting from the interruption of heme biosynthesis and are rare causes of peripheral neuropathy. Though the most important sites for heme synthesis are the bone marrow and liver, neuropathy is only seen in the hepatic porphyrias. Disturbances in heme biosynthesis result in the accumulation of porphyrins with acute attacks being precipitated by stress, drugs, and hormones. Neuropathy is described in the four hepatic porphyrias: acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP), and aminolevulinic acid (ALA) dehydrase deficiency.

Clinical Presentation

The cardinal features of neuropathy, central nervous system manifestations, and abdominal involvement characteristic of an acute attack of porphyria are similar in all of the hepatic porphyrias. Classically acute attacks of porphyria are characterized by severe abdominal pain that is often concerning for an acute abdomen and may be accompanied by nausea, vomiting, constipation, diarrhea, distention, or ileus, but 5 % of patients may present without abdominal complaints. Brain involvement manifests as almost any acute psychiatric symptom most commonly agitation and nightmares, which may progress to florid psychosis and, eventually, to seizures and coma that may be exacerbated by hyponatremia. A peripheral neuropathy that is diffuse, sometimes asymmetric and often rapidly progressive resembling Guillain-Barré syndrome, develops a few days after the onset of symptoms. Limb pain may be the first feature followed by motor involvement. In contrast to the generalized hyporeflexia of Guillain-Barré syndrome, reflex loss is patchy in proportion to the degree of muscle weakness [41]. Isolated mononeuropathies may occur, e.g., bilateral wrist drop [42]. Overall, 40 % of patients with porphyria develop a neuropathy, even between attacks [43]. Cranial nerves are often involved as is the autonomic

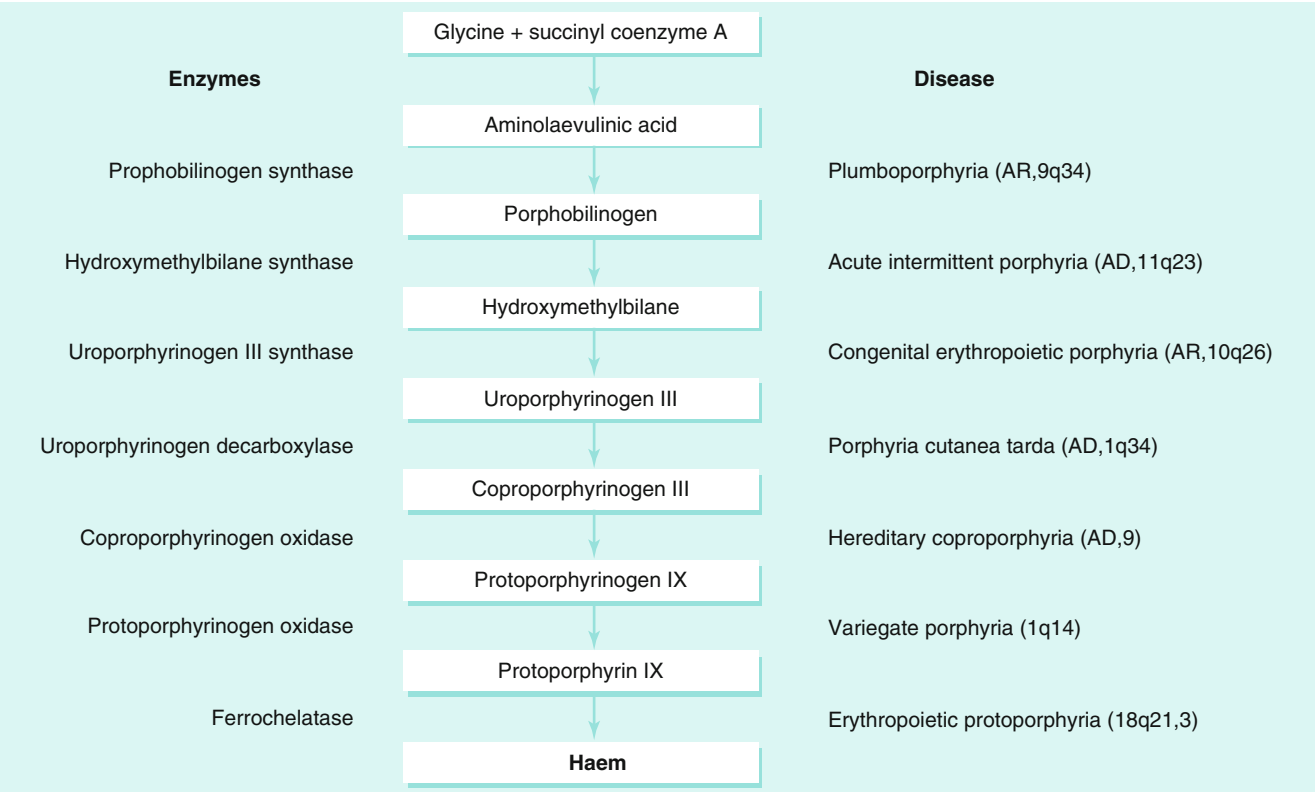

Fig. 27.4 The heme biosynthesis pathway with the enzymes that catalyze each step and the corresponding disease associated with dysfunction of those enzymes (From Thadani et al. [196]. Used by permission)

nervous system. Bulbar manifestations can be severe and paralysis of the respiratory muscles may necessitate intubation and ventilation. Urine will appear red to reddish-brown during an acute attack. The clinical history should seek to identify typical triggers of acute attacks, e.g., drugs or hormones that induce the hepatic microsomal cytochrome P450 system [44], although fasting, alcohol, stress, and infection are also known triggers. Acute attacks are about five times more common in women than men presumably due to hormonal influences. Blisters and skin fragility may occur in HCP and VP.

Pathology and Pathogenesis

Axonal degeneration of peripheral nerves and central chromatolysis are the pathological features described in porphyria, although detailed pathological studies have rarely been undertaken [45]. Patchy demyelination is also described. The pathogenic mechanisms leading to the peripheral neuropathy in porphyria are not completely understood, but two main theories are considered. One is that excess ALA is neurotoxic [46] and the other posits heme deficiency could lead to decreased levels of cytochromes, with detrimental metabolic effects on nervous tissue [47], perhaps through oxidative stress and free radical formation. A recent study showed evidence of Na/K pump dysfunction in the peripheral nerves of patients during an acute attack that may be related to decreased energy supply and reduced heme availability [48].

Etiology

There are eight enzymes involved in heme synthesis. Deficiency of any of these enzymes results in decreased heme production and accumulation of porphyrin precursors and porphyrins in various tissues (Fig. 27.4). Table 27.3 summarizes the distribution of the resulting byproducts.

The estimated prevalence of acute porphyria in most Western countries is 1–2 per 100,000, most of whom have *acute intermittent porphyria (AIP)*. In Sweden the gene frequency is higher at 1 per 10,000 [49]. AIP is an autosomal dominant disorder caused by a partial deficiency of porphobilinogen (PBG) deaminase. This disease is characterized by incomplete penetrance with 90 % of individuals being clinically latent. The *HMBS* gene for PBG deaminase is on the short arm of chromosome 11. Two distinct mRNAs are produced from this gene by alternative transcription and splicing resulting in two forms of PBG deaminase, one of which is erythrocyte specific. Over 100 different mutations are described in the PBG deaminase gene including single-base

Table 27.3 The differential accumulation of heme synthesis substrates in the blood and urine as well as ALAD activity

	Urinary excretion			Stool excretion				
Disorder	ALA	PBG	Copro-porphyrin	Copro-porphyrin	Proto-porphyrin	ALAD activity	Neurovisceral attacks	Photocutaneous symptoms
AIP	↑	↑	Normal or ↑	Normal	Normal or ↑	Normal	+	–
Hereditary coproporphyria (HCP)	↑	↑	↑	↑	Normal	Normal	+	+
Variegate porphyria (VP)	↑	↑	Normal or often ↑	Normal or often ↑	↑	Normal	+	+
ALAD porphyria (ADP)	↑	Normal or slightly increased	↑	Unknown	Unknown	↓	+	–
Hereditary tyrosinemia type 1	↑	Normal	Normal	Normal	Normal	↓	+	–

From genereviews.org
Hereditary tyrosinemia type 1, although not a porphyria, has been included as well for clinical comparison

substitutions, small insertions, and deletions. Partial deficiency of PBG deaminase gives rise to elevated PBG and ALA in the urine and in the serum during acute attacks, with decreased PBG deaminase activity in erythrocytes (except in those patients where the erythrocyte-specific enzyme is normal).

Variegate porphyria (VP) is also autosomal dominant, caused by a partial deficiency in protoporphyrinogen (PPG) oxidase. In the UK, this form of porphyria is about one-third as common as AIP, but the highest prevalence of 3 per 1,000 occurs in South Africa [50]. During acute attacks of VP, urinary ALA, PBG, and coproporphyrin are increased and fecal protoporphyrin and coproporphyrin are elevated. PPG oxidase activity in leukocytes is decreased.

Hereditary coproporphyria (HCP), an autosomal dominant disorder due to partial deficiency of coproporphyrinogen (CPG) oxidase, is much less frequent than AIP or VP. During acute attacks, urinary and fecal coproporphyrin are elevated as well as urinary ALA, PBG, and uroporphyrin. CPG oxidase activity is reduced in leukocytes.

Aminolevulinic acid (ALA) dehydrase deficiency is an extremely rare autosomal recessive disorder due to a homozygous deficiency of the enzyme ALA dehydrase on chromosome 9. This causes a markedly elevated urinary ALA and a minimally elevated urinary porphobilinogen (PBG) with a profound reduction in serum ALA dehydrase activity. Note that in hereditary tyrosinemia, type I dysfunction of fumaryl acetoacetate hydrolase leads to accumulation of 4,6-dioxoheptanoic acid, a potent inhibitor of ALA dehydrase, and thus mimics ALA dehydrase deficiency.

Diagnosis

The main clinical differential diagnosis for porphyric neuropathy is Guillain-Barré syndrome, but abdominal symptoms are more severe in porphyria. A history of urine color change, brain involvement, and electromyographic findings of an axonal polyneuropathy also helps distinguish porphyria from Guillain-Barré syndrome. Previous skin involvement or photosensitivity raises the possibility of VP and HCP. Arsenic, thallium, or lead poisoning may cause a similar presentation with abdominal and neuropathic symptoms, and heavy metal intoxications may also cause a rise in urinary coproporphyrins.

When an acute porphyric attack is suspected, a rapid screening test for urinary porphobilinogen (PBG) should be performed using the Watson-Schwartz [51]. If positive, the diagnosis should be confirmed by specific quantitative assays of urinary PBG and measurement of fecal and plasma porphyrins (PBG and ALA), which will also characterize the type of acute porphyria. Although PBG excretion is usually increased in AIP in the asymptomatic phase, PBG excretion in HCP and VP usually returns to normal. All of the hepatic porphyrias cause an elevated urine ALA and this can be measured where clinically indicated.

Electromyography and nerve conduction studies reveal a predominantly motor axonal neuropathy, with relatively persevered sensory nerve action potentials, H-reflexes, and F-waves [52]. Genetic testing should be undertaken for any new diagnosis of porphyria, and family members should be tested where appropriate.

Treatment

Care of the acute attack often requires hospitalization. The most important first step is to withdraw potentially exacerbating drugs. Relief of pain and vomiting may be required. In mild cases, hydration and glucose are adequate treatment. The most effective therapy is now accepted to be the intravenous administration of heme, particularly in severe attacks. Heme arginate is said to be preferable to hematin as it is

more stable and has less side effects [53]. Patients may require nasogastric feeding to obtain adequate calorie intake during the acute phase. Assisted ventilation may be necessary. During an acute attack, plasma PBG levels have been shown to be the most reliable marker of improvement [54]. Treatment of confusion and seizures may be difficult because of the limited number of drugs that are safe, e.g., gabapentin [55]. Menses-related attacks can be difficult to manage since hormones may exacerbate porphyria.

There have been recent trials of recombinant human porphobilinogen deaminase in patients with AIP. Although this therapy is still in early stage evaluation, results suggest safety and evidence of improved enzymatic activity [56]. The mainstay of treatment of porphyria is the prevention of attacks. A current drug list should be consulted before any drug is prescribed to a patient with porphyria (www.drugs-porphyria.org). Mortality is now less than 10 % and decreasing with growing awareness [57]. Although the abdominal and central nervous system complications improve, recovery from the neuropathy may be incomplete. Repeated acute attacks may lead to chronic renal failure.

Leukodystrophies

Metachromatic Leukodystrophy

The leukodystrophies are lysosomal storage disorders (lipidoses) affecting myelin. The metachromatic leukodystrophies (MLD) are a heterogeneous group of disorders characterized by demyelination in the central and peripheral nervous system and accumulation of galactosyl sulfatide (cerebroside sulfate) in glia, Schwann cells, and macrophages. The inheritance pattern is autosomal recessive. The *ARSA* gene resides on chromosome 22q13.33 and codes for arylsulfatase A.

The finding of metachromatic lipid deposits in nervous system tissue is pathognomonic for MLD. Metachromasia refers to the staining properties of the abnormal tissue. When frozen tissue is stained with acidified cresyl violet (Hirsch-Peiffer stain) or with toluidine blue or thionine, sulfatide-rich storage deposits stain a golden brown. Fixing the tissue with lipid solvents like alcohol before staining abolishes the metachromatic reaction. Urinary sediment may also show metachromatic material.

Late-infantile, juvenile, and adult-onset forms are recognized; most cases are due to a deficiency of arylsulfatase A, which results in the accumulation of sulfatide in many tissues, particularly in the nervous system and kidneys. The AB variant, where arylsulfatase activity is normal, is due to a deficiency of the sphingolipid activator protein B. Multiple sulfatase deficiency, a genetically distinct condition, has features of both late-infantile MLD and mucopolysaccharidosis.

Clinically, the late-infantile form of the disease (50–60 % of cases) begins by age 30 months with preceding normal development. The disease evolves rapidly over 2–3 years from a predominantly hypotonic neuropathic form to one in which central nervous system dysfunction predominates. The disease usually starts with hypotonia and walking, sitting, or crawling difficulty progressing to inability to stand without support. At this stage, the reflexes are often absent with motor weakness in the feet. Slowed nerve conduction velocity is a common finding [58]. Regression of mental development may begin. As the disease progresses, ataxia becomes more prominent and spasticity develops accompanied by limb pain, dementia, and dysarthria. In the terminal stages, the child develops quadriplegia or decerebrate rigidity, blindness, deafness, seizures, and myoclonic jerks or opisthotonus. Juvenile MLD (20–30 % of cases) presents between the ages 3 and 20 years. Symptoms include reduced school performance, clumsiness, dysarthria, seizures, and behavioral problems. Survival from 10 to 20 years is common. Adult-onset MLD (15–20 % of cases) can present at any age beyond puberty, often with a behavior change suggesting psychosis, with poor job performance, alcoholism, and emotional instability [59]. A mild peripheral neuropathy is often found, with reduced motor nerve conduction velocity. Ataxia and spasticity generally supervene and inexorable progression occurs with disabling speech, vision, and UMN signs.

Many variations to the clinical types described above have been reported. Childhood-onset peripheral neuropathy without central manifestations [60], hypotonia suggestive of spinal muscular atrophy or myopathy [61], adult-onset isolated demyelinating neuropathy [62], multifocal nonuniform slowing [63], mirroring chronic inflammatory demyelinating neuropathy [64, 65] may all be encountered within MLD.

The gene frequency is about 1/40,000; however, from 13.7 to 17 % of normal individuals may have reduced level of arylsulfatase A without disease. These pseudoarylsulfatase deficiency states may cause confusion when screening with enzyme levels for genetic counseling or disease detection; thus, DNA analysis is the recommended method for prenatal and preimplantation detection. An immune-based assay of blood spot samples can differentiate MLD and pseudodeficiency and offer the possibility of effective newborn screening [66]. Because there are alleles that result in either no enzyme (O allele) or residual enzyme (R allele) activity, genotype-phenotype correlations exist. Late-infantile disease is associated with the presence of two O alleles, adult-onset MLD with two R alleles, and juvenile cases one of each.

Pathologically, there is degeneration of myelinated fibers in the brain and peripheral nerves. Brain MRI shows white matter abnormalities that may be confluent. CSF protein is elevated. Segmental demyelination-remyelination and small onion bulbs may be found [67]. On light microscopy, lipid

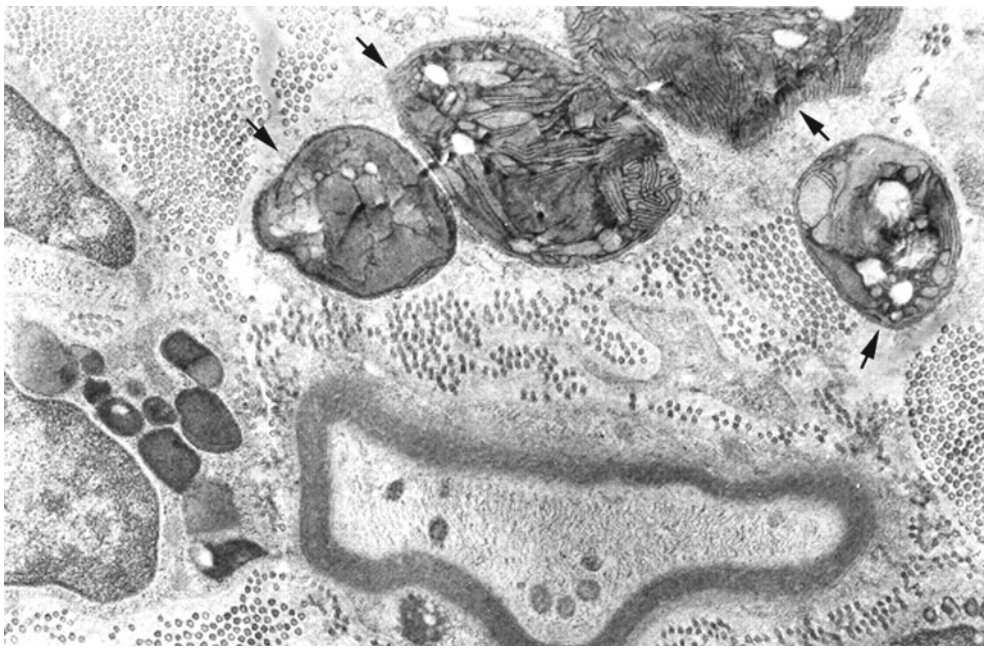

Fig. 27.5 Electron micrograph showing tuff stone inclusion bodies composed of stacks of lamellar discs and plates (*arrows*) enclosed within a membrane in the endoneurium. Original magnification, ×10,000 (From Bindu et al. [197]. Used by permission)

accumulation with metachromatic granules is found in glia, macrophages, and Schwann cells and viscera, especially the kidney and gall bladder [68]. Ultrastructurally, the metachromatic granules are found in relation to Schwann cell nuclei along with inclusions of various types, some of which are thought to be specific to this disease. The earliest reported are membrane-bound concentric lamellated figures exhibiting a periodicity of 5.6–5.8 nm [69]. Myelin figures have a periodicity of 8 nm between their major dense lines. Tuffstone bodies, prismatic stacks, and zebra bodies are also seen (Fig. 27.5) [70]. These inclusions are not derived from myelin breakdown, as they are present in Schwann cells associated with unmyelinated axons and in fetal nerves before demyelination is evident. Inclusions are found less in the juvenile and adult-onset forms. Mouse models show accumulation of sulfatides but not significant peripheral nerve demyelination.

The pathogenesis of the demyelination is uncertain. Sulfatides comprise about 5 % of myelin lipids, and their accumulation may interfere with normal oligodendrocyte and Schwann cell function [71], attract toxic cations or other metabolites [72], or contribute to temperature-dependent myelin instability [73].

Reduced arylsulfatase A levels are found in serum, but diagnosis requires either molecular genetic analysis or demonstration of abnormal urinary sulfatide excretion or of metachromatic lipid deposits in nervous tissue. Brain MRI may suggest a leukodystrophy. Motor nerve conduction velocity as low as 10–20 m/s and reduced or absent sensory action potentials [61] may precede symptoms [74, 75], but these may be less obvious in the adult-onset MLD.

The prognosis is poor in untreated late-infantile MLD, with death usually by age six. Bone marrow transplantation is the only treatment that influences the neurologic progression of the disease [76]. Later age of onset and minimal clinical involvement before transplantation are the best prognostic factors [77]. NAA levels by magnetic resonance spectroscopy correlate with function and can be used to monitor disease progression [78].

Efforts underway to improve bone marrow transplant include using autologous stem cells, combined therapy with bone marrow and mesenchymal stem cell transplant, or ARSA genetically engineered to cross the blood–brain barrier. Gene therapy has not yet reached human subjects, but potential strategies are reviewed by Biffi [79] and Gieselmann and Krageloh-Mann [80].

Multiple Sulfatase Deficiency (O Variant)

Multiple sulfatase deficiency was described in 1973 [81] and is caused by a defect in formylglycine-generating enzyme (FGE), responsible for activating most sulfatases. Patients have deficiencies of arylsulfatases A, B, and C and iduronate sulfatase (Hunter type) and have features of both late-infantile MLD and mucopolysaccharidosis, with earlier onset and death usually by age 12 years. Dementia and spasticity with reduced tendon reflexes are combined with ichthyosis, coarse facial features, and skeletal changes (flared ribs, broad phalanges) in classic cases. A demyelinating neuropathy similar to MLD is found and nerve biopsy shows metachromatic inclusions. Urine and tissue show accumulation of both sulfatides and mucopolysaccharides.

Saposin B Deficiency (AB Variant)

Another variant of MLD is described with normal activity of arylsulfatase A and B but with a deficiency of the cerebroside sulfate activator protein, saposin B (AB variant) [82].

The gene is on chromosome 10q21-23. The age of onset is variable but clinically and pathologically, this variant is indistinguishable from MLD. The diagnosis of activator deficiency is suspected in a child who appears to have MLD but with normal ARSA activity and evidence of excess urinary sulfatide excretion and/or tissue storage.

Globoid-Cell Leukodystrophy (Krabbe's Disease)

Globoid-cell leukodystrophy is an autosomal recessive disease caused by a deficiency of galactocerebrosidase-β-galactosidase (aka galactosylceramide-β-galactosidase-GALC). This leads to nervous system damage by accumulation of psychosine and galactocerebroside in oligodendrocytes and Schwann cells, demyelination, and variable axon loss. The pathologic hallmark in brain tissue is multinucleated globoid cells of macrophage origin, containing prismatic and tubular inclusions found around small blood vessels. In peripheral nerve, macrophages and endoneurial Schwann cells contain similar inclusions, but frank globoid cells are rare. The gene is on chromosome 14q31.3 and many mutations are known.

In the era of molecular diagnosis the stereotypical presentation of this disease as one of early infancy is being reconfigured, with late-infantile, juvenile, and even adult-onset cases now described. In the classical form, onset is usually between 3 and 6 months, with the child developing irritability and motor and intellectual delay. Spasticity, opisthotonus, nystagmus, optic atrophy, deafness, tonic seizures, and intermittent fevers develop. Deep tendon reflexes are reduced after about 6 months as neuropathy develops, though Babinski signs are present. Death usually occurs by age 2 years.

Later onset comprises 10–15 % of patients. These patients have intellectual regression, visual difficulty, and spastic paraparesis but with variable peripheral neuropathic features. Several reviews detail the clinical and biochemical features of cases across the age spectrum [83–85]. Neuropathy may be the presenting feature [86].

Laboratory testing reveals MRI evidence of symmetric white matter changes or sometimes calcifications in the brain. Enhancement of cranial nerves [87] or roots [88] may be found. EMG shows uniform slowing of motor NCV consistent with an inherited demyelinating neuropathy [89–91]. Sural nerve biopsy is diagnostic but rarely needed today as the diagnosis is made by assay of GALC activity in leukocytes, serum, or cultured fibroblasts.

Pathologically, the brain has myelin loss with globoid cells with characteristic inclusions described below. Peripheral nerves show thinning of myelin sheaths or segmental demyelination, and dense material may be seen near blood vessels. Ultrastructurally, the pathognomonic inclusions are seen in Schwann cells and macrophages as nonoriented straight or curved, prismatic or tubular structures. Depending on their plane of section, they may appear as empty clefts [92].

In a natural animal model of the disease, the "twitcher" mouse, hematopoietic stem cell transplantation can reduce globoid cells and induce remyelination [93]. Nerve conduction was shown to improve in humans treated with hematopoietic stem cell transplantation [94]. Clinical improvement after donor umbilical cord blood transfusion suggests this may be a breakthrough therapy for this disorder [95].

Adrenoleukodystrophy/ Adrenomyeloneuropathy

Diseases affecting peroxisomal function include those that interfere with peroxisome biogenesis (neonatal adrenoleukodystrophy, infantile Refsum disease) or disorders with deficiency of single peroxisomal enzymes or proteins. The latter category is associated more often with peripheral neuropathy and includes adrenoleukodystrophy and classical Refsum disease.

Adrenoleukodystrophy (ALD) is an X-linked recessive disorder that affects primarily the nervous system myelin, the adrenal cortex, and the Leydig cells of the testes. The associated gene, *ABCD1*, is on chromosome Xq28 near the color vision gene, and its product is not actually an enzyme but a membrane transport protein in the ATP-binding cassette subfamily (ALDP) [96]. The pathologic substance, very long-chain fatty acids (VLCF), can be detected in several organs, plasma, and cultured skin fibroblasts. Adrenomyeloneuropathy (AMN) is a variant of later onset with peripheral neuropathy.

This disease has marked phenotypic heterogeneity even in families with the same mutation and between monozygotic twins, suggesting environmental modifiers [97]. Families have been described harboring both ALD and AMN patients with identical haplotypes [98]. There are many de novo mutations. Heterozygous females may develop symptoms later in life to a milder degree than males and pass on the disease to each male offspring. If both hemizygote and heterozygotes are included, it is estimated to occur in 1:16,400 live births [99].

Schilder (1913) described the pathology of a case originally published by Haberfeld and Spieler (1910) under the title "encephalitis periaxialis diffusa." Griffin and Schaumburg (1977) are credited with distinguishing adrenomyeloneuropathy (AMN) as a distinctive phenotype [100]. Hugo Moser, a preeminent scientist of this disease, described seven phenotypes [101], but for simplicity, three main symptom sets will be described here. The classic ALD patient is a boy developing attention deficit disorder-like behavior changes and regressing school performance between ages 4 and 8 years, with rapidly progressing spasticity, visual difficulty, dementia, pseudobulbar palsy, seizures, and adrenal insufficiency

with its associated skin hyperpigmentation. Untreated, the boy becomes bedridden with death ensuing over the next 1–2 years. This is estimated to occur in about 35 % of affected individuals.

Adrenomyeloneuropathy (AMN), caused by the same mutation, occurs in about 40–45 % of patients and generally presents in the third decade with slowly progressive spastic paraparesis, peripheral neuropathy, and sexual dysfunction with hypogonadism. There may be antecedent adrenal dysfunction, recognized by pigmentation, nausea, vomiting, weakness, and hypotensive episodes in about 70 % of men. On exam, the AMN patient may have hypotension, bronzed skin, gait stiffness with mild spasticity early on, but reduced deep tendon reflexes. Reduced vibration and proprioception, indicative of large myelinated peripheral nerve fiber dysfunction, is often found. On electromyographic testing, slowed motor nerve conduction velocities, indicating a demyelinating neuropathy, are most common, but mixed axonal and demyelinating or predominantly axonal changes have been reported. Brain MRI is generally normal, but van Geel found that about 20 % of patients with AMN had radiographically apparent cerebral demyelination [102]. The prognosis is one of slowly progressive spasticity that may require assistive devices for ambulation, social and emotional support, and treatment of libido and erectile dysfunction. Truncation of the initial 65 amino acids of the ALD protein has been correlated with the AMN phenotype [103].

Female carriers are heterozygous and may develop slowly progressive spastic paraparesis and sphincter dysfunction in adulthood; adrenal insufficiency is much less common. Peripheral neuropathy could be detected electrodiagnostically in about two-thirds of women and close to 90 % of men, showing mixed multifocal demyelination and axon loss [104].

The pathogenesis of these subtypes is similar, though different in degree, for unclear reasons. The transport protein facilitates β-oxidation of long-chain fatty acids. The defect leads to accumulation of lipid material consisting of unbranched saturated fatty acids with a chain length of 24–30 carbons, especially hexacosanoate (C26:), in many cells. Detection of elevated levels of these VLCF is the basis for diagnosis. The pathophysiologic link between these findings and the cellular damage is uncertain. Loss of microglia in regions of the brain with intact myelin has been observed and suggests that VLCF accumulation causes microglia apoptosis early, then leading to demyelination [105]. VLCF are apparently toxic to oligodendrocytes and to mitochondrial function in vitro [106].

Pathologically, massive myelin degeneration is found in the brain with sudanophilic staining and pockets of inflammatory infiltrates. The most common finding on microscopy is lipid-laden macrophages and gliosis. The ultrastructural changes are nonspecific to this disease, but include lamellar cytoplasmic inclusions ("zebra bodies") in central nervous system white matter, adrenals, and Schwann cells [107]. Atrophic changes and inclusions are also found in the adrenal cortex and testes. Sural nerve biopsies show loss of both myelinated and unmyelinated axons, increased endoneurial collagen, and small onion bulbs without inflammation. Teased fiber preparations may show demyelination with remyelination [108]. Mitochondria in dorsal root ganglion neurons show lipid inclusions [109]. These changes have been difficult to recapitulate in knockout mouse models. Oligodendrocyte and myelin damage can be ameliorated with IGF-1 and NT-3 introduced via a viral vector [110].

The diagnosis is made by demonstrating elevated levels of C26 fatty acid or elevated C26:C22 ratios in plasma or skin fibroblasts. Prenatal testing via amniocentesis is available. In heterozygotes, plasma levels are normal in 15 %, and thus, genotyping with DNA analysis may be tried next. ALD should be considered in boys with progressive cognitive or behavioral problems associated with visual loss and UMN signs. AMN should be suspected in young or middle-aged men and women with progressive gait and sphincter dysfunction, especially with hypoadrenalism. In classic cases, brain MRI is abnormal with often dramatic white matter damage. CSF protein may be elevated. Evaluation should include measurements of electrolytes, serum testosterone, and cortisol.

For ALD, a three-pronged treatment is currently recommended: early dietary adjustment, adrenal hormone replacement, and hematopoietic stem cell transplantation if MRI abnormalities develop. Corticosteroid and mineralocorticoid therapy is essential for those patients with adrenal insufficiency. Physical therapy, bladder relaxants, drugs for erectile dysfunction, and testosterone therapy may be helpful.

Variable but sometimes significant success has been reported with bone marrow transplantation, hematopoietic stem cell transplantation, and, in asymptomatic patients, dietary strategies ("Lorenzo's oil"). Because of phenotypic heterogeneity, there is no one treatment recommended for all, and the timing of marrow and stem cell transplantation is controversial. Some individuals with ALD remain asymptomatic until middle age or later.

Bone marrow transplant is recommended for boys in early stages of classic ALD, ideally with minimal intellectual and motor deficit (e.g., performance IQ >80) [111]. Hematopoietic stem cell transplantation can restore intact ALD protein in tissues [112], and a 5-year survival rate of 56 % was reported [113]. Bone marrow transplant is not recommended for AMN as this can be a slowly progressive disorder.

Dietary restriction of long-chain fatty acids alone is not effective. Lorenzo's oil is a mixture of oleic acid and erucic acid. Incorporated with a low-fat diet, it was hoped that this treatment could stabilize or improve the disease, but trials in symptomatic patients have not shown success [114, 115]. An open trial using Lorenzo's oil in asymptomatic boys with normal brain MRI showed reduction in plasma C26:0 levels and reduced risk of developing MRI lesions. The amount of

C26:0 reduction correlated with reduction of risk [116]. The treatment is still considered investigational. Gene therapy may be considered in those patients without suitable donors for hematopoietic stem cell transplantation [117].

A separate disease, neonatal ALD, has autosomal recessive inheritance and is due to abnormalities of peroxisomal biogenesis or assembly rather than a single enzyme defect. Clinically, neonatal ALD is characterized by seizures, hypotonia, facial dysmorphism, blindness, deafness, hepatomegaly, and diffuse amyotrophy. Tendon reflexes may range from absent to brisk. Slow nerve conduction velocity and denervation may occur. Nerve biopsy shows decreased density of myelin sheaths without inclusions. Disease onset is in infancy with rapid progression due to white matter degeneration in the brain. Adrenal insufficiency does not occur. Plasma shows elevations in VLCF and, occasionally, phytanic acid [118].

Tangier Disease

Tangier disease (TD) is a rare disorder of lipid metabolism caused by mutations in the *ABCA1* gene. ATP-binding cassette A1 (ABCA1) normally is a transmembrane protein that transports free cholesterol from cells into the circulation to bind with apoliporotein-A1 and become high-density lipoprotein (HDL). Peripheral neuropathy occurs in half of patients with variable features, though upper body sensorimotor dysfunction is a clinical clue to diagnosis.

The disease was first described in 1960 when enlarged tonsils containing cholesterol-laden macrophages were removed from a boy living on Tangier Island, off the Virginia coast [119]. This finding was linked to markedly low serum HDL levels, and the gene defect was discovered in 1998. A related disorder, familial HDL deficiency, is seen in patients with one mutant allele but does not lead to peripheral neuropathy.

There is no typical clinical presentation, family history may be lacking, and errors in diagnosis are common. Hand or face weakness and numbness may lead patients to seek medical attention. Loss of pain and temperature sensation is common, with motor weakness evident in some, either with a distal predominance in the feet or hands or with bilateral facial weakness, causing patients to sleep with eyes partially open [120]. Transient ptosis and diplopia may occur. Pain is not a common feature, and there is no significant autonomic dysfunction.

When sensory manifestations are confined to the arms and face, a syringomyelia-like pattern is suggested, but MRI of the spinal cord is normal [121]. An asymmetric or multifocal pattern of deficit may cause confusion with the Lewis-Sumner syndrome [122]. A relapsing-remitting clinical course occurs and contributes to diagnostic inaccuracy.

Nerve conduction studies typically show no recordable SNAPs in the arms and legs, consistent with the hypothesized pathology of dorsal root ganglia damage with secondary axonal degeneration. Motor nerve conduction are often markedly slow, with prolonged distal motor latencies and occasional conduction block resembling that found in chronic progressive demyelinating neuropathy [123].

Other clinical findings represent cholesterol deposition and include enlarged yellow-orange tonsils, xanthomas, corneal clouding, hepatosplenomegaly, lymphadenopathy, and coronary and carotid artery disease, with a sixfold increased risk of myocardial infarction [124].

The *ABCA1* gene resides on chromosome 9q31. The defect leads to impaired removal of cellular cholesterol. Lipoproteins render lipids soluble in the circulation for transport. They are composed of cholesterol, phospholipids, triglycerides, and apolipoproteins. The latter are responsible for targeting the hydrophobic lipid to the appropriate cellular receptor or enzyme. Apolipoprotein-A1 is the major structural component of high-density lipoproteins. Point mutations, deletions, and compound heterozygosity have been reported in the *ABCA1* gene leading to reduced levels of apolipoprotein-A1. A defect in the reverse cholesterol transport pathway prevents transfer of cholesterol via the ABCA1 transporter to high-density lipoprotein leading to elimination of lipid-poor high-density lipoproteins by the kidneys [125].

Nerve pathology shows loss of small myelinated and unmyelinated axons. There are prominent lipid vacuoles in Schwann cells but not in neurons [126, 127]. Demyelination and remyelination is seen in the subtype with relapsing-remitting multifocal neuropathy. The precise pathogenesis of the neuropathy is unknown, but cholesterol deposition in Schwann cells is theorized to cause paranodal dysfunction and tomacula are described [128]. Lipid-laden macrophages are found in the bone marrow, liver, tonsils, and other organs.

It is suggested that lipid profiles be included in patients with neuropathy resembling those described above in order to detect the characteristic reduced high-density lipoprotein (<5 mg/dL) and cholesterol (usually <150 mg/dL, but may be normal) levels and increased triglyceride (>300 mg/dL) levels of Tangier disease. The diagnosis is secured by demonstrating reduced or absent apolipoprotein-A1 levels (<5 mg/dL) and a relevant gene mutation by DNA analysis. Reduced HDL levels may also be seen in chronic infection and lymphoproliferative disease, but finding reduced HDL levels in family members (who are obligate heterozygotes) strengthens the likelihood of TD. There is no specific treatment, and dietary management of lipids is the mainstay of therapy.

Bassen-Kornzweig Disease (Abetalipoproteinemia)

Abetalipoproteinemia is a rare autosomal recessive disorder that presents in infancy or childhood with hyporeflexia, ataxia, sensory peripheral neuropathy, and acanthocytosis.

The disorder was first clinically described in 1950 and in 1993 mutations in the gene on chromosome 4q23 encoding the microsomal triglyceride transport protein (MTP) identified [129]. The basic biological defect is an inability of the body to synthesize the proteins of cell membranes because of the impaired absorption of fat and fat-soluble vitamins through the mucosa of the small intestine. This results in markedly reduced concentrations of the apolipoprotein-B (ApoB)-containing lipoproteins (very low-density lipoproteins, low-density lipoproteins), with decreased levels of chylomicrons, cholesterol, and triglycerides. Serum HDL is normal in this disease. Vitamin E deficiency likely contributes to the pathology.

The disease has a heterogeneous clinical presentation with the fat malabsorption syndrome causing steatorrhea and failure to thrive. Neurological manifestations occur in infancy in about a third of patients with visual deterioration from retinal and macular degeneration associated with reduced tendon reflexes and progressive ataxia with features of both large fiber sensory loss and cerebellar ataxia. The child may be unable to stand or walk in adolescence, and many patients are confined to a wheelchair by age 30 [130]. In addition to impaired vibration and proprioception, titubation, dysarthria, muscle weakness, and oculomotor abnormalities, extensor plantar reflexes, pes cavus, and scoliosis reminiscent of Friedreich's ataxia occur. Sensory nerve action potentials are reduced in amplitude or absent, and motor nerve conduction velocity is normal or mildly slowed, reflecting a predominantly axonal sensorimotor neuropathy [131]. Other clinical findings in some include anemia, cardiomyopathy with congestive heart failure, mild clotting dysfunction due to vitamin K deficiency, and mild mental retardation.

Blood smears reveal acanthocytes, the characteristic spiky erythrocytes caused in this case by a defective lipid layer of the red cell membrane. Foamy vacuoles are seen in cells of the intestinal mucosa. Loss of myelinated fibers in the sural nerve and degeneration of the posterior columns and cerebellar Purkinje and granule cells is observed. Anterior horn cells, retinal ganglion cells, muscle fibers, and myocardium show degenerative changes.

The diagnosis should be suspected in a child presenting with progressive ataxia and acanthocytes on peripheral blood smear and is supported by finding markedly low levels of very low- and low-density lipoproteins in the serum. Treatment with high-dose vitamins E, A, and K (if warranted) may stabilize the disease or reverse symptoms if given early [132]. Dietary restriction of very long-chain fatty acids can reduce steatorrhea. The prognosis is poor in untreated patients, and most are bedridden by early adulthood.

Familial hypobetalipoproteinemia is another disorder of the ApoB-containing lipoproteins with the same serum profile as abetalipoproteinemia. Its inheritance is autosomal dominant. Homozygotes are clinically similar to abetalipoproteinemia. Some patients have mutations in the ApoB gene, most of which cause ApoB truncations, or PCSK9 mutations [133]. Dietary fat restriction and vitamin E supplementation may stabilize deterioration.

Anderson's disease (chylomicron retention disease) is another rare autosomal recessive ApoB-deficient disease. Chylomicrons in plasma after fat ingestion are absent due to an inability to secrete ApoB-containing chylomicrons from the intestine. Neurologic manifestations and acanthocytosis occur in some patients. MTP is normal, but mutations of the SARA2 gene are reported [133].

Fabry's Disease

Fabry's disease is a lysosomal storage disorder caused by mutations in the α-galactosidase-A (*GLA*) gene on chromosome Xq22. The enzymatic defect results in deposition of glycosphingolipids including globotriaosylceramide (Gb3) in cells throughout the body, especially affecting vascular endothelial and perineurial cells. Phenotypic diversity is noteworthy, with the classic phenotype of most neurologic interest, but there are variant phenotypes affecting cardiac and renal function that may be misdiagnosed. The classic clinical features include acroparesthesias, angiokeratomas, hypohidrosis, corneal and lens opacities, and progressive renal failure. Although classically affected males have almost no GLA, others with over 1 % GLA function may have cardiac or renal variant phenotypes, and heterozygous females may be variably symptomatic (Table 27.4). Enzyme replacement therapy is safe and effective in reducing symptoms, and gene therapy is successful in reducing storage in knockout mice.

The first patients were reported independently by Anderson and Fabry in 1898 [134]. Neurological manifestations predominate in the classic form, with intense burning pain in the distal arms and legs beginning often in childhood, reflecting a small fiber peripheral neuropathy. Hypohidrosis is linked to deposition of storage material in sweat glands, as there is little evidence of autonomic failure despite small fiber involvement. EMG studies may be normal, but thermal threshold testing [135] and intraepidermal nerve fiber density [136] are abnormal. Angiokeratomas, small telangiectasias with keratin and epidermal cell proliferation, can be widespread or limited to the lower "bathing trunk" area of the body (Fig. 27.6). They are found in two-thirds of men and about one-third of women, and their presence correlates with disease severity [137]. Proteinuria may be detected early, and renal failure may ensue if untreated. Cerebrovascular disease may be a presenting feature or a variant of the disease. A *GLA* mutation was found in 5 % of men and half that percentage of women with cryptogenic stroke under age 55 [138].

Death is caused by cardiac or renal disease with median survival in men of about 50 years. Stroke occurs in up to a

Table 27.4 Major manifestations in classic and atypical Fabry's disease

Manifestation	Classic	Renal variant	Cardiac variant
Age at onset	4–8 years	>25 years	>40 years
Average age of death	41 years	>60 years	>60 years
Angiokeratoma	++	–	–
Acroparathesias	++	∓	–
Hypohidrosis/anhidrosis	++	∓	–
Corneal/lenticular opacity	+	–	–
Heart	LVH/ischemia	LVH	LVH/myopathy
Brain	TIA/stroke	–	–
Kidney	ESRD	ESRD	Proteinuria
Residual α-Gal A enzyme activity	<1 %	>1 %	>1 %

(+)-Present
(–)-Absent
LVH-left ventricular hypertrophy
TIA-transient ischemic attack

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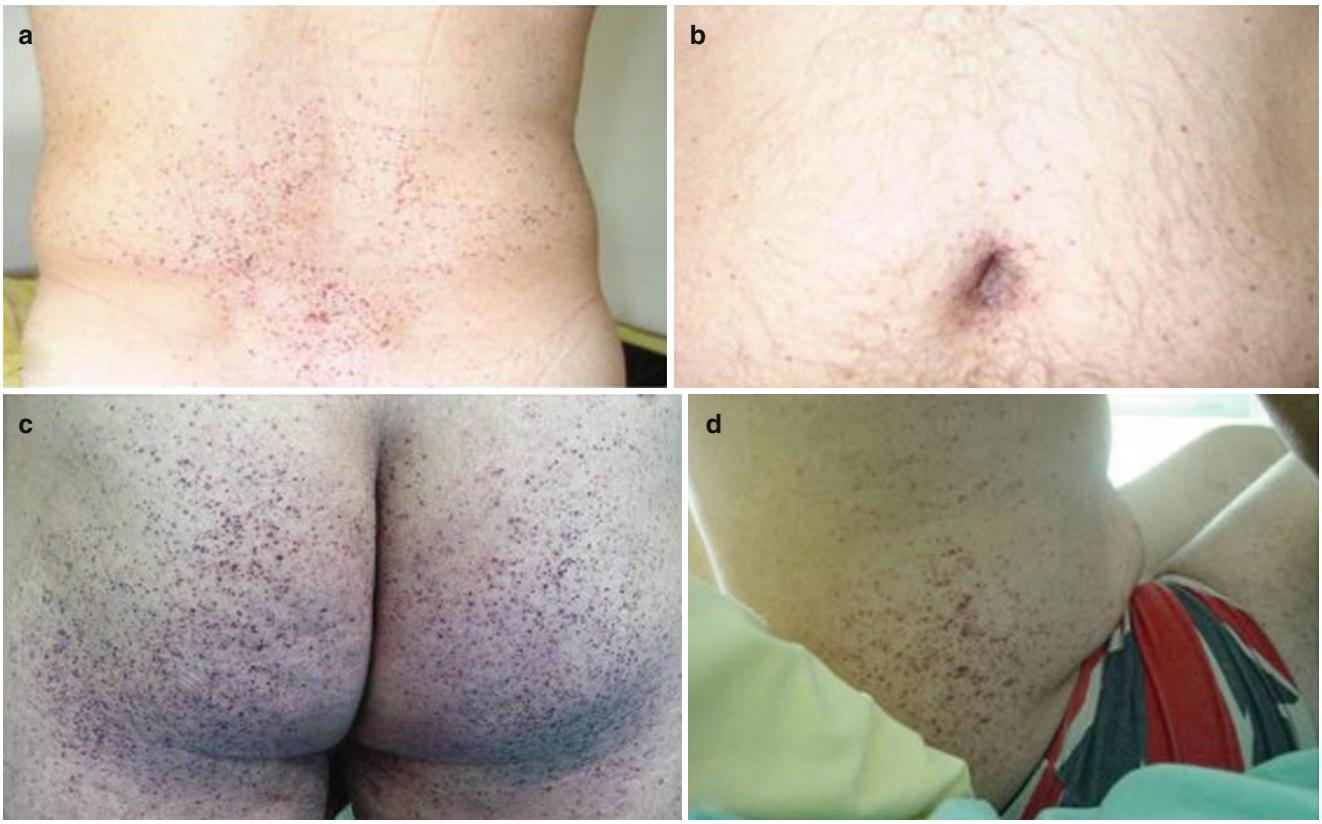

Fig. 27.6 Fabry's disease Angiokeratoma: the angiokeratoma are small, raised, dark-red spots that increase in number and size with age and can occur singly or in clusters. They are typically found on the lower back (**a**), buttocks (**c**), groin, flanks (**d**), and upper thighs, but their distribution may be restricted to a limited area, such as the umbilicus (**b**) (This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited)

quarter of patients [139], and increased cerebral vessel tortuosity and basilar artery dilatation was found on MRA in nearly 90 % of patients [140]. End-stage renal disease usually occurs by the third to fifth decade, and hemodialysis and renal transplantation have improved survival. Hearing loss, corneal dystrophic changes (cornea verticillata), cataracts, early myocardial infarction, and left ventricular hypertrophy are also common. Heterozygous women often develop similar

but milder manifestations as men, with later onset and less severe renal disease, about 10 % requiring dialysis or transplantation [141].

The genetic defect is on Xp22 with over 300 mutations described. Missense mutations correlate with the lowest enzyme levels, but nonsense, frame shift, and splice site defects have all been described. Variation in the endothelial nitric oxide synthase gene (*NOS3*) may also have a role in determining the phenotype [142].

Among men diagnosis is confirmed by deficiency of GLA activity in plasma or leukocytes, and DNA analysis for one of the reported *GLA* mutations provides additional confirmation. Women demonstrate markedly decreased GLA activity, which confirms a carrier state; however, enzyme activity may be normal, in which case molecular genetic testing is necessary to clarify the genetic status. Prenatal diagnosis and preimplantation genetic diagnosis are available but require prior identification of the responsible mutation in the family.

The incidence of Fabry's disease is estimated to be 1:50,000 male births and occurs among all ethnic and racial groups [143]. Atypical forms of the disease present in later life with hypertrophic cardiomyopathy or renal failure and may be misdiagnosed as idiopathic cardiac disease, atherosclerotic disease, or chronic glomerulonephritis [144]. A newborn screening study of GLA activity in Italy showed an incidence of 1:3,100. Molecular modeling studies and in vitro mutant enzyme activity yielded a ratio of 11:1 of individuals with the later onset: classic phenotype [145].

Pathologically, lipid may be seen in multiple organs and skin on light microscopy, with more characteristic findings seen on ultrastructural examination. PAS and acid phosphatase-positive storage material consists of Gb3 and is found deposited mainly in arterial endothelium, vascular smooth muscle, cardiac muscle, skin, and variably in neurons, muscle, liver, and sinusoidal histiocytes of lymph nodes. The kidney shows mesangial widening and glomerular endothelium and tubules contain foam cells. In the peripheral nervous system, glycolipid granules and concentric laminated cytoplasmic inclusions termed zebra bodies are seen under EM in ganglion cells and perineurium, with loss of small myelinated and unmyelinated nerve fibers [146, 147]. Punch biopsy of skin can demonstrate reduced intraepidermal nerve fiber density. Proliferation of vascular smooth muscle cells in the brain and a prothrombotic state contribute to cerebral infarction [148]. Evaluation should include renal and cardiac function studies, hearing, eye, and neurological examinations. Current or potential treatment strategies include symptom management and hemodialysis, enzyme replacement therapy, chaperone therapy, gene replacement therapy, and substrate reduction therapy.

Gabapentin, carbamazepine, and phenytoin may reduce pain. For hypertension, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are preferred for their renal protection. Enzyme replacement therapy currently consists of two drugs: agalsidase β and α. They markedly reduce Gb3 in tissues and urine sediment, and clinical trials successfully achieved their hope for outcome endpoints of reduction of neuropathic pain and improvement in cardiac and renal function [149, 150]. Enzyme replacement therapy improves peripheral nerve and sweating function [151] although intraepidermal nerve fiber density is less likely to improve in patients with impaired renal function [152]. Enzyme replacement therapy should be initiated early in all men with Fabry's disease and in female carriers with significant disease [153, 154]. It is also recommended to start enzyme replacement therapy in asymptomatic boys at age 12–13. Its role in long-term prophylaxis of clinical symptoms, especially stroke, is unproven.

Gene replacement using viral vectors or bone marrow transplantation shows promise in a mouse model of Fabry's disease, but there is no human data [155]. Chaperone therapy, using drugs such as 1-deoxygalactonorijimycin, DGJ, to enhance GLA activity is now in clinical trials in humans after success in the mouse model [156]. A modified enzyme (α-N-acetylgalactosaminidase, NAGA) with GLA-like effect was shown to cleave accumulated Gb3 in a patient's fibroblasts and improve pathology in Fabry mice, implying potential therapeutic application to humans [157].

The Fabry Outcome Survey [158] and the Fabry Registry [159] are sources of updates on the disease, and a Prognostic Index has been developed [160].

Cerebrotendinous Xanthomatosis (Cholestanolosis)

Cerebrotendinous xanthomatosis is a rare autosomal recessive disorder manifest by late-infantile diarrhea, childhood cataracts, and later characteristic tendon xanthomas and progressive neurological dysfunction. The gene defect on chromosome 2q35 causes a defect in sterol 27-hydroxylase, leading to impaired bile acid synthesis with accumulation of cholestanol in tissues. The neurological features include neuropsychiatric symptoms, dementia, pseudobulbar palsy, ataxic or spastic gait, and a mild distal peripheral neuropathy [161].

Nerve biopsy shows a reduction in large myelinated fibers, and although demyelination is described, other reports suggest primarily an axonopathy [162, 163]. The diagnosis is suggested by the clinical signs and by finding a high plasma cholestanol with normal cholesterol. Genetic analysis of the *CYP27A1* gene allows an accurate diagnosis. Without treatment, patients die in the fourth decade. Early diagnosis is important, because therapy with oral chenodeoxycholic acid results in clinical improvement [164].

Refsum Disease

Classical Refsum disease is an autosomal recessive disease characterized by accumulation of phytanic acid in serum and tissue and is recognized by the clinical triad of retinitis pigmentosa, peripheral neuropathy, and cerebellar ataxia plus a raised cerebrospinal fluid protein. Patients usually present between age 10 and 30 years although both younger and older onset patients occur. The earliest manifestation is usually night blindness due to the retinitis pigmentosa. A sensorimotor demyelinating polyneuropathy affecting all aspects of the peripheral nervous system including the autonomic system will eventually develop and is associated with palpably thickened peripheral nerves, atrophy, and areflexia in the late stages. Nerve hypertrophy may not be clinically evident as it is most severe in the brachial and lumbosacral plexus. These manifestations are progressive but can be episodic in the earlier stages of the disease. Sudden increases in dietary phytanic acid, rapid weight loss, or illness may temporarily worsen the symptoms. Other abnormalities may include sensorineural deafness, anosmia, ichthyosis, skeletal deformities, and cardiac abnormalities that can lead to sudden death.

In Refsum disease, the branched-chain fatty acid phytanic acid accumulates because of a deficiency of the chromosome 10 encoded peroxisomal enzyme phytanoyl-CoA hydroxylase (*PHYH*) gene, which catalyzes the first step in the α-oxidation of phytanic acid to pristanic acid [165, 166]. This in turn prevents adequate fatty acid catabolism via β-oxidation. The mechanism by which accumulation of phytanic acid leads to the phenotype of Refsum disease is unclear. Rat and mouse models suggest the pathogenesis is a combination of oxidative stress, release of intracellular calcium stores, and mitochondrial respiratory chain dysfunction [167]. Accumulation of phytanic acid has also been shown to lead directly to Purkinje cell death [168]. There are recent reports of *PEX 7* mutations resulting in a disorder phenotypically indistinguishable from Refsum disease [169].

The finding of raised serum phytanic acid and defective α-oxidation in cultured skin fibroblasts with the appropriate clinical picture is highly suggestive of Refsum disease, but these biochemical alterations are not specific and may be found in disorders of peroxisomal biogenesis, including infantile Refsum disease and in some isolated peroxisomal β-oxidation defects [170]. Mutational analysis of the *PHYH* or *PEX7* genes is the best way to confirm the diagnosis. Nerve conduction studies show a sensorimotor demyelinating polyneuropathy. Segmental demyelination, depletion of myelinated fibers, and onion bulbs are described. Nonspecific Schwann cell inclusions (osmiophilic bodies and crystalline bodies) are reported [171].

The treatment of Refsum disease is well established. Phytanic acid is derived exclusively from external sources, e.g., ruminant products, cod, and some nuts, so dietary adjustment is key [172]. Plasma exchange or extracorporeal lipid apheresis can reduce serum phytanic acid levels more quickly in acute situations if necessary [173]. Before treatment was available, 50 % of patients died by the age of 30. In vitro phytanic acid can be catabolized by omega-oxidation via enzymes expressed in some human cells. Significant research has been done to push Refsum disease patients enzymatically into omega-oxidation through manipulation of CYP-450 and other mechanisms [174].

Infantile Refsum disease is a disease of abnormal peroxisomal biogenesis. The patients have mental retardation, sensorineural deafness, pigmentary retinopathy, dysmorphic features, and hepatomegaly, and some have peripheral neuropathy. Nerve conduction studies confirm a sensorimotor neuropathy with moderately reduced motor conduction velocities. Nerve biopsy is reported to show loss of myelinated nerve fibers without hypertrophic changes [175]. Another peroxisomal disorder, methylacyl-CoA racemase deficiency, is associated with pristanic acid dysregulation and causes an adult-onset sensorimotor neuropathy that may be either demyelinating or axonal [176].

Niemann-Pick Disease (Sphingomyelin Lipidoses)

Historically four types of autosomal recessive Niemann-Pick disease (NPD) are described (types A–D). The first two types (A,B) are due to mutations in the *SMPD1* gene on chromosome 11, with a deficiency of sphingomyelinase (ASM) causing accumulation of sphingomyelin in a variety of tissues. However, types C and D have normal ASM activity and result from mutations in *NPC1* and, more rarely, *NPC2* genes, causing abnormalities in cholesterol transport with accumulation of sphingomyelin and cholesterol in lysosomes [177]. Since these are different disorders albeit causing lipid storage, the classification system will need revision [178].

Type A NPD is a fatal disorder of infancy characterized by hepatosplenomegaly, retinal cherry red spots, severe developmental delay, occasional seizures, and rarely a peripheral neuropathy. The peripheral neuropathy is characterized by reduced motor nerve conduction velocities with pathological findings of segmental demyelination and remyelination, Schwann cell and axon lipid inclusions, and endothelial foam cells [179, 180]. Type B NPD, classically referred to as the non-neurologic form, presents in childhood with hepatosplenomegaly and demonstrates a wide phenotypic variation. A review of 64 patients reported that about a third of type B patients had neurologic involvement, 22 % mild and nonprogressive, but 8 % with severe and progressive involvement. All severe progressive patients were found to have the Gln294Lys mutation and onset between the ages of 5 and 7 years [181].

Types C and D NPD are allelic and usually present in childhood with hepatosplenomegaly, ataxia, vertical gaze palsy, and motor and intellectual decline. There are case reports with a mild demyelinating peripheral neuropathy though this is not a main feature [182].

Markedly deficient ASM activity in leukocytes or cultured fibroblasts confirms the diagnosis of types A and B and reduction of cholesterol esterification for *NPC1/2*. Enzymatic and molecular analysis may also be used on cultured amniocytes and chorionic villi for prenatal diagnosis. Although new mutations are being described frequently, there are targeted DNA tests available based on the patient's origins (e.g., Ashkenazi Jew or North African).

There is no curative treatment for NPD. In type A death usually occurs by age 2 or 3 years, whereas patients with type B frequently survive into adulthood. Orthotopic liver transplant and amniotic cell transplant have not been effective therapy. Hematopoietic stem cell therapy on the other hand has shown some benefits but does not seem to help with neurological deficits [183]. Recombinant Hsp70 has been shown to stabilize lysosomes and may be therapeutic for *SMPD1* patients [184]. Preliminary data using the glycosphingolipid inhibitor miglustat show evidence of stabilization or benefit in some individuals with NPD-C [185]. Studies of neurosteroid replacement therapies are underway [186].

Disorders with Defective DNA Repair

Xeroderma Pigmentosum

Xeroderma pigmentosum (XP) is a rare autosomal recessive disease characterized by an increased frequency of sunlight-induced skin cancers as a result of defects in DNA repair or replication after damage by ultraviolet irradiation or various chemical carcinogens. Eight genes have now been linked to XP. Seven are involved in nucleotide excision repair (XPA-XPG) and one, yet to be cloned (XP variant), in replication of damaged DNA.

Patients usually present between age 1 and 2 years with increased sensitivity to sunlight. XP may be divided into non-neurological and neurological forms. Patients with the non-neurological forms (XPC, E, and F) have a 2,000-fold increase in skin cancer occurrence for individuals under the age of 20 years. The neurological forms (XPA, B, D, and G) manifest with mental retardation, microcephaly, spasticity, seizures, sensorineural hearing loss, cerebellar ataxia, and dystonia. An axonal or mixed neuropathy may be present as evidenced by absent tendon reflexes and reduced amplitude or loss of sensory nerve action potentials [187]. Overall, 25 % of patients with XP have neurologic manifestations [188]. The severe form is historically referred to as De Sanctis-Cacchione syndrome; however, the neurologic manifestations may be limited to isolated hyporeflexia. XP has significant genetic and phenotypic overlap with Cockayne syndrome.

Pathologically, there is a loss of myelinated and unmyelinated axons with sensory fibers being affected to a greater extent than motor. Autopsies have demonstrated axonal degeneration and secondary demyelination [189]. The diagnosis can be made by laboratory testing of UV sensitivity of fibroblasts and excision repair; however, this is not universally available. Genetic tests are currently commercially available for XP types A, C, D, E, and G. There is a 30-year estimated reduction in life span, mainly due to neoplasia, but also related to neurologic complications. Life expectancy is 29 years with neurologic manifestations compared to 37 years without. Treatment is aimed at early diagnosis, genetic counseling, and skin care including protection from sunlight and monitoring and treatment of skin cancers.

Cockayne Syndrome

Cockayne syndrome (CS) is a rare disorder mainly characterized by sun sensitivity, short stature, and neurological dysfunction without increased frequency of skin cancer. There are three forms of CS (although other classifications schemes have been used): types I and II exist on a spectrum with type I typically presenting around age two with survival into the second decade, associated with mutations of *ERCC8* (25 % of CS patients). Type II is characterized by failure to thrive and meet neurologic milestones from birth and is associated with mutations in *ERCC6* (75 % of CS). Of note there is significant overlap with XP discussed above. *ERCC6* mutations are also associated with the De Sanctis-Cacchione form of XP. Type III is a milder form with little or late-onset neurologic symptoms. There is also an XP-CS combination disease with skin lesions and some of the neurologic disease of CS.

Patients with CS usually present early with sun sensitivity. Other clinical features include growth retardation, progeria, mental retardation, microcephaly, normal pressure hydrocephalus, deafness, pigmentary retinopathy, and ataxia. A demyelinating polyneuropathy is a common finding with hyporeflexia, reduced motor conduction velocities, and segmental demyelination on sural nerve biopsy [190]. Primary demyelination is also seen in the CNS. The diagnosis may be made by the demonstration of hypersensitivity of cultured CS cells to killing by UV light and by delayed recovery of DNA and RNA synthesis following UV radiation. Genetic testing is commercially available for both *ERCC6* and *ERCC8.* It is reasonable to start testing with *ERCC6,* as this represents 75 % of CS patients. Treatment is supportive.

Ataxia-Telangiectasia

Ataxia-telangiectasia (AT) is an autosomal recessive disorder characterized by neurological symptoms, oculocutaneous telangiectasia, and immunologic deficiency and, at the cellular level, by radiosensitivity, chromosomal instability, and impaired induction of ionizing radiation-induced cell cycle controls. The gene for AT (*ATM*) is localized to chromosome 11q22-23. The ATM protein is a member of the chemical family that phosphorylates key substrates involved in DNA repair.

Patients usually present in early childhood with a slowly progressive cerebellar ataxia, oculomotor apraxia, and oculocutaneous telangiectasia. Other neurological manifestations appear with time and include choreoathetosis and neuropathy, as evidenced by hyporeflexia, distal sensory loss, and distal motor weakness [191]. A variant presenting as adult-onset spinal muscular atrophy is reported [192]. Nerve conduction studies show reduced SNAP amplitudes and a slight reduction of motor conduction velocities. The pathology is a loss of large myelinated fibers. Endocrine abnormalities may occur and include growth retardation, delayed sexual maturity, and glucose intolerance. There is evidence of impaired humoral and cellular immunity with an increased incidence of infections and lymphoreticular malignancies. Lymphocytes and fibroblasts have increased sensitivity to ultraviolet, gamma, and x-irradiation.

The diagnosis is suggested by the clinical features, cerebellar atrophy on MRI, and high levels of circulating α-fetoprotein (>10 ng/ml). Lymphocytes and fibroblasts may be tested for irradiation sensitivity or ATM levels by immunoblot. Ninety percent of patients with AT have no detectable ATM and about 10 % have trace amounts; less than 1 % have normal ATM. Although *ATM* gene sequencing is available, it is less sensitive for AT than immunoblotting for ATM levels as only 90 % of patients have an identifiable *ATM* gene mutation. 7,14 translocation is present in 5–15 % of patients and should be checked with high-resolution karyotyping. There is no effective specific treatment. Pulmonary disease secondary to immunodeficiency and recurrent aspiration are common causes of death. Replacement IVIg may be necessary for frequent infections. Betamesthasone was shown to provide some neurologic improvement [193, 194]. Patients should avoid radiation therapy and high-dose radiologic exams as they have reduced ability to recover from the effects of radiation.

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Guillain-Barré Syndrome and Related Disorders

28

Ezequiel Agustin Piccione, Karim Salame, and Bashar Katirji

Introduction

Guillain-Barré syndrome (GBS), also known as Landry-Guillain-Barré-Strohl syndrome, was described in 1916 [1, 2]. GBS is usually a predominantly motor disorder with areflexia and subjective more than objective sensory symptoms. GBS is the most common cause of acute flaccid paralysis worldwide, particularly with the almost complete eradication of poliomyelitis. Its incidence in North America and Europe ranges from 0.8 to 1.9 cases per 100,000 population. GBS affects individuals of all races and ages, but is more common in subjects above 50-year-old [3, 4], and the incidence increases by 20 % for every 10-year increase in age [5]. The annual incidence of GBS increased with age from 1.7/100,000 before 50 years to 3.3/100,000 after 50 years. The annual incidence in children less than 15 years old is between 0.34 and 1.34 per 100,000 population [4]. GBS affects males more than females with a male to female ratio of 1.78.

For many years since its original description, GBS was considered to be a single disorder and interchangeably named acute inflammatory demyelinating polyradiculoneuropathy (AIDP), based on evidence of acute immune attack on myelin and resemblance to experimental allergic neuritis. In addition, criteria for the published diagnosis of GBS have been based on AIDP clinical and electrophysiological features (Table 28.1).

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Table 28.1 Diagnostic features of the typical form of Guillain-Barré syndrome, acute inflammatory demyelinating polyradiculoneuropathy (AIDP)

Clinical features
Required for the diagnosis:
Progressive weakness in both arms and legs
Areflexia or hyporeflexia (generalized or in weak limbs)
Strongly supporting the diagnosis:
Progression of symptoms over days to 4 weeks
Relative symmetry of symptoms
Mild sensory symptoms or signs
Cranial nerve involvement, especially facial diplegia
Recovery beginning 2–4 weeks after progression ceases
Autonomic dysfunction
A preceding upper respiratory or gastrointestinal illness
Absence of fever at the outset
Making the diagnosis doubtful:
Well-demarcated sensory level
Marked, persistent asymmetry of symptoms or signs
Severe and persistent bladder or bowel dysfunction
Excluding the diagnosis:
Diagnosis of botulism, myasthenia gravis, poliomyelitis, or toxic neuropathy
Abnormal porphyrin metabolism
Recent diphtheria
Meningeal carcinomatosis or lymphomatosis
Laboratory criteria
Elevated CSF protein concentration with no pleocytosis or fewer than 10 cell/mm^3
Electrophysiological criteria (any 3 of 4 criteria)
Reduction in conduction velocity of 2 or more motor nerves <80 % lower limit of normal (LLN) if amplitude >80 % of LLN; <70 % of LLN if amplitude <80 % of LLN
Prolonged distal latencies in 2 or more motor nerves >125 % of the upper limit of normal (ULN) if amplitude >80 % of LLN; >150 % of ULN if amplitude <80 %
Absent or prolonged minimum F-waves in 2 or more motor nerves, >120 % of ULN if amplitude >80 % of LLN; >150 % of ULN if amplitude is <80 % of LLN
Conduction block or abnormal temporal dispersion (>20 % drop in amplitude or >15 % change in duration between proximal and distal sites) in 1 or more motor nerves

Adapted with revisions from Asbury and Cornblath [6], pp 521–524

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Table 28.2 Classification of Guillain-Barré syndrome

GBS types
Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)
Acute motor-sensory axonal neuropathy (AMSAN)
Acute motor axonal neuropathy (AMAN)
GBS variants
Miller Fisher syndrome
Ataxic variant (acute ataxic neuropathy)
Pharyngeal-cervical-brachial variant
Multiple cranial neuropathy variant
Facial diplegia with paresthesias
Paraparetic variant
Acute pandysautonomia (acute autonomic neuropathy)
Others

More recently, it has become clear that AIDP represent only the prototype of GBS, and other related immune polyneuropathies that cause acute generalized weakness but with different etiologies and pathophysiologies have been grouped together and called GBS. These GBS types comprise most commonly the axonal subtypes of GBS, in which the primary pathology is axonal degeneration and not segmental demyelination, including acute motor axonal neuropathy (AMAN), a pure motor disorder, and acute motor-sensory axonal neuropathy (AMSAN), an acute mixed sensorimotor axonopathy (Table 28.2).

In addition to these three major subtypes of GBS, several GBS variants have been described. These variants deviate significantly from the flaccid weakness and areflexia of typical GBS. Their link to GBS is supported by preceding infectious episodes, diminished reflexes, elevated CSF protein levels, and a presumed immune-mediated origin. Of these, Miller Fisher syndrome is the most widely known, but others include facial diplegia with paresthesias, pure sensory or ataxic forms, a pharyngeal-cervical-brachial regional form, and an acute dysautonomia (see Table 28.2).

Etiology

Although the topography, pathological features, pathophysiology, prognostic features and, more recently, immunopathogenesis of GBS are well understood, the etiology of the disease remains uncertain. There are no genetic factors that are known to predispose individuals to develop GBS, nor is there evidence that GBS is communicable. There have been reports of clusters of cases without an obvious source, but these have been thought to represent random variations [7].

The association of GBS with vaccinations has been suspected and debated for more than four decades. Reports of a definite association of GBS and conventional influenza, hepatitis B, and Gardasil vaccines have been published [8–10]. An "epidemic" of GBS, more accurately, an approximately fivefold increase in the incidence of cases over the estimated natural occurrence, was reported following the swine influenza vaccination program in 1976 [11]. However, lack of clarity in case ascertainment still generates controversy regarding the validity of this association [12–14]. Nonetheless, the risk of developing GBS is one to two additional GBS cases per one million vaccinated persons. The incidence of GBS was higher among conventional influenza vaccinees that were younger than 65 years, but the morbidity was higher among those older than 65 years [10]. Following the recent pandemic swine flu in 2009, another specially designed H1N1-influenza vaccine was introduced. Though epidemiological studies from North America and Europe did not find an increase in incidence of typical GBS among contemporary H1N1-influenza vaccinees [15, 16], atypical GBS cases and cases with GBS variants were recently reported [17].

An upper respiratory tract viral illness, diarrhea, or other infectious illness occurs 1–4 weeks before the onset of GBS in approximately two-thirds of patients (Table 28.3) [2, 18].

Table 28.3 Antecedent illnesses associated with Guillain-Barré syndrome

Viral infections
Cytomegalovirus
Influenza
Parainfluenza
Epstein-Barr virus
Cocksackie
Echo
Measles
Mumps
Rubella
Herpes simplex virus
Herpes Zoster virus
Hepatitis A and B virus
Human immunodeficiency virus
Bacterial and other infections
Campylobacter jejuni
Mycoplasma pneumoniae
Typhoid
Shigella
Legionella pneumonia
Cyclospora
Systemic illnesses
Hodgkin's lymphoma
Thyroid disease
Addison's disease
Leukemia
Paraproteinemia
Solid tumors (lung cancer)
Sarcoidosis
Systemic lupus erythematosus
Surgery
Trauma
Vaccination
Pregnancy

In any individual case, the relationship between an antecedent illness and GBS may be less certain. Respiratory or gastrointestinal syndromes are the most common antecedent illnesses. In most patients, the infection resolves by the time the neurological condition develops.

Campylobacter jejuni (*C. jejuni*) is the most frequently identified bacterial infection preceding GBS. In addition to its peculiarity of being a bacterial rather than a viral infection, it is implicated in up to 30 % of GBS cases studied prospectively with serological studies [19, 20]. Patients with *C. jejuni* enteritis develop fever, watery diarrhea, and abdominal cramping with GBS typically developing days later. However, a substantial number of patients have only serological evidence of recent *C. jejuni* infection without enteritis [19]. *C. jejuni*-related GBS has more severe axonal loss on electrodiagnostic (EDX) studies, elevated anti-GM1 antibodies, and a more protracted recovery compared to cases without the infection (see Sect. "Acute Motor Axonal Neuropathy" below) [19, 21]. The immunologic implications of *C. jejuni* as a triggering agent for GBS are of great interest because this sequence of events supports postinfectious nerve inflammation as a pathogenetic theory. Certain strains of *C. jejuni* are the cause of enteritis in a disproportionate number of GBS patients [22]. The lipopolysaccharides of these organisms share ganglioside-like epitopes with peripheral nerves (such as GM1, GQ1b, and GalNAc-GD1a) and are thought to induce a form of molecular mimicry in which the immune system, in its efforts to eradicate *C. jejuni,* elaborates antibodies against neural antigens and secondarily produces GBS [21, 23].

The most commonly identified viral infection is *cytomegalovirus* (CMV), with serological evidence of preceding infection in 10–15 % of cases [18, 24]. In some instances, the only indication that CMV is the preceding infectious agent may be an elevation in liver enzymes concomitant with the onset of GBS symptoms. GBS triggered by CMV infection tends to occur in younger individuals and to produce a more severe course with respiratory failure, prominent sensory loss, more frequent cranial nerve involvement, and raised antibodies directed against the ganglioside GM2 [18, 25]. Similarly, judging by serological studies, Epstein-Barr virus infection precedes GBS in approximately 10 % of patients, and the infectious clinical syndrome varies from mononucleosis to pharyngitis or hepatitis [18]. The relationship between GBS and other viruses reported to precede the condition, such as respiratory syncytial virus, parainfluenza virus, echovirus, coxsackie virus, measles, mumps, rubella, herpes zoster and simplex virus, influenza, and hepatitis A and B, is less certain (see Table 28.3). GBS may occur soon after seroconversion with human immunodeficiency virus (HIV) [26]. There are no clinical or EMG features that distinguish these patients from non-HIV-related forms of GBS, except for a prominent lymphocytic pleocytosis in the spinal fluid of patients with HIV, which may therefore complicate the CSF formula in GBS [26]. GBS has also been reported following immune reconstitution from highly active retroviral immunotherapy [27].

Among other bacteria, *Mycoplasma pneumoniae* (*M. pneumoniae*) has been reported to precede GBS in approximately 5 % of cases and should be considered when weakness develops after a prodromal illness characterized by fever, headache, and severe dry cough [18]. Infection with *M. pneumoniae* is supported by the presence of cold agglutinin antibodies in the serum and is confirmed by complement-fixing antibody tests. Lyme disease is a bacterial illness caused by a spirochete, *Borrelia burgdorferi* in the United States and *Borrelia afzelii* in Europe. It is transmitted by infected hard ticks belonging to a few species of the genus Ixodes. Lyme disease may cause a chronic axonal sensorimotor polyneuropathy, a painful polyradiculitis (Bannwarth's syndrome), or acute facial diplegia [28, 29]. This may mimic GBS, but the presence of a true postinfectious polyneuritis with Lyme is still somewhat uncertain. As with HIV, a lymphocytic pleocytosis in the spinal fluid may distinguish these patients from typical cases of GBS [28, 29]. Shigella, salmonella, typhoid, brucella, cyclospora, and yersinia enterocolitica also have preceded GBS during epidemics or in single cases [30].

Several systemic illnesses also have been tenuously linked to acute GBS, but most of these are implicated more often with CIDP. For example, a GBS-like syndrome has been described in patients with Hodgkin's disease, lung cancer, thyroid disease, systemic lupus erythematosus, paraproteinemia, and sarcoidosis in single case reports or small series [31, 32]. It is difficult to be certain that these are anything more than chance associations.

Many GBS series have included a small proportion of cases that occurred after surgery, and only few cases genuinely appear to have been triggered by an operation. It is now considered that some of these patients who develop weakness after being admitted to the intensive care unit have a "critical illness polyneuropathy" rather than GBS as a consequence of multiorgan failure and sepsis or other factors associated with a prolonged postoperative course in an intensive care unit (see Chap. 76). It is also unlikely that the axonal loss and prognosis in GBS patients worsen after admission to the intensive care unit due to concomitant critical illness polyneuropathy [33]. Trauma has rarely been reported as a precipitant to GBS, and we have seen several such cases, but the association remains uncertain. In one study reported in 2006, 16 patients receiving tumor necrosis factor-alpha antagonist therapy developed GBS and were reported to the US Food and Drug Administration [34]. Other medications, drugs of abuse, bone marrow transplantation, and spinal epidural anesthesia all have been reported to precede GBS, but these connections also remain unproven. GBS may occur at any time during pregnancy, but the risk is maximal during the first 2 weeks after delivery [35].

Pathogenesis

A number of immune mechanisms involving humoral and cellular immunity, complement deposition, proinflammatory cytokines, and other inflammatory mediators are theorized to be involved in the pathogenesis of GBS [36]. Many of these purported mechanisms have been gleaned from studies in an experimental model of the disease—experimental autoimmune neuritis (EAN) that represents a fair version of the human disease. The extent to which each of these immune processes is related to various clinical and electrophysiological patterns, and the implications for treatment and prognosis, is of great interest but has not been fully studied. In EAN, rabbits, guinea pigs, or rats are immunized with autologous peripheral nerve tissue and Freund's adjuvant (a nonspecific stimulator of immune reactions). After a latency of several days, they develop a rapidly progressive paralytic illness with the pathologic features of endoneurial inflammation and demyelination, identical to the clinical and pathological manifestations of GBS [37]. This inflammatory response is mediated by T cells that are directed against epitopes on peripheral nerve myelin including PO, P2, and PMP 22, and by implication, this immune attack leads to macrophage invasion and demyelination [38].

In classical pathological studies of GBS, demyelination was most prominent adjacent to regions of intense perivenular inflammation [39, 40]. Pathological material from patients with GBS shows a similar accumulation of lymphocytes and macrophages in a perivascular distribution scattered throughout the peripheral nervous system with a predilection for spinal roots [39–41]. Macrophages and T cells express major histocompatibility (MHC) class II antigens which are upregulated on Schwann cells in the region of inflammatory lesions in patients with GBS. One hypothetical sequence that has been offered is that activated T cells, stimulated by a preceding infection and by an interaction with antigen presenting cells that express MHC class II antigens, disrupt the blood nerve barrier, attack endoneurial antigens, and release inflammatory cytokines such as interleukin-2 and tumor necrosis factor (TNF) [36]. In keeping with this hypothesis, several investigators have demonstrated elevated levels of TNF and soluble TNF receptor in the serum of patients with acute GBS [42, 43]. These cytokines attract macrophages that are capable of producing nerve demyelination and damage Schwann cells and axons [36, 42, 43].

There is also evidence that humoral factors are central to the development of GBS. Passive transfer studies have shown that sera from GBS patients injected into the nerves of animals induces local demyelination. Furthermore, the observed clinical recovery following removal or neutralization of autoantibodies (or other pathogenic humoral factors) by plasmapheresis or intravenous immune globulin (IVIG) supports a role for B-cell-mediated processes in the pathogenesis of GBS [44]. Koski et al. demonstrated that elevated serum levels of complement-fixing anti-myelin antibodies correlated with disease activity in patients with GBS [45, 46]. Recent autopsy studies revealed that local complement activation occurs at the site of nerve lesion, such as the axolemma in patients with AMAN and the Schwann cell membrane in patients with AIDP [47, 48]. There is now evidence, using high-resolution immunocytochemistry, of early complement activation and deposition of activated complement components along the outer surface of the Schwann cell. The presence of terminal complement complex is associated with vesiculation of the outermost myelin lamellae. This occurs before and within 1 week of invasion of macrophages [48]. In patients with AMAN associated with axonal loss, the complement activation product binds to the axolemma of motor fibers and, in severe cases, immunoglobulin and activated complement within the periaxonal space of myelinated internodes [47].

Numerous studies have demonstrated the presence of anti-neural antibodies directed against acidic glycoconjugates in the serum of patients with GBS. These peripheral nerve antigens are usually gangliosides (GM1, GD1a, GQ1b, and GT1a) which differ with regard to the position and number of their sialic acid. There is solid indication that *anti-ganglioside antibodies* play a pathogenic role in the pathophysiology of GBS [49]. In clinical practice, these antibodies are found in only a minority of patients since autoantigens have not been well identified in AIDP. The anatomic distribution of the gangliosides within the peripheral nervous system may explain some of the observed clinical variants of GBS [36, 49]. For example, GQ1b is strongly expressed in the oculomotor, trochlear and abducens nerves, as well as the muscle spindles in the limbs, which explain the distinct Miller Fisher syndrome (ophthalmoplegia, ataxia, and areflexia), frequently associated with anti-GQ1b antibody [50–52]. There is also strong evidence currently that the axonal subtypes of GBS, particularly AMAN and less commonly AMSAN, are associated with antibodies directed against GM1 and GD1a at the axolemma. This eventually attracts macrophages invading the nodes of Ranvier and inserting between the axon and the axolemma, resulting in axonal degeneration. In AMAN, the myelin sheath also remains intact, and there is no lymphocytic inflammation [53]. In AMAN, only the axons of the ventral roots are involved, while in AMSAN, both the dorsal and ventral roots are affected [38, 41].

Increasing evidence supports that *molecular mimicry* plays an important role in the pathogenesis of GBS. It is likely that genetic polymorphism in various strains of *C. jejuni* determines the specificity of the antiganglioside antibodies and the associated variant of GBS. Lipooligosaccharide, a major component of the outer membrane of *C. jejuni*, has ganglioside-like products; sensitization with GM1-like

lipooligosaccharide by injecting it, rabbits induced a neuropathy resembling AMAN [54]. *C. jejuni* bacterial isolates from patients with AMAN have GM1-like and GD1a-like lipopolysaccharides, whereas bacterial isolates from patients with the Miller Fisher syndrome usually express GQ1b-like lipopolysaccharides [55, 56]. It is now evident that *C. jejuni* is composed of several classes that have diverse lipooligosaccharide biosynthesis genes. *C. jejuni* is now grouped into several classes based on the organization of these genes. A specific class carrying a sialyltransferase gene (cst-II) is associated with the development of GBS. Patients infected with a specific strain (Thr51), which expressed both GM1-like and GD1a-like lipooligosaccharides, had anti-GM1 or anti-GD1a IgG antibodies and present with typical GBS manifestations including limb weakness. In contrast, patients infected with another strain (Asn51), which expresses GT1a-like or GD1c-like lipooligosaccharides, have anti-GQ1b IgG antibodies and present with the Miller Fisher syndrome including ophthalmoplegia and ataxia [55–58]. On the basis of the above findings, one may conclude that *C. jejuni*-associated/GM1-related GBS represents at least true instance of a molecular-mimicry-related disease.

Clinical Features

GBS in its typical form is a predominantly motor neuropathy, although acral paresthesias are almost always present at the onset of the illness (Table 28.4). Tingling, prickling, or pins and needles sensations are usually followed within hours or days by symmetrical leg weakness and trouble walking. The presence of acral paresthesias increases the probability of the correct diagnosis of GBS [2]. Difficulty climbing stairs or arising from a chair or commode is typical. Weakness of the upper limbs, ocular, oropharyngeal, and facial muscles develops with variable frequency and severity.

The *weakness* is often bilateral but some degree of asymmetry is common. Rarely, the weakness begins in one limb hours or a day before involving the contralateral limb. Proximal weakness is more frequent than distal and often more severe. In contrast to diseases that affect the muscle or neuromuscular junction, weakness rarely remains restricted to the shoulder or hip girdle muscles; some degree of hand or distal leg weakness develops after the proximal muscles. The weakness often moves to the upper limbs resulting in an *ascending paralysis*. Weakness that remains limited to the legs or, alternatively, weakness that begins in the hands or shoulder girdle and involves the legs may occur as the condition advances. A pattern of *descending paralysis* occurs in 10–15 % of cases, with symptoms beginning in the cranial nerves or arms and spreading to the legs. Approximately one-third of fully developed cases have a degree of weakness that is similar in the arms and legs. Fasciculations or myokymia are observed in a small number of patients.

Table 28.4 Frequency of clinical features in Guillain-Barré syndrome

	Initially	In fully developed Illness
Paresthesias	70	85
Weakness		98
Legs > arms	54	
Arms > legs	14	
Approximately equal	32	
Ophthalmoparesis	5	15
Facial weakness	35	50
Bulbar weakness	25	50
Respiratory failure	10	30
Ataxia	10	15
Sphincter dysfunction	15	5
Areflexia	75	95
Pain	25	30
Sensory loss	40	85

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The second hallmark sign of GBS is *reduced or absent deep tendon reflexes*, presumably reflecting desynchronization or dispersion of impulses carried by myelinated fibers in the afferent arm of the reflex arc. Approximately 70 % of patients have absent deep tendon reflexes at the time they are first examined. Reflexes occasionally remain elicitable until weakness or large fiber sensory loss advances. Reflexes are almost always unobtainable in limbs that are too weak to resist gravity. Yuki et al. found that the myotatic reflexes were normal or exaggerated during the entire clinical course in approximately 10 % of GBS patients, more commonly in patients with AMAN than AIDP [60]. However, the diagnosis of GBS must remain questionable in this group, and upper motor neuron causes of weakness should be excluded.

More than half of GBS patients experience *paresthesias* of the distal extremities as the initial symptom. Most patients complain of "pins and needles," "prickling," or "tingling" feelings, likened to an "asleep feeling" in an arm or leg following compression of the limb. In contrast to most length-dependent axonal polyneuropathies, patients with GBS often develop paresthesias in the fingertips soon after the feet are affected and sometimes beforehand. The sensory symptoms are symmetric and often precede weakness by a few days, ascending to the ankles and wrists as the illness progresses. Paresthesias of the trunk or face are infrequent. Patients may also describe an acral numb, heavy, or dead sensation as the disease evolves. Some experience sensory loss over the trunk, and a well-demarcated sensory level simulating spinal cord disease has been described, but only to the extent of a noticeable change in sensation, not analgesia below the level. The detection of a genuine thoracic sensory level should prompt further evaluation with an MRI of the spinal cord to exclude a myelopathy including transverse myelitis. Reduced

vibration sense and proprioception in the distal limbs are the most common findings. A substantial number have sensory ataxia that is soon obscured by weakness. Pinprick sensation may also be impaired in distal parts in severely affected patients.

Pain is a common but underappreciated symptom in GBS. Pain may precede the onset of weakness by 2 weeks in 1/3 of patients [61], and about 2/3 of patients have modest discomfort early in the illness [62]. Pain, when not severe, may be overlooked by medical staff who are preoccupied with more pressing medical complications, and intubated patients often are unable to convey their discomfort. The discomfort in GBS has been described as (1) aching, usually confined to muscles of the back, hips, or upper legs (the most common type); (2) shooting or stabbing, radicular pain radiating from the back to one or both legs; or (3) chronic and unrelenting, burning, dysesthetic feelings in the distal limbs [61–63]. Rarely, back and radicular pain can precede weakness and paresthesias and be attributed to sciatica or a spinal condition [63]. At 1-year follow-up, pain is reported in 38 % of patients, and the pain intensity was highest in patients with typical GBS and in those with sensory disturbances and with higher level of weakness and disability [61].

Approximately one-half of GBS patients will have *cranial nerve involvement* at some time in the course. The facial nerve is most commonly affected, and facial weakness typically occurs when there is substantial limb weakness. Conversely, lack of facial weakness in a patient with severe generalized paralysis should at least raise concerns about the accuracy of the diagnosis. As with limb weakness, facial paralysis is often bilateral, but occasionally asymmetrical, and rarely unilateral. Weakness of the ocular muscles arises in 10–20 % of patients, the abducens nerve being most commonly affected. Impaired abduction is usually bilateral and occasionally asymmetrical. Oropharyngeal weakness occurs in up to one-half of patients during the course of the illness and presents great problems in terms of aspiration. In severely affected patients, there may be paralysis of all the cranial muscles, ventilatory failure, and flaccid paralysis of all the limbs, simulating the "locked-in" state [64].

Weakness of the diaphragm that leads to *respiratory failure* and a requirement for ventilator support occurs in approximately 20–30 % of patients with GBS [65–67]. Most such patients are quadriparetic, although patients with a bibrachial pattern of weakness may also have pronounced oropharyngeal and respiratory muscle involvement (see Sect. "Guillain-Barré Syndrome Variants"). Weakness of the neck muscles, tongue, and palate tends to parallel involvement of the diaphragm and respiratory muscles. Diaphragmatic weakness, which causes reduced vital capacity, inspiratory force, and tidal volume, invariably causes atelectasis. Coughing and clearing of oral secretions are then impaired, generating progressive atelectasis, arteriovenous shunting, and mild hypoxia. These changes further aggravate ventilatory failure by causing tachypnea and an increased work of breathing. As the respiratory rate increases, levels of carbon dioxide actually may be reduced in the early stages of respiratory compromise. However, as the diaphragm, intercostal, and accessory muscles become further exhausted, hypercapnea ensues and patients may rapidly deteriorate with hypercarbia and respiratory arrest. If diaphragmatic and respiratory muscle weakness have not occurred 2 weeks into the course of the illness, assisted ventilation should not be necessary unless other pulmonary or medical complications ensue. The main predictors of mechanical ventilation include shorter days between onset of weakness and admission, higher Medical Research Council (MRC) sum score, and presence of facial and/or bulbar weakness (see Sect. "Prognosis") [65]. Patients with GBS who require ventilator support have a less favorable prognosis for neurologic recovery, longer hospitalization, and higher mortality.

Dysautonomia is a less common but well-recognized feature in patients with fully developed GBS, occurring up to 65 % of cases [68, 69]. This number is certainly overestimated if one considers only changes of clinical significance. Autonomic nervous system complications tend to occur more frequently in those with severe paralysis and ventilatory difficulties, but rarely may develop in otherwise mild cases. The most common cardiac manifestations include sinus tachycardia, sinus bradycardia, sinus arrest and other supraventricular arrhythmias, paroxysmal hypertension, hypotension (especially postural hypotension), and so-called vagal spells that consist of bronchorrhea, bradycardia, and hypotension. Infection, hypoxia, pulmonary embolus, and other medical complications should be excluded before attributing cardiovascular disturbances to dysautonomia. Because of the potential for complete heart block, sinus arrest or other life-threatening cardiac arrhythmias (e.g., ventricular tachycardia), and the risk of rapidly progressive respiratory failure, most patients with GBS require monitoring in an intensive care setting early in the illness (see Sect. Supportive Care in under the Sect. Treatment and Management). Other features of autonomic instability include ileus, urinary retention (surprisingly common—seen in one-quarter of patients and suggesting a myelopathy), and inappropriate antidiuretic hormone secretion leading to hyponatremia [70]. Many patients have minor aspects of dysautonomia that are clinically insignificant, such as altered sweating, mild orthostatic hypotension, and acral cyanosis from vasomotor instability.

GBS can have sometimes unusual features such hearing loss, meningeal signs, vocal cord paralysis, papilledema, and mental status changes [71]. Recently, cases of GBS has been associated with posterior reversible encephalopathy syndrome (PRES) [72]. One explanation for the PRES is that the cytokines, produced in the context of GBS, may increase the permeability of the blood–brain barrier.

Guillain-Barré Syndrome Subtypes

For many years, the term AIDP was interchangeably used with GBS. It is now well recognized, particularly during the last two decades, that axonal forms of GBS exist and these are distinguished from AIDP using electrophysiological and pathological characteristics. These disorders, AMAN and AMSAN, remain under the same umbrella term of GBS because they share many of the clinical findings, including flaccid weakness and areflexia, preceding infectious episode, and a presumed immune-mediated origin (see Table 28.2). These disorders are also often preceded by infections, but may be occasionally associated with connective tissue disorders [73, 74]. Also, these disorders may be difficult to distinguish on early electrodiagnostic studies since the nerve conduction changes may overlap and sequential studies are often necessary.

Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP)

AIDP is the prototype of GBS and characterized by peripheral nerve and spinal root demyelination. This disorder accounts for up to 90 % of GBS cases in North America and Europe [75] but only 22–46 % of cases in China, Japan, India, Southeast Asia, and Mexico [76, 77]. This disorder is characterized by vesicular degeneration of myelin triggered by membrane-attack complex formation on the outer surface of Schwann cells. AIDP has not been strongly associated with antiganglioside antibodies [78].

Acute Motor Axonal Neuropathy (AMAN)

McKhann, Griffin, and colleagues described an acute paralytic syndrome in patients from regions of northern China and coined the term acute motor axonal neuropathy (AMAN) [79–81]. It is now clear that this disorder is as common as AIDP in Mexico, China, Japan, India, and Southeast Asia, accounting for 30–65 % of cases [76, 77]. In contrast, AMAN is rare in North America and Europe, probably accounting for less than 10 % of cases [75].

The disorder primarily afflicts children and young adults [79, 82] and causes symmetrical limb weakness, areflexia, facial diplegia, and oropharyngeal and respiratory muscle weakness that evolves over several weeks. The extraocular muscles are spared. There are no sensory features although mild changes in sensory nerves may occur [83]. The condition occurs as an annual epidemic during summer months. Most cases are preceded by a gastrointestinal illness with abdominal pain, cramps, and diarrhea and elevated antibody titers to Campylobacter jejuni, anti-GM1, and anti-GD1a [84–86]. The spinal fluid protein concentration is usually slightly elevated after several days of the illness, but EDX studies show reduced or absent compound muscle action potential amplitudes with normal conduction velocities, no conduction blocks, normal sensory potentials, and early active denervation, thus implicating a process similar or identical to AMSAN, with the exception of the normal sensory potentials (see below) [79–81].

Autopsy findings have confirmed widespread axonal degeneration with little demyelination or inflammation [48, 81]. Pathologic studies using electron microscopy have demonstrated the presence of macrophages in the periaxonal space of myelinated internodes [48, 53, 87]. The pathogenesis of AMAN has not been fully elucidated, but there is convincing evidence for an antibody- and complement-mediated process directed primarily at motor axons. There is evidence to suggest that IgG anti-GM1 or anti-GD1a antibodies bind to the axolemma at the node of Ranvier leading to membrane-attack complex formation. This results in the loss of voltage-gated sodium channels and leads to conduction failure. These rapidly reversible immune-mediated changes at the nodes of Ranvier may explain the puzzling speedy recovery that occurs in some patients with AMAN, a rate that is comparable to patients with AIDP. Another explanation for the rapid recovery is selective degeneration and subsequent quick regeneration of intramuscular motor nerve terminals in AMAN [86, 88, 89].

Acute Motor-Sensory Axonal Neuropathy (AMSAN)

In 1986, Feasby and coworkers described an axonal form of GBS, challenging the existent notion of GBS being a primarily demyelinating disease. These patients developed rapidly progressive paralysis, areflexia, and distal sensory loss [90, 91]. All of their patients required assisted ventilation and recovery was poor. The spinal fluid protein level was increased, but in contrast to the demyelinating features of typical GBS, EDX evaluation showed numerous inexcitable nerves, widespread active denervation, and no evidence of demyelination. An autopsy in one case showed axonal degeneration without inflammation or primary demyelination in the spinal roots and peripheral nerves. Since then, several studies have suggested that this syndrome, now termed acute motor-sensory axonal neuropathy (AMSAN), represents a variant of GBS that is clinically indistinguishable from typical, albeit very acute, cases but in which axons are the targets of the immune reaction. Virtually all patients become quadriplegic within days and require ventilator support and most have substantial residual weakness after recovery from the acute illness; some remain ventilator dependent for prolonged periods. Nerve conduction studies indicate an acute and widespread axonal sensory and motor neuropathy without demyelinating features.

It has also been argued that complete, distal conduction block and reversible conduction failure can simulate the finding of nerve inexcitability that is at the core of the diagnosis [92]. Subsequent pathological material from a few cases has shown axonal degeneration in the motor nerves

with macrophages insinuated in the periaxonal space of internodes; some patients also had axonal loss in the spinal roots [41].

Recent evidence suggests that AMAN and AMSAN share a common immunological profile and represent a continuum within the spectrum of axonal GBS [41]. Anti-GM1, anti-GM1b, and anti-GD1a, immunological markers for AMAN, are seen in high percentage of patients with AMSAN [93]. Also, sensory fiber involvement which distinguishes AMSAN from AMAN has been shown to be often involved subclinically in AMAN patients [83].

Evaluation and Diagnosis

Electrodiagnostic Studies

Electrodiagnostic (EDX) studies are very important in the diagnosis of GBS. Abnormalities on nerve conduction studies (NCS) are seen in up to 95 % of cases, and these findings are diagnostic in large number of GBS patients at some time during the course of the illness [94–96]. Unfortunately, NCS may be normal or show only modest nondiagnostic changes early in the course of GBS, at a time when treatment decisions have to be made. Repeat studies are often necessary, particularly when initial NCS findings are not specific [94]. The nature of the abnormalities detected by NCS depends upon the timing of the study in relation to disease onset and the number of nerves studied. Extensive testing of multiple nerves and multiple nerve segments in multiple limbs including evaluation of F-waves, H-reflexes, and blink reflexes is essential. The aim of NCS is to show evidence of *multifocal acquired nerve demyelination,* the hallmarks of AIDP, which represents the majority of patients with GBS in the Western World [75].

Abnormal Electrodiagnostic Parameters in GBS

The EDX studies in GBS include a variety of NCS parameters which may become abnormal during the course of illness. These include motor distal latencies, motor conduction velocities, CMAP amplitude and waveform configuration, sensory studies, late responses, and needle EMG. Although these EDX abnormalities are common in GBS, they vary in specificity which renders some of them less useful than others. The following are the most common abnormalities seen in GBS, with varying degree of specificity:

Abnormal H-Reflex

The tibial H-reflex is a sensitive test for detecting abnormalities of the S1 nerve root and early polyneuropathy and correlates fairly well with the Achilles reflex [97]. Absent H-reflexes correlate well with the areflexia in the lower extremities of GBS patients. The H-reflexes are absent bilaterally in almost all patients with GBS, including in 95–100 % of patients during the first 1–2 weeks of illness [98–100]. Hence, the H-reflex is the most sensitive EDX test. However, absent H-reflexes are not specific for GBS since it a common finding in the elderly and occurs in the majority of large fiber sensory and sensorimotor peripheral polyneuropathy such as diabetic and critical illness polyneuropathies, as well as S1 radiculopathies, cauda equina, and conus medullaris lesions.

Abnormal F-Waves

Multifocal acquired nerve demyelination, the hallmark of GBS [6], preferentially affects proximal and distal portions of the peripheral nerves [101]. Therefore, a common finding in early GBS is prolonged F-waves [94–96]. Prolonged or absent F-responses have been reported in as many as 40–80 % of GBS patients early in the illness [100, 102]. It may be the sole electrodiagnostic abnormality in about one-fourth of patients [101, 102]. The yield of F-wave studies improves by assessment of additional multiple F-wave parameters, including chronodispersion, mean latency, and mean amplitude [101]. However, these parameters are difficult to quantitate and are subject to variability.

Multiple and Complex A-Waves

A-waves are reproducible intermediate-to-late responses that are distinguished from F-waves and H-reflexes and usually seen during routine F-wave studies. A-waves may be recorded in normal individuals of the foot muscles while stimulating the tibial nerve. A-waves are commonly seen in multiple nerves and often with complex morphology in about 2/3 of patients with GBS [103, 104]. Their precise mechanism is not known, but they may be due to ephaptic transmission between axons or proximal re-excitation of the axon. Although prevalent in GBS, A-waves are not specific for GBS since they may be seen in other acquired and inherited demyelinating polyneuropathies (such as chronic inflammatory demyelinating polyneuropathy and Charcot-Marie-Tooth disease type I) and, less often, in axonal polyneuropathies, radiculopathies and motor neuron disease [103].

Motor Conduction Blocks

This is defined as a reduction (usually >20–50%) in the amplitude and area of the compound motor action potential (CMAP) following proximal nerve stimulation (Fig. 28.1). To be more specific and to avoid confusing GBS with polyneuropathies associated with compressive mononeuropathies, the conduction blocks in GBS should be located at non-entrapment sites (Fig. 28.2). This is a highly specific finding but is found in only about one-third of patients with GBS, dependent on the number of nerves and nerve segments studied [95, 98, 100]. Conduction block is often a sign of segmental demyelination, but transient conduction and block may be seen as the early manifestations of axonal loss such during the early stages of AMAN [105, 106]. Sequential studies are necessarily before a final diagnosis of axonal loss

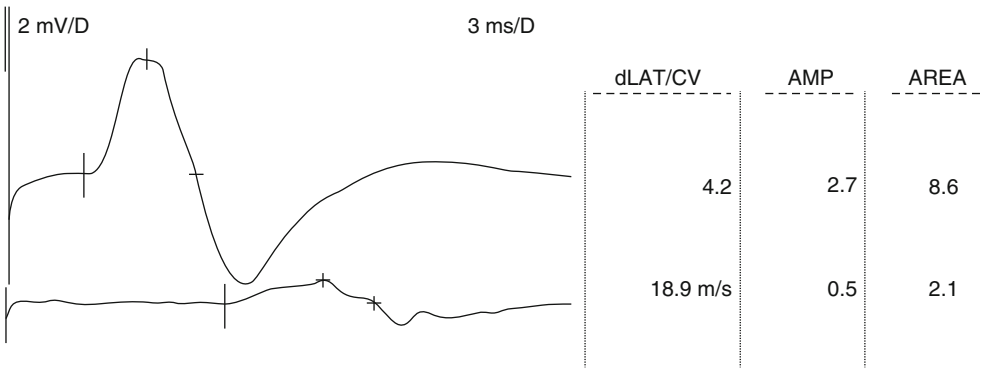

Fig. 28.1 Median motor nerve conduction study in a 35 year old patient with GBS examined at week 2 of illness. Note the forearm conduction block as evidenced by the significant drop in CMAP amplitude (80 %) and area (76 %) when CMAP obtained with distal stimulation at the wrist (*upper tracing*) is compared to proximal stimulation at the elbow (*lower tracing*). There is also marked slowing of forearm conduction velocity (18.9 m/s). *dLAT/CV* distal latency/conduction velocity, *AMP* amplitude

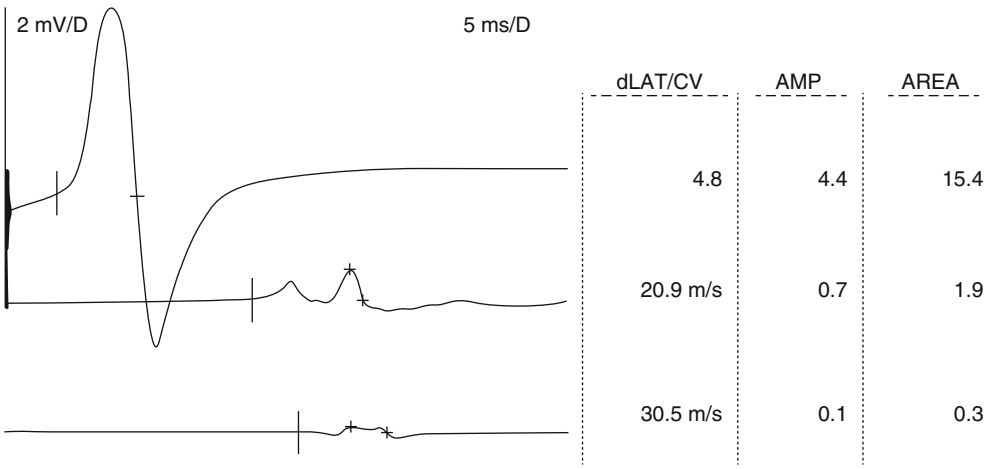

Fig. 28.2 Peroneal motor nerve conduction study in a 55 year old patient with GBS examined at week 4 of illness. Note the significant drop in CMAP amplitude (84 %) and area (88 %), with CMAP dispersion, when CMAP obtained with distal stimulation at the ankle (*upper tracing*) is compared to proximal stimulation below fibular neck (*middle tracing*) and popliteal fossa (*lower tracing*). The conduction block is distal to the fibular neck, not at a common entrapment site (i.e., fibular tunnel). *dLAT/CV* distal latency/conduction velocity, *AMP* amplitude

is made. Also, low distal CMAPs may be due to distal demyelination with distal conduction block and often mimic axonal loss. Rapid recovery of low distal CMAPs and SNAPs on sequential studies is a necessary confirmatory sign of distal demyelination [106].

Nerve Conduction Velocities Slowing

Significant slowing of nerve conduction velocities was first reported by Lambert and Mulder who reported in 60 % of their patients with GBS. During the early stage of disease, however, 80–90 % of patients with AIDP have normal conduction velocities [95]. It is now clear that prominent slowing of nerve conduction velocities is uncommon and is detected in only approximately 25 % of cases [98, 100]. Slowing is particularly uncommon during the first 2 weeks of illness in AIDP, and conduction velocities become paradoxically slower between 3 and 6 weeks from onset and during the recovery phase, presumably due to nerve fiber remyelination [95]. Additionally, controversies remain regarding the exact cutoff of conduction velocity that distinguishes primary demyelination from axonal loss, particularly in the presence of low CMAP amplitude. These values have varied from 60 to 80 % of the lower limits of the normal conduction velocity values [94, 95, 107].

Distal Latency Slowing

Since multifocal acquired nerve demyelination in GBS preferentially affects proximal and distal portions of the peripheral nerves, common findings in early GBS are prolonged distal motor latencies [94, 95]. Although this finding is common, it lacks specificity except when the latencies are significantly delayed and are within the demyelinating ranges. Similar to velocities, these ranges have also been controversial since demyelinating ranges have varied from 120 to 150 % of the upper limit of normal values [107–110].

Compound Muscle Action Potentials (CMAPs) Dispersion

The CMAP duration may be prolonged in GBS, and this is attributed to varying degrees of conduction slowing in demyelinated motor nerve fibers. Dispersion of the CMAP has only been considered as a criterion of demyelination in one study [108, 109]. Adding this fairly specific finding to other EDX parameters improved the sensitivity of EDX studies without worsening its specificity [111]. Distal CMAP durations of median, ulnar, peroneal, or tibial nerves measuring more than 8.5 ms are strong evidence for the presence of demyelination [111, 112].

Abnormal Sensory Nerve Action Potentials (SNAPs)

Earlier EDX criteria of GBS overlooked sensory nerve conduction studies by emphasizing abnormalities of motor NCS, such as conduction block, CMAP dispersion, abnormal F-waves, and slowing of latencies and velocities. It is now clear that SNAPs abnormalities are common and sometimes specific for AIDP. SNAP are abnormal in about 75 % of patients sometimes during the illness [94, 95, 100, 102]. The most common findings are reduced SNAPs amplitudes. This may reflects axon loss but is more likely caused by conduction block and phase cancellation. Slowing of sensory nerve conduction velocities is detected less frequently because the SNAP potential usually drops out before severe slowing is found.

Sensory NCS is now recognized to be important in providing EDX evidence that might distinguish primary demyelinating from axonal polyneuropathy. A *sural-sparing pattern*, also known as a "normal sural-abnormal median" pattern, is now recognized to be a common and specific finding in GBS and in particular AIDP [94, 100, 113, 114]. In contrast to the majority of length-dependent axonal polyneuropathies, the median and ulnar SNAPs are frequently reduced or absent when the sural nerve is normal ("sural sparing"), presumably as a consequence of random, multifocal demyelination. This pattern is the most specific sensory abnormality in AIDP and is present in about 50 % of patients during the first 2 weeks of illness [98, 100].

There are several limitations of the sural-sparing pattern which affects its sensitivity and specificity in the diagnosis of GBS. First, the sural SNAP may be either low in amplitude or absent in elderly patients and in those with underlying diabetic polyneuropathy [98]. Second, technical considerations in hospitalized or critically ill patients or those on mechanical ventilation render it difficult to study the sural SNAP. Third, the median sensory study may be abnormal in patients with preexisting carpal tunnel syndrome. Hence, sural sparing is better defined by preservation of sural SNAP in the presence of normal or near normal median *and* ulnar SNAPs in the upper extremity [98, 100].

Comparing several SNAP amplitudes in the upper and lower extremities is a useful exercise, particularly in elderly where the sural may be unobtainable. Among them, a sensory ratio (sural + radial SNAPs/median + ulnar SNAPs) is a good substitute for sural-sparing pattern. Patients with AIDP are 12 times more likely to have an elevated sensory ratio (>1) compared to patients with axonal polyneuropathies such as diabetic or critical illness polyneuropathies [115]. It is not known whether another lower limb SNAP, such as the superficial peroneal, could substitute for the sural.

Needle Electromyography (EMG)

Needle EMG is the least helpful EDX tool in the evaluation of patients with GBS, mostly since the EDX studies are often done early in the disease before signs of axonal degeneration are apparent on needle EMG. The initial finding in patients with GBS is reduced recruitment with the degree of abnormality proportional to the degree of muscle weakness. Early on, the combination of normal or virtually normal motor unit action potentials (MUAPs), reduced MUAP recruitment, and absent fibrillation potentials detected by needle EMG is characteristic. However, similar needle EMG findings are also seen in other acute axonal nerve lesions. The detection of abnormal spontaneous activity (fibrillation potentials) indicates axonal damage and occurs in 20–60 % of GBS patients in the first 4 weeks of the illness [95, 107]. This is seen in the demyelinating and axonal subtypes of GBS and signifies a variable element of axonal loss in all patients. Abnormal spontaneous activity is found more often during follow-up studies, 2–4 months after onset, and may be observed in proximal and distal muscles, consistent with multifocal nerve degeneration [95]. MUAP morphology changes start to occur after the fourth week of illness with an increased percentage of polyphasic MUAPs as the early change. Myokymia may be found in limb or facial muscles in some GBS patients, usually early in the course of the disease [94].

Electrodiagnostic Criteria in GBS

Various sets of EDX criteria for the detection of demyelination have been developed. These were mostly made by consensus or as part of the methods utilized in GBS studies [94, 95, 107, 109, 110]. However, most of these criteria were not subjected to vigorous scrutiny or applied to other neuropathies, and their specificities in GBS diagnosis were not well tested. For example, classic published diagnostic criteria of AIDP in GBS are fulfilled in 20–70 % of the cases based on the specific criteria utilized [99, 116]. This variation depends on how strict these criteria are in excluding patients with equivocal EDX findings.

Although it is intuitive to conclude that EDX studies are sensitive in confirming demyelination, EDX studies often reveal abnormalities that are not specific of primary demyelinating polyneuropathy during the early phases of the disease. Common abnormalities seen during the first few weeks of illness include absent or delayed H-reflexes, F-responses or blink reflexes, "sural sensory sparing," distal CMAP temporal dispersion, or frequent A-waves [95, 98–100]. During the first 4 days of weakness GBS, about 1/2 of the patients have normal NCSs (except for absent H-reflex in the majority of

Table 28.5 Diagnostic power of nerve conduction studies findings in the first 2 weeks of patients with AIDP

	Abnormalities	Sensitivity (%)	Specificity (%)
1. Nondiagnostic	Nonspecific abnormalities that are not specific for GBS, including absent H-reflexes, borderline or low CMAPs and/or SNAPs, minimal slowing of latencies or velocities	–	19
2. Suggestive	Upper extremity sensory sparing pattern *or* Absent or prolonged minimal F-wave latencies in at least 2 motor nerves with absent H-responses	26	86
3. Highly suggestive	Upper extremity sensory sparing pattern *and* Absent or prolonged minimal F-wave latencies in at least 2 motor nerves with absent H-responses	29	96
4. Definite	Signs of multifocal demyelination including: 1. Marked slowing of motor conduction velocity, distal latency and temporal dispersion 2. Conduction blocks in at least 2 motor nerves 3. Absent or prolonged minimal F-wave latencies in at least 2 motor nerves with absent H-responses	35	100
Highly suggestive or definite findings	3 and/or 4	64	96–100

SNAP sensory nerve action potential, *CMAP* compound muscle action potential

them), while only about 10 % of them have normal studies by the first week of illness [98]. Another 5–10 % have only nonspecific nerve conduction abnormalities, such as mild slowing, absent and/or prolonged H-reflexes or F-waves (due to spinal root demyelination), or low-amplitude CMAPs (due to intramuscular motor nerve terminals involvement).

We recommend using EDX criteria that include these different variables and have increasing levels of certainty in confirming the diagnosis of demyelination in AIDP [100] (Table 28.5). These criteria are designed to grade the level of confidence of the EDX studies, ranging from normal study to definite findings of acquired multifocal demyelination. Using these criteria, about 2/3 of patients with GBS meet the highly suggestive or definite criteria for AIDP during the first two weeks of illness with a very high specificity of 96–100 %. The remainder likely includes patients with the axonal subtypes of GBS, AMAN, and AMSAN, who do not have evidence of demyelination.

Electrodiagnostic Studies in GBS Subtypes

The EDX studies in GBS and its subtype may be confusing at the early stage of the disease when it is often difficult to determine the subtype classification of the disease (axonal vs. demyelinating) [105]. AIDP, AMAN, and AMSAN may have similar findings during the first weeks of illness. As outlined above, sensory conduction abnormalities are seen in patients with AMAN, making the distinction with AMSAN sometimes difficult [83]. Also, transient conduction slowing and block may be encountered during the early stages of AMAN, leading to incorrect diagnosis of AIDP [106, 117]. Similarly, some patients initially classified as "axonal" by nerve conduction studies have distal conduction block, and follow-up studies demonstrate rapid recovery of motor and/or sensory amplitudes typical of distal demyelination as seen in AIDP [92]. A useful diagnostic clue is the time course of EDX abnormalities. The nadir of conduction slowing in AIDP is 3–6 weeks after onset of symptoms, and this corresponds with the beginning of the clinical improvement [95]. In contrast, when conduction slowing or block is present in AMAN, it is evident early during the first 3 weeks of illness and rapidly resolves in parallel with clinical improvement [106, 117].

Prognosis of GBS Using Electrodiagnostic Studies

It has been long known that this presence of axonal damage in GBS is generally associated with worse outcome. In contrast, there is no association between slowing of nerve conduction velocities or F-wave latencies and clinical recovery. Early studies indicated a relationship between the detection of fibrillation potentials and poor outcome [118], but others have failed to confirm this finding as fibrillation potentials may occur when minimal amount of axonal loss has occurred [75, 107]. Also, fibrillation potentials may take several weeks to appear which renders needle EMG findings less useful.

Reduced CMAP amplitude is the most important predictor of outcome in GBS. Reduced mean CMAP amplitude (<20 % of the lower limit of normal) or absent CMAPs are strongly associated with a poor prognosis [66, 75, 119]. Hadden and colleagues demonstrated that 42 % of patients with an axonal loss pattern, on follow-up studies, were nonambulatory after 48 weeks [75]. On individual basis, one should be careful in making definite prognostic implications based on EDX studies only during the first 2–3 weeks of illness for several reasons: (1) Patients with axonal GBS studied early may show normal CMAP amplitude before the onset and completion of Wallerian degeneration [120]; (2) EDX evidence of conduction block when the site of stimulation is

advanced proximally does not always imply segmental demyelination since primary axonal degeneration may manifest with conduction block before the completion of Wallerian degeneration [121]; and (3) although low distal CMAP amplitudes imply almost always axonal loss, a severe distal demyelinative conduction block may mimic axonal degeneration and shows improvement of CMAP over a short period of time with good prognosis [94].

Serial EDX studies are extremely useful in GBS for the accurate diagnosis and prognosis of GBS. The disorder often evolves over several days to weeks, and a single early EDX study and before the illness reaches its nadir may be misleading. This lone study may miss the pathological changes that may have not been completed including Wallerian degeneration and sometimes rapid remyelination. Also, signs of segmental demyelination are most evident during the third and fourth weeks of illness [95]. These serial EDX studies are also mandatory for proper diagnosis and classification of GBS subtypes (AIDP, AMAN, and AMSAN). In many cases, the relative contributions of primary demyelination and axonal degeneration, or a combination of the two, cannot be determined with any certainty except if EDX studies are performed many weeks after the onset of disease and corroborated by the outcome.

Cerebrospinal Fluid Studies

Typically, the CSF protein level is elevated in the majority of patients at some time during the course of the illness. The protein concentration is elevated in only 50 % of patients during the first week of illness and is elevated in 75 % by the third week [2]. Usually, the protein level peaks in the second or third weeks of the illness followed by a slow decline towards normal that may take several months. The cause of increased CSF protein is not known but presumably results from abnormalities in the blood-CSF barrier due to inflammation at the level of the spinal nerve roots. Patients with GBS and exceptionally high protein levels (e.g., 1,500 mg/dL) may develop papilledema and symptoms of pseudotumor cerebri. Patients with AMAN and AMSAN also tend to have elevated CSF protein levels, but the frequency of this finding and the protein concentration is usually lower compared to patients with AIDP; normal values are not unusual. There is also correlation between the presence of demyelination on EDX studies and the CSF protein concentration during the first 2 weeks of illness [100]. There is no apparent correlation between the CSF protein level and clinical findings or outcome.

The increase in CSF protein is not usually associated with a cellular response. This "cyto-albuminologic dissociation" was observed first by Guillain-Barré and Strohl in their first cases and made the disease credible by differentiating it from a number of febrile paralytic disorders, particularly poliomyelitis [1]. However, in most large series, minorities, usually less than 10 %, of patients have a slight lymphocytic CSF pleocytosis greater than 10 cells/mm. GBS that follows Lyme or HIV infection often has a more prominent pleocytosis that reflects a concurrent meningeal reaction [26, 122]. Therefore, the presence of cells in the CSF certainly does not exclude the diagnosis, but other infectious disorders, such as Lyme and HIV [26, 122], or malignant conditions, such as lymphoma [32], should be excluded.

Antiganglioside Antibodies

Gangliosides are a large family of glycosphingolipids, predominantly distributed on the cell-surface membrane. Although antibodies against many of these gangliosides have been detected in sera of GBS patients, including LM1, GM1, GM1b, GM2, GD1a, GalNAc-GD1a, GD1b, GD2, GD3, GT1a, and GQ1b, the pathological significance of some of these antibodies is not known. In addition, most of these antibodies are found in subgroups of GBS patients. Antibodies to GD3, GT1a, and GQ1b are often seen in high percentage of patients with GBS associated with ophthalmoplegia, and antibodies to GQ1b are detected in 95 % of patients with MFS [123]. Antibodies to GM1, GM1b, GD1a, or GalNAc-GD1a are associated with about 50 % of patients with AMAN or axonal variants of GBS [78]. When strict criteria for GBS subtypes are used, IgG autoantibodies against GM1 or GD1a are associated with AMAN, AMSAN, and acute motor-conduction-block neuropathy (see below), but not with AIDP. No specific ganglioside antibody appears to be associated with AIDP, the prototypical and most common form of GBS in North America and Europe. This explains why these ganglioside antibodies are not clinically useful in clinical practice in these countries.

Imaging Studies

Magnetic resonance imaging (MRI) is most useful in excluding central nervous system disorders which may mimic GBS in their presentations. This includes MRI of the brain to rule out brainstem pathology and MRI of the cervical and thoracic spine to exclude cord compression or transverse myelitis. MRI of the lumbar spine, however, is often abnormal and shows nerve root enhancement of the cauda equina with gadolinium. This occurs in up to 80–90 % of patients particularly in children and in patients with severe weakness and severe leg and back pain (Fig. 28.3) [124, 125]. Occasionally, the facial nerves may also enhance with gadolinium in GBS patients with facial palsies [126].

Other Laboratory Studies

Routine laboratory studies are usually normal in patients with GBS. The erythrocyte sedimentation rate or liver function studies are infrequently elevated, although these

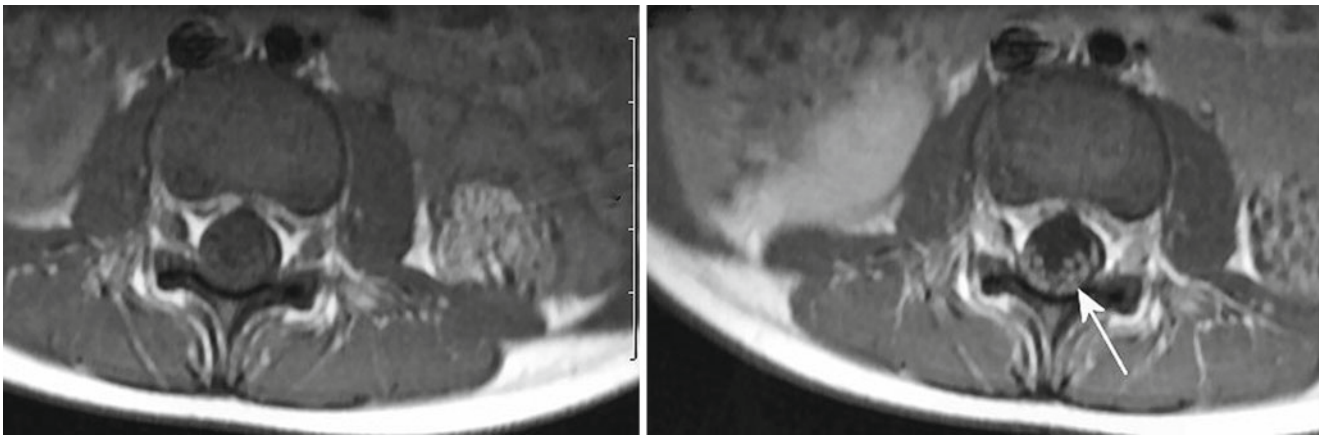

Fig. 28.3 MRI of lumbar spine in a 4 year old with GBS showing enhancement of cauda equina. T1 weighted image (*left panel*) is normal while T1 weighted image following contrast shows enhancement of nerve roots (*white arrow*, *right panel*)

findings most likely reflect a recent, preceding infectious illness and have little diagnostic utility. Viral antibody titers, particularly EBV and CMV, may be increased and thus help to identify the triggering infectious agent in individual cases. Prior infection with C. *jejuni* may be confirmed by detecting elevated serum IgM antibodies or culturing the bacteria from the stool [19].

An HIV titer should be obtained in patients with GBS who have CSF pleocytosis, risk factors for HIV or reside in geographic regions where AIDS is prevalent. Urine porphyrin screen, heavy metal testing, and Lyme titer may be indicated in selected cases but are rarely necessary. Stool culture and serum titers for *C. botulinum* and anti-acetylcholine receptor antibodies are helpful in patients when the ocular-pharyngeal-brachial variant is considered or when electrophysiological studies are consistent with a disorder of neuromuscular transmission. Creatine kinase (CK) may be slightly elevated, particularly in patients with muscle pain and tenderness [63]. A very high serum CK level distinguishes GBS from rhabdomyolysis or acute myopathies. Severe electrolyte imbalance may cause generalized weakness that rarely mimics GBS, and levels of magnesium, phosphorus, and potassium should be checked.

Differential Diagnosis

Acute GBS is easily recognized in typical cases, but unusual presentations expand the differential diagnosis to many other central nervous system and neuromuscular diseases (Table 28.6). With several subtypes and variant syndromes (see below), GBS may mimic a variety of neurological disorders [127]. Careful history and examination, coupled with cautious interpretation of diagnostic testing, is often necessary for accurate diagnosis. The first step is to establish that the clinical features are a consequence of a peripheral nerve condition.

Table 28.6 Differential diagnosis of Guillain-Barré syndrome

Peripheral neuropathies
Toxic neuropathies
Heavy metals—arsenic, lead, thallium, gold
Medications—vincristine, disulfiram, nitrofurantoin, isoniazid
Organophosphate poisoning
Hexacarbon (glue-sniffer's neuropathy)
Acute intermittent porphyria
Vasculitic neuropathy
Poliomyelitis
Diphtheria
Tick paralysis
Lyme disease
Critical illness polyneuropathy
Polyradiculopathies and ganglionopathies
Carcinomatous or lymphomatous meningitis
Acute sensory neuronopathy syndrome
Disorders of neuromuscular transmission
Botulism
Myasthenia gravis
Hypermagnesemia
Antibiotic-induced paralysis
Snake envenomations
Myopathies
Polymyositis
Other acute myopathies, e.g., drug induced
Metabolic abnormalities
Hypokalemia
Hypophosphatemia
Central nervous system disorders
Basilar artery thrombosis with brainstem infarction
Locked-in syndrome
Brainstem encephalomyelitis
Transverse myelitis
Acute necrotic myelopathy
Cervical cord or foramen magnum neoplastic compression
Hysteria
Malingering

Acute Peripheral Neuropathies and Poliomyelitis

Apart for GBS, the majority of acute peripheral neuropathies are toxic in nature. Acute toxic neuropathies are axonal and evolve in a subacute or chronic fashion. There are numerous environmental, industrial (heavy metals), and occupational toxins that cause a neuropathy, resembling GBS, following an acute exposure, including if a history of ingestion is lacking. Acute arsenic poisoning may have a presentation that is indistinguishable from GBS and AIDP. The EDX studies may show findings of acquired demyelinating polyneuropathy, which when repeated, convert to a dying-back neuropathy [128]. Thallium, lead, n-hexane (glue-sniffers neuropathy), and organophosphate poisoning are other examples of acute toxic neuropathies. In most instances, intoxication is heralded by gastrointestinal symptoms, and usually there is involvement of other organ systems, skin lesions, alopecia, and encephalopathy, coma, or other features of central nervous system toxicity. Acute toxic neuropathies are distinguished from GBS by the history of preceding toxic ingestion and by detecting suspected toxins in the serum or urine. Acute demyelinating neuropathies mimicking GBS have been linked to certain medications, such as amiodarone, perhexiline, and gold therapy for rheumatoid arthritis. An acute, rapidly progressive neuropathy, similar to GBS, has been described in alcoholics [129, 130]. These patients invariably have a long-standing history of alcohol abuse prior to onset of the acute neuropathy. Most develop progressive generalized weakness, severe distal sensory loss, and areflexia over days to weeks. The condition is distinguished from GBS by a normal CSF protein concentration and axonal features on EDX studies.

Patients with acute intermittent porphyria (AIP) may develop a neuropathy that resembles GBS [131–133]. A variety of medications or infections may trigger an acute attack. Initial symptoms include vomiting, constipation, and abdominal pain. Seizures occur in 10–20 % of cases and delirium or other psychiatric symptoms occur in most. The weakness is symmetric and begins in proximal muscles of the arms, but widespread weakness develops in most as the syndrome progresses. Hypertension, arrhythmias, or other features of dysautonomia are common. The cranial nerves are typically spared. EMG shows an axonopathy rather than demyelination, thus differentiating this condition from typical GBS. Increased urinary excretion of delta-aminolevulinic acid and porphobilinogen during an acute attack of AIP establishes the diagnosis.

Neuropathy is a common complication of systemic vasculitis and usually evolves in a subacute fashion; rarely, acute mononeuritis multiplex may have a fulminant course that simulates an acute polyneuropathy. Polyarteritis nodosa, and hepatitis B or C-associated vasculitis Churg-Strauss syndrome are the vasculitides most likely to cause a rapidly progressive polyneuropathy [134]. Focal or multifocal onset, severe pain, lack of diaphragmatic weakness or cranial nerve involvement, and electrophysiological features of a multifocal axonopathy distinguish acute vasculitic neuropathy from GBS in most cases. Furthermore, the CSF protein level is normal in the former condition. The diagnosis is established by pathologic evidence of vasculitis on biopsy material. Nonsystemic vasculitic neuropathy is generally an indolent condition that is rarely mistaken for GBS.

Lyme disease, a tick-borne illness, may be a consideration in cases of GBS presenting with facial diplegia or when there is a CSF pleocytosis. However, as already noted, most cases of Lyme neuropathy are characterized by chronic, slowly progressive, distal sensory loss or an asymmetric, painful polyradiculopathy.

Poliomyelitis, once the most common cause of acute paralysis in the world, is now a rarity except in few underdeveloped countries (see Chap. 19). The condition is most commonly contracted by non-vaccinated individuals after exposure to infants who recently were vaccinated against the poliovirus. A number of other viruses, typically the enteroviruses such as the West Nile virus, may produce an identical poliomyelitis syndrome and are a more common cause of acute motor neuronopathy simulating GBS. Affected individuals have a febrile illness, usually a gastroenteritis, followed by a paralytic phase 7–14 days later. The neurologic syndrome begins with fever, headache, and neck stiffness, followed by muscle pain, asymmetric flaccid limb paralysis, and fasciculations, and reaches a nadir within 4 weeks. Mild confusion may occur early in the illness. Diaphragmatic and oropharyngeal weakness are common but the extraocular muscles and sensory functions are spared. The CSF shows a lymphocytic pleocytosis and a normal or mildly elevated protein concentration, in contrast to GBS. Similarly, nerve conduction studies in poliomyelitis show reduced or absent motor amplitudes with normal conduction velocities and no conduction block. Sensory potentials are normal. Fibrillations are prominent in weak muscles early in poliomyelitis. Culture of the poliovirus from the pharynx or stool or detection of elevated antibodies directed against poliovirus with acute and convalescent sera establishes the diagnosis.

During the West Nile encephalitis epidemic in North America in the late 1990s and early 2000s, many patients with weakness were diagnosed mistakenly as GBS. Upon further studies, it was clear that these were cases of West Nile-induced poliomyelitis with evidence of anterior horn cell damage [135, 136]. When motor weakness occurs in West Nile, it may be asymmetric with paralysis of one limb (monoparesis) or fairly symmetric affecting four limbs (quadriparesis), with or without brainstem involvement and respiratory failure. EDX studies also reveal normal SNAPs, low-amplitude CMAPs recorded from weak muscles, signs

of diffuse active denervation (including the paraspinal muscles), and generalized or focal loss of motor units [137]. The pathology is consistent with poliomyelitis with identified neuronal loss, perivascular chronic inflammation, and microglial proliferation in the ventral horns of the spinal cord, especially in the cervical and lumbar segments [138].

Diphtheria is also a rare cause of acute polyneuropathy in developed countries because of effective vaccination programs. It is also reported in closed communities in countries where diphtheria remains endemic despite prior vaccination [139]. Infection with *Corynebacterium* diphtheria produces a febrile syndrome with severe pharyngitis, followed by palatal weakness and descending paralysis that develops weeks later. A membranous exudate over the tonsils and pharynx is present in most cases, and cervical adenopathy may be prominent. Bulbar weakness is present in the majority of patients. Over half the patients develop paralysis of accommodation. Symmetric limb weakness may be mild or severe with a predilection for proximal muscles. There is generalized areflexia, minimal sensory loss, and no dysautonomia. The course is slower than GBS, with maximal paralysis developing as long as 3 months after the onset of palatal weakness. The CSF profile demonstrates a cyto-albuminologic dissociation, similar to GBS, and EDX studies show an acute demyelinating neuropathy. Differentiation from GBS may be impossible if the early facial involvement is not recognized, but the low prevalence of diphtheria in developed countries makes GBS a more likely cause of acute, generalized, areflexic paralysis.

Critical illness polyneuropathy (CIP) was once frequently mistaken for GBS in the intensive care setting (see Chap. 76). It is now recognized as a common cause of limb weakness and failure to wean in ventilated patients in intensive care units (ICU). CIP is encountered most often in patients who have had sepsis and multiorgan failure [140–142]. Flaccid limb weakness, muscle atrophy, and generalized hypo- or areflexia are found in most patients. A small minority have facial weakness or ophthalmoparesis. Accurate sensory examination may be difficult in ventilated ICU patients, but most patients appear to have distal loss of all sensory modalities. Dysautonomia does not occur. The CSF protein concentration is normal and EDX studies demonstrate axonal loss with diffuse denervation without demyelination. Critical illness myopathy and prolonged exposure to neuromuscular blocking agents are other conditions that may simulate GBS in the ICU.

Disorders of the Neuromuscular Junction

Botulism is a rare condition that begins with cranial nerve dysfunction followed by generalized paralysis and can be confused with the oropharyngeal or ophthalmoparetic regional variants of GBS (see Chap. 50). Food-borne botulism usually begins hours to days after the ingestion of the neurotoxin produced by *Clostridium botulinum* types A, B, or E by way of contaminated food. Nausea and vomiting are followed by constipation and neurological symptoms. Blurred vision is an early complaint. Initial findings include dilated pupils in most patients, with paralysis of accommodation, ptosis, and oropharyngeal weakness. Diaphragmatic weakness with ventilatory failure is common and may be more severe than limb weakness. In contrast to GBS, the deep tendon reflexes are usually preserved. EDX studies show reduced amplitudes of the motor potentials with an incremental increase of the amplitude (usually >100 % above baseline) following high-frequency repetitive nerve stimulation, indicating a presynaptic neuromuscular junction abnormality. The CSF is normal. Detection of botulinum toxin in the serum, contaminated food source, or culture of *Clostridium botulinum* from the stool confirms the diagnosis.

In myasthenia gravis (MG), the slow onset of weakness, prominent fluctuation, fatigue, and the regional pattern of involvement usually poses little difficulty distinguishing these cases from GBS, but rarely patients with MG have a fulminant course with rapidly progressive limb and respiratory muscle weakness resembling an ocular-pharyngeal-brachial variant of GBS (see below) [143]. Although ptosis occurs in a minority of patients with GBS and may be transiently responsive to edrophonium, though it does not fatigue. Similarly, oropharyngeal weakness, nasal speech, and hypophonia do not fluctuate in GBS patients. Preserved deep tendon reflexes and lack of sensory symptoms or signs, dysautonomia, or an elevated CSF protein level are other features that differentiate MG from variant patterns of GBS. Patients with MG usually have transient improvement in strength following administration of edrophonium. EDX studies easily differentiate the two conditions; in MG, nerve conduction studies are normal and low-frequency repetitive nerve stimulation recording from a clinically affected muscle demonstrates a decrement (>10 %) of the amplitude characteristic of a postsynaptic neuromuscular junction abnormality.

Tick paralysis causes rapidly progressive paralysis that perhaps simulates GBS more closely than any other condition [144]. The illness is rare and affects mostly children in the northwestern United States in the spring and summer. A short prodrome characterized by fatigue, paresthesias, and ataxia is followed by generalized, areflexic weakness that occurs 3–5 days after attachment of the tick. The CSF is normal throughout the illness. The EDX studies show reduced motor amplitudes without demyelinating features; sensory studies are normal. The diagnosis is established by finding the tick, usually located at the hairline, and removal is followed by rapid recovery.

Central Nervous System Disorders

Occlusion of the basilar artery with pontine infarction may produce flaccid quadriparesis with ocular and bulbar findings. The symptoms usually begin suddenly and often there is a history of preceding transient ischemic attacks. Deep tendon reflexes may be reduced at the initial evaluation although hyperreflexia develops after a few days or weeks. Babinski signs are usually present. Vertical eye movements are preserved and other cranial nerve findings may be present but are usually asymmetrical. Most patients with brainstem stroke are somnolent or comatose because of involvement of the ascending reticular activating system.

Acute cervical transverse myelitis may cause a rapidly progressive quadriparesis. The detection of a spinal sensory level on the trunk and upper motor neuron findings (hyperreflexia, extensor plantar responses) differentiates this condition from GBS, but in the spinal shock stage of an acute myelopathy, flaccid limb weakness and areflexia simulate a lower motor neuron condition. In the acute inflammatory myelopathies (multiple sclerosis, neuromyelitis optica, or acute disseminated encephalomyelitis), weakness is often asymmetric, bowel and bladder dysfunction is an early and prominent finding, and the cranial nerves are normal. There is usually an inflammatory response with lymphocytes in the spinal fluid. Increased signal abnormalities on T2-weighted MRI or gadolinium enhancement of the cervical or thoracic cord establish the diagnosis.

Anxiety or a panic attack may be considered early in the illness when paresthesias are the only symptom of emerging GBS and deep tendon reflexes may be preserved. These patients may be labeled as "anxious" with symptoms attributed to hyperventilation and are often discharged from the emergency room, only to return later with generalized and diaphragmatic weakness.

Treatment and Management

Supportive Care

Most patients with GBS require admission to an intensive care unit (ICU) under the care of physicians who are familiar with the medical complications that develop in paralyzed ICU patients (Table 28.7) [146, 147]. The timely and skillful management of medical problems is as important as immune therapy in the outcome of patients with GBS.

Ventilatory failure is a central issue and should be anticipated in any GBS patient with progressive limb or oropharyngeal weakness. About 15–30 % of patients with GBS will need ventilatory support [65, 147]. Atelectasis develops early and leads to mild hypoxemia. Hypercarbia and hypoxemia is a later finding as ventilatory failure advances; therefore, arterial blood gases are not as helpful as respiratory mechanics in monitoring the evolution of diaphragmatic weakness in GBS patients. Vital capacity (VC), tidal volume, and negative inspiratory force are reasonably sensitive reflections of diaphragmatic power, and progressive decline in these values indicates impending mechanical respiratory failure and the need for ventilatory support (Fig. 28.4) [146]. These measures should be obtained early on in the course and repeated as frequently as dictated by the clinical state (up to every 4–6 h). Bulbar dysfunction including swallowing problems with difficulty in clearing secretions increases the odds of needing ventilator support. In general, if the forced vital capacity is less than 15–20 mL/kg, the maximum expiratory pressure is less than 30 cmH_2O and the maximum inspiratory pressure is less than 30 cmH_2O, impending respiratory arrest is present and intubation should be performed [148]. Also, PCO_2 above 48 mmHg or PO_2 less than 56 mmHg on room air are definite indications for intubation [2, 149].

Prediction for respiratory failure in patients with GBS is important in order to improve outcome and reduce mortality. Several studies have recently tried to answer this question. Walgaard et al. found that patients who required ventilatory support had facial and/or bulbar weakness, shorter days between onset of weakness and admission, and more limb weakness (higher Medical Research Council sum score) [65]. Sharshar et al. proposed that patients should be monitored in ICU setting if at least one of the following predictors of respiratory failure is present: (1) time from onset to admission of <7 days, (2) inability to cough, (3) inability to

Table 28.7 Guidelines for the general management of patients with Guillain-Barré syndrome

Measure vital capacity as indicated by rapidity of deterioration:
Vital capacity 12–15 mL/kg: intubate
Vital capacity 15–19 mL/kg: intubate if bulbar paralysis
Incentive spirometry to prevent atelectasis
Bronchial clearing and assisted coughing
Chest X-ray examination weekly, or more often
Biweekly serum albumin, sodium, BUN, calcium measurements
Urinalysis weekly
Pulmonary embolism prophylaxis: 5,000 U heparin every 12 h subcutaneously
Peristalsis checked
Gastrointestinal bleeding prophylaxis: magnesium-containing antacid 30–120 mL or sucralfate
Decubitus prophylaxis: frequent position changes; air-floating bed or water mattress and skin care
No antibiotic prophylaxis; urine and pulmonary infections treated with antibiotics after bacterial sensitivities available, unless septic
Tube feeding when swallowing is impaired (start with continuously administered fiber-enriched mixtures)
Inquiries daily concerning pain, sleep, and hallucinosis; administration of adequate pain treatment
Limitation of antecubital phlebotomy if plasma exchange anticipated

Reprinted with permission from Ropper et al. [145]

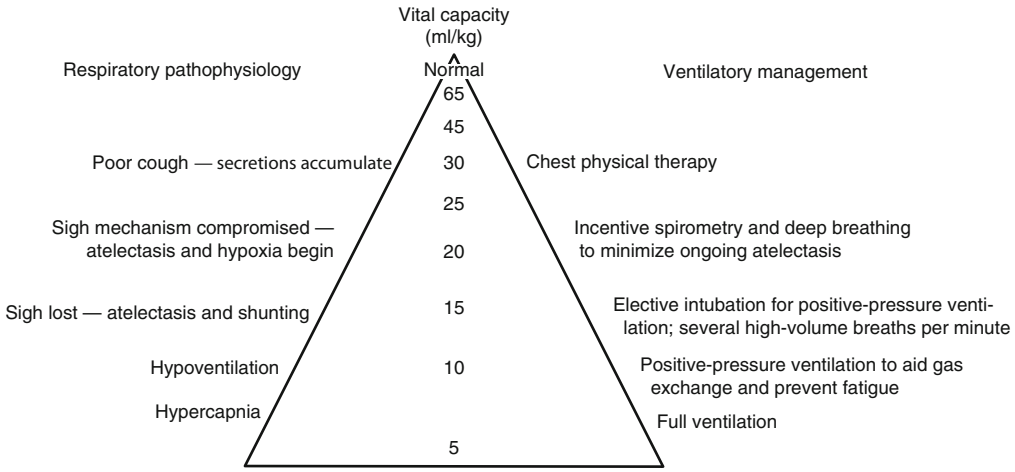

Fig. 28.4 Schematic diagram of pathophysiologic events in patients with ventilatory failure and Guillain-Barré syndrome, with corresponding suggested management (Reprinted with permission from Ropper AH [190])

stand, (4) inability to lift the elbows, (5) inability to lift or head, or (6) vital capacity <60 % of predicted. More than 85 % of patients with 4 out of these 6 predictors were intubated [150]. Moreover, Durand et al. found that the EDX is a predictor for mechanical ventilation. They found that the risk of respiratory failure was very low in GBS patients with less than 55.6 % conduction block of the common peroneal nerve [151].

Incentive spirometry is useful in the early stages of the illness to prevent atelectasis. Frequent suctioning and chest physiotherapy minimize the accumulation of secretions and prevent aspiration and bronchopneumonia, but patients with moderate oropharyngeal weakness (e.g., those who cannot safely swallow liquids) will probably require intubation for protection of the airway. Most patients with severe, ventilator-dependent GBS who have no improvement after 2 weeks require tracheostomy to secure long-term airway management, avoid tracheal stenosis, facilitate suctioning, and maximize patient comfort. However, tracheostomy can be deferred for another week if pulmonary function tests show any significant improvement form baseline. Older patients with preexisting pulmonary disease are more likely to require tracheostomy [152].

Autonomic dysfunction is a well-recognized feature of GBS and a significant source of mortality. It is present in 70 % of patients, but serious and potentially fatal dysautonomia occurs in 20 % of patients. Severe autonomic disturbances affect mainly patients with severe weakness and those with respiratory failure. Many of the features of autonomic dysfunction are self-limited and require no intervention. For example, resting tachycardia is common in GBS patients and does not require treatment except in those with active coronary artery disease and acute myocardial ischemia. Hypertension often develops as a consequence of a procedure (e.g., suctioning or catheter placement) but is usually transient and does not require therapy. Sustained high blood pressure (e.g., >180/95) may be managed with angiotensin-converting enzyme inhibitors or beta-blocking agents. Short-acting intravenous medications, such as nitroprusside or esmolol, are preferred for patients who have severe, labile hypertension and require immediate therapy. Conversely, postural hypotension, often precipitated by only minor position changes, can be effectively treated with a bolus of intravenous saline or by placing the patient in the supine position. Norepinephrine and other sympathomimetic agents generally should be avoided because of the risk of rebound hypertension, but vasopressors may be necessary for those with persistent supine hypotension. Invasive procedures or cholinergic medications may trigger excessive vagal discharges ("vagal spells") and precipitate bradycardia, asystole, or other vagally mediated arrhythmias [153, 154]. These episodes are usually transient, but anti-arrhythmic medications (atropine) or cardiac pacing may be necessary [154]. Micturitional disturbances are common and can be managed with intermittent catheterization or an indwelling catheter [147, 155].

Nosocomial infections are probably the most common medical complication that develops in GBS patients in the ICU with pulmonary infections predominating [156]. Other infections include urinary tract infections and central venous catheters sepsis. Tracheitis and sinusitis are other considerations in intubated patients who have a persistent fever and no apparent source of infection. Every effort should be made to identify the organism to guide appropriate antibiotic therapy. Routine monitoring of the chest X-ray and sputum and urine cultures are useful. However, bacterial colonization occurs frequently, and patients should receive antibiotic therapy only when there is clinical evidence of an infection; inappropriate treatment only increases the risk of infection with resistant pathogens. Although indwelling urinary catheters are often necessary in GBS patients, the risk of colonization and infection increases after several days.

Immobilization that is associated with GBS predisposes to deep venous thrombosis and pulmonary embolism. Subcutaneous heparin or intermittent pneumatic compression

boots should be used routinely, and chronic anticoagulation with warfarin may be considered for those who are bedbound or ventilator dependent for long periods. Low molecular weight heparin has become popular, but the value of neither the old nor new type of heparin has been established by a trial; they are presumed from experiences in general medicine to be helpful. Although mucous plugging is probably the most common cause of acute respiratory decompensation in ventilated patients with GBS, any unexplained episode of acute oxygen desaturation requires evaluation for pulmonary embolism.

Patients who are intubated or have dysphagia due to oropharyngeal weakness require nasogastric tube feedings to maintain long-term nutritional support. A gastrostomy tube can be placed at the time of tracheostomy in patients with prolonged recovery. Hyperalimentation may be necessary in patients with an ileus. Neostigmine or erythromycin can be effective to treat ileus [147]. Moreover, daily abdominal auscultation and monitoring of opioid administration should be performed. Judicious intravenous hydration is essential because insensible fluid losses may be substantial, leading to dehydration and exacerbating autonomic instability. Hyponatremia may develop, usually as a consequence of inappropriate antidiuretic hormone secretion. Hyponatremia is an independent indicator of poor prognosis [70].

Pain is a common symptom in patients with GBS and is often underappreciated by the medical staff [61, 63]. Narcotics are almost always needed to manage pain, and the use of nonnarcotic, chronic analgesics often provides additional relief. Carbamazepine and gabapentin are usually successful in alleviating pain during the acute phase of GBS and may be used for long-term management of neuropathic pain [147]. An excellent alternative for severe pain in the back or legs is epidural analgesia [157]. Most patients benefit from early physical and occupational therapy [158]. For example, passive range of motion of paralyzed joints prevents contractures, foot boards minimize the risk of foot drop and shortening of the Achilles tendon, and frequent turning and air mattresses reduce the risk of skin breakdown and development of decubitus ulcers. Symptoms of anxiety and depression are also common, occur at all stages of the illness, and should not be overlooked. Those who are paralyzed, intubated, and unable to communicate with their caregivers are most likely to experience fear and helplessness. Communication boards allow patients to maintain a connection with their families, nurses, and medical staff. Facilitating contact with recovered GBS patients provides additional psychological support.

Immunotherapy

Several large, randomized, controlled trials have demonstrated the benefits of *plasma exchange* when performed within the first 2 weeks of the illness. The North American study involved 245 patients randomized to receive plasma exchange, 200–250 mL/kg over five sessions within 2 weeks, or supportive care [159]. Treated patients improved more rapidly and regained the ability to walk earlier (an average of 53 days for the plasma exchange group vs. 85 days in untreated patients). Furthermore, those who required ventilator assistance and were treated with plasma exchange weaned sooner than controls (24 vs. 48 days). Similar findings were reported from French and Swedish trials [160, 161]. Severely affected patients with features that are associated with a poor prognosis (see below) also benefited from treatment, but probably less so than others. The efficacy of plasma exchange is reduced if therapy is initiated after 3 weeks from the onset of symptoms [159, 162]. Plasma exchange is most effective when started within the first 2 weeks of symptom onset [159], but benefits are still seen if started within 30 days of symptom onset [163]. Improvement may occur after as few as two exchanges in patients with mild GBS, but four exchanges, performed approximately on alternate days, appear necessary in those with moderate or severe forms of the illness [164]. Adding more exchanges is not indicated, since six exchanges are not superior to four in severe GBS [163, 164]. A recent report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology found that plasmapheresis is effective for the treatment of moderate and severe GBS (class I studies, level A) and probably effective in mild disease (level B) [165].

Patients treated with plasma exchange generally experience few serious adverse effects. Treatment-related complications include pneumothorax at the time of placement of central venous catheters, line infection with bacteremia or sepsis, cardiac arrhythmias, hypotension from rapid fluid shifts, and excessive bleeding. In some patients, generally large men, the high volume of exchange necessary may be accomplished through antecubital veins, thus obviating the risk of a central venous catheter. Plasma exchange is difficult to conduct in young children and patients with severe dysautonomia, especially those with hypotension, or with active cardiac disease, coagulopathy, or hepatic failure. Plasma exchange is safe to perform in children and pregnant women.

Intravenous immune globulin was introduced as an alternative to plasma exchange because of its efficacy in other immune-mediated disorders, its relative safety, and ease of administration. A randomized trial comparing IVIG (400 mg/kg/day for 5 days) to plasma exchange in 150 patients with GBS established that (1) IVIG is an effective therapy for GBS, (2) the efficacy is comparable to plasma exchange, and (3) there was a low frequency of adverse effects [166]. A larger, international, randomized, multicenter, controlled trial of 379 patients with GBS (the "Sandoglobulin trial") subsequently compared IVIG (400 mg/kg/day for 5 days),

plasma exchange (50 mL/kg exchanges over 8–13 days), and combined therapy. It established that IVIG and plasma exchange had equivalent efficacy and that plasma exchange followed by IVIG provided no additional benefit [167]. There was no difference in functional disability scores at 4 and 48 weeks between IVIG, plasma exchange, and combined therapy, nor was there any difference in secondary outcome measures (time required to wean from mechanical ventilation, number of days to recover ambulation, and the proportion of patients unable to walk after 48 weeks). These findings were subsequently confirmed by several studies and meta-analysis, despite the lack of placebo studies in IVIG [163, 168, 169]. A recent report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology concurred also that there is strong evidence (level A) to support the use of IVIG in GBS which should be initiated during the first 2 weeks of disease onset [169]. Also, the analysis concluded that the combination of plasmapheresis and IVIG is probably not better than either treatment alone.

The beneficial immunomodulator effects of IVIG are complex and not completely understood, but probably include neutralization of proinflammatory cytokines (especially tumor necrosis factor-alpha and interleukin-1 beta), downregulation of pathogenic antibodies, modulation of Fc-receptor-mediated phagocytosis, inhibition of complement deposition, and promotion of remyelination [36, 44].

Headache is probably the most common side effect of IVIG occurring in up to 16 % of patients [169]. It may be prevented by premedication with analgesics or corticosteroids and by slowing the rate of infusion. Other minor complications include transient fever, chills, and transient hypertension. Serious adverse effects are currently rare and occur in less than 5 % of patients. These include serum sickness reaction, aseptic meningitis, acute renal tubular necrosis (possibly due to a high osmotic load), and a hypercoagulable state with risk of deep vein thrombosis, especially in nonambulatory patients, and myocardial infarction or stroke, especially in patients with risk factors for cardiovascular disease. IVIG should not be administered to patients with known IgA deficiency, a rare genetic trait, because of a high risk of developing an anaphylactic reaction. Transmission of HIV has not been reported, and infection with hepatitis C virus has been reported during the 1990s but not since. Recent improvement of IVIG manufacturing using nanofiltration or caprylate (a saturated medium-chain fatty acid) has essentially eliminated the risk of viral transmission. IVIG can be administered safely to pregnant patients [170]. Because IVIG is generally well tolerated and easy to administer, it has become the preferred therapy for GBS in the United States [171].

The optimal IVIG dose needed for patients with GBS remains somehow controversial. The dose of IVIG was set arbitrarily at 400 mg/kg/day for 5 days (total dose 2 g/kg) based on its use in hematologic disorders. This dose was used in most subsequent studies of IVIG in patients with GBS. A longer duration or higher dose of IVIG treatment in patients with severe disease may be beneficial. Indeed, Raphael et al. found that, in select patients on mechanical ventilation, a 6-day course of IVIG (total dose 2.4 g/kg) is more beneficial than a 3-day treatment (total dose 1.2 g/kg) with more rapid rate of recovery [172]. More recently, Kuitwaard et al. compared IgG level in serum before and 2 weeks after infusion with the standard dose of IVIG (total dose 2 g/kg) [173]. They identified a large variation of IgG levels at 2 weeks following the infusion of the same standard dose and a dose–response relationship. More significantly, patients with slight or no increase in serum IgG at 2 weeks had more severe clinical deficit at nadir, and fewer were able to walk at 6 months. An international study is currently assessing whether additional IVIG in patients who do not show a meaningful rise in IVIG level is beneficial.

Approximately 10 % of GBS patients treated with plasma exchange or IVIG relapse after initial treatment. This rate is equal with the use of plasma exchange or IVIG [167, 174]. The cause of these relapses is unknown but may be related to persistence of active disease after completing therapy or a rebound in antibody production. Patients with a more protracted course may be at higher risk for a relapse, but no other predictive factors have been identified [175]. Occasionally, a relapse may be triggered by an intercurrent infection or an ongoing CMV or EBV infection. A single study indicated that a repeated course of IVIG administered to patients who do not respond or relapse following the initial treatment may be of some benefit [176], but this regimen is currently being evaluated by a controlled study. A GBS relapse raises the concern of more chronic disorder, namely, CIDP. Ruts and colleagues found recently that GBS patients deteriorate more rapidly (15–27 days) while CIDP worsen much slower (31–63 days) [177]. Also, CIDP is the likely diagnosis if patients diagnosed with GBS exhibit more than two treatment-related fluctuations.

The difficult issue of how to treat patients with severe GBS who have not improved with standard therapies remains not well clarified. The "Sandoglobulin trial" showed that a course of plasma exchange followed by IVIG is not better than plasma exchange of IVG alone [167]. A repeated dose of IVIG has only been shown to be effective in a small study [176]. An international study is being conducted in assessing the use of additional IVIG in unresponsive server GBS patients or those who relapse.

A discussion on GBS treatment cannot be completed without addressing *corticosteroids.* Anecdotal reports indicated for decades that *corticosteroids* were beneficial to patients with GBS, but larger, prospective studies showed subsequently that oral and intravenous high-dose corticosteroids made no difference in outcome [178, 179]. There is also limited evidence suggesting that oral corticosteroids may

slow recovery from GBS [180]. In combination with intravenous immunoglobulin, intravenous methylprednisolone may have a short-term effect and hasten recovery but does not significantly affect the long-term outcome [181].

The efficacy of other pharmacological agents is unknown. A small randomized controlled trial demonstrated that interferon beta 1a (Rebif®) was not associated with significant clinical improvement [182]. A recent meta-analysis concluded that there are no beneficial effects on GBS from brain-derived neurotrophic factor or cerebrospinal fluid filtration [183].

Prognosis

The majority of patients with GBS have a rapidly progressive course followed by a plateau phase of varying duration. Three-quarters of patients reach a nadir by 1 week and virtually all (98 %) do so by 4 weeks (Fig. 28.5) [77, 184–186]. Approximately 15 % of patients have a mild condition, remain ambulatory, and recover after a few weeks. Conversely, 5–20 % of patients have a fulminant course and develop flaccid quadriplegia, ventilator dependence, and axonal degeneration, often within 2 days from the onset of symptoms [110, 187]. This group is often caused by axonal loss (AMSAN subtype); The recovery is delayed and virtually always incomplete [90]; at 1-year follow-up, most have substantial residual motor deficits [187]. In contrast to AMSAN, patient with AMAN have a prognosis which is comparable to patients AIDP. This may be due to rapidly reversible immune-mediated changes at the nodes of Ranvier (conduction failure) that occur in some patients with AMAN or the selective degeneration and subsequent quick regeneration of intramuscular motor nerve terminals [87, 89, 188].

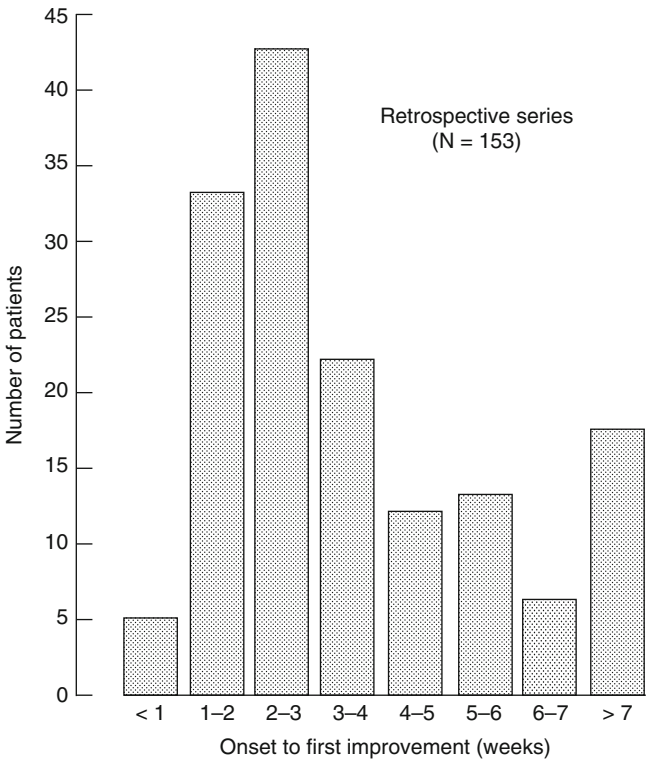

Fig. 28.5 Time from onset of the illness to onset of improvement (end of the plateau phase) in the Massachusetts General Hospital retrospective series. (Reprinted with permission from Ropper AH et al. [145])

Neurologic disability advances steadily until a plateau is reached. The plateau phase usually lasts several weeks but may be only a few days in mild cases or persist for months in patients with quadriplegia and ventilator dependence. At the time of the maximum deficit, approximately one-third of patients require assisted ventilation, almost half are wheelchair or bedbound, 7 % have trouble walking, and the remainder are ambulatory [189]. Once recovery begins, improvement follows a predictable course; patients who were quadriparetic often recover to walk in a few months, although about half have persistent symptoms at 1 year. An earlier study reported that at 1-year follow-up, 62 % had recovered completely, 14 % could walk but not run, 9 % could not walk without assistance, 4 % remained bedbound or ventilated, and 8 % died [190]. In a more recent study, full recovery or minor deficits were observed in 41 % of patients in the first month, 71 % in the third month, 86 % in the sixth month, and 92 % by the first year [184].

Features that predicted a poor recovery (inability to walk independently) in various studies include older age (>60 years), history of preceding diarrheal illness, recent CMV infection, fulminant and rapidly progressive course, ventilator dependence, hyponatremia, peroneal nerve conduction block, and greatly reduced CMAP mean amplitudes (<20 % of the lower limit of normal) or inexcitable nerves [66, 70, 159, 191].

Several clinical scoring systems to predict prognosis have been used in the past. The Erasmus University scales have been validated. The scales uses the GBS disability score [179] (Table 28.8) and the Medical Research sum (MRC) score [166] (Table 28.9), as well as several simple and easily obtainable clinical data. The Erasmus GBS Outcome Score (EGOS) was developed based on a prognostic model that uses easy-to-obtain patients' clinical characteristics during

Table 28.8 GBS disability score

0	A healthy state
1	Minor symptoms and capable of running
2	Able to walk 10 m or more without assistance but unable to run
3	Able to walk 10 m across an open space with help
4	Bedridden or chairbound
5	Requiring assisted ventilation for at least part of the day
6	Dead

the acute phase of illness to accurately predict the chance of being able to walk independently at 6 months. The EGOS is based on age, diarrhea, and GBS disability score at 2 weeks after hospital admission that accurately predicts the chance of being able to walk independently at 6 months [185]. A final score higher than four correlates with poor recovery (Table 28.10). The modified EGOS (mEGOS) model replaced the GBS disability score by the more detailed MRC sum score [186]. It is also applicable at hospital admission as well as 1 week after hospital admission (see Table 28.10). It is used to predict inability to walk independently at 4 weeks, 3 months, and 6 months. The mEGOS is advantageous because it can predict groups with poor prognosis early in the disease when treatment is considered to be most effective. In addition, the Erasmus respiratory insufficiency score was also validated with specific parameters which predict mechanical ventilation at the time of hospital admission. These include the time between onset of weakness and admission, the MRC sum score, and presence or absence of facial and/or bulbar weakness (see Table 28.10) [65].

The mortality from GBS, once reported to be as high as 10–20 % [192, 193], has been reduced to 1–5 % in North America and Europe, most likely because of the advent of critical care units with experience in the management of this disorder [194–196]. The predictors of death are similar to the predictors of poor disability outcome [194].

Approximately 3–6 % of patients with typical GBS develop a chronic relapsing course consistent with CIDP. These cases are referred to as *acute-onset CIDP*. There are no distinctive features that allow early recognition of these patients; however, CIDP should be considered very likely in patients with GBS whose relapses reach nadir after 8 weeks or have more than two relapses [177]. Some patients with a progressive phase of 4–8 weeks and a monophasic course have been labeled *subacute inflammatory demyelinating polyneuropathy (SIDP)* [197]. These patients fall between CIDP and a relapsing GBS. These patients often do not relapse and treatment could be completely tapered over several months. A few patients had bouts of *recurrent GBS* completely remitting and separated by long asymptomatic intervals [198, 199].

Table 28.9 Medical Research Council (MRC) sum score

Sum of Medical Research Council scores of six muscle groups tested bilaterally:	
Shoulder abductors	0–5
Elbow flexors	0–5
Wrist extensors	0–5
Hip flexors	0–5
Knee extensors	0–5
Foot dorsiflexors	0–5
MRC sum score	60 (normal) to 0 (quadriplegic)

Medical Research Council score of an individual muscle group ranges from 0 to 5:

0 No visible contraction
1 Visible contraction without movement of the limb
2 Active movement of the limb, but not against gravity
3 Active movement against gravity over (almost) the full range
4 Active movement against gravity and resistance
5 Normal power

Table 28.10 Erasmus GBS outcome score and respiratory insufficiency score

		Erasmus GBS outcome score	Modified Erasmus GBS outcome score		Erasmus GBS respiratory insufficiency score
Prognostic factors	Categories	At day 14 of hospital admission	At hospital admission	At day 7 of hospital admission	At hospital admission
Age at onset	<40 years	1	0	0	
	41–60 years	0.5	1	1	
	>60 years	0	2	2	
Diarrhea during 4 weeks prior to onset	Absent	0	0	0	
	Present	1	1	1	
Time between onset of weakness and admission	>7 days				0
	41–60 days				1
	>60 days				2
Facial or bulbar weakness	Present				1
	Absent				0
MRC sum score	60–51		0	0	0
	50–41		2	3	1
	40–31		4	6	2
	30–21				3
	≤20				4
	≤30		6	9	
GBS disability score	0 or 1	1			
	2	2			
	3	3			

Guillain-Barré Syndrome Variants

Miller Fisher Syndrome

The triad of acute ophthalmoplegia, ataxia, and areflexia, initially described by Fisher in 1956, has been recognized as a variant of GBS on the basis of shared clinical features with the typical disease and EDX findings indicating an acute sensory neuropathy [200]. Miller Fisher syndrome accounts for approximately 5 % of GBS cases in North America and Europe but may represent as high as 20–25 % of GBS patients in Eastern Asia [201, 202]. In some patients, the illness progresses to generalized GBS that overtakes the other features [184, 203].

Diplopia is usually the first symptom, followed by limb or gait ataxia that appears within days. Additionally, there may be mild distal paresthesias, dysphagia, or mild proximal limb weakness in up to one-third to one-half of cases. In some patients, frank GBS develops with respiratory failure requiring ventilator support. In patients with the classical syndrome, respiratory failure is, however, rare [201, 202]. Unilateral or bilateral asymmetric abducens weakness is a common initial finding and often evolves to complete external ophthalmoplegia. Ptosis is present in the majority of patients but pupillary function is usually preserved (a small proportion do have internal ophthalmoplegia). Ataxia typically involves all the limbs and gait but may be asymmetric early in the illness. Large amplitude, discoordinated, and poorly metricated limb movements are indistinguishable from a cerebellar efferent ataxia. The deep tendon reflexes are absent in all fully developed cases. The Fisher syndrome can be confused with brainstem lesions such as encephalitis or infarction, but the presence of other central nervous system features (confusion, seizures, alternating hemiparesis, Babinski signs, etc.) and normal electrophysiologic studies in the latter conditions clarify the diagnosis.

The CSF protein level may be elevated in Fisher syndrome but less frequently than in typical cases of GBS [201]. The EDX findings are abnormal in half of the patients with absent or low-amplitude SNAPs or a sural spaing pattern. Motor conduction abnormalities are rare [204]. In almost all patients (95–98 %) with Fisher syndrome studied, there has been elevated antiganglioside antibodies directed against the epitope GQ1b (Table 28.11) [51, 205]. The observation that paranodal regions of the oculomotor, trochlear, and abducens nerves are enriched with GQ1b ganglioside supports a role of anti-GQ1b antibodies in the pathogenesis of ophthalmoplegia. Indeed, patients with incomplete forms (acute ataxic neuropathy and acute ophthalmoplegia), generalized GBS with ophthalmoplegia, and Bickerstaff's encephalitis also display the antibody [51, 205, 206]. Sera from patients with anti-GQ1b antibodies and Fisher syndrome induced rapid and reversible failure of release of acetylcholine from presynaptic motor nerve terminals and motor nerve terminal blockade [207, 208]. The ataxia is believed to be secondary to selective involvement of muscle spindle afferents [52, 205, 206].

Table 28.11 Clinical spectrum of the anti-GQ1b antibody syndrome

Disorder	Clinical features	Frequency of anti-GQ1b Ab (%)
MFS	Ataxia, areflexia, ophthalmoplegia	~95
Ataxic GBS	Ataxia, sensory loss and areflexia	~65
Bickerstaff encephalitis	Ataxia, ophthalmoplegia, hyperreflexia, and impaired consciousness	~70
GBS	Weakness, sensory loss, areflexia, cranial neuropathy	~25

About 20 % of patients with Miller Fisher syndrome have followed *C. jejuni infection* and 8 % followed *H. Influenzae* infection [209, 210]. The majority of patients peak at a median of 1 week and improvement starts at a median of 2 weeks [211]. Most patients are recovered completely by 6 months.

Miller Fisher Syndrome (MFS) and Bickerstaff's encephalitis with variable CNS and PNS involvement are considered now part of a continuous clinical spectrum with a common pathogenesis related to the presence of anti-GQ1b antibody. Ataxia and ophthalmoplegia are common to both conditions. Impaired consciousness and upper motor neuron signs are more characteristic of Bickerstaff's encephalitis. The current hypothesis is that this antibody reaches the brainstem via area postrema, attacking the reticular formation and corticospinal tract, among other structures. Hyperreflexia and Babinski's sign are present in 1/3 of the Bickerstaff's encephalitis patients. CSF albuminocytological dissociation occurs in around 25 % of patients during the first week of illness, increasing to 50 % in the second week. Pleocytosis is present in 30 % of cases, much more frequently than in the Fisher syndrome (around 5 %). MRI detects CNS lesions (brainstem and cerebellum) in 1/10 of the Bickerstaff's encephalitis patients [205]. Elevated anti-GQ1b antibody is seen in up to 70 % of patients with Bickerstaff's encephalitis (see Table 28.11).

Immunotherapy has been found to be effective only in retrospective studies [202, 212, 213]. IVIG slightly hastens the recovery of ophthalmoplegia and ataxia, but does not seem to influence patients' outcomes, presumably because of the good natural history of Fisher syndrome. However, plasma exchange or IVIG should be administered as early as possible when the disorder overlaps with GBS or Bickerstaff brainstem encephalitis, because these conditions may not have as good a natural course as the Fisher syndrome [202]. Animal models of MFS with transference of GQ1b antibodies have showed efficacy of C5 complement inhibitors as

promising treatment. Clinical application in human being is yet to be reported [214, 215].

Ataxic Variant (Acute Ataxic Neuropathy)

In 1962, Richter quoted the term ataxic GBS and described a patient with acute severe "cerebellar type ataxia" without proprioceptive sensory loss or ophthalmoplegia [216]. This group of patients presents with a rapid-onset ataxia, hypo- or areflexia, distal paresthesias, and CSF albuminocytological dissociation [206]. They have negative Romberg test with intact proprioception, and 65 % of them have elevated GQ1b antibodies (see Table 28.11). SNAPs are intact in 60 % and reduced or absent in the rest [206]. Clinically, this variant is similar to the Miller Fisher syndrome, except for the lack of ophthalmoplegia and reduced occurrence of elevated GQ1b antibodies (65 % vs. 98 % in Miller Fisher syndrome). Another group of acute ataxic patients, labeled "acute sensory ataxic neuropathy", has similar presentation but positive Romberg test and marked proprioceptive sensory loss [217, 218]. About 90 % of these patients have low-amplitude or absent SNAPs [206]. Antibodies against the epitopes GQ1b or GD1b are present in about 50 % of these patients. It is now likely that the ataxic GBS, originally described by Richter, and the acute sensory axonal neuropathy form a continuous spectrum and represent an incomplete form of the Miller Fisher syndrome with similarly good prognosis. Some authors recently proposed the terms "acute ataxic neuropathy" [206] or "acute sensory axonopathy-ganglionopathy" to encompass both of these disorders [219]. The main differential diagnoses of ataxic GBS are subacute paraneoplastic sensory neuronopathy (anti-Hu syndrome), Sjögren syndrome, pyridoxine intoxication, and vitamin B12 and thiamine deficiency. Anecdotal reports have shown improvement with IVIG or plasma exchange [206].

Pharyngeal-Cervical-Brachial Variant

A regional pattern of weakness of the cervical, brachial, and oropharyngeal muscles exclusively is a rare variant of GBS [143, 220]. The clinical picture is characterized by a recent history of viral illness followed by severe weakness limited to pharyngeal and neck muscles at the onset, with spread to the arms and legs only after several weeks. However, upper limb weakness may sometimes precede the dysphagia. Muscle power, reflexes, and sensation are entirely spared in the legs. Facial weakness and respiratory failure also may occur, thus simulating a disorder of neuromuscular transmission. Curiously, ptosis is almost universal, further emulating myasthenia gravis [143, 184]. Ophthalmoparesis is rare. Aspiration is a common complication and most require intubation for airway protection. The CSF protein concentration is usually slightly increased. About half of the patients exhibit elevated anti-GT1a antibodies, perhaps reflecting an immune attack that is restricted to nerves with that particular epitope serving as an antigenic target [221]. Antibodies against GQ1b are also present in around a third of patients [221]. Nerve conduction studies may demonstrate demyelinating and axonal changes limited to the upper limbs. The blink reflexes are very useful and often show demyelinative changes that are commensurate with the severity of facial paralysis. Some patients with the pharyngeal-cervical-brachial variant of GBS show low-amplitude distal CMAPs and SNAPs and partial motor conduction blocks which normalized within 4 weeks [222]. This is consistent with reversible conduction failure in both motor and sensory fibers which can account for a better prognosis and similar to what is observed in AMAN. In the rest of the patients, recovery may take months and many patients need a gastrostomy tube for nutritional support and a tracheostomy for airway management. Case reports have shown improvement with IVIG or plasma exchange [223].

Multiple Cranial Neuropathy Variant

This GBS variant is characterized by acute onset of multiple cranial nerve dysfunction, multiple ocular motor nerve palsies, and facial and bulbar dysfunction [224]. This form accounts for around 5 % of GBS patients in Taiwan [224]. The findings are often due to involvement of individual cranial nerves, often bilaterally and symmetrically. This also helps distinguish this from the pharyngeal-cervical-brachial variant of GBS. Bilateral IX, X, and XI cranial nerve impairment, resulting in dysphagia, laryngopharyngeal discomfort, and slurred speech, is the initial symptom in most cases [203]. The second most common mode of presentation is facial nerve palsy, which is usually bilateral and of the peripheral type [223]. Complete or partial bilateral extraocular nerve palsies may later develop. Although not initially present, within 2–3 weeks most patients will develop sensory symptoms and limb weakness. Areflexia is usually present.

CSF analysis shows the characteristic albuminocytologic dissociation in half of the patients in the first week after disease onset, a somewhat higher rate and earlier occurrence than that seen in typical GBS [223]. Most case series report abnormalities in motor and sensory conduction velocities and abnormal F-wave responses. The characteristic rapid, progressive course with respiratory paralysis makes early recognition and prompt treatment very important. IVIG was effective in most case series and this is considered the preferred therapy [223, 224].

Facial Diplegia with Paresthesias

A syndrome of acute-onset facial diplegia often associated with distal limb paresthesias is another GBS variant [225]. Other cranial nerve involvements, limb weakness, or ataxia are absent. The majority of patients have hyporeflexia, while hyperreflexia has been described in this syndrome [226, 227]. More than 2/3 of them have a preceding infectious illness. One-third of the patients have positive serology for a recent CMV infection. All the patients had elevated CSF protein. Nerve conduction studies shows demyelinating changes in limb nerves in 60 % of patients. Favorable outcome occurred in the majority of patients and in some have residual facial weakness [225].

Paraparetic Variant

Another regional variant of GBS has features of isolated leg weakness and areflexia simulating a cauda equina or spinal cord syndrome [143]. The arms, ocular, facial, and oropharyngeal muscles are spared, and sphincteric function is normal. Radicular leg pain is common and may be severe, but other sensory features are more variable. The spinal fluid protein level is elevated in the majority. EDX studies show typical demyelinating features of GBS restricted to the legs. MRI of the spinal cord and lumbar roots should be obtained in these patients to exclude a lesion of the caudal spinal cord or cauda equina. Imaging may also show gadolinium enhancement of the lumbosacral nerve roots, as also occurs in many typical GBS cases [124].

Acute Pandysautonomia (Acute Autonomic Neuropathy)

An acute autonomic neuropathy is thought to be another rare variant of GBS [184, 228, 229]. Gastrointestinal symptoms are commonly the initial features, namely, abdominal pain, vomiting, constipation, or diarrhea, all following a viral syndrome. Gastroparesis or abdominal distention with an ileus may develop. Patients complain of lightheadedness due to orthostatic changes in blood pressure following positional changes, and in extreme forms, severe orthostatic hypotension with recurrent syncope are seen. Additional manifestations that are acquired in the first week or two include erectile dysfunction, urinary frequency, urgency, and retention; vasomotor instability with acrocyanosis; and reduced salivation, lacrimation, or sweating. Sensation is normal initially but most patients develop various degrees of sensory impairment without motor dysfunction [230]. The sensory symptoms tend to be segmental and asymmetrical, often associated with pain. The majority of patients have reduced or absent deep tendon reflexes after several weeks. Routine nerve conduction studies are typically normal or show reduced SNAPs particularly in patients with sensory ataxia. Specialized testing of autonomic functions (heart rate variability testing, quantitative axon reflex studies, tilt table testing) are abnormal. The CSF protein concentration is usually mildly elevated. Combined sensory and autonomic GBS variants are probably common [219, 231].

In order to diagnose this condition, one has to rule out a large number of disorders that may cause autonomic dysfunction (cancer, multiple system atrophy, Parkinson's disease, amyloidosis, and others). Autoantibodies specific for nicotinic acetylcholine receptors in the autonomic ganglia are present in about 30 % of the paraneoplastic form and 50 % of the idiopathic autonomic ganglionopathies [232]. The seropositive group has less frequently a preceding viral illness but more frequently a subacute onset, abnormal pupillary responses, sicca complex, and lower gastrointestinal dysautonomia [233].

This GBS variant characteristically progresses and then plateaus after a few weeks, and approximately half the patients recover slowly after several months. There have been case reports of improvement with immunomodulatory therapy, including plasmapheresis or infusion of IVIG [234–236].

Other Possible GBS Variants

A number of other peculiar constellations of neuropathic disorders that develops acutely, often after a minor infectious illness, are possible variants of GBS. These conditions begin acutely, are mostly bilateral in one region, evolve over days or weeks, and are monophasic. Most are associated with an elevated spinal fluid protein concentration without a cellular response and with features of demyelination on EDX studies. These syndromes include acral paresthesias with diminished reflexes in either the arms or legs, abducens nerve palsies with distal paresthesias and hypo- or areflexia, isolated ophthalmoplegia (e.g., asymmetric oculomotor nerve palsies), and bilateral foot drop with upper limb paresthesias [237, 238]. A small fiber sensory neuropathy was also described and considered by some authors to be a GBS variant [239, 240]. The outcome in these patients was favorable.

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Chronic Inflammatory Demyelinating Polyradiculoneuropathy and Related Disorders

29

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Introduction

The chronic acquired demyelinating polyneuropathies constitute a rather heterogeneous group of disorders of the peripheral nervous system whose common feature is demyelination of peripheral nerves. They may be symmetric or asymmetric, predominantly motor, predominantly sensory, or sensorimotor. Most patients with these disorders can be treated successfully. The first disorder described within this group is chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Other different clinical phenotypes have been subsequently identified and were variably considered to be variants of CIDP or separate clinical entity. Major related disorders which are currently considered to be a variant of CIDP are the Lewis–Sumner syndrome (multifocal acquired demyelinating sensory and motor neuropathy, MADSAM neuropathy), distal acquired demyelinating symmetric neuropathy (DADS neuropathy), purely motor CIDP, purely sensory CIDP including chronic immune sensory polyradiculopathy (CISP), and focal CIDP. Other chronic acquired demyelinating neuropathies are considered separate diseases from CIDP and include multifocal motor neuropathy (MMN) and demyelinating neuropathy associated with an IgM monoclonal gammopathy, mostly of undetermined significance (MGUS), with antibody activity against the myelin-associated glycoprotein (MAG). This is in contrast to CIDP associated with IgG or IgA MGUS that is considered a form of CIDP associated with other diseases.

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Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a chronic disorder of the peripheral nervous system. A variety of names have been used to describe CIDP over the years, including chronic relapsing polyneuropathy, chronic relapsing Guillain–Barré polyneuritis, relapsing corticosteroid-dependent polyneuritis, steroid-responsive recurrent polyneuropathy, chronic relapsing polyneuritis, and chronic inflammatory polyradiculoneuropathy [1–4]. The disease may have either a relapsing or progressive course, and, after the initial reports on its response to steroids [5, 6], it has been now shown that it improves after therapy with steroid, plasma exchange, or high-dose intravenous immunoglobulin (IVIg) [7–9]. Several large series of patients with CIDP reported in the last years have provided insight into the clinical presentation, electrodiagnostic findings, clinical course, and prognosis [10–15]. In addition, a number of recent reviews addressed the most important aspects of the disease [16–19] and analyzed its possible variants [20–22].

Prevalence

The prevalence of CIDP ranges in different studies from 0.8/100,000 in Japan [23] to 1.32/100,000 in England [24]; 3.5/100,000 in Piedmont, Italy [25]; and 8.9/100,000 in Olmstead County, USA [26], with an annual incidence ranges from 0.50 to 1.60 per 100,000. These differences are probably more related to the use of different diagnostic criteria (see below) [27] than to geographical diversity. CIDP may affect individuals at any age ranging from early childhood to the ninth decade though the mean age of onset ranges from 30 to 50 years. The disease is slightly more common in men than in women.

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Etiology and Pathogenesis

There is a general consensus that CIDP is an immune-mediated disorder affecting peripheral nerve myelin even if this has not been yet formally proved [17–19, 28]. This hypothesis is supported by several observations and data. The onset and relapses are sometime triggered by infections or immunizations which were reported in 20–30 % of the patients and inclusive of upper respiratory infections, gastroenteritis, other infections, vaccinations, surgery, and trauma [10, 13–15, 29–32]. More recent epidemiological studies showed, however, that the prevalence of antecedent infection is around 10 % and does not differ from what was observed in the control population [25]. Patients who developed CIDP after vaccination have been reported, however, to have an increased risk of relapse after vaccination [31]. These figures are, though, different from what were observed in the Guillain–Barré syndrome (GBS) where the incidence of antecedent events ranges from 60 to 70 % [33, 34]. Pathological studies on nerve biopsy of affected patients (see below) reveal the presence of infiltrates of macrophages and T cell infiltrates and of immunoglobulin deposits [16]. In addition, it was recently shown that the T cell receptor repertoire of infiltrating cells has a strong mono- or polyclonal restriction which corresponds to that of circulating T cells favoring an antigen-driven T cell attack [35]. Serum and cerebrospinal fluid levels of cytokines are often increased in CIDP and, in particular, those associated with cellular (Th1) immunity [36, 37]. On the other side, antibodies against several myelin antigens including the glycolipids GM1, LM1, asialoGM1, sulfatide, and chondroitin sulfate and the proteins P2, P0, PMP22, and β-tubulin have been reported in patients with CIDP [37–46] even if none of these antibodies was convincingly shown to be more frequent or consistently associated with CIDP [28]. Experimental studies on animals have demonstrated a similarity of CIDP with chronic experimental allergic neuritis (EAN) [47] induced in Lewis rat by immunization with the protein P0 or P2 and in rabbit with myelin or galactocerebroside C. Most importantly, however, the vast majority of patients with CIDP improve after receiving immune therapies (see below).

Clinical Presentation

CIDP is a chronic disorder that may have either a chronic progressive or a relapsing course. As in the case of multiple sclerosis, young patients tend to have a relapsing course, while older patients more frequently have a chronic progressive course [48]. This distinction is not always easy with available current therapies since patients with a progressive course may deteriorate after therapy suspension or reduction mimicking a relapse while this is only a wear-off effect of therapy. Initial symptoms may progress over several weeks to months, though in some patients a rapid progression over a few days or weeks leads to the diagnosis of GBS. These patients are initially treated and respond to therapy as if they had GBS even if the subsequent relapsing course eventually leads to the diagnosis of CIDP. Acute-onset CIDP may occur in up to 16 % of all CIDP patients and should be suspected if deterioration continues >2 months from onset or if ≥3 treatment-related fluctuations occur in GBS patients [49]. Prominent sensory symptoms and signs at presentation should also raise this suspicion [50]. These patients were initially considered to have GBS that had subsequently become chronic while they are now considered to have a GBS-like onset CIDP. This is also supported by the observation that during the course of the disease, a few patients may have subacute relapses leading them to a wheelchair in only a few days. The initial diagnosis of CIDP is, however, often delayed after the initial presentation by, in some series, 12–24 months [15, 29].

Most patients with CIDP present with sensory and motor symptoms, although a minority of them present predominantly with motor or sensory involvement. Over 90 % of patients have weakness at presentation. This may be severe in 17 % of patients resulting in marked disability and total dependence [15]. Numbness and paresthesias, usually of the feet and hands, occur at onset in 64–82 %. Pain at onset is less frequent but may occasionally be the presenting symptom [51]. Gait unbalance and upper-limb tremor may also occur in some patients. Cranial nerve symptoms, including dysarthria, dysphagia, facial numbness, facial weakness, blurred or double vision, and ptosis, occur in a minority of patients [10, 13–15], even if these are the symptoms that might raise the suspicion of CIDP in a patient with chronic neuropathy. Respiratory failure may seldom occur in CIDP [52]. When inquired, over 80 % of the patients reported fatigue as a major symptom [53], and this may occasionally be the presenting symptom when weakness is not yet present [54]. Symptoms of dysautonomia are considered uncommon [13], even if impotence [10] and micturition manifestations, including voiding difficulty, urgency, frequency, and incontinence, have been reported in up to 25 % of the patients [55]. More recent data shows however that symptoms of a usually mild autonomic dysfunction may be present in 65 % of the patients [56].

On examination, proximal and distal weakness is common, usually in a symmetric manner. The presence of proximal weakness is indeed considered one of the clues to the clinical diagnosis of CIDP in patients with chronic neuropathy. Distal weakness is, however, more common and severe than proximal weakness. Reflexes are classically deemed to be absent in CIDP even if total areflexia only occurs in 70 % of patients. Most other patients have a mixture of decreased and absent reflexes with ankle reflexes being most often

absent. Sensory deficits are present in over 80 % of patients, with vibratory impairment more common than deficits to pinprick. A postural action tremor in upper-limb and gait ataxia is seen in some patients. Cranial nerve dysfunction occurs in up to 16 % and may include ophthalmoplegia, facial weakness, and bulbar weakness. Papilledema may occur [10, 13–15]. In occasional patients, nerve root hypertrophy may lead to cervical myelopathy [57] or lumbar radiculopathy [58–60].

CIDP is a severe disease. In previous studies, 11 % of the patients were reported to die from CIDP, 11 % to be in a wheelchair or in bed at last follow-up, and 64 % to be ambulatory and working [10]. Subsequent studies showed that 73–87 % of patients had a good recovery and were independent [13, 61], with a death rate from CIDP of 3–6 % [13, 14, 61]. Recent epidemiologic studies showed that over 50 % of the patients have at least temporary severe disability in the course of the disease including temporary restriction to a wheelchair or inability to walk without support and approximately 10 % eventually become persistently disabled or die because of the illness [24, 25]. A few patients have, however, a disturbing but functionally indolent course with minimal weakness and minor sensory symptoms and are considered to have a clinically minimal and sometime asymptomatic CIDP [62].

Diagnosis of CIDP

Even if the diagnosis of CIDP is often easy in clinical practice, the use of expensive therapies for this disease and the description of a number clinical variants have led to the necessity to define the clinical boundaries of this neuropathy in order to avoid the inappropriate use of expensive therapies but at the same to include under this diagnosis the largest proportion of patients who might benefit from immune treatment. This is why, even if CIDP is not a common disease, at least 17 diagnostic criteria for CIDP [17, 63] have been proposed in the last few years. These selective criteria try to achieve the best compromise between the desire to include under this diagnosis, and treat, as many patients as possible and to avoid the inclusion of patients with similar but different neuropathies and the consequent expectation of potential benefit from ultimately ineffective therapies. For the same reason, despite the presence of a number of differences, variants of CIDP were variably included under the term of CIDP to allow affected patients to be reimbursed for the same therapies of CIDP. Most of these criteria have similar clinical feature and differ in term of the electrophysiological criteria necessary for its diagnosis [63]. Recently, Koski and colleagues [64] proposed a new set of criteria which also allowed the diagnosis of CIDP on clinical ground only. The presence of a symmetric neuropathy affecting four limbs with proximal weakness in at least one limb in the absence of a serum paraprotein or documented genetic abnormality was considered sufficient for the diagnosis. It was recently shown, however, that the sensitivity of these criteria (63 %) for the diagnosis of CIDP [65] was higher than that of the criteria of the American Academy of Neurology (45.7 %) [66] but lower than that of the European Federation of Neurological Sciences and Peripheral Nerve Society (EFNS/PNS) (81.3 %) [67] with a comparable specificity. The recently revised criteria of the EFNS/PNS (Tables 29.1, 29.2, and 29.3) have the great advantage of including patients with typical and atypical presentation of CIDP including a number of variants and of allowing the diagnosis of CIDP even in patients with demyelinating abnormalities in a single nerve when other supportive criteria for the diagnosis of CIDP are present. A few aspects of these diagnostic criteria will be now addressed.

Table 29.1 EFNS/PNS (2010) clinical diagnostic criteria for CIDP [67]

(1) Inclusion criteria
(a) Typical CIDP
Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 months; cranial nerves may be affected
Absent or reduced tendon reflexes in all extremities
(b) Atypical CIDP (still considered CIDP but with different features). One of the following, but otherwise as in (a) (tendon reflexes may be normal in unaffected limbs):
Predominantly distal (distal acquired demyelinating symmetric, DADS)
Asymmetric (multifocal acquired demyelinating sensory and motor neuropathy [MADSAM], Lewis–Sumner syndrome)
Focal (e.g., involvement of the brachial or lumbosacral plexus or of one or more peripheral nerves in one upper or lower limb)
Pure motor
Pure sensory (including chronic immune sensory polyradiculopathy affecting the central process of the primary sensory neuron)
(2) Exclusion criteria
Prominent sphincter disturbance
Lyme disease (Borrelia burgdorferi infection), diphtheria, drug or toxin exposure likely to have caused the neuropathy
Hereditary demyelinating neuropathy
Multifocal motor neuropathy (MMN)
IgM monoclonal gammopathy with high-titer antibodies to myelin-associated glycoprotein (MAG)
Other causes for a demyelinating neuropathy including POEMS syndrome, osteosclerotic myeloma, diabetic and nondiabetic lumbosacral radiculoplexus neuropathy, PNS lymphoma, and amyloidosis

Clinical Criteria

All the criteria for CIDP, as well as some clinical series [10, 14], require a minimum 2-month period of symptoms. Others have accepted a shorter period of progression.

Table 29.2 EFNS/PNS (2010) electrodiagnostic criteria for CIDP [67]

(1) Definite: at least one of the following
(a) Motor distal latency prolongation ≥ 50 % above ULN in 2 nerves (excluding median neuropathy at the wrist from carpal tunnel syndrome)
(b) Reduction of motor conduction velocity ≥ 30 % below LLN in 2 nerves
(c) Prolongation of F-wave latency ≥ 20 % above ULN in 2 nerves (≥ 50 % if amplitude of distal negative peak CMAP <80 % of LLN values)
(d) Absence of F-waves in 2 nerves if these nerves have distal negative peak CMAP amplitudes ≥ 20 % of LLN + ≥ 1 other demyelinating parameter[a] in ≥ 1 other nerve
(e) Partial motor conduction block: ≥ 50 % amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP ≥ 20 % of LLN, in 2 nerves, or in 1 nerve + ≥ 1 other demyelinating parameter[a] in ≥ 1 other nerve
(f) Abnormal temporal dispersion (>30 % duration increase between the proximal and distal negative peak CMAP) in ≥ 2 nerves
(g) Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in ≥ 1 nerve (median ≥ 6.6 ms, ulnar ≥ 6.7 ms, peroneal ≥ 7.6 ms, tibial ≥ 8.8 ms) + ≥ 1 other demyelinating parameter[a] in ≥ 1 other nerve
(2) Probable
≥ 30 % amplitude reduction of the proximal negative peak CMAP relative to distal, excluding the posterior tibial nerve, if distal negative peak CMAP ≥ 20 % of LLN, in 2 nerves, or in 1 nerve + ≥ 1 other demyelinating parameter[a] in ≥ 1 other nerve
(3) Possible
As in (1) but in only 1 nerve

CMAP compound muscle action potential, *ULN* upper limit of normal values, *LLN* lower limit of normal values
[a]Any nerve meeting any of the criteria (a–g)

Table 29.3 EFNS/PNS (2010) diagnostic categories for CIDP [67]

Definite CIDP
Clinical criteria 1 (a or b) and 2 with electrodiagnostic criterion 1
Probable CIDP + at least one supportive criterion[a]
Possible CIDP + at least two supportive criteria[a]
Probable CIDP
Clinical criteria 1 (a or b) and 2 with electrodiagnostic criterion 2
Possible CIDP + at least one supportive criterion[a]
Possible CIDP
Clinical criteria 1 (a or b) and 2 with electrodiagnostic criterion 3
CIDP (definite, probable, possible) associated with concomitant diseases

[a]*Supportive criteria for CIDP*
1. Elevated CSF protein with leukocyte count <10/mm3
2. MRI showing gadolinium enhancement and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses
3. Abnormal sensory electrophysiology in at least one nerve:
   (a) Normal sural with abnormal median (excluding median neuropathy at the wrist from carpal tunnel syndrome) or radial sensory nerve action potential (SNAP) amplitudes
   (b) Conduction velocity <80 % of lower limit of normal (<70 % if SNAP amplitude <80 % of lower limit of normal)
   (c) Delayed somatosensory evoked potentials (SSEP) without central nervous system disease
4. Objective clinical improvement following immunomodulatory treatment
5. Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination by electron microscopy or teased fiber analysis

McCombe et al. [13] found that 16 % of patients in their CIDP series reached a nadir within 4 weeks but went on to develop a relapsing or progressive course. Prineas and McLeod [11] found four CIDP patients whose nadir was reached in 2 months or less. Similarly, Simmons et al. [15] found that 16 of 77 patients (21 %) reached peak impairment less than 2 months after symptom onset, with a small number having an acute presentation indistinguishable from GBS. Treatment is often instituted less than 2 months after onset if the deficit was sufficiently severe and progressive. In these patients, the subsequent relapsing or progressive course supports the diagnosis before the classic 2 months even if theoretically none of the proposed criteria would allow the treatment of the patients as CIDP. A prominent sensory impairment is often helpful in distinguishing acute-onset CIDP from GBS [50].

Electrodiagnostic Studies

With the only exception of Koski's criteria, electrodiagnostic (EDX) studies have been always considered fundamental for the diagnosis of CIDP by demonstrating various typical features of demyelination in motor and sensory fibers. These criteria mainly differ in the number of abnormal nerves needed and in the degree of these abnormalities. Motor nerve conduction abnormalities are similar to those seen in GBS and generally demonstrate multifocal demyelination in motor nerves, characterized by prolonged distal latencies, slowed conduction velocities, prolonged F-wave latencies, and evidence of partial conduction block or abnormal temporal dispersion (Fig. 29.1). However, not all motor nerves demonstrate such abnormalities, due to the multifocal nature of the demyelination in CIDP. A review of the EDX studies of 70 patients who carried the diagnosis of CIDP found that only 48–64 % of those in whom a sufficient number of nerves were tested fulfilled the EDX criteria for CIDP, depending upon which criteria were used [68]. One of the advantage of the revised EFNS/PNS criteria [67] is to allow the diagnosis of definite CIDP even in the presence of a single motor nerve as far as two other supportive criteria are found (see Table 29.3). In addition, if EDX criteria for definite CIDP are not met initially, repeated study at a later date may help in the diagnosis. In any case, even if EDX tests are considered mandatory for the diagnosis of CIDP, they should be considered in conjunction with other clinical and laboratory features. Patients with POEMS or IgM monoclonal gammopathy with anti-MAG or anti-sulfatide antibodies also fulfill the EDX criteria for CIDP. The clinical presentation including skin changes and

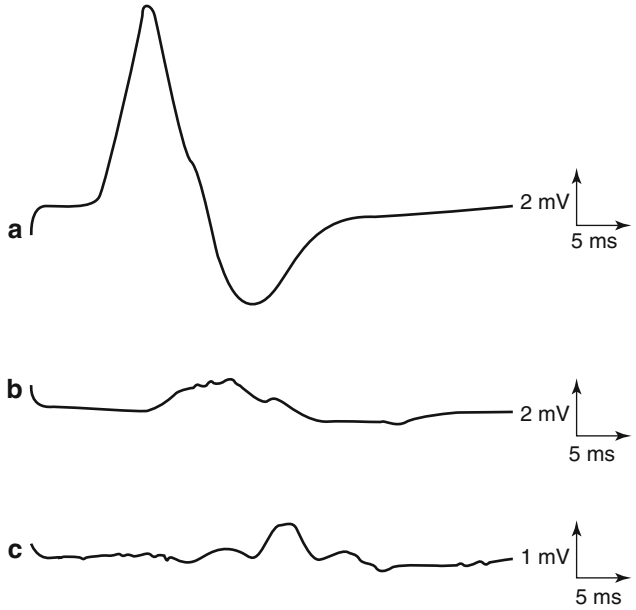

Fig. 29.1 Ulnar motor nerve conduction study in a CIDP patient, recording with surface electrodes over the abductor digiti quinti muscle and stimulating at the wrist (**a**), below elbow (**b**), and above elbow (**c**). There is a partial conduction block and abnormal temporal dispersion with proximal stimulation

serum VEGF levels may help in identifying patients with POEMS [69] while serum protein electrophoresis and antibody testing in patients with IgM monoclonal gammopathy (see below) [70]. Occasional patients with amyloidosis or nerve or root lymphoma may also have some EDX features suggestive for CIDP.

Electrodiagnostic studies of motor nerves are also helpful in distinguishing CIDP from hereditary demyelinating polyneuropathies (most commonly type I Charcot–Marie–Tooth disease) [71]. Patients with CIDP generally demonstrate differences in the degree of slowing of conduction velocity between different segments of a given nerve and between similar segments of different nerves, while those with hereditary neuropathies are more likely to demonstrate uniform slowing of conduction velocity both within and between nerves. In addition, temporal dispersion and conduction block on proximal stimulation are characteristics of acquired but not hereditary demyelinating polyneuropathies with the only exception of hereditary neuropathy with liability to pressure palsy (HNPP), which can be easily confirmed by demonstration of deletion of one allele of the PMP22 gene. Occasional patients with other forms of inherited neuropathy associated with conduction block have been, however, reported [72, 73].

Early reports demonstrated absent sensory responses in virtually all patients with CIDP [11, 12], but it is now clear that sensory responses vary from absent to normal [13, 15]. The most common sensory nerve pattern in CIDP is for both the median and sural sensory responses to be abnormal. An abnormal median sensory response in association with a normal sural sensory study may help to distinguish acquired demyelinating polyneuropathies such as CIDP from other neuropathies in the proper clinical setting [74], even if its specificity is quite low [75]. Similarly sensitive but also not specific is the reduction of sensory conduction velocities [76]. Somatosensory evoked potentials (SSEP) can be also useful in CIDP by demonstrating abnormal proximal sensory conduction, particularly in patients with sensory CIDP or with chronic immune sensory polyradiculopathy (see below) [77, 78].

The findings on needle electromyography (EMG) depend on the degree of secondary axonal degeneration. If there is no axonal loss, decreased recruitment may be the only finding. Otherwise, there may be variable amounts of acute and chronic partial denervation and reinnervation, including fibrillation potentials; positive sharp waves; high-amplitude, long-duration motor unit action potentials; and increased polyphasia [79]. Single-fiber EMG is often mildly abnormal in CIDP, demonstrating increased jitter in most patients and increased fiber density in a minority [80].

Cerebrospinal Fluid Analysis

Patients with CIDP generally have increased levels of proteins in the cerebrospinal fluid (CSF) with normal cell count (albuminocytologic dissociation). In large series of patients, CSF proteins were increased in 83–95 % of the patients with mean values ranging from 134 to 145 mg/dl and individual values varying between 20 and 1200 mg/dl [10, 13–15]. While most diagnostic criteria recommend CSF examination for the diagnosis of CIDP, this was only considered a supportive criteria by the EFNS/PNS [67] and was considered useful as supportive criteria only in patients in whom clinical and EDX criteria are not sufficient for the diagnosis of CIDP (see Table 29.3). This is not always accepted by neurologists who still consider this test fundamental in the diagnosis of CIDP. It is not so infrequent, however, to encounter patients with unclear EDX findings in whom a diagnosis of CIDP is based on increased CSF protein and who eventually prove to have POEMS, amyloidosis, lymphoma, or IgM monoclonal gammopathy.

Sural Nerve Biopsy Findings

As in the case of cerebrospinal fluid analysis, sural nerve biopsy is only considered by the EFNS/PNS as one of the supportive criteria for CIDP in patients in whom clinical and EDX criteria are not sufficient for the diagnosis of CIDP [67]. Supportive features for the diagnosis of CIDP are macrophage-associated demyelination, onion-bulb formation, demyelinated and to a lesser extent remyelinated nerve fibers, endoneurial edema, endoneurial mononuclear cell infiltration, and variation between fascicles [16]. Even if demyelination is relatively common, the degree of demyelination varies widely among patients [10, 11, 14, 81]. A study on a large series of

patients found that demyelination was the predominant histologic finding in only about half of the patients, while 21 % demonstrated predominantly axonal degeneration and 13 % a mixed axonal and demyelinating picture [14]. Another report indicated that demyelination was more severe than axonal degeneration in only half of 14 patients studied [81]. Dyck et al. [10] reported that Wallerian degeneration was the most common finding on nerve biopsy. A minority of biopsies demonstrate endoneurial mononuclear inflammatory infiltrates (commonly perivascular and usually rather mild), endoneurial edema, and onion-bulb formations. The presence of cluster of macrophages around endoneurial vessels in sural nerve biopsy was shown to represent an additional marker for the pathological diagnosis of CIDP [82]. Some patients with CIDP (15 %) have normal sural nerve biopsies [14], possibly reflecting a sampling error. In any case, sural nerve biopsy findings should be considered in the clinical context and cannot be relied upon in isolation to make the diagnosis of CIDP. It is also often recommended to perform sural nerve biopsy in patients with suspected CIDP not responsive to immune therapy in the context of a diagnostic reevaluation, even if this has not been formally proved to be effective. Sural nerve biopsy may be, however, useful in patients with a long-lasting story in whom several nerves are not excitable and therefore not helpful in the diagnosis of CIDP. In these patients nerve biopsy can help excluding axonal damaged caused by amyloidosis, nerve vasculitis, or lymphoma.

Radiologic Studies

Gadolinium-enhanced MRI of spinal roots and brachial or lumbar plexus may demonstrate hypertrophy and gadolinium enhancement of cervical and lumbosacral nerve roots in CIDP patients, some of whom have symptoms of radiculopathy, but also of brachial or lumbar plexus. The MRI findings appear to be due to demyelinating and remyelination with onion-bulb formation [58–60, 83–85]. This test is not recommended for patients with a definite clinical and EDX diagnosis of CIDP but may support the diagnosis in patients with inconclusive findings. Some recent report also suggests that nerve echography may help identify an increased size of nerve and may help support the diagnosis of CIDP [86, 87].

Response to Immune Therapy (See Below)

Response to immune therapy has been proposed to be a supportive criterion for the diagnosis of CIDP. This should be, however, considered with some caution since a few diseases that should be differentiated from CIDP including POEMS, IgM monoclonal gammopathy, and vasculitis may also improve with immune therapy. Response to therapy is particularly useful in patients in whom the EDX studies do not fulfill the diagnosis of CIDP for the absence of recordable nerves and not in those in whom recordable nerves are normal or show signs of axonal pathology.

Central Nervous System (CNS) Demyelination

Several patients with CIDP have been reported to have clinical, MRI, and electrophysiological (evoked potential) evidence of a CNS demyelination [88–90]. This has raised the hypothesis of a shared myelin antigen for both peripheral and CNS demyelination even if this has never been proved. The vast majority of patients with CIDP do not have evidence of a CNS demyelinating disease, either clinically or by MRI [91–93], and only occasional patients with multiple sclerosis have signs of CIDP. Unless signs of a possible involvement of CNS are present, patients with CIDP should not be routinely investigated for CNS abnormalities.

Variants of CIDP

Sensory CIDP

Some patients with CIDP may present with a pure sensory syndrome with a proportion in different series ranging from 5 to 15 % [20, 21]. Most of these patients have normal strength even if they also have EDX evidence of demyelination also on motor nerves [94–96]. A few patients have, however, a clinically and electrodiagnostically pure sensory neuropathy and are considered to represent the variant of sensory CIDP [97]. Follow-up studies in these patients reveal that while some of them evolve into a typical sensorimotor CIDP, others remain purely sensory even during long-term follow-up [18, 98]. The pathological features of CIDP were also reported on sural nerve biopsy in eight patients who presented with a clinical picture of cryptogenetic sensory neuropathy, four of whom improved with immune therapy [99]. It is, however, not so infrequent that patients with sensory CIDP have an unsatisfactory response to immune therapy and two patients were recently reported to deteriorate after plasma exchange [100].

A particular form of sensory CIDP is *chronic immune sensory polyradiculopathy* (*CISP*). This entity has been highlighted by Sinnreich et al. [78] who reported 15 patients who had only sensory symptoms for a few years with normal nerve conduction studies. Somatosensory evoked potentials were delayed, and CSF proteins were increased. Lumbar MRI revealed an enlargement of lumbar roots, and root biopsy confirmed the inflammatory nature of the process. All treated patients improved with IVIg or steroids.

Motor CIDP

A few patients have been reported to have purely motor impairment throughout the course of the disease [101, 102]. They represented 4–5 % of the patients with chronic demyelinating neuropathy, in two series of patients with CIDP [21]. There are, however, only a few reports of patients with motor CIDP, while most patients are only mentioned in series of patients with CIDP. Some patients have an asymmetric

presentation with partial conduction block and no slowing of motor conduction velocity that is somehow reminiscent of multifocal motor neuropathy (MMN) [101]. Even if motor CIDP is generally considered to be a variant of CIDP, most affected patients were reported to worsen after steroids and to improve with intravenous immunoglobulins [101–103] raising the possibility that this variant may represent more a diffuse variant of MMN (that also deteriorates under steroids) than a motor form of CIDP.

Focal CIDP

A few patients have been reported with a more restricted distribution of weakness and sensory loss which is often restricted to one or both arms. Thomas et al. [104] reported nine patients including five who had a sensorimotor impairment in one or both arms, one with a sensory monomelic impairment, and three with a purely motor impairment in one or two arms. One of these patients could be now considered to have MMN, while in the other patients impairment was not restricted to the distribution of individual nerves to raise the suspicion of Lewis–Sumner syndrome or of MMN. Seven of these patients improved with either steroids or IVIg. This clinical presentation is now classified as a focal variant of CIDP. A few other patients with upper-limb predominant multifocal CIDP have been reported even if the clinical features were more consistent with the diagnosis of Lewis–Sumner syndrome [105].

Lewis–Sumner Syndrome

In 1982, Lewis and colleagues [106] described five patients with a chronic, acquired, asymmetric sensorimotor demyelinating polyneuropathy which clinically resembled a mononeuritis multiplex. Electrodiagnostic studies demonstrated multifocal conduction block in motor nerves. CSF protein was normal to mildly elevated. Two patients were treated with prednisone and improved. Several similar patients have been subsequently reported under the name of Lewis–Sumner syndrome, motor and sensory demyelinating mononeuropathy multiplex, multifocal motor and sensory demyelinating neuropathy, multifocal inflammatory demyelinating neuropathy, and multifocal acquired demyelinating sensory and motor neuropathy (MADSAM neuropathy) [107–113]. This syndrome is now considered to be a variant of CIDP. It is, however, unclear why only 50 % of the affected evolve into CIDP within 4 years, while the remaining 50 % maintain a multifocal distribution [112].

There is no difference in age distribution compared to CIDP. Similarly to CIDP, patients have relapsing or progressive course. The arms are usually involved before the legs. Both weakness and numbness are present at onset in approximately 50–60 % of the patients, while 30 % of the patients have a selective sensory loss and 10 % a predominant motor impairment [112, 113]. The pattern of involvement is asymmetric, usually in the distribution of individual nerves as seen with mononeuritis multiplex. Pain is present in a minority. Cranial neuropathies occur in 10–20 % of the patients [112–114]. Reflexes are usually decreased in an asymmetric multifocal manner but rarely are completely absent [108, 109].

Electrodiagnostic studies in preliminary studies focused on the frequent presence of partial conduction block in motor nerve with normal conduction velocities [106]. Subsequent studies focused on the asymmetric mononeuropathy multiplex type of presentation with the concomitant presence of prolonged distal latencies, slowed conduction velocities, temporal dispersion, and prolonged F-wave latencies in an asymmetric manner. Sensory studies are abnormal as well. Needle EMG examination demonstrates active and chronic denervation. CSF protein levels are usually normal but may be mildly elevated in one-third of the patients [112], even if very high levels have been seldom reported. Anti-GM1 antibodies are either absent or present in less than 10 % of the patients [106–109, 112, 113]. Nerve biopsies demonstrate multifocal asymmetric demyelination as the primary process, and inflammatory infiltrates have been reported in some patients [110, 114, 115]. MRI imaging of the brachial plexus revealed in some patients swollen nerves and increased signal intensity on T2-weighted imaging [110].

Response to therapy is similar to CIDP (see below) even if more frequent response to IVIg than to steroids has been reported [112]. In a retrospective analysis on 120 patients, patients with a predominant impairment in arms had a more frequent response to steroids than to IVIg (74 % versus 52 %), while the reverse occurred in patients more impaired in lower limbs (25 % versus 80 %) [113].

Distal Acquired Demyelinating Symmetric (DADS) Neuropathy

Katz et al. [116] first introduced the term of DADS neuropathy to describe a group of patients with predominantly distal symmetric sensory ataxic demyelinating neuropathy. This clinical phenotype corresponded to what was observed in patients with neuropathy associated with IgM monoclonal gammopathy and antibodies to the myelin-associated glycoprotein (MAG) (see later). Not all patients with this phenotype had, however, IgM monoclonal gammopathy [116] or anti-MAG antibodies [117]. Other patients with IgM monoclonal gammopathy and this phenotype had antibodies to sulfatide [118] even if the specificity of this reactivity is still matter of controversy. This clinical pattern is now considered to represent a clinical phenotype more than a definite syndrome, and patients without IgM monoclonal gammopathy or anti-MAG antibodies are now considered to have a DADS variant of CIDP [117]. These patients have a chronic, slowly progressive polyneuropathy characterized by distal sensory loss, gait ataxia, normal strength or mild distal weakness, and demyelinating features on nerve conduction studies, generally

without conduction block. They have low motor conduction velocities and prolonged distal motor latencies. There is often an associated action tremor. Similarly to what was observed in patients with anti-MAG neuropathy, these patients tend to have a less satisfactory response to the therapy than was observed in patients with typical CIDP [22, 116].

CIDP with Associated Diseases

CIDP may coexist with a number of other diseases. In most of these conditions, the pathogenesis and pathology of CIDP are thought to be the same as in CIDP without a concomitant disease (usually referred to as idiopathic CIDP) [67]. These diseases include diabetes mellitus, HIV infection, chronic active hepatitis, IgG or IgA monoclonal gammopathy of undetermined significance (MGUS), systemic lupus erythematosus or other connective tissue diseases, sarcoidosis, thyroid disease, inflammatory bowel disease, membranous glomerulonephritis, or organ transplantation. In these conditions, treatment is the same than in idiopathic CIDP with the only caution derived from the possible effect of treatment on the associated condition.

In other conditions, the pathogenesis and pathology may be different from idiopathic CIDP and treatment is mainly directed at treating the associated disease. These include infection with Borrelia burgdorferi (Lyme disease), IgM monoclonal gammopathy with antibodies to myelin-associated glycoprotein (MAG) or other antigens, POEMS syndrome, osteosclerotic myeloma, and hematological and non-hematological malignancies, including lymphoma and Castleman's disease.

Some specific aspects of these related or unrelated conditions are addressed below, while neuropathy associated with anti-MAG antibodies will be addressed in a separate section.

Diabetes Mellitus

Patients with diabetes may develop a symmetric sensorimotor polyneuropathy which fulfills research criteria for CIDP. It is important to recognize CIDP in diabetic patients, since this neuropathy responds to immunomodulating therapy [119, 120]. It has been widely discussed in the recent years whether the prevalence of diabetes is increased in patients with CIDP or whether the prevalence of CIDP is increased in patients with diabetes. It has been also discussed whether patients with diabetes and CIDP have a different response to therapy [120]. Two recent epidemiological studies have shown that the association of these two diseases is not higher than would be expected from a casual association [26, 121]. It is, however, important to consider that diabetes is a contraindication to steroid therapy which should be avoided or used with caution in patients with CIDP and diabetes. In addition, steroids may induce diabetes in patients with a familial history of diabetes or glucose intolerance. In patients not responsive to the other effective therapy for CIDP, including IVIg and plasma exchange, a course of steroid should be not, however, denied even if blood glucose levels need to be strictly monitored in these patients and therapy accordingly adapted. A similar caution should be given to patients with CIDP and chronic active hepatitis.

IgM Monoclonal Gammopathy

The association of IgM monoclonal gammopathy of undetermined significance (MGUS) with a demyelinating neuropathy has been known for several years, and the pathogenetic relevance of this association has been widely debated [70]. It is now accepted that patients with a demyelinating neuropathy associated with IgM monoclonal gammopathy with IgM antibodies to the myelin-associated glycoprotein (MAG) have a distinct disorder caused by the binding of these antibodies to nerve. This neuropathy will be separately addressed.

More controversial is the association of neuropathy with IgM monoclonal antibodies directed against other neural antigens. IgM antibodies to sulfatide antibodies were originally associated with an axonal neuropathy [122] even if, in subsequent studies, they were associated with sensorimotor demyelinating neuropathy with prominent limb weakness and gait ataxia [118, 123, 124]. The clinically heterogeneous association of this reactivity has induced some skepticism on the pathogenetic relevance of this reactivity so that the EFNS/PNS did not consider it a causal factor for the neuropathy in patients with IgM monoclonal gammopathy [70] or an exclusion criterion for the diagnosis of CIDP. Morphological studies on nerve biopsy showed, however, in some patients the same abnormalities observed in patients with anti-MAG antibodies including abnormally spaced myelin lamellae and myelin deposits of the M-protein and complement [118, 125] supporting the hypothesis of a similar pathogenetic mechanism. In our opinion, unless a patient with IgM monoclonal gammopathy with or without anti-MAG antibodies has a clinical relapsing course compatible with the clinical diagnosis of CIDP, he/she should be considered to have a separate disease from CIDP and treated as patients with anti-MAG neuropathy.

IgG and IgA Monoclonal Gammopathy

It has been debated for several years whether patients with otherwise typical CIDP and IgG or IgA MGUS should be distinguished from patients with idiopathic CIDP and should require different therapies. Even if some clinical differences between the two groups have been observed by some [61, 126] but not other authors [29], there is little evidence that the presence of IgG or IgA MGUS has a role in the neuropathy or that it may affect its treatment [127]. A few reactivities of IgG or IgA M-proteins with nerve antigens have been reported in these patients, but these were seldom confirmed or were equally frequent in patients with and without

neuropathy [128]. In addition, in most patients the M-protein becomes manifest several months to years after onset of the neuropathy [128], making it unlikely a causative role of the M-protein in the neuropathy. The panel of experts of the EFNS/PNS concluded that patients with CIDP associated with IgG or IgA MGUS should be considered indistinguishable from patients with idiopathic CIDP and treated in the same way [67]. These patients have indeed an identical response to therapy compared to patients with CIDP with more than two-thirds of them responding to the same immune therapies known to be effective in CIDP [129] including steroids, IVIg [130], and plasma exchange [131].

HIV Infection

CIDP may occur early in the course of HIV infection and has clinical and EDX features similar to HIV-negative patients. The main distinguishing feature is that HIV-positive patients may have increased CSF cells compared to normal CSF cell count in HIV-negative patients and that HIV viral antigens can be found in the CSF. Prominent inflammatory infiltrates have been also reported in sural nerve biopsy. Effective treatments include intravenous immunoglobulin (IVIg), plasma exchange, and steroids [132].

Malignancies

CIDP has been reported in patients with pancreatic adenocarcinoma, rectosigmoid adenocarcinoma, cholangiocarcinoma, hepatocellular carcinoma, seminoma, melanoma [133–138], and hematological malignancies [139–141]. Some of these patients improved with treatment of the malignancy or with prednisone. It has been debated whether CIDP may be considered a paraneoplastic neuropathy or whether this association is merely casual. In a recent epidemiological study, 12/294 (4 %) patients with a diagnosis of CIDP or idiopathic demyelinating neuropathy had a malignancy [25]. The data from an aged-matched control population was not, however, available. Some interest derives from the association of malignant melanoma with CIDP that may improve with prednisone [137, 138]. A possible causal relationship was given by the observation that melanoma and Schwann cells are both of neuroectodermal origin and that they share surface antigens including the ganglioside GM2 [138], suggesting that in some patients a mechanism of molecular mimicry might have played a role in the induction of CIDP.

Diagnostic Evaluation of the Patient with Suspected CIDP

As for any patient, a comprehensive history and physical examination are keys in the evaluation of patients with suspected CIDP and should help the differential diagnosis. If CIDP is suspected on the basis of a relapsing course, a progressive impairment which might not be as slow as usually observed in other chronic acquired neuropathy or proximal muscle weakness, motor and sensory nerve conduction studies are usually sufficient to establish the diagnosis of CIDP. When, however, nerve conduction studies do not show unequivocal signs of multifocal demyelination with reduced conduction velocities, increased latencies, and conduction block, the diagnosis of CIDP may be supported by cerebrospinal fluid examination which might disclose an increase of CSF proteins with normal cells. MRI may be also helpful by revealing gadolinium enhancement or hypertrophy of spinal roots and brachial or lumbosacral plexus. As mentioned above, sural nerve biopsy is not necessary in most patients with suspected CIDP, since the findings are neither sensitive nor specific. In addition, it is an invasive procedure technique that should be probably considered only when other tests are inconclusive. In these patients nerve biopsy may occasionally identify vasculitis, amyloidosis, sarcoidosis, or neoplastic infiltration of the nerve.

Other laboratory tests may be done to exclude other possible causes for either a demyelinating neuropathy or axonal neuropathy [67]. In patients with a demyelinating neuropathy, serum and urine immunofixation or immunoelectrophoresis and serum immunoglobulin dosage should be performed looking for a monoclonal gammopathy in the serum and Bence-Jones proteins in the urine. If immunofixation reveals a previously unknown paraproteinemia, evaluation by a hematology specialist is warranted. In these patients skeletal surveys, looking for the possibility of osteosclerotic myeloma should be also considered [67, 70]. If the IgM level is elevated, antibody titers to myelin-associated glycoprotein (MAG), sulfatide, and disialoglycolipid such as GD1b or GQ1b should be determined [70]. Serum VEGF levels may help exclude the diagnosis of POEMS syndrome in patients with other possible features of this syndrome including a tanned skin, recent cutaneous hemangiomata, distal edema, recent thrombocytosis, hepatomegaly or splenomegaly, recent onset of severe diabetes, or other endocrinopathy [69]. Signs of cardiomyopathy, renal dysfunction, or autonomic impairment may raise the suspicion of amyloid neuropathy which should be investigated with periumbilical fat biopsy or genetic test to exclude transthyretin mutation. Genetic test for PMP duplication, connexin 32 mutation, or P0 mutation should be considered in patients with a very slowly progressive demyelinating neuropathy without conduction block and negative or unclear history of familial neuropathy.

In patients with an axonal neuropathy, the diagnosis of CIDP is often excluded unless the patient has a very long-lasting disease that might have led to secondary axonal degeneration. In these patients increased sedimentation rate, C-reactive protein, antinuclear factor (ANA), anti-extractable nuclear factor (ENA) and antinuclear cytoplasmic (ANCA) antibody, and complement levels may help exclude a vasculitic neuropathy [142]. A blood glucose level and a glycosylated hemoglobin or glucose tolerance test should be

performed to exclude diabetes. Even if a positive test does not exclude the diagnosis of CIDP (see above), this diagnosis should not be probably considered in a patient with axonal neuropathy. Screening tests for other causes of polyneuropathy [67], including thyroid function tests, vitamin B12 level, VDRL, antibodies to hepatitis C or B virus, and, in some geographic regions, Lyme titer, are helpful. Patients with a risk for HIV infection or with a significant CSF pleocytosis should be evaluated for HIV infection. Angiotensin converting enzyme is usually considered useful in the diagnosis of sarcoidosis. This diagnosis is usually considered in the presence of a pulmonary symptoms with evidence of enlarged lymph node on chest CT and can be only confirmed by the biopsy of an affected lymph node.

Tests to search for an associated condition should be only performed in the presence of suggestive symptoms, while the search for an underlying malignancy should be only considered if other symptoms or laboratory tests raise the suspicion of their presence. If a superimposed CNS demyelinating disorder is suspected, CSF studies for multiple sclerosis can be helpful including MRI of the brain and spinal cord.

Treatment and Management

Several controlled studies and retrospective series on large series of patients and a few randomized controlled trials have shown the efficacy of steroids, plasma exchange, and IVIg in CIDP [7–9] with approximately 50–70 % of the patients responding to each of these treatments. In addition, almost 50 % of patients not responding to one of these treatments respond to the second therapy used leading to 80 % of the proportion of patients improving with these therapies [143, 144]. The efficacy of these therapies was confirmed in recent Cochrane Reviews [7–9] and in the recently updated guidelines of the EFNS/PNS [67]. Also, the efficacy of IVIg was set in a consensus statement of the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) [145] and in a more recent evidence-based guideline of the American Academy of Neurology (AAN) on the use of IVIg in neurological diseases [146].

It is often difficult for the clinician to decide what therapy should be first used in CIDP. This decision should consider the efficacy, cost, and side effects of each of these therapies. A few randomized trial have shown a comparable short-term efficacy of IVIg and oral corticosteroids [147] and of IVIg and plasma exchange [148] in CIDP, and more recent trials have shown that both IVIg [149, 150] and steroids [151, 152] have prolonged efficacy in CIDP. A recently published randomized controlled trial comparing the 6-month efficacy of IVIg and intravenous methylprednisolone showed that IVIg was more frequently effective and tolerated than steroids during the first 6 months of treatment, although, when effective, steroids were less frequently associated with deterioration than IVIg after therapy discontinuation [153]. There were not significant differences in the proportion of patients experiencing adverse events even if slightly more adverse events were observed after steroids. It remains unclear whether these advantages are sufficient to balance the much higher cost of IVIg compared to steroids [154, 155]. Even if similarly effective to IVIg, plasma exchange is usually considered the third choice since it is more invasive for the patients and has an higher prevalence of side effects, mostly related to hemodynamic changes and vascular access, that make it less suitable for the long-term treatment of the patients [67].

Several anecdotal reports have shown the efficacy of other immune therapies that have been used to reduce the cost and frequency of IVIg and the side effects of steroids or to treat patients not responding or becoming resistant to these therapies [156]. None of the randomized controlled trials so far performed with these therapies confirmed however their efficacy which remains therefore unclear [157–160].A summary of the major treatment modalities in CIDP is here provided.

Corticosteroids

A prospective, randomized, placebo-controlled trial of prednisone demonstrated a small but significant improvement in patients who were treated with prednisone compared to those with no treatment [161]. The effects of prednisone are not immediate since the mean time for improvement and to reach a clinical plateau is often delayed by several weeks [14]. In the recent PREDICT study, the median time to disability improvement in patients treated with pulsed monthly oral dexamethasone was indeed 17 weeks (range 13–20) and with daily oral prednisolone 39 weeks (range 30–48 weeks) [151, 152]. In the same study, the median time to remission was 20 weeks (range 12–28) with pulsed dexamethasone and 39 weeks (range 30–48) with oral prednisolone. This finding of a long delay before the therapy is effective is, however, rarely expected by the treating physicians (and by the patients) who might early decide failure of the therapy since previous recommendations indicated that 8–12 weeks is needed before considering the therapy ineffective.

The standard initial dose of corticosteroids in CIDP is considered to be 60 mg/day of prednisolone, i.e., the dose that was shown to be effective in a randomized controlled trial [161]. In the recent PREDICT study, the pulse dose of oral dexamethasone of 160 mg/month, divided in 4 consecutive days, was used for 6 moth and was found to be similarly effective than the standard daily prednisolone dose [151]. Side effects were usually minor and comparable among the two groups even though sleeplessness and Cushing's face were less frequent in the dexamethasone group. A similar efficacy of pulsed steroid therapy in CIDP was reported in an

uncontrolled study on 10 patients treated for at least 22 months with pulsed oral methylprednisolone therapy [162], with 60 % of the patients entering an off-treatment remission. Pulsed intravenous methylprednisolone and oral steroids (and IVIg) were reported to be similarly effective over 6 months, with over 80 % of the patients responding to therapy but with less weight gain and cushingoid features in the methylprednisolone group [163]. In a recent study [153], intravenous methylprednisolone was given at the dose of 0.5 g/day for 4 consecutive days for 6 months and was effective in 48 % of the patients, none of whom relapsed within 6 months after therapy discontinuation. All these studies support the notion that steroids are similarly effective in CIDP when given either daily orally or by monthly oral or intravenous pulse, with the suggestion that the pulse doses may be better tolerated.

Steroids are usually well tolerated over the short term even if agitation and hyperglycemia may early occur. Most common side effects over the long term include hyperglycemia, hypertension, gastritis and gastrointestinal bleeding, osteoporosis, glaucoma, cataracts, poor wound healing, susceptibility to infection, weight gain, depression, psychosis, and insomnia.

Plasma Exchange

Many case reports, uncontrolled studies, and prospective, double-blind, sham-controlled studies have shown the efficacy of plasma exchange in some patients with CIDP [9, 164, 165]. The time to improvement is generally short, with one series demonstrating a response beginning 2 days to 3 weeks after initiating plasma exchange [166]. The duration of response varies, but two-thirds of responding patients were reported to require repeated exchange to maintain improvement since they relapsed after about 7–14 days [164, 165]. Thus, concomitant immunosuppressive therapy is often suggested even if its efficacy has still to be proved (see below). A course of about five treatments on consecutive or alternate days is commonly used to initiate treatment, but regimes vary and single exchanges every few weeks are sometimes used for long-term treatment. Plasma exchange was similarly effective as IVIg over 6 weeks in a small randomized controlled trial on 20 patients [148]. In a larger retrospective study on 105 patients, a similar proportion of patients responded to plasma exchange (23/33; 70 %) or IVIg (14/22; 64 %). More complications were, however, observed after PE (10) than after IVIg (0) [167]. A higher prevalence of side effects after plasma exchange (19 %) than after steroids (12.5 %) and IVIg (4 %) was also observed in a recent retrospective study on 267 patients with CIDP [143]. Plasma exchange is therefore effective as initial treatment since neurological disability improves rapidly. However, adverse events related to difficulty with venous access, use of citrate, and hemodynamic changes are not uncommon, and this together with the inconvenience related to the necessity of frequent hospital admissions for repeated exchanges makes it less suitable for the chronic treatment of CIDP patients [67].

Intravenous Immunoglobulin

A number of retrospective, uncontrolled, or nonrandomized studies have shown the efficacy of IVIg in some patients with CIDP when administered at a dosage of 2 g/kg divided over 3–5 consecutive days [8]. Controlled studies confirmed that IVIg is effective in over 60 % of patients [149, 168–171] and is equally effective as oral prednisolone [147] and plasma exchange [148] over the short period. Improvement usually begins in 3–8 days but may occur as early as 2 days, while some patients only improve after 6 weeks and a second course of IVIg [171, 172]. In the IMC trial [153], IVIg was more frequently effective or tolerated (87.5 %) than intravenous methylprednisolone (47.6 %) over 6 months. Almost 40 % of the patients treated with IVIg deteriorated, however, in the 6 months following therapy discontinuation compared to none of the patients treated with steroids. These data confirm that while a few patients may have a monophasic course with a sustained response, the duration of efficacy in many patients lasts a few weeks with a reported range of 3–22 weeks and a mean of 6 weeks [170–173]. In one series, several patients who did not improve had predominantly sensory deficits [170].

IVIg was also shown to be effective as long-term treatment of CIDP. Patients with relapsing courses continue to respond to intermittent infusions of IVIg for 4 years or longer [167, 173]. For patients who require regular IVIg infusions to prevent or treat relapses, the necessary dose and interval vary greatly, with one series reporting maintenance IVIg doses ranging from 0.025 g/kg every 10 days to 0.4 g/kg once every 2–4 days [148]. Another series reports that IVIg was regularly administered at the dose of 1 g/kg or less prior to the expected relapse, which occurred 3–22 weeks after prior IVIg therapy [165]. The long-term efficacy of IVIg was recently confirmed in the ICE study [149] that showed that this treatment was safe and effective for 24 and possibly 48 weeks. During the first 24 weeks, treatment with IVIg resulted in a significantly greater improvement in disability and impairment compared to placebo, while continuing treatment for the following 24 weeks was associated with a significantly lower proportion of relapses. Though the 48-week duration of the study is by far the longest randomized controlled study conducted in CIDP to date, it only partially resolves the issue of the long-term treatment of this disease whose course is measured in several years. In an ancillary study, the authors also reported that this treatment not only improved weakness and disability but also had a significant beneficial effect on health-related quality of life [150].

The possibility to reduce the cost and the inconvenience of repeated hospital admissions for chronic IVIg therapy in

CIDP (and MMN; see below) was recently addressed with the use of subcutaneous immunoglobulin (SCIg). Two patients with CIDP were reported to maintain the improvement achieved with IVIg assuming the same dose subcutaneously at home during the week [174]. These observations were recently confirmed in a randomized placebo-controlled study on 15 patients indicating that SCIg is safe and effective in CIDP and may improve the quality of life of the patients who do not need to suspend their daily activities to receive periodic infusions [175].

Therapy with IVIg is usually well tolerated, even if fever, flu-like syndrome, and headache are not so uncommon. Serious adverse effects are rare and can include thromboembolic events, renal failure (mainly in patients with preexisting renal failure), anaphylaxis (especially in patients with IgA deficiency), or aseptic meningitis.

Immunosuppressive or Immunomodulating Agents

The necessity for long-term periodic treatments with IVIg or PE, the serious adverse events frequently associated with the chronic use of steroids, and the not so uncommon development of resistance to these therapies have led to the use of immunosuppressive or immunomodulating agents in CIDP. These agents are widely used in CIDP even in the early stage of the disease. Several uncontrolled studies have reported the efficacy of these therapies in CIDP [156], even if none of the randomized controlled trials performed with any of these agents in CIDP confirmed their efficacy. The first randomized trial with azathioprine (2 mg/kg) or placebo in addition to oral prednisolone (120 mg on alternate day tapered to 0 mg) given for 9 months to 27 patients with CIDP did not show any difference between the two groups [157]. In this study, the dose and duration of treatment with azathioprine were, however, smaller and shorter compared to what were later found to be effective in a similar trial in patients with myasthenia gravis [176]. In addition, only the adjunctive effect of azathioprine was analyzed and not its capability to reduce the dosage of steroids. A second randomized study was performed with oral methotrexate in addition to IVIg or steroids [159]. This therapy was well tolerated but was not more effective than placebo in reducing the dose of steroids or IVIg used to maintain the improvement in 60 patients with CIDP. In particular, 52 % of the patients taking oral methotrexate, 15 mg weekly, and 44 % of those assuming placebo reduced by at least 20 % the associated initial dose of IVIg or steroids by the end of the 40 weeks of the study. Similar negative results were obtained in two trials with intramuscular interferon beta-1a (IM IFNβ-1a) on a total of 77 patients [158, 160]. In the larger study on 67 patients with CIDP under chronic IVIg therapy [160], treatment for 32 weeks with either 30 or 60 μg of IM IFNβ-1a once or twice weekly was not more effective than placebo in reducing the mean dose of IVIg with 47 % of the patients in both groups not needing to restart IVIg after their suspension after 16 weeks of therapy with IFNβ-1a. The subgroup of patients severely affected or taking high baseline dose of IVIg could, however, reduce more IVIg after IM IFNβ-1a than after placebo. Both the study with methotrexate and IM IFNβ-1a showed that a consistent proportion of patients with CIDP are probably overtreated with steroids or IVIg since more than 40 % of them could reduce or suspend the therapy without worsening.

Despite the negative results from these randomized studies, immunosuppressives are still widely considered a valid option in the treatment of CIDP patients. This derives from the results of a number of uncontrolled or retrospective trials on small series of patients showing an overall efficacy in up to 80 % of patients treated with cyclosporin (82 %), cyclophosphamide (75 %), rituximab (anti-CD20) (75 %), methotrexate (70 %), azathioprine (64 %), interferon alfa (64 %), alemtuzumab (57 %), mycophenolate mofetil (46 %), interferon beta-1a (35 %), etanercept (30 %), tacrolimus, and autologous hematopoietic stem cell transplantation (reviewed in [156]). These figures should be considered however at the light of the above-mentioned consistent proportion of patients not worsening after therapy discontinuation even when assuming placebo. In a more recent retrospective multicenter study on 110 patients with CIDP not adequately responsive to IVIg, steroids, or plasma exchange, the proportion of patients responding to these therapies ranged between 20 and 30 % with 10–20 % of treated patients having adverse events related to the use of these therapies [177]. In a session on the use of immunosuppressive agent in CIDP at the Congress of the Peripheral Nerve Society hold in Wurzburg in 2009, the vast majority of the experts supported the used or oral azathioprine at the above-mentioned dose in patients with mild to moderate CIDP and of cyclophosphamide in severely affected patients. Cyclophosphamide was reported to be effective when given intravenously (1 g/m^2 of body surface area monthly for 6 months) in 75 % of patients unresponsive to standard treatment [178]. Higher dose of intravenous cyclophosphamide (200 mg/kg over 4 days without stem cell rescue) was also reported [179, 180]. Oral cyclosporine was also effective in inducing remission or reducing other therapies in CIDP patients when used at the dose of 3–5 mg/kg divided into two daily doses [181]. In recent studies, however, 50 % of treated patients had adverse events mainly related to renal dysfunction that we observed even using lower dosage of cyclosporin (2–3 m/kg/day) after a few months [177].

A Personal Approach to Treatment of the Patient with CIDP

Patients with mild sensory deficits and no weakness may be observed without treatment for days to weeks, since

spontaneous improvement may occur [67]. In those who do not improve, continue to worsen, or have motor as well as sensory deficits at presentation or are disturbed by their sensory symptoms, treatment with oral or intravenous steroids or IVIg should be first considered after discussing with the patients the pro and cons of each treatment. Contraindications to corticosteroids will influence the choice toward IVIg and vice versa. For pure motor CIDP, IVIg treatment should be the first choice, and if corticosteroids are used, patients should be monitored closely for deterioration. Steroids may become the preferred choice for economical problems related to either health insurance or national economy. Patients not responding to IVIg or steroids should be shifted to the other therapy considering that 50 % of patients not responding to one treatment respond to the alternative therapy [143]. We should, however, remember that steroids may become effective after several weeks and that over 50 % of the patients responsive to IVIg do so after the second course of IVIg [172]. We prefer to use plasma exchange in patients not responsive to the other two therapies.

For IVIg, we start at the dose of 2 g/kg body weight over 3–5 consecutive days. The onset of action is rapid, and the side effect profile is rather benign. In a few patients, the effects of IVIg are sustained, and the disease course is monophasic, eliminating the need for additional treatment. If improvement occurs but is unsustained, IVIg is then given periodically at the dose of 1 g/kg at a frequency sufficient to prevent the wear-off effect of the therapy. The dosage of IVIg is subsequently slowly reduced to achieve the minimal effective dose. The use of subcutaneous immunoglobulin has become a valid alternative for chronic therapy with immunoglobulins when given at the same monthly effective dosage for IVIg.

For steroids, we now prefer to use monthly course of intravenous methylprednisolone at the starting dose of 0.5 g for 4 consecutive days. Pulsed oral dexamethasone (40 mg for 4 days) is a valid alternative. This pulsed regimen can be also performed in patients with diabetes or glucose intolerance in whom we prefer to admit patients to better monitor and adjust glucose levels with insulin. Daily oral steroids can be also used at the standard daily dosage of 60 mg/day of prednisone or prednisolone even it may have more frequent adverse events than pulsed therapy. Patients should be educated regarding the side effects of steroids and instructed in the use of supplemental calcium and vitamin D, on gastroprotection, and on the need for monitoring of blood pressure, glucose, and electrolytes. After 2–3 months, the dose of pulsed steroid can be reduced and eventually suspended after 6 months closely monitoring the possible worsening of the patients in which case the effective therapy is resumed. Daily oral steroids are often initially shifted after 6–8 weeks to an alternate day regimen that is assumed to be better tolerated than the daily regimen and subsequently reduced and suspended over 1–2 years.

In patients who are nonresponsive or having contraindications to IVIg and steroids, we perform plasma exchange (usually 4–5 courses of one plasma volume on alternate days). The onset of action generally is rapid. If the effect is sustained, no further treatment is required. If improvement occurs but the patient relapses, plasma exchange may be repeated and progressively tapered possibly at the frequency of 1 course every 1–2 months.

Due to lack of consistent evidence supporting the use of immunosuppressive agents, we reserve them to patients who remain disabled despite the above-mentioned therapies or who have failed to respond to all of them, while we do not use them just to save on their cost. In these patients, we use intravenous cyclophosphamide at the monthly dose of 1 g/m^2 for 6 months.

Neuropathy Associated with IgM Monoclonal Gammopathy and Anti-MAG Antibodies

Introduction

In 1980 Latov et al. [182] first reported on a patient with neuropathy associated with IgM monoclonal gammopathy in whom the paraprotein reacted with a myelin antigen that was later characterized as the myelin-associated glycoprotein (MAG) [183]. MAG is a minor constituent of both central and peripheral nervous system myelin membranes that is deemed to have an important role on axonal–myelin interactions [184]. Since then several other laboratories reported this reactivity that is present in almost 50 % of patients with neuropathy associated with IgM monoclonal gammopathy [123, 185]. In these patients, the paraprotein also reacts with other nerve glycoconjugates (P0, PMP-22, SGPG, and SGLPG) sharing with MAG the HNK-1 carbohydrate epitope [186–189]. Even if this is considered a rare neuropathy, its prevalence has been estimated to be of at least 20–40 per 100,000 in the population above 50 years [190].

Clinical Features

High titers of anti-MAG IgM antibodies are almost invariably associated with a homogeneous clinical pattern with a DADS neuropathy phenotype [190]. The majority of affected patients are men presenting their first neuropathy symptoms in the sixth or seventh decade. Almost 80 % of them have IgM MGUS, while most remaining patients have Waldesntröm's macroglobulinemia that is frequently indolent [191]. Most patients present with sensory symptoms in legs including paresthesias, hypesthesias, dysesthesias, cramps, or other pains and unsteadiness of gait. Weakness is frequently absent at onset. An intentional and postural tremor in the upper limbs is often reported

and is sometimes quite disabling. In some patients, it can be the presenting symptom [192]. On neurological examination, the neuropathy is characterized by a distal and symmetric, predominantly large fiber sensory involvement, gait ataxia, and postural tremor in the upper limbs, while motor impairment is usually less prominent and often appears later.

The vast majority of patients with anti-MAG antibodies have a relatively favorable long-term prognosis. Approximately 25 % of the patients were reported to become at least moderately disabled (Rankin disability score higher that 2) after 10 years and 50 % after 15 years [193]. This was recently confirmed in a series of 140 patients with neuropathy associated with IgM monoclonal gammopathy [194], 44 % of whom had anti-MAG IgM. In these patients, the presence of anti-MAG antibodies reduced the probability of becoming disabled (approximately 50 % after 18 years in the MAG-positive group compared to 13 years in the MAG-negative group). Unfortunately, the possible effect on the prognosis of the therapies performed during the follow-up was not assessed.

Diagnosis

Anti-MAG IgM antibodies are currently examined in serum by western blot [123] or ELISA [195]. For both systems, it is, however, necessary to establish a normal range since low titers (usually 1/3,200 or less) can be encountered in some normal subjects. It was recently shown that a commercially available ELISA system was more sensitive but less specific than the western blot. This system has, however, the advantage to avoid the cumbersome procedure required for myelin isolation and western blot assay [195].

Electrodiagnostic studies in patients with anti-MAG antibodies are consistent with a demyelinating neuropathy with markedly reduced motor and sensory conduction velocities often in the range of 15–25 m/s [123, 196] and an even more pronounced delay of distal motor latencies [197, 198]. Conduction blocks are rarely observed in these patients facilitating the distinction from CIDP [199]. The severity of EDX abnormalities is often discrepant with the relatively mild clinical impairment of the patients and may induce the unexperienced clinician to formulate an unappropriately severe prognosis.

Morphological studies on sural nerve biopsy are consistent with a demyelinating neuropathy with reduced number of myelinated fibers, demyelination and remyelination on teased fibers, and, in over 90 % of examined patients, typical widely spaced myelin lamellae on ultrastructural studies [200]. In most patients deposits of IgM and complement around the myelin sheaths are found on immunohistochemical studies [201, 202]. Recent studies have shown that these deposits may be also found on myelinated nerve fibers obtained by skin biopsy [203]. Sural nerve biopsy is, however, unnecessary to confirm the diagnosis in patients with a clinically typical presentation and elevated antibody titers.

Pathogenesis

Several data support the pathogenetic role of anti-MAG IgM in the neuropathy [185, 190]: (1) high titers of anti-MAG IgM antibodies are almost invariably associated with an homogeneous clinical pattern or predict the development of a symptomatic neuropathy in asymptomatic patients with IgM monoclonal gammopathy [204]; (2) pathological studies on nerve biopsies show segmental demyelination with deposits of IgM M-protein and complement on nerve myelin, i.e., the target of the anti-neural reactivity, and loss of MAG in nerve biopsy correlates with antibody titers [205]; (3) complement-mediated demyelination of nerve has been experimentally induced in animals by intraneural or systemic injection of anti-MAG IgM M-proteins [206–209]; (4) more recently, immunization of cats with the cross-reacting glycolipid SGPG was shown to cause a sensory ataxic neuronopathy [210]; and (5) therapeutical reduction of anti-MAG IgM, though difficult to achieve, often correlates with clinical improvement (see below).

Therapy

The importance of the diagnosis of a demyelinating neuropathy associated with IgM monoclonal anti-MAG antibodies is highlighted by the fact that in these patients response to therapy is different from that observed in CIDP. Clinical improvement in patients with anti-MAG IgM most often correlates with the reduction of antibody titers even if this may be difficult to achieve [193]. Almost 50 % of reported patients improved, at least temporarily, after one of more immune therapies including steroids, plasma exchange, a number of cytotoxic agents, and, more recently, high-dose intravenous immunoglobulin, fludarabine, cladribine, interferon-α, and the anti-B lymphocyte (CD20) humanized monoclonal antibody rituximab [211]. The efficacy of these therapies has not been so far confirmed in randomized controlled trials, most of whom showed at the most a marginal effect [70]. More recently a number of open pilot trials have suggested the efficacy of the humanized monoclonal antibody rituximab directed against the CD20 antigen, in patients with anti-MAG IgM neuropathy [212–215]. The efficacy of rituximab in anti-MAG neuropathy was recently assessed in two randomized controlled trials, 1 on 26 patients [216] and the other on 54 patients [217]. Even if neither trials met the prespecified primary outcome measures, both studies showed a 20–30 % absolute improvement in the number of patients

improving in the disability scale in patients treated with rituximab compared to placebo, a figure which is higher than observed with approved immune therapies in other immune diseases such as multiple sclerosis. In responding patients the benefit was reported to last up to 2 years in 80 % of the patients and 3 years in 60 % of them [218]. This aspect is important for the long-term management of the patients and should be balanced with the side effects of this therapy including the possible development of progressive multifocal leukoencephalopathy [219].

We think that until therapies with a better efficacy/safety profile become available, symptomatic therapy for tremor and paresthesias and reassurance on the usually favorable functional prognosis for several years may be sufficient in patients not impaired in their daily life, while rituximab should be considered for patients worsening or impaired in their daily life [70]. The recent observations on the possible efficacy of the association of rituximab with other therapy used in WM such as fludarabine need to be confirmed in larger population and possibly in RCT [220].

Multifocal Motor Neuropathy

Introduction

The term multifocal motor neuropathy (MMN) was first introduced in the literature in 1988 by Pestronk et al. [221] who reported two patients with a progressive purely motor, predominantly distal, asymmetric neuropathy with multifocal persistent conduction blocks (CB) on motor but not sensory nerves. A few similar patients had been reported some years before [222–224], but Pestronk et al. highlighted two of the main features of this neuropathy, i.e., its frequent association with anti-GM1 IgM antibodies and response to immune therapies. Between 1992 and 1993, a number of authors independently reported the effectiveness of IVIg in MMN, which is now considered the gold standard for the treatment of this neuropathy [225, 226]. Even if MMN was originally variably related to CIDP or to motor neuron disease (MND), it is now considered a well-defined separate clinical entity [227, 228].

Prevalence

The prevalence of MMN has been originally estimated to be of 1–2 person per 100,000 [227] and was recently shown to be 0.6 per 100,000 inhabitants in the Dutch population [229]. Men are more frequently affected than women with a ratio of 2.6–2.7:1. The mean age of onset is around 40 years with 80 % of reported patients presenting their first symptoms between 20 and 50 years [227]. Onset in childhood has been occasionally reported.

Clinical Features

MMN almost invariably presents with progressive, usually distal, asymmetric arm weakness which can be often related to the distribution of individual nerves [227, 228]. Weakness remains occasionally confined to the territory of a single nerve for several years [230]. Some patients may present with more proximal weakness or with symptoms in their legs. The disease usually steadily progresses to affect other nerves sometime with a typical initial crossed distribution (one arm and contralateral leg). It is not so infrequent however that the disease has a stepwise progression with an interval of months or even years before spreading to other nerves with sometime a partial spontaneous remission of initial deficit [222, 231]. Asymmetry and predominance of arm weakness may become less evident during the course of the disease even if they are usually still present even after several years of disease. Localized muscle atrophy may be mild or irrelevant in the early stage of the disease but may become prominent during the course of the disease when it is usually associated with the development of signs of axonal degeneration. Fasciculations, cramps, and myokymia have been variably reported in these patients making the similarity of MMN with MND even more evident. Their clinical distinction may become even more difficult in the 20–30 % of patients in whom tendon reflexes, which are often reduced in a patchy way or diffusely, are normal or even brisk [221, 229, 232]. In these patients a marked asymmetry in the degree of clinical impairment and EDX abnormalities between contiguous nerves may orient the examiner toward a diagnosis of purely motor multiple neuropathy. Cranial nerve involvement or respiratory failure due to unilateral or bilateral phrenic nerve palsy may seldom occur in these patients. Even if some patients may report mild sensory symptoms sometime in the course of the disease, only a minority of them have a definite though minor sensory loss. It is still unsettled, however, the degree that sensory impairment should attain for a diagnosis of Lewis–Sumner syndrome instead of that of MMN. Based on the list of the above-mentioned symptoms and signs, it is not surprising that early and even recent reports [229] of MMN highlighted its similarity with MND, a diagnosis that, together with entrapment neuropathy, is not so infrequent for MMN patients to receive before they are correctly diagnosed.

Most patients with MMN carry an overall good prognosis *quoad vitam*, with only few of them having a fatal outcome after several years of disease. Still the majority of patients become somehow disabled in their daily life because of a reduced dexterity in manual activities, while very few of them become disabled in their deambulation. In our series, the proportion of patients with a disability score above 2 on the Rankin scale before starting effective therapy was 12 % at 5 years, 25 % at 10 years, and 60 % at

Table 29.4 EFNS/PNS (2010) clinical diagnostic criteria for MMN [235]

Core criteria (both must be present)
1. Slowly progressive or stepwise progressive, asymmetric limb weakness, or motor involvement having a motor nerve distribution in at least two nerves, for more than 1 month[a]
2. No objective sensory abnormalities except for minor vibration sense abnormalities in the lower limbs
Supportive clinical criteria
3. Predominant upper-limb involvement[b]
4. Decreased or absent tendon reflexes in the affected limb[c]
5. Absence of cranial nerve involvement[d]
6. Cramps and fasciculations in the affected limb
Exclusion criteria
7. Upper motor neuron signs
8. Marked bulbar involvement
9. Sensory impairment more marked than minor vibration loss in the lower limbs
10. Diffuse symmetric weakness during the initial weeks

[a]Usually more than 6 months
[b]At onset, predominant lower limb involvement account for nearly 10 % of the cases
[c]Slightly increased tendon reflexes, in particular, in the affected arm have been reported and do not exclude the diagnosis of MMN provided criterion 7 is met
[d]Twelfth nerve palsy reported

Table 29.5 EFNS/PNS (2010) electrophysiological criteria for conduction block in MMN[a] [235]

1. Definite motor CB
Negative CMAP area reduction on proximal versus distal stimulation of at least 50 % regardless of the nerve segment length (median, ulnar, and peroneal). The negative CMAP amplitude (baseline negative peak) on stimulation of the distal part of the segment with motor CB must be >20 % of the lower limit of normal and >1 mV and an increase of proximal negative peak CMAP duration must be ≤30 %
2. Probable motor CB
Negative CMAP area reduction of at least 30 % over a long segment of an upper-limb nerve with an increase of proximal negative peak CMAP duration ≤30 %
Negative CMAP area reduction of at least 50 % (same as definite) with an increase of proximal negative peak CMAP duration >30 %
3. Normal sensory nerve conduction in upper-limb segments with CB and normal SNAP amplitudes (see exclusion criteria)

[a]Evidence for conduction block must be found at sites distinct from common entrapment or compression syndromes

15 years, although most of them could still walk independently [233].

Diagnostic criteria for MMN have been proposed by several groups including the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) [234] and more recently the Joint Task Force of the EFNS/PNS (Tables 29.4, 29.5, and 29.6) [235].

Table 29.6 EFNS/PNS (2010) diagnostic categories for MMN [235]

Definite MMN
Clinical criteria 1, 2, and 8–11 (Table 29.4) and electrophysiological criteria 1 and 3 in one nerve (Table 29.5)
Probable MMN
Clinical criteria 1, 2, and 8–11 (Table 29.4) and electrophysiological criteria 2 and 3 in two nerves
Clinical criteria 1, 2, and 8–11 (Table 29.4), electrophysiological criteria 2 and 3 in one nerve (Table 29.5), and at least two supportive criteria[a] 1–4
Possible MMN
Clinical criteria 1, 2, and 8–11 (Table 29.4) and normal sensory nerve conduction studies and supportive criteria 4
Clinical criteria 1 with clinical signs present in only one nerve, 2 and 8–11 (Table 29.4) and electrophysiological criteria 1 or 2 and 3 in one nerve (Table 29.5)

[a]*Supportive criteria for MMN*
1. Elevated IgM anti-ganglioside GM1 antibodies
2. Laboratory: increased CSF protein (but <1 g/l)
3. Magnetic resonance imaging showing increased signal intensity on T2-weighted imaging associated with a diffuse nerve swelling of the brachial plexuses
4. Objective clinical improvement following IVIg treatment

Differential Diagnosis

MMN should be clinically differentiated from MND, from which it can be distinguished by its weakness that follows multiple nerves distribution (and not simply asymmetric pattern of motor impairment), absence of bulbar involvement, and slower progression. The absence of a concomitant sensory impairment helps to distinguish MMN from entrapment neuropathies, vasculitic neuropathy or hereditary neuropathy with liability to pressure palsy (HNPP). More subtle is the distinction from Lewis–Sumner syndrome, which mainly relies on the absence in MMN of definite sensory impairment although this distinction may be difficult in patients with minor sensory symptoms (Table 29.7). Another diagnosis to be considered is pure motor CIDP where weakness is often symmetrical and proximal and the course is often relapsing with a more severe progression of symptoms.

Electrodiagnostic Features

The diagnosis of MMN mainly relies on the presence of persistent, multifocal, partial conduction blocks (CB) in motor nerves outside the usual sites of nerve compression. CB has been defined as a reduction in the amplitude or area of the compound muscle action potential (CMAP) on proximal compared to distal stimulation, accompanied by no significant or only focal abnormal temporal dispersion (TD) [236]. Unfortunately, no uniformly accepted criteria exists for CB

Table 29.7 Comparison of three different acquired demyelinating polyneuropathies: chronic inflammatory demyelinating polyneuropathy (CIDP), Lewis–Sumner syndrome, and multifocal motor neuropathy (MMN)

Feature	CIDP	Lewis–Sumner syndrome	MMN
Age at onset	Adults of all ages, children rarely	Adults of all ages	Adults of all ages
Sex	Slight male predominance	Males more common	Males more common
Duration of illness at presentation	Varies widely – days to years. Usually months	Usually years	Usually years
Weakness	Symmetric	Asymmetric, in the distribution of peripheral nerves UE>LE	Asymmetric, in the distribution of peripheral nerves UE>LE Distal>proximal
Sensory impairment	Symmetric	Asymmetric, in the distribution of sensory nerves	Minimal or none
Reflexes	Generally absent	Focally decreased or absent	Focally decreased or absent
Sensory nerve conduction studies	Usually abnormal	Usually abnormal	Normal
Motor nerve conduction studies	Acquired demyelination: conduction block, abnormal temporal dispersion, slowed conduction velocities, prolonged distal latencies, prolonged F-wave latencies	Acquired demyelination: conduction block, abnormal temporal dispersion. Other focal, and usually mild, abnormalities including slowed conduction velocities, prolonged distal latencies, prolonged F-wave latencies	Acquired demyelination: conduction block, abnormal temporal dispersion. Other focal and, usually mild, abnormalities including slowed conduction velocities, prolonged distal latencies, prolonged F-wave latencies
Anti-GM1 antibodies	May be present, usually not at high titers	Usually absent	High titers in about half
CSF protein	Usually elevated	Usually elevated	Usually normal. May be elevated to <100 mg/dl
Sensory nerve biopsy	Demyelination, axonal degeneration, mononuclear inflammation, endoneurial edema	Demyelination	Normal or minor abnormalities
Usual treatment	Prednisone, IVIg, plasma exchange	Prednisone, IVIg	IVIg
Course	Relapsing, monophasic, or progressive	Progressive until treated	Progressive or stepwise until treated

UE upper extremities, *LE* lower extremities, *IVIg* intravenous immunoglobulin

identification, as the reduction of CMAP amplitude or area required to be significant for CB varies considerably among different authors. Consensus criteria for the diagnosis of CB have been proposed by the AANEM [234] and by the EFNS/PNS (see Table 29.5) [235]. If the application of these criteria is useful for the inclusion of patients in therapeutic trials, it may risk to underestimate the presence of CB in the early phases of the disease and possibly delay the diagnosis of a potentially treatable disease. One of our patients initially presented with a 24 % reduction of proximal versus distal CMAP amplitude without temporal dispersion in the right ulnar and median nerves which, 2 years later, as the patient became more severely affected, increased to 70 and 88 %, respectively [237]. In addition, there are patients in whom typical CB may decrease or even disappear in some nerves after several years of the disease because of a progressive reduction of the distal CMAP amplitude, which may reflect either secondary axonal degeneration or the appearance of unrecognized very distal CB. CB is not specific for MMN (and Lewis–Sumner syndrome), as it can also be found in CIDP and Guillain–Barré syndrome (GBS), where it is associated with other abnormalities suggestive of demyelination; in acute compressive neuropathy or nerve entrapment, in which CB is found at the usual sites of nerve compression or entrapment; and in nerve ischemia, in which it rapidly evolves into axonal degeneration.

In some nerves, CB can be diagnosed, even if it does not attain the above-mentioned level, by stimulation at several sites as close as 2–2.5 cm apart ("inching" technique) [238, 239]. Magnetic or transcutaneous cervical stimulation may help in the localization of proximal CB in patients suspected of having MMN [240, 241]. This was more evident using the magnetic fatigue test that allowed to reveal increased CB or temporal dispersion after prolonged exercise [242]. More recently, a novel triple stimulation technique was reported to be more sensitive in detecting CB by revealing the presence of CBs proximal to Erb's point not detectable by routine nerve conduction studies [243]. The presence of CB distal to the most distal site of stimulation is suggested by a low-amplitude CMAP recorded by a weak, but not wasted, muscle [244].

Nerve conduction velocity across the regions with CB is usually reduced although it may be normal or only slightly reduced. Other, usually mild, features of demyelination, including prolonged distal CMAP latencies and prolonged or absent F-waves may be also found in affected nerves. Sensory nerve conduction studies are usually normal or only minimally affected in MMN, even in the nerves where motor CB has been detected. A possible concomitant proximal sensory impairment has been revealed in some patients with MMN by somatosensory evoked potentials [245]. More recently, a few studies have shown that 30–60 % of MMN patients develop some degree of electrophysiological sensory impairment in the course of the disease even if most of them remained clinically asymptomatic [246–248].

Laboratory Findings

Routine hematological and biochemical laboratory findings are usually normal in MMN apart from slightly to moderately increased serum creatine kinase activity, observed in up to two-thirds of patients [249]. Cerebrospinal fluid (CSF) examination shows slightly increased protein levels (usually up to 80 mg/dl) in one-third of MMN patients, with normal CSF findings in the others, including absence of oligoclonal bands [227, 248]. This finding may help in the distinction with CIDP where CSF proteins are often markedly increased. Serum protein electrophoresis may occasionally reveal the presence of a monoclonal or polyclonal gammopathy, mostly of IgM isotype.

The most typical laboratory findings in MMN are the presence of increased levels of serum IgM antibodies to the ganglioside GM1 and, to lesser extent, to other glycolipids including asialo-GM1, GD1a, or GM2, with frequency in most laboratories of 40–50 % [250]. These antibodies have been rarely reported in other immune neuropathies and in approximately 5–10 % of patients with MND. Attempts to identify differences in the fine specificity of the antibodies associated with these different diseases or to improve the sensitivity or specificity of anti-GM1 testing in MMN did not produce consistent results. This has led to some divergences on the interpretation of the diagnostic relevance of anti-GM1 IgM in the diagnosis of MMN [251]. Elevated antibodies were included as supportive criteria by the EFNS/PNS [235] (see Table 29.6) but not by the AANEM [234]. A few large studies indicated, however, that their presence may help in distinguishing MMN from MND even if their absence does not permit to exclude MMN [252–256]. Several attempts have been performed to improve the sensitivity of anti-GM1 antibodies in MMN using more sophisticated techniques [257] or testing GM1 in addition to other glycolipids [258]. The combination of GM1 with cholesterol and galactocerebroside increased indeed the sensitivity of GM1 testing in MMN of approximately 20 % with a marginal reduction of the specificity and positive predictive value for MMN [259]. More recently increased titers of IgM antibodies to a disulfated heparin disaccharide (NS6S) were also reported to increase the sensitivity with MN [260], but this was associated, in our hands, with a reduced specificity and positive predictive value for MMN [261]. In conclusion, testing for anti-GM1 and related antibodies may help in the diagnosis in patients in whom this cannot be established after comprehensive clinical and EDX evaluations, even though the absence of these antibodies does not exclude the diagnosis of MMN.

Magnetic resonance (MR) imaging studies of the forearm or brachial plexus may show in some patients an asymmetrically increased signal intensity in T2-weighted images or in T1-weighted images after gadolinium enhancement associated with diffuse nerve swelling of the brachial plexus [262]. Similarly promising results were observed with ultrasonographic study of the nerves [263].

Nerve biopsy is seldom useful in the diagnosis of MMN because it is routinely performed on the sural or other sensory nerves, which typically are clinically and electrophysiologically normal in MMN. In these patients, pathological studies on sural nerve were either normal or showed mild axonal degeneration or demyelination or both [227]. Mild pathological abnormalities consistent with a demyelinating process were however reported on ultrastructural studies [264]. Motor or mixed nerve biopsy adjacent to the site of CB revealed in two patients demyelination with onion bulbs without inflammatory infiltrates [265, 266]. These pathological findings were not subsequently confirmed in seven patients with typical MMM in whom fascicular nerve biopsy at the site of CB only disclosed multifocal fiber degeneration and loss and clusters of regenerating fibers without obvious sign of demyelination [267]. More recently, biopsy of motor nerves was shown to be helpful in the distinction of MMN from MND showing in the former a significantly higher density of clusters of regenerative small myelinated fibers compared to MND [268, 269].

Pathogenesis

The frequent association of MMN with anti-glycolipid antibodies and the improvement observed in most patients after IVIg or other immune therapies (see below) support the opinion that the disease is immunologically mediated and possibly caused by anti-GM1 IgM binding to neural structures (reviewed in [250]). There are, however, some aspects that still need to be clarified. Even if anti-GM1 IgM antibodies are significantly associated with MMN, their absence in the majority of patients makes it unclear what would cause the disease in negative patients, most of whom respond to immune therapies similarly to GM1-positive patients. The presence of anti-GM1 IgM in some patients with MND or

other immune neuropathies makes it unclear how similar antibodies cause different diseases. Similarly inconclusive are the results of experimental studies directed at testing the capacity of these antibodies to cause CB. Intraneural injection or exposure to sera from patients with high anti-GM1 antibodies and MMN but not with MND was able to induce focal CB in vivo or in vitro [270–272] even if the same results were not confirmed using purified anti-GM1 antibodies [273]. In addition, a similar blocking effect on mouse distal motor nerve conduction was induced in vitro by sera from MMN patients with and without high anti-GM1 antibodies [274]. These findings suggest that sera from patients with MMN contain indeed soluble factors able to affect the neural transmission even if the role of anti-GM1 antibody in this blocking effect remains unclear.

Therapy

Almost 80 % of patients with MMN respond to IVIg [225], whose efficacy has been confirmed in four randomized, double-blind, placebo-controlled trials on a total of 34 patients [275–278] and in a yet unpublished trial [279]. IVIg induces a rapid improvement which often occurs within 1 week of treatment and is usually more evident in recently affected regions with minor or no effect on older and stabilized deficits. Only a few patients have persistent improvement after a single or few courses of therapy, while in most patients the effect of IVIg only lasts for a few weeks and has to be maintained with periodic IVIg infusions for long periods of time, if not indefinitely [229, 233, 280–283]. IVIg therapy in MMN is usually started at the standard dose of 2 g/kg on 2–5 consecutive days followed by maintenance infusions ranging from 0.4 g/kg once a week to 1–2 g/kg every 2–5 weeks. Maintenance therapy may be also performed at home with subcutaneous immunoglobulin (SCIg) whose efficacy as maintenance treatment has been confirmed in two small randomized controlled trials [284, 285]. The long-term efficacy and adverse events of this therapy related to the repeated local injections still need to be clarified. Over time, several patients become progressively less responsive to IVIg and require increasing dosage (in case of insufficient response) or frequency (in case of reduced duration of the response) of IVIg to maintain improvement [233, 281].

A minority of patients with MMN do not respond or become resistant to IVIg, while in others IVIg infusions may be challenging to implement because of their elevated cost. Steroids are, however, ineffective in MMN, even when given at high-dose intravenously, and almost 20 % of treated patients were reported to worsen under this therapy [102]. Similarly ineffective is plasma exchange [286], and it can be also associated with clinical worsening [287]. This highlights the importance of the distinction of MMN from CIDP and Lewis–Sumner syndrome where steroids and plasma exchange are often effective. Cyclophosphamide given intravenously at high doses followed by oral doses was found effective in approximately 50 % of the patients [221, 288]. This drug has, however, several side effects and may be unsuitable for a nonfatal disorders and for young patients. Occasional patients were reported to improve or stabilize with azathioprine [232], while interferon beta-1a (IFN-β1a) was found effective in some patients with MMN, some of whom had failed to respond to other therapies including IVIg [289, 290]. The only randomized double-blind controlled trial with immunosuppressant in MMN showed, that mycophenolate mofetil did not permit to increase the effectiveness or to reduce the dose of IVIg [291]. More recent open trials showed that oral methotrexate [292] and eculizumab [293] were marginally effective in some patients but did not permit to consistently reduce the dose of IVIg therapy. A positive effect was initially reported with rituximab [212], but subsequent studies inconsistently confirmed these results [294, 295]. A recent Cochrane Review concluded that at the present time there is little evidence to support the use of any immunosuppressant in MMN [296] and confirmed that at the present time IVIg remains the gold standard for the treatment of MMN [235].

MMN Without CB and Axonal MMN

It is still debated whether the presence of CB is a mandatory criteria for the diagnosis of MMN for patients with otherwise typical clinical presentation. Some patients have lesser degree of amplitude reduction than required by the current diagnostic criteria [297, 298], while others neither have CB nor other features of demyelination [299, 300] leading to the diagnosis of axonal MMN [301]. Some of these patients have anti-GM1 antibodies and improve with IVIg similarly to patients with CB, while pathological evidence of immune-mediated axonal damages was observed in one patient [302]. Though the presence of CB should be considered crucial for the diagnosis of MMN, a course of IVIg therapy might be considered for patients with otherwise clinically typical MMN. A positive response to IVIg in these patients would support the diagnosis of MMN, as also indicated by the EFNS/PNS criteria [235] where a diagnosis of possible MMN can be posed under these conditions.

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Dysproteinemic Neuropathies

30

Elham Bayat and John J. Kelly

Epidemiology and Pathogenesis

Approximately 10 % of patients with idiopathic peripheral neuropathy have an associated monoclonal gammopathy [1]. The frequency of monoclonal gammopathy in general population is around 2 % in those aged 50–70 years and 3 % in individuals older than 70 years [2, 3]. Most of these patients have monoclonal gammopathies of undetermined significance (MGUS) (Tables 30.1 and 30.2) with a risk of progression to malignant gammopathy of 1 % per year [5]. About half of MGUS neuropathies are associated with an IgM gammopathy [4, 6], and of these, about half have antibody activity against myelin-associated glycoprotein (MAG) [7]. MAG antibody neuropathy has an estimated prevalence of 1–5 per 100,000 adults [6]. The other half of the MGUS group is associated with IgG or IgA gammopathies, which are a much more diverse group in antibody activity [1]. The prevalence of peripheral neuropathy in multiple myeloma (MM) is low with 3–5 % of patients having neuropathy [8, 9], but subclinical neuropathy may be detected by nerve conduction study or histopathological evaluation in up to 60 % of patients [10–12]. In this category, osteosclerotic myeloma has the highest incidence of polyneuropathy reported at 50–80 % of patients [13, 14].

Peripheral neuropathy is the most common neurological manifestation in primary amyloidosis (AL) with sensory motor neuropathies present in 15 % of AL patients [15, 16]. Peripheral neuropathy is the presenting sign of systemic amyloidosis or multiple myeloma in about 15 % of patients [16–18] and may be the cardinal manifestation.

Plasma cell dyscrasias (paraproteinemias or dysproteinemias) (Table 30.1) are a group of disorders characterized by the proliferation of a single clone of plasma cells, which produces an immunologically homogeneous protein commonly referred to as a paraprotein or monoclonal protein (M protein) [4, 19]. The M protein (monoclonal immunoglobulin) can be an intact immunoglobulin (containing two light (L) chains and two heavy (H) chains). Occasionally, only the

Table 30.1 Classification of common plasma cell dyscrasias

Disorder	Diagnostic criteria
Monoclonal gammopathy of undetermined significance	MP in serum < 3 g/dl and no malignancy or amyloid
Osteosclerotic myeloma	Solitary or multiple plasmacytomas
Multiple myeloma	>10 % abnormal plasma cells in bone marrow or plasmacytoma and MP in serum or urine or osteolytic lesions
Waldenström's macroglobulinemia	IgM-MP >3 g/dl, >10 % lymphs or plasma cells in bone marrow
Primary systemic amyloidosis	Light-chain amyloid by histology
Gamma-heavy-chain disease	Monoclonal heavy chain in serum or urine

Adapted from Kelly et al. [4]
Abbreviations: *MP* monoclonal protein

Table 30.2 Hematologic diagnosis of 28 patients with PCD and polyneuropathy

Diagnosis	Number
Monoclonal gammopathy of undetermined significance	16
Primary systemic amyloidosis	7
Multiple myeloma (includes osteosclerotic myeloma)	3
Waldenström's macroglobulinemia	1
Gamma-heavy-chain disease	1

Data from Kelly et al. [1]
Abbreviation: *PCD* plasma cell dyscrasia

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Table 30.3 Features of dysproteinemic polyneuropathy syndromes

Class	Weakness	Sensory	Autonomic	CSF	MNCV loss
MGUS–IgM	+	+++	–	++	D
MGUS–IgG, A	++	++	–	+	D
Amyloidosis	+/++	+++	+++	+	A or D
OSM	+++	++	–	+++	D
WM	++	++	–	++	D or A

Data from Kelly et al. [4]
Abbreviations: *CSF* cerebrospinal fluid protein concentration, *MNCV* motor nerve conduction velocities, *MGUS* monoclonal gammopathy of undetermined significance, *OSM* osteosclerotic myeloma, *WM* Waldenström's macroglobulinemia, *D* segmental demyelination pattern, and *A* axonal degeneration pattern

light chain or heavy chain may be secreted (light- or heavy-chain disease). M proteins are identified by the heavy-chain class (IgM, IgG, IgA, IgD, and IgE) that is produced. The light chains may be either kappa (k) or lambda (L).

Serum protein electrophoresis (SPEP) [4, 19] is the preferred method to screen M proteins [20, 21]. Among patients where a spike is identified by the SPEP and among all patients who are suspected to have a monoclonal gammopathy, such as idiopathic polyneuropathy, immunoelectrophoresis (IEP) or immunofixation (IFE) should be performed, even with a normal SPEP [19]. IEP and IFE are more sensitive than SPEP for detection of a small M protein and allow characterization of the single heavy and light chain, thus verifying the monoclonal nature of the immunoglobulin. Of the two, IFE is more sensitive and will detect M proteins occasionally when IEP and SPEP are negative. Urine should also be examined since monoclonal light chains (Bence-Jones proteins) may appear in urine when the serum is normal. Presence of a light chain in urine suggests either a malignant PCD or light-chain amyloidosis (AL). Measurement of serum free light chains (FLC) was introduced into clinical practice in 2002 [22]. The presence of abnormal kappa/lambda ratio indicates the presence of PCD. In such situations, a 24-h urine for protein electrophoresis and IFE are indicated to detect and quantify the M protein in the urine [20].

After identification and characterization of the M protein in serum or urine, further hematologic evaluation should be done to classify the PCD (Table 30.1) [4, 19]. If a diagnosis of MGUS is made, M-protein levels should be monitored on a yearly basis since a sudden increase may indicate malignant transformation of a benign plasma cell dyscrasia, which occurs in up to 20 % of patients.

Polyneuropathy Syndromes

MGUS-Associated Neuropathies

MGUS is the most common PCD and detectable in 0.1 % of the normal population by the third decade [21, 23], and the frequency increases with age to 3 % by the eighth decade [23]. MGUS may be a contributing factor to neuropathy pathogenesis in 5 % of all neuropathies and 10 % of idiopathic neuropathies (Table 30.3) [1]. MGUS-associated neuropathies comprise the largest number of polyneuropathies associated with PCD [1]. These can be divided into IgM associated and non-IgM associated [13, 24]. The IgM group is further divided into those with and without anti-MAG (myelin-associated glycoprotein) antibody.

Table 30.4 Antibody activities of IgM in peripheral nerve disorders

Antibody activity	Clinical syndrome	Pathology
MAG	Sensory > motor polyneuropathy	SD
Acidic glycolipids	Polyneuropathy	?
Gangliosides GM1 and GD1b	Motor neuron disease	SD, ?AD
Chondroitin sulfate C	Sensory polyneuropathy	AD
Intermediate filaments	Polyneuropathy	SD
Neurofilament	Polyneuropathy	AD
Sulfatide	Sensory polyneuropathy	AD, SD
SGPG	Polyneuropathy	AD, SD

Data from Steck et al. [30]
Abbreviations: *MAG* myelin-associated glycoprotein, *SD* segmental demyelination, and *AD* axonal degeneration

IgM Monoclonal Gammopathy

MGUS-IgM Anti-MAG Antibody Neuropathy (Latov's Syndrome)

Latov and colleagues first described this syndrome in 1980 [6, 7], and now multiple studies have shown that about 50 % of all polyneuropathies associated with PCD are of the IgM type and, of these, half have anti-MAG activity [6, 7, 24–29]. Anti-MAG is a glycoprotein with neural adhesion properties located in the myelin sheath of peripheral and central nervous system. Other anti-nerve antibodies (Table 30.4) are much less common and are less clearly related to the polyneuropathy.

Table 30.5 Major electrodiagnostic features of PN associated with PCD

Type of PN	demyelination	Axonal	CTS	Pure sensory	Other
MGUS-IgM	+++	+	–	++	+
MGUS-IgG,A	++	++	–	+	+
OSM	+++	+	–	–	–
PSA	–	+++	++	+	+++[a]
MM	+	++	+	+	++[b]

Data from Kelly [13]

Abbreviations: *PN* polyneuropathy, *PCD* plasma cell dyscrasia, *CTS* carpal tunnel syndrome superimposed on polyneuropathy, *MGUS* monoclonal gammopathy of undetermined significance, *OSM* osteosclerotic myeloma, *PSA* primary systemic amyloidosis, *MM* multiple myeloma

[a]Autonomic involvement

[b]Root involvement and polyradiculopathies superimposed on PN

Clinical Presentation

Anti-MAG neuropathy is the most firmly this established and best characterized of the anti-nerve antibody neuropathy syndromes. The frequency of detection of this syndrome has increased steadily due to better recognition of the syndrome and the wider availability of the anti-MAG antibody test. As mentioned, the estimated frequency is 1–5 per 10,000 adults [6]. Based on our experience and that of others, a fairly consistent clinical picture has emerged. Patients are usually older (sixth through ninth decades) and predominately men [24, 31]. These patients typically present with the slow and insidious onset, over months to years, of sensory gait ataxia and progressive ascending numbness, usually with minimal pain or autonomic involvement. Intention tremor may be prominent in some [14, 24, 32–35]. Weakness is usually much less pronounced, and indeed, early on, the clinical picture may resemble the sensory neuronopathy syndrome with predominant discriminatory sensory loss (i.e., vibration and joint position sense) and preserved power. The manifestations are quite symmetric and progress in a slow and steady distal to proximal fashion, similar to a length-dependent axonopathy. However, most patients have palpable thickening of proximal nerves, a finding generally associated with demyelination and re-myelination, which are absent in axonopathies.

Diagnostic Studies

ELISA and Western blot both have been used to detect anti-MAG antibody; however, ELISA testing for MAG antibody is more sensitive and easier to perform than Western blot and the preferred assay [36]. Electrodiagnostic studies, especially nerve conduction and electromyography (Table 30.5), are helpful in suggesting the diagnosis. Sensory nerve action potentials are absent or severely attenuated. Despite the fact that weakness is generally not pronounced in these patients, there is often marked slowing of motor conduction velocities and severely prolonged distal latencies in the "demyelinating"

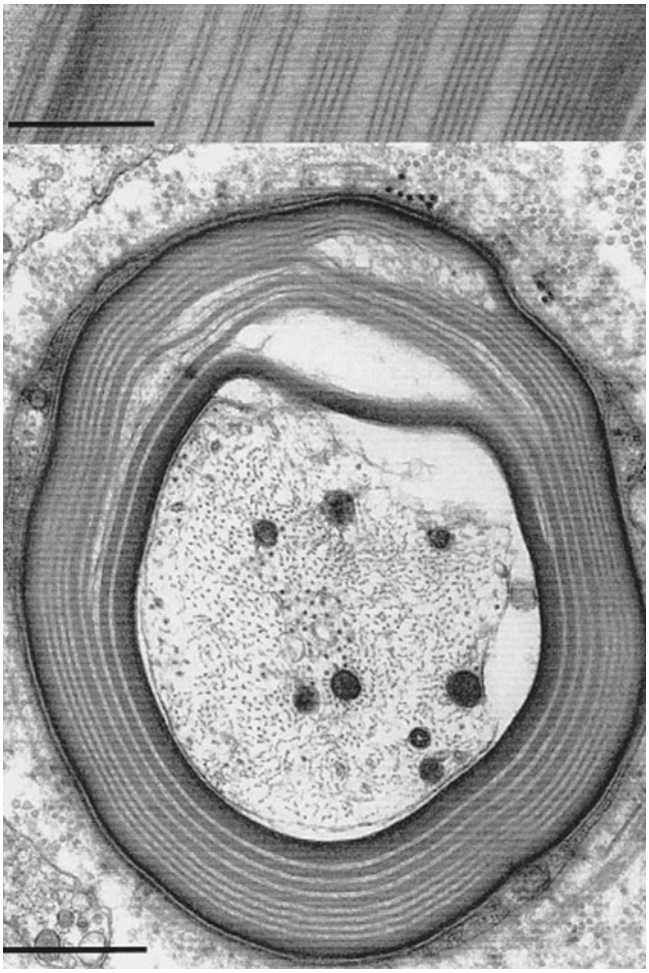

Fig. 30.1 Electron micrograph of a transverse section through a nerve fiber with enlarged periaxonal space and myelin splitting (Adapted from Cai et al. [38], with permission from Wiley publishing)

range associated with conduction blocks and focal areas of dispersion of the motor-evoked potentials. In one study, the highest anti-MAG titers correlated with the most delayed distal latencies and slowest motor conduction velocities [37]. Cerebrospinal fluid protein concentration is usually increased to greater than 100 mg/dl in advanced cases. Although spinal fluid and electromyography can suggest the etiology in the proper clinical setting, the diagnosis is firmly established by nerve biopsy and serological studies. Electron microscopic examination of nerve biopsy specimens has demonstrated widening of the myelin lamellae in more than 95 % of patients [29], as well as segmental demyelination with deposits of M protein and complement in the myelin sheath (Fig. 30.1) [39–42].

Anti-MAG antibodies may predict the subsequent development of neuropathy in asymptomatic patients [43] with the ELISA disclosing high titers of serum MAG antibodies in these patients. The IgM appears to react with a carbohydrate epitope which is shared by MAG and other glycoproteins

and glycolipids of the nervous system [44]. Recognition of these patients is important since treatment which lowers anti-MAG antibody levels can stabilize these patients or promote recovery.

Treatment

Treatment of these patients is difficult. They are often elderly and tolerate immunosuppressive drugs poorly. In addition, current therapies are effective temporarily and associated with side effects. Therefore, until more effective or safer treatments become available, aggressive treatment should be reserved for patients with progressive disease or those with disability due to neuropathy [14]. In general, therapeutic reduction of anti-MAG IgM levels correlates with improvement of neuropathy [7, 24, 45, 46]. Therefore, treatment in patients with anti-MAG neuropathy is directed at reducing the antibody concentration either by depleting the monoclonal B cells or by passive removal. Plasma exchange was effective in 25–50 % of patients in two randomized trials [43, 47]. Rituximab, a B cell-depleting monoclonal antibody, is an effective therapy in anti-MAG neuropathy and particularly for sensory impairment [48–52]. It is emerging as the best agent available, providing long-term benefits to almost half of these patients [53]. In the first controlled study done by Dalakas et al., rituximab showed encouraging results in treating anti-MAG neuropathy [54, 55] with up to 65 % of MAG neuropathies, unresponsive to other treatments, improved after 8 months, and sometimes with long-lasting remission [54, 56]. The authors have a similar experience with rituximab; however, further trails required to evaluate the long-term toxicity and safety of this new treatment. Rituximab appears to work by suppression of the IgM as well as the anti-MAG antibodies and by inducing immunoregulatory T cells [53]. Cyclic intravenous or oral high dose of cyclophosphamide when used with corticosteroids [44] or plasma exchange [57] was effective in two open-label trials. The first double-blind randomized trial with cyclophosphamide and prednisone in IGM MGUS neuropathy showed same beneficial effect on muscle strength and sensation but no beneficial effect on functional scales [58]. In our experience, a 6–9-month course of oral cyclophosphamide allows stabilization or recovery in the majority of patients who can tolerate the treatment [24]. Other treatment options including interferon-alpha, chlorambucil, fludarabine, and high-dose chemotherapy followed by autologous bone marrow transplant have been reported in small series; however, all need to be confirmed in controlled randomized studies [59–62].

In general, it is desirable to lower the serum M-protein level by at least half although clinical response does not always correspond to success in lowering the M-protein level [63]. The clinical remission is often prolonged. Based on our experience, after therapy is stopped, the M-protein level gradually rises to pretreatment levels, the deficit begins to slowly re-accumulate, and re-treatment may need to be considered.

Although the tremor may improve in some patients who respond to immunotherapy, it remains disabling in most. Recently, unilateral thalamic deep brain stimulation (DBS) was applied in a patient unresponsive to plasma exchange, cyclophosphamide, corticosteroids, primidone, and gabapentin [53, 64]. The rationale was that thalamic stimulation interferes with the cerebellar circuits implicated in the generation of tremor. A sustained improvement in tremor control was identified.

MGUS-IgM Non-MAG Neuropathies

These neuropathies are more diverse and represent a quarter of the MGUS neuropathies [17, 26, 27, 65]. Some patients have axonal polyneuropathy by electrodiagnostic evaluation and biopsy [4, 65]. However, many have demyelinating features similar to anti-MAG neuropathy and are difficult to distinguish without serologic testing [26, 27]. Immunofluorescent studies are generally negative, and myelin lamellar splitting is not observed. IgM antibodies in these patients may react with a variety of antigens (Table 30.4), but these reactions are, for the most part, less clearly related to disease activity than in the case of MAG antibody neuropathy. Anti-Ganglioside antibodies are significantly associated with demyelinating neuropathy and specially the IgM isotype [66]. Anti-GD1b and anti-GQ1b are associated with predominantly large-fiber sensory ataxic neuropathy in one series and with predominantly motor neuropathy in another [41]. Anti-sulfate-3-glucuronyl paragloboside (anti-SGPG) antibodies have been identified in 91 % of demyelinating and 50 % of axonal neuropathies associated with IgM monoclonal gammopathy [67]. Anti-sulfatide neuropathy associated with an M protein is associated with both demyelinating and axonal neuropathy without pain component [41, 68, 69]. These demyelinating neuropathies may also respond to treatment with steroids and cytotoxics [70]. Some resemble chronic inflammatory demyelinating polyneuropathy (CIDP) and respond to more conventional treatment with steroids, plasmapheresis, and IVIG. Patients with primarily axonal polyneuropathy must be evaluated for amyloidosis [71]. Axonal neuropathies respond poorly to any presently available therapies.

IgG and IgA MGUS-Associated Polyneuropathies

This group accounts for about half of MGUS neuropathies and the nature of polyneuropathies is much less clear [1, 17, 65, 72]. These both are heterogeneous disorders. IgG MGUS neuropathy can mimic anti-MAG neuropathy with late-onset, distal sensory motor large-fiber dominant neuropathy

Table 30.6 Medical syndromes in amyloid polyneuropathy

Syndrome	Percent frequency (%)
Orthostatic hypotension	42
Nephrotic syndrome	23
Cardiac failure	23
Malabsorption	16

Data from Kelly et al. [17]

associated with tremor and sensory ataxia [23]. IgG MGUS type sometimes fits the picture of chronic relapsing and remitting demyelinating polyneuropathy similar to CIDP [73]. Finally, it may present with painful axonal neuropathy similar to amyloid neuropathy. IgA MGUS neuropathies can present with a distal sensorimotor neuropathy [23] or a CIDP-like picture as well [74].

In general, patients with axonal polyneuropathies respond poorly to therapy, while those with demyelinating features (CIDP form) are more likely to respond to conventional immunosuppressive treatment. In studies comparing IgM with non-IgM neuropathies, the non-IgM patients were found to have less sensory loss than those with IgM gammopathies and less demyelination on EDX studies [26, 27]. It is important to exclude amyloidosis, especially when there is a recent onset axonal neuropathy, with rapid progression, and pain or autonomic manifestations [71].

Primary Systemic Amyloidosis (PSA) and Light-Chain Amyloidosis (AL)

Clinical Presentation: PSA generally presents as a multisystem disease due to the deposition of fragments of the variable portion of a monoclonal light chain in tissue, most often lambda in 75 % of patients and kappa in the remainder [75–80]. PSA can occur alone or in association with MM or, much less often, Waldenstrom's macroglobulinemia. Patients present with either a medical disease with associated (sometimes incidental) polyneuropathy or with severe polyneuropathy with minimal organ involvement. A similar illness can occur in a variety of inherited amyloid polyneuropathies due to an abnormal circulating prealbumin (transthyretin) protein with a single amino acid substitution. Polyneuropathy does not occur in amyloidosis secondary to chronic inflammatory disease or familial CNS amyloidosis.

Peripheral neuropathy is the most common neurologic manifestation in PSA [16, 17]. PSA is perhaps the best characterized of the polyneuropathies associated with M proteins and accounts for up to one-quarter of cases in some series [71]. This neuropathy characteristically occurs in older men and is rare prior to the sixth decade. Most patients are not associated with an underlying illness, but a few are associated with hematologic malignancies such as myeloma and Waldenström's macroglobulinemia (see below). More commonly, however, patients have major systemic disease, and neuropathy is diagnosed as a result of neurologic examination or EMG to investigate associated neuropathic manifestations [81].

Medical complications (Table 30.6) include the nephrotic syndrome due to amyloid infiltration of the kidneys, cardiac failure due to amyloid cardiomyopathy, chronic diarrhea with wasting due to amyloid infiltration of the gut wall, and autonomic neuropathy with prominent orthostatic hypotension. General laboratory studies reflect the medical syndromes, with proteinuria occurring in a high-percentage, elevated erythrocyte sedimentation rate in about half and mild increase in benign-appearing plasma cells in bone marrow in many. Up to 90 % have an M protein in serum or a monoclonal light chain in urine when thoroughly screened with serum and urine IFE. Those patients lacking an M protein, if not an inherited condition, are called "nonsecretory," although immunocytologic studies of their tissue disclose that the amyloid derives from single (monoclonal) light chains. Presumably, the serum concentration is too low to detect light chains in these patients. The light chains are deposited in tissue where they are digested by macrophages with the production of insoluble amyloid fibrils.

The polyneuropathy has been well characterized [71]. Sensory symptoms are typically most prominent and the earliest to appear. Almost all present with numbness of the hands and legs with complaints such as burning, aching, stabbing, and shooting pains. In greater than half of patients, cutaneous sensations (light touch, pain, temperature) are more frequently and severely affected than discriminative sensations (vibration and position sense). About 20 % present with typical symptoms of carpal tunnel syndrome before distal neuropathy symptoms appear, due to amyloid infiltration of the flexor retinaculum of the wrist [17]. Amyloid neuropathy can rarely present with a relatively pure autonomic neuropathy due to amyloid deposition restricted to dorsal root ganglia, autonomic fibers, and ganglia [82, 83]. An asymmetric presentation of chronically progressive peripheral motor and sensory deficit has been associated with amyloid involvement of lumbosacral plexus and nerve roots, causing distal axonal degeneration [84]. Otherwise, the findings tend to be symmetric and predominant distally with gradual proximal spread. Most patients soon complain of autonomic dysfunction with orthostatic lightheadedness and syncope, bowel and bladder disturbances, impotence, and sweating disturbances. Hypoactive pupils and orthostatic blood pressure drop with a fixed heart rate are the most easily detected autonomic signs at the bedside.

Laboratory Studies: EDX studies (Table 30.5) confirm the presence of a distal sensorimotor axonal neuropathy, which is most severe in the legs [17]. Motor conduction velocities in the "demyelinating" range (<60 % of the mean normal for

Table 30.7 Results of biopsy in primary systemic amyloidosis with neuropathy

Site positive	Number of patients	Percent
Rectum	25	88
Kidney	4	75
Liver	2	100
Small intestine	2	100
Bone marrow	21	33
Sural nerve	10	100
Other (skin, gingiva)	2	100

Data from Kelly et al. [17]

that nerve) occur rarely and then only in severely affected nerves where the evoked compound muscle action potential is very low in amplitude. Sensory nerve action potentials are usually absent. Often, there is evidence of carpal tunnel syndrome, which can suggest the diagnosis. Needle EMG shows the changes expected of a distal axonopathy, with abundant signs of distal denervation and reinnervation. CSF is usually acellular, often with mild elevation of protein level in the 50–70 mg/dl range.

Serum protein electrophoresis (SPE) is abnormal in up to 33 % of patients with PSA. Urine or serum immunofixation electrophoresis (IFE) may detect M protein in 80–90 % of patients. In patients without detectable M protein with routine laboratory tests, serum free light-chain immunoassay or clonal assay of plasma cells on bone marrow biopsy may be helpful [85, 86]. Free light-chain assay is useful for follow-up of patients with amyloidosis who have undergone stem cell transplantation [85]. Autonomic function tests can detect abnormalities early in the disease even in asymptomatic familial amyloidosis carriers [87].

Diagnosis depends on the identification of amyloid in tissue. Sural nerve biopsy is useful in detection of amyloid, although occasionally it has to be sought through multiple sections. One study reported that 6 of 10 patients with PSA neuropathy had negative nerve biopsies [12]; therefore, biopsy of two high-yield sites is generally recommended, such as sural nerve and fat pad. Other useful tissues to biopsy (Table 30.7) include rectum, skin, bone marrow, salivary glands, and other affected organs. Abdominal fat-pad aspiration is simple, rapid, and effective technique for diagnosis with 80–90 % sensitivity [79, 88, 89]. Rectal and skin biopsy are also positive in more than 80 % of patients [16, 90]. Bone marrow biopsies show amyloid deposit in up to 60 % of specimens [91]. On nerve biopsy, amorphous deposits of amyloid on congo red or cresyl violet stains typically appear in the perivascular regions of the epineurium or occasionally in the endoneurium. Amyloid is classically defined by its appearance under polarized light where the congo red-stained deposits emit an apple-green birefringence. Electron microscopy can also be used to identify the characteristic beta-pleated fibrils. Immunofluorescent staining for monoclonal light-chain fragments is helpful but is technically difficult [92, 93]. However, newer molecular techniques such as mass spectrophotometry and immunohistochemistry of amyloid show promise in determining types of amyloidosis [94, 95]. Teased fiber studies show predominant axonal degeneration. The reason for nerve fiber damage, however, is not always readily apparent in all patients. In some instances, marked axonal degeneration appears with minimal amyloid infiltration, possibly caused by more proximal amyloid, perhaps at the level of the dorsal root ganglion.

Pathogenesis: Pathologic findings have led to many theories of the pathogenesis of the neuropathy including vascular and pressure changes by the amyloid deposits. However, direct toxic effects of the amyloid fibrils on nerve fibers and dorsal root ganglion cells seem more likely.

Treatment: Treatment is challenging. The amyloid fibrils are insoluble once deposited in tissue. Thus, it is unlikely that much improvement would appear, even with cessation of amyloid deposition. Melphalan and prednisone, with or without colchicine and other chemotherapeutic agents, have been tried in multiple prospective trials [65, 96–98]. Overall, melphalan and prednisone treatment, continued for at least 1 year, has resulted in increased survival rates. The highest response rate (39 %) was obtained in patients with nephrotic syndrome with normal serum creatinine levels and no echocardiographic evidence of cardiac amyloidosis. However, peripheral neuropathy did not respond [16, 17, 96, 98]. The combination of melphalan and prednisone has proved superior to colchicine [96], and the addition of colchicine to the above regimen did not add any benefit in one randomized trial [65]. Thus, a trial of alkylating agents and prednisone is warranted in every patient. Treatment with cyclophosphamide and dexamethasone with either lenalidomide [99] or bortezomib [100] has been found to be effective. There have been reports of benefit from high-dose chemotherapy with melphalan and steroids followed by peripheral blood stem cell transplantation [101–107]. Small numbers of bone marrow transplants have been reported to date; however, the reports have been encouraging. In one study, neurologic improvement occurred in 4 of 5 neuropathy patients [101]. Another group reported that 12 of 20 patients with amyloidosis had improved organ function following transplantation [102]. Thus, early peripheral blood stem cell transplantation in the first year for those with minimal organ involvement is now the treatment of choice if the patient qualifies [103, 104, 108, 109]. Unfortunately, many patients by the time of diagnosis are too advanced to benefit from this treatment. The number of organs involved is the most important factor in predicting survival [103]. Treatment of peripheral neuropathy is mainly symptomatic, with tricyclic antidepressants, analgesics, and neuropathic pain medication. Dysautonomia, particularly orthostatic hypotension, can be controlled with medication and compressive stockings.

Multiple Myeloma (MM) Neuropathy

Multiple myeloma is a malignant PCD with high serum and urinary concentrations of MP, infiltration of bone marrow by malignant plasma cells, and multiple bone plasmacytomas. Diagnostic criteria require the presence of at least 10 % plasma cells on examination of the bone marrow, M protein in the serum or urine, and evidence of organ damage [110]. Most neurologic complications are due to secondary effects of the tumor (hypercalcemia, infections), malignant infiltration of nerve roots, or secondary compression of spinal cord or nerve roots due to vertebral fractures. Polyneuropathies are uncommon with MM and reported as high as 3–5 % in large series [8, 9]. They occur in only a few percent of MM patients and are diverse in nature [111], similar to the polyneuropathies associated with other malignancies. The exception is osteosclerotic myeloma, discussed separately below. Subclinical neuropathy, however, can be detected in up to 40–60 % of patients with MM using electrodiagnostic tests or histopathologic evaluation [11, 12].

Peripheral Neuropathy in Typical Lytic Multiple Myeloma Without Amyloidosis

Neuropathy associated with typical lytic MM includes distal sensorimotor axonopathy, CIDP-like syndrome, and sensory neuropathy [13]. The sensorimotor neuropathy is often mild and slowly progressive. A pure sensory neuropathy variant resembles the sensory neuropathy associated with small cell carcinoma [13, 112]. Patients usually have disabling sensory ataxia with minimal weakness. The CIDP syndrome is a pure motor neuropathy with symmetrical proximal and distal weakness [13].

Peripheral Neuropathy in Typical Lytic Multiple Myeloma with Amyloidosis

Twenty to forty percent of patients with typical MM can develop neuropathies due to deposition of light-chain amyloid in nerves. In this case, the clinical picture is similar to primary amyloidosis without MM with typical distal axonal sensorimotor neuropathy and dysautonomia [13]. Superimposed root involvement may confuse the clinician by mistakenly suggesting a picture of mononeuritis multiplex. The root and cord compressive syndromes should be managed by conventional therapy, but, like nonmalignant primary systemic amyloidosis, the amyloid neuropathy does not respond to chemotherapy.

Osteosclerotic Myeloma (OSM) and Polyneuropathy (and Related Syndromes)

Osteosclerotic myeloma is a rare accounting for only 5 % of all myelomas and is relatively benign variant of MM [13, 113–116]. While polyneuropathy is rare with typical MM, it occurs in 50 % or more of reported cases with OSM. In contrast to typical MM, patients with OSM are usually not systemically ill. They present because of the neuropathy or other remote effects of the malignancy, rather than as a direct effect of the malignancy. Anemia, hypercalcemia, and renal insufficiency are uncommon in OSM. The bone marrow is rarely infiltrated with malignant plasma cells, and the serum M-protein concentration is low. Finally, the course of OSM is indolent; these patients have prolonged survivals even without treatment. Thus, there is something singular about the syndrome of OSM and its paraneoplastic accompaniments. For these reasons, the syndrome can be difficult to diagnose even by experienced clinicians.

Clinical Features: Unlike MM, the polyneuropathy accompanying OSM is distinctive and homogeneous. Deficits are mainly motor and slowly progressive without sudden changes in severity or tempo of progression. Patients present with the onset of weakness, mostly in distal limbs initially, with gradual proximal spread accompanied by reflex loss. Sensory loss is typically less striking and tends to disproportionately affect the larger sensory fibers with greater loss of discriminative than cutaneous sensation. Pain and autonomic dysfunction, with the exception of impotence (actually due to endocrine insufficiency), are very uncommon. Nerves are often palpably thickened. The deficit is usually symmetrical and the speed of progression is slow, often over months to years.

Laboratory Studies: General laboratory studies are usually relatively uninformative. The best clue to the diagnosis is the presence of a serum M protein, which is present in about 75–80 % of patients. However, the M protein may be small and obscured by the normal serum protein components in the electrophoresis, emphasizing the importance of obtaining an IEP or IFE in all patients with idiopathic polyneuropathy. The M protein is characteristically IgG or IgA, lambda light chain (rarely kappa), and rarely present in the urine, as opposed to MM and AL. EDX studies are helpful but nonspecific (Table 30.5) and reveal a mixed axonal and demyelinating picture which is also nonspecific but helpful in categorizing the neuropathy into the group with clear-cut demyelinating features and thus more likely to be diagnosed. Nerve biopsy studies disclose a reduced concentration of myelinated fibers with mixed demyelination and axonal degeneration. There may be foci of mononuclear cells in the epineurium surrounding blood vessels. These changes are nonspecific and observed in a number of neuropathies, including CIDP and diabetic polyneuropathy. The clinical and laboratory picture thus resembles CIDP. However, these patients are resistant to the usual therapies used to treat CIDP, such as steroid and IVIg. Therefore, all patients with progressive CIDP should have been evaluated for PCDs including serology testing for M protein and skeletal X-ray surveys.

CSF typically is acellular but with a high protein concentration, generally greater than 100 mg/dl and sometimes as high as several 100 mg/dl. Since these findings are nonspecific, the diagnosis often hinges on the discovery of the characteristic bony lesions and subsequent bone biopsy. The osteosclerotic lesions may be solitary or multiple. They tend to affect the axial skeleton and very proximal long bones but spare the distal long bones and skull. They may be purely sclerotic or mixed sclerotic and lytic. Radioactive bone scans, although more sensitive than X-rays as a rule in detecting myeloma and other bony metastases, are not as sensitive as X-rays in detecting OSM lesions, probably due to the indolent nature of these plasmacytomas. Thus, all patients with unexplained polyneuropathies who fit the clinical profile described above should be screened with a radiographic skeletal survey. On occasion, these lesions are misinterpreted by radiologists who are unfamiliar with their appearance and significance. Three of our patients were felt to have benign osteosclerotic lesions (fibrous dysplasia in a rib in two and a vertebral hemangioma in one) with negative radionucleotide bone scans. We typically pursue biopsy based on the clinical picture and the presence of a serum M protein, and with plasmacytomas being discovered, leading to institution of treatment. Thus, if there is any question of the significance of a bony lesion in a patient with a suggestive clinical picture, the neurologist with the radiologist should review the X-rays, and the lesion should be biopsied if doubt remains. Open biopsy is often preferable to needle biopsy in our experience.

Pathogenesis: The cause of the polyneuropathy is not known, but most theories focus on the disease being induced by a secreted product of the tumor, most likely the M protein itself. The tumor does secrete cytokines, interleukin-a beta, tumor necrosis factor-alpha, and interleukin-6, which may play a role in pathogenesis [59]. Studies of anti-nerve antibody activity in the serum of these patients and immunocytochemical studies of nerves have been negative. The pathogenesis of nerve damage and even whether it is an axonopathy or a primary demyelinating disorder remains unresolved.

Treatment: The diagnosis of this disorder is of more than academic interest since these patients may be helped by tumoricidal therapy. Patients with solitary lesions do best. Radiation therapy to the lesion or surgical excision results in elimination of the M protein from the serum and gradual recovery from the neuropathy and other symptoms over the ensuing months in most patients. However, these patients should continue to be followed since they have a tendency to relapse with the development of new lesions months to years later [117]. This is usually heralded by the return of the neuropathy and other symptoms and the reappearance of the serum M protein. Patients with multiple lesions are more difficult to treat, and in general, the outcome is less favorable than for solitary lesions. Radiation therapy is usually not an option due to the risk of toxicity. In some patients, aggressive chemotherapy, with or without local radiation therapy to large lesions, can be helpful [117–119]. Treatment usually requires large doses of steroids and alkylating agents. Treatments which are usually effective in autoimmune inflammatory neuropathies, such as steroids, azathioprine, plasmapheresis, and IVIG, are typically ineffective in these patients.

Systemic Features

The disorder is of clinical and scientific interest since many patients develop a multisystem syndrome, which goes by a variety of names including the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes) or the Crow-Fukase syndrome. More than 95 % of patients with POEMS syndrome have a monoclonal lambda sclerotic plasmacytoma or bone marrow infiltration [120]. Manifestations of peripheral neuropathy usually dominate their clinical picture and begin in the feet with tingling, paresthesia, and coldness [1]. Motor involvement follows the sensory symptoms. The course is usually progressive. Bone pain and fractures rarely occur [121]. NCS has typical demyelinating features. Conduction blocks, the hallmark of acquired demyelination, occur in only 6 % of patients with POEMS syndrome [122, 123]. In contrast to MM, the course is chronic with a reported median survival of 13.8 years [121].

The pathology of POEMS is an area of active research. These patients have, in addition to polyneuropathy, other features (Table 30.8) suggesting an underlying endocrinopathy or malignancy. The etiology of the endocrinopathy is unclear. Limited data suggests a disturbance of the hypothalamic-pituitary axis rather than primary end-organ failure, possibly due to antibody activity against pituitary tissue. Vascular endothelial growth factor (VEGF) and cytokines have been proposed as possible causes of POEMS syndrome, as an increase in the blood level of VEGF is usually present in these patients. VEGF may increase the permeability of the blood-nerve barrier, leading to the exposure of nerves to complement, thrombin, and other substances that are toxic to nerves [124–127]. Plasma VEGF is also useful in monitoring disease activity after treatment and correlates with clinical improvements better than hematologic response [128]. Patients are frequently found to have higher levels of interleukin (IL) B, IL-6, and tumor necrosis factor compared with MM [129]. Biopsy of affected lymph nodes generally discloses hyperplastic changes, sometimes resembling the pathologic findings in the syndrome of angiofollicular lymph node hyperplasia (Castleman's disease), which is a benign localized or generalized hyperplastic lymph node syndrome of unknown etiology. Patients with generalized angiofollicular lymph node hyperplasia without bony lesions may also have the manifestations of Crow-Fukase syndrome associated with serum M proteins or polyclonal gammopathies. Thus, it is likely that the main pathogenetic determinant of these syndromes is the presence of a serum product, most

Table 30.8 Non-neurologic abnormalities in 16 patients with OSM and polyneuropathy

Abnormality	Patients
Gynecomastia	2
Hepatomegaly	5
Splenomegaly	2
Hyperpigmentation	5
Edema	3
Lymphadenopathy	2
Papilledema	4
Digit clubbing	3
White nails	2
Hypertrichosis	3
Atrophic testes	3
Impotence	4
Polycythemia	5
Leukocytosis	3
Thrombocythemia	12
Hypotestosterone	5
Hyperestrogen	3
Hypothyroid	2
Hyperglycemia	1

Abbreviation: *OSM* osteosclerotic myeloma
Data from Kelly et al. [117]

likely the IgG or IgA lambda M protein or polyclonal antibodies with similar specificity, directed against neural and other tissue. For these patients, the term POEMS syndrome, which focuses attention on a small number of patients to the exclusion of others, is not entirely accurate [130]. For example, of the patients with OSM polyneuropathy, most have features other than neuropathy which are fragments of a multisystemic disorder, but only a few would qualify for the term POEMS (Table 30.8). Also, patients without myeloma may develop all the features of the POEMS syndrome. Thus, I prefer the term Crow-Fukase syndrome when referring to patients with polyneuropathy and multisystemic disorder.

There is no standard therapy for POEMS syndrome; however, radiation of isolated plasmacytoma or multiple lesions in a limited area, systemic chemotherapy (alkylating agents and corticosteroids), and peripheral blood stem cell transplantation should be considered [131].

Miscellaneous Syndromes

Waldenström's macroglobulinemia (WM) is a rare disorder and characterized by a monoclonal IgM paraprotein and morphological evidence of lymphoplasmacytic lymphoma [132]. Seventy percent of MPs in WM are kappa light chains. It is sometimes difficult to differentiate WM from IgM-MGUS, and the latter may evolve into WM over time (Table 30.1). Demyelination in electrophysiologic studies is much more commonly seen in IgM-MGUS compared with WM neuropathy [133]. This difference may reflect varied immune mechanism(s) in the two disorders. The most frequent neuropathy in WM is a distal symmetrical and slowly progressive sensorimotor neuropathy causing paresthesia and weakness that affect lower extremities predominantly [134, 135]. Other patients may have a CIDP-like picture, a typical amyloid polyneuropathy, or even the sensory neuronopathy syndrome usually seen with small cell cancer of the lung. MAG antibody is found in about half of these patients with features similar to anti-MAG neuropathy in MGUS. Dimopoulos and colleagues classified neuropathies in WM into five categories [135]:

1. IgM anti-MAG demyelinating neuropathy
2. Monoclonal IgM non-MAG with ganglioside reactivity and demyelinating neuropathy
3. Monoclonal IgM (with no known antibodies) neuropathy
4. Cryoglobulinemic neuropathy
5. Amyloid neuropathy

Many of the same treatments used for MGUS-associated neuropathy have been used for WM, including rituximab in IgM-related neuropathy [52, 55, 136]. In moderate to severe IgM neuropathy, a combination of cyclophosphamide, prednisone, and rituximab is recommended [137, 138]. In refractory cases, bortezomib or thalidomide, in combination with rituximab, has been used [139, 140], although bortezomib or thalidomide usage is limited due to their neurotoxic effect. High-dose chemotherapy and peripheral blood stem cell transplant may be considered as other therapeutic options [59, 121].

Cryoglobulinemia: Cryoglobulins are circulating immunoglobulins that reversibly precipitate at temperatures lower than 37 °C. Their presence in serum is referred to as cryoglobulinemia. This disorder is usually divided into 3 types [141]. In type 1, accounting for about a quarter of patients, the M protein itself is a cryoglobulin in the setting of a plasma cell disorder. Type 2 involves another 25 % of patients; the cryoglobulin is a mixture of an M protein of IgM type with rheumatoid factor activity against polyclonal immunoglobulins, usually occurring in the setting of a lymphoproliferative disorder. Type 3 occurs in the setting of a collagen-vascular or other chronic inflammatory disease, and the cryoglobulin consists of polyclonal immunoglobulins. The polyneuropathy in all these syndromes is painful, symmetrical or asymmetrical, sensorimotor, and axonal in nature. Gemignani and colleagues reported that sensory neuropathy, often in the form of small-fiber sensory neuropathy (76 %), is by far the commonest form of neuropathy in mixed cryoglobulinemia [142]. They reported sensory motor polyneuropathy in 15 % of patients. In this large series, sensory neuropathy was found to mainly affect women in the sixth and seventh decades and was the initial manifestation of mixed cryoglobulinemia in about half of the patients. About one out of ten patients have an extensive mononeuritis multiplex of acute or subacute

onset, frequently reflecting a necrotizing vasculitis of the nerve [142–146]. Purpura occurs in distal limbs in a high percentage of patients, and the neuropathy is generally considered to be due to a vasculopathy or vasculitis of skin and vasa nervorum. Symptomatic treatment includes low-dose steroid and analgesic and avoidance of cold exposure [121]. High-dose steroid, plasmapheresis, and cytotoxic therapy are indicated for severe cases [121, 147]. Several reports have emphasized the usefulness of rituximab in cryoglobulinemia [148–151]. A few case series and a recent randomized controlled trial demonstrate improvement of peripheral neuropathy with rituximab [150, 152–154].

Lymphoma and Leukemia. These cancers can be associated with MP and polyneuropathy. In lymphoma with IgM M protein, the IgM may have anti-MAG activity with the usual associated clinical and pathological features. Other syndromes without clear anti-nerve activity in the M-protein fraction may respond to ablation of the malignancy. Still others have an unclear relation to the malignancy and show little response to tumoricidal treatment or to lowering of the M-protein concentration in serum.

Conclusion

The topic of plasma cell dyscrasias and neuromuscular diseases has been a fruitful area for active research over the last decade. These patients are of great importance to recognize since treatment may lead to remission. Also, careful study of these patients may lead to a better understanding of the pathogenesis of polyneuropathies and possibly motor neuron disease. This may in turn lead to effective treatment for conditions for which there are now no effective treatments. Therefore, despite their relative infrequency, increased recognition of these disorders will continue to be a high priority for peripheral nerve specialists and general neurologists.

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Diabetic Neuropathies

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Shawn J. Bird and Mark J. Brown

Introduction

Diabetic polyneuropathy (DPN) is the most common neuropathy and possibly the neuromuscular disorder most frequently encountered by internists and general physicians. DPN is responsible for substantial morbidity and is associated with increased cardiac mortality. Much is known about the clinical, electrophysiological, and neuropathological features of DPN. Excellent glycemic control has been shown to slow the progression of diabetic neuropathy. Despite many intriguing scientific observations, and decades of clinical neuropathy treatment trials, we still do not have disease-modifying therapies for those who cannot achieve good control. Diabetes mellitus is also associated with other forms of neuropathy, some of which are distinctive and yet subject to misdiagnosis and inappropriate management. Comprehensive publications have reviewed clinical and basic aspects of DPN and related disorders [1–4].

Overview of Diabetes Mellitus (Diabetes)

Diabetes is a metabolic syndrome with multiple causes. About 5 % of diabetics have the type 1 or ketosis-prone form, previously called juvenile diabetes. The usual cause is autoimmune necrosis of pancreatic β (beta) cells. Other causes of type 1 diabetes include pancreatitis, other illnesses, and pancreatectomy. The mainstay of treatment is insulin replacement. Patients with type 1 diabetes have fewer complications and a better prognosis than 30 years ago [5]. About 90 % of diabetics have type 2 diabetes, formerly called adult-onset diabetes. This results from relative insensitivity to insulin, often with gradual insulin loss. The pathogenesis of type 2 diabetes is multifactorial, with genetic predisposition, obesity, and inactivity as contributing influences [6]. Basic treatments include diet modification, weight loss, exercise, oral medications to increase insulin availability or improve insulin sensitivity, and insulin replacement. Individuals with type 2 diabetes may be undiagnosed for 5 or more years after laboratory and clinical evidence of the condition [7]. Less common types of diabetes include genetically determined insulin deficiency disorders and medication-induced diabetes [4]. Taken together the prevalence of diabetes is enormous. There are an estimated 25.8 million diabetics in the United States alone, including 26.9 % of persons age 65 or older [8].

Acute diabetic complications like ketoacidosis and hypoglycemia are generally associated with type 1 diabetes. Late complications occur with all types of diabetes. There is a strong correlation between the presence of late complications and the duration and severity of a patient's hyperglycemia. Late medical complications include atherosclerosis, cardiac disease, cataracts, retinopathy, and nephropathy. Late neurologic complications include neuropathies, cognitive impairment, Alzheimer disease, shingles, and other nervous system infections. Genetic factors, age, male gender, smoking, greater height, and other comorbid conditions are thought to influence susceptibility to late medical and neurologic complications. DPN, retinopathy, and nephropathy often coexist. However, the rate of progression for each may vary in the same individual.

Criteria for the Diagnosis of Diabetes

Internationally agreed-upon standards for the diagnosis of diabetes are regularly reviewed and updated by the American Diabetes Association and published on-line and in Diabetes Care [9]. The diagnostic gold standard remains the 2-h fasting

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glucose tolerance test (GTT), done with a 75 g glucose load. The test should be repeated once if other measures do not support the diagnosis of diabetes. A fasting plasma glucose (FPG) of ≥126 mg/dL, or a 2-h glucose of ≥200 mg/dL, indicates diabetes. Plasma glucose levels are about 10–12 % higher than comparable whole blood glucose measurements. Diabetes can be diagnosed if plasma glucose is ≥200 mg/dL in association with symptoms of hyperglycemia.

The hemoglobin A1c (A1c) test is invaluable for monitoring glycemic control over the previous 3 months. More recently the A1c has been accepted as a screening tool for populations at risk for diabetes [9]. The A1c test has advantages over the GTT. There is no need for fasting and only a single blood specimen is required. An A1c value of ≥6.5 % indicates diabetes if the test method is certified and standardized. The test should be repeated if there is no supporting evidence of diabetes. A disadvantage is that the A1c level is not as sensitive for detecting new cases as GTT or FPG measurements [10].

Individuals with elevated blood glucose levels or glucose intolerance not meeting criteria for diabetes are called "borderline diabetic" or "prediabetic." Borderline diabetics are at a higher risk for developing diabetes than controls. Individuals with an FPG of 100–125 mg/dL or a 2-h post-glucose load PG of 140–199 mg/dL, or with AIC levels in the 5.7–6.4 % range, meet current criteria for borderline diabetes. About 3 % will develop overt diabetes each year. Those with a fasting glucose of 110–125 mg% should be followed, usually with a GGT. The relationship between neuropathy and borderline diabetes remains uncertain. There is a general understanding that borderline-diabetic individuals are more likely to have a coexisting sensory neuropathy than controls without IFG or IGT, but the epidemiologic importance of this association remains uncertain.

Classification of the Diabetic Neuropathies

Studies of large North American and European diabetic populations have shown that about 50 % have symptoms and/or signs of polyneuropathy. Diabetes specialists may use the designation "typical diabetic neuropathy" to indicate DPN, the most common phenotype. Patients with other patterns of neuropathy are classified as having "atypical diabetic neuropathy" and are often candidates for neurologic referral. Another classification scheme is based on the clinical course. "Chronic diabetic neuropathy" in this context usually means DPN. "Acute diabetic neuropathy" encompasses mononeuropathies, radiculopathies, radiculoplexopathies, and polyneuropathies with acute or subacute onset. In this chapter, we use a third classification scheme system that considers the topography of peripheral nervous system involvement along with the clinical course (Table 31.1).

Table 31.1 Classification of diabetic neuropathies by clinical course and topography

Diabetic polyneuropathy (DPN)
Mixed sensory-autonomic-motor polyneuropathy
Predominantly small-fiber polyneuropathy
Predominantly large-fiber polyneuropathy
Predominantly autonomic neuropathy
Asymptomatic polyneuropathy
Subacute painful polyneuropathy with changing glycemic control
Other patterns of polyneuropathy associated with diabetes
Chronic inflammatory demyelinating polyneuropathy (CIDP) with DPN
Distal motor polyneuropathy
Proximal motor neuropathy (also known as diabetic amyotrophy or diabetic lumbosacral radiculoplexus neuropathy)
Mononeuropathies and radiculpathies without focal nerve compression
Cranial mononeuropathies
Truncal radiculoneuropathies
Limb mononeuropathies
Mononeuropathies with focal nerve compression

Diabetic Polyneuropathy

Diabetic polyneuropathy (DPN) is a very slowly progressive disorder that may be asymptomatic for many years before discovery. The clinical features are those of a distal sensory-motor axonal polyneuropathy. The clinical and electrodiagnostic features of DPN are often indistinguishable from a wide range of acquired and genetically determined axonal neuropathies. There is no diagnostic test that can confirm DPN as the cause of polyneuropathy. The diagnosis is made by demonstrating that the patient has diabetes, that the pattern of neuropathy is consistent with DPN, and that a careful work-up has not shown another cause. The presence of other late diabetic complications, especially retinopathy and neuropathy, is strongly supportive evidence that the neuropathy is from diabetes. However and since diabetes is common, DPN may coexist with another peripheral nervous system disorder.

Symptoms of DPN

Because of the high prevalence of neuropathy with diabetes, every diabetic patient, with or without neuropathy symptoms, should be considered at high risk for having DPN. The earliest symptoms are distal, typically involving the toes and then the balls of the feet. For some, finger numbness is an early symptom. Over years, the entire sole, lower leg, and hands will become insensitive. Symptoms may include foot numbness with painless injuries; the false perception of cold, swollen, or hot feet; and the sense of walking on sponges or cotton. There may be spontaneous distal shock-like feelings

(paresthesias), burning pain, bone-deep aching, altered feelings when skin is lightly touched (dysesthesias), excessive responses after painful stimuli (hyperpathia), and discomfort with normally non-painful skin contact (allodynia). There may be non-healing ulcers and painless foot and finger injuries. Some report small foot muscle cramps early in the course, later followed by calf and finger cramps. Foot and leg discomfort may interfere with sleep. The patient or his family may be aware of leg restlessness, especially at night. Foot and hand weakness are late features that may not be recognized by the patient.

It is important to inquire about autonomic symptoms since they are underreported, often disabling, and an indicator of possible increased mortality from cardiac involvement. A report of dizziness on standing suggests orthostatic hypotension. There may be blurred vision in bright light from pupillary involvement. GI autonomic and somatic neuropathy leads to dysphagia, abnormal food absorption, gastric distention, constipation, diarrhea, and fecal incontinence. There may be overflow urinary incontinence. Standard doses of medications with anticholinergic properties may precipitate urinary retention. Male erectile dysfunction is common and an early symptom. Patients with longstanding diabetes may recognize that hypoglycemia no longer produces the warning uncomfortable autonomic symptoms. Most will not mention decreased sweating, especially if it is limited to the feet and small patches elsewhere. However, they will often express concern about compensatory hyperhidrosis of the trunk, neck, and face. Gustatory sweating is an unusual, incompletely understood autonomic symptom.

DPN and the Neurologic Examination

The resting pulse may be elevated because of cardiac autonomic neuropathy. Cardiac autonomic tests that can be done in the clinic with an EKG machine may show loss of normal R-R variability with breathing and decreased R-R variability with the Valsalva maneuver. Bedside tests for orthostatic hypotension may show a drop of systolic pressure of more than 20 mm after 1–3 min of standing [11]. When inspected the feet may be cool, suggesting diminished blood flow. Alternatively, diabetic foot temperature may be surprisingly warm with full pedal pulses and dilated foot veins, a manifestation of precapillary A-V shunting in the feet. In advanced cases, there may be signs of toe and foot vascular insufficiency from proximal leg artery disease. A potentially serious problem, and a predictor of future need for amputation, is foot pressure sores and ulcers. There may be unilateral or bilateral foot and ankle bone and joint degeneration with misshapen feet (Charcot foot). The degree of foot deformity is typically much greater than would be expected for the extent of foot proprioception loss. The cause of Charcot foot is not well understood. Lyons [12] opined that there is merit to both the "German" theory (micro-neurotrauma to insensate joints and ligaments) and the "French" theory (hyperemia followed by bone absorption).

Pupils may be irregular and react sluggishly. The sensory examination requires techniques that are able to detect loss of unmyelinated and small caliber myelinated sensory functions. Early findings are distal pin prick and cold temperature sensation loss. Since patients with longstanding distal neuropathies may judge blunted cold or pin prick feelings as normal, it is important to test proximal sites first to establish a baseline. Like other length-dependent polyneuropathies, finger sensory loss does not become evident until foot sensory loss has ascended to the calf. If there is loss of cold or pin prick sensation up to the mid-thigh, then expect hand and distal arm sensory loss. It is helpful to document the level of lower and upper limb sensory loss. It is likely to ascend proximally if the neuropathy progresses. Vibration sensation loss typically follows small-fiber sensory loss. An examiner without special training in sensory testing may detect vibration sensation loss first, using the examiner's sensibility as a control. The Rydel-Seiffer tuning fork provides a numeric value indicating when vibration is no longer detected. Tests of toe and ankle position sensation are relatively insensitive and may appear to be normal even though the patient has sufficient proprioception loss to cause gait imbalance. Inability to feel the touch of a 10 g calibrated filament on the feet is a late neuropathy sign but an important one. Patients who cannot feel the filament have an increased likelihood of developing foot ulcers and subsequent amputations [13].

Once the sensory level has ascended to the calf, then ankle jerks are likely to disappear. Arm reflexes typically remain until late in the course of DPN. Clinically, motor involvement comes long after distal sensory signs and symptoms. Bedside testing of foot and toe strength may give unreliable results. An early sign is the inability of non-obese patients under age 60 to heel walk without shoes. This presages foot drop, tripping, and falls. Late in the course of DPN, toes may be excessively flexed, arches may be high or flat, and there may be abnormal areas of callous over the metatarsal-phalangeal joints. Hand weakness and atrophy are late features. Surprisingly advanced hand muscle weakness and atrophy may be evidence of a coexisting focal median or ulnar neuropathy. Weakness of cranial nerve-innervated muscles and proximal limb muscles is unusual with DPN and indicates another cause.

Most patients with DPN have slow neuropathy progression, year after year, with a mixture of sensory, autonomic, and motor symptoms. There are others with symptom patterns that appear to reflect selective nerve fiber-type vulnerability or an atypically rapid rate of progression. It is likely that these are outliers in the DPN spectrum. However, one

cannot exclude the possibility of a fundamental difference in neuropathy pathogenesis among symptom subtypes.

DPN with Predominantly Small Fiber-Type Sensory Symptoms

This is an especially challenging group of patients because the diagnosis may be elusive and pain symptoms may be slow to respond to conventional treatments. Burning pain, paresthesias, and allodynia are prominent and often intense. Pain distribution may be distal, starting in the feet, or may be generalized, affecting limbs, trunk, abdomen, face, and scalp areas. There may be autonomic symptoms with anorexia, gastroparesis, and orthostatic hypotension. Physical findings are typically limited to distal loss of small-fiber-type sensory modalities. Position sensation may be normal or mildly affected. Reflexes and strength are often preserved. A physical examination that does not focus on small-fiber-type sensory modalities may be misleadingly normal. If an expert's examination does not give clear results, then QST or quantitative assessment of cutaneous axons with a skin punch or blister biopsy may be helpful.

These patients tend to be young type 1 diabetics with poor glycemic control. If the patient has type 2 diabetes with recent weight loss, then plasma glucose levels may be in the normal or near-normal range. Treating physicians may be reluctant to accept diabetes as the cause of the patient's symptoms if glucose and Hgb A1c measurements are not elevated. If the diagnosis of diabetes is in doubt, then tests for other causes of small-fiber-type sensory neuropathy should be carried out.

The basis for the pain in this and other forms of DPN is not known. Nerve fiber analyses from patients with and without painful neuropathy have not demonstrated neuropathological differences that might be responsible for neuropathic pain. Standard neuropathic pain medications may be ineffective for diabetic small-fiber sensory neuropathy. Narcotics are often required when pain is most severe. For most patients, the pain resolves over 6 months to 2 years. Many are then able to return to their previous activities. The small-fiber-type sensory loss persists. Over time there may be progression to mixed modality DPN.

DPN with Predominantly Large-Fiber Sensory Symptoms

A subgroup of older patients with chronic poorly controlled DPN for decades has prominent loss of large-caliber sensory function. The presenting problem may be imbalance, frequent falls, or hand clumsiness. Most often they have long-standing DPN that is relatively painless. They may attribute unsteadiness to age or vertigo and not neuropathy. The neurologic examination shows loss of proprioception and vibration sensation below the upper arms and thighs, ankle and knee reflex loss, and weakness of toe and foot dorsiflexion. There may be dysautonomia. Since the likelihood for neuropathy reversal at this stage is small, glycemic control should not be intensified at the risk of hypoglycemic episodes. If the degree of neuropathy is greater than expected for the known duration and severity of the neuropathy, then other causes of neuropathy must be considered.

DPN with Predominantly Autonomic Neuropathy

These are typically type 1 diabetic patients with brittle diabetes. Autonomic dysfunction may be so severe that in-hospital care is required. There are almost always symptoms and signs of a coexisting sensory polyneuropathy that often are painful. Orthostatic hypotension may make walking unsafe. Gastric motility slowing may lead to delayed food absorption, anorexia, and obstipation. Bladder enlargement and urinary retention are expected features. There may be blunting of hypoglycemic awareness. Diabetic control may be poor and there is weight loss. Symptoms respond in part to supportive treatments. There is usually substantial functional improvement over months or several years. Successful efforts to reverse weight loss are often associated with symptomatic improvement.

Asymptomatic DPN

About half of patients with diabetes and neuropathy are not aware of neuropathy symptoms. This is because the neuropathy is mild, or the patients do not question the meaning of toe tingling or foot numbness, especially if progression has been slow. It is important to identify patients with subclinical neuropathy early because improved blood glucose control appears to be most successful if started early. Asymptomatic individuals who are told about DPN may be more willing to take the steps necessary to improve glycemic control. All patients with diabetes who are not known to have neuropathy should be tested for foot sensory loss at least yearly with a calibrated filament, especially if no other neurologic evaluation is planned.

Subacute Painful Polyneuropathy with Changing Glycemic Control

Diabetic patients may develop intense diffuse neuropathic pain after declining or improving glycemic control. These patients appear acutely ill and typically report unwanted

weight loss. The rapid onset and pain severity may suggest an acute vasculitic or toxic neuropathy. These are described here as a variant of DPN, but sudden worsening or improvement could reflect a process that is unique to the disorder.

Subacute painful neuropathy with *declining glycemic control*, referred to as "subacute cachexic neuropathy" or "diabetic neuropathic cachexia" [14, 15], is primarily a disorder of young adults with poorly controlled type 2 diabetes. Anorexia and unintentional weight loss are common, and there may be gastroparesis. Pain may be intense, requiring narcotics for control. There may be small-fiber-type sensory loss or more generalized axonal breakdown. Nerve conduction abnormalities may be surprisingly mild for the extent of pain and cutaneous hypersensitivity. Improvement is slow, over months, perhaps related to the rate of axonal regeneration. Weight gain usually precedes improvement and may be necessary for recovery. Symptoms improve over months or several years. There is a residual sensory neuropathy.

In contrast, subacute neuropathy with *improved glycemic control* ("insulin neuritis") appears after the initiation of treatments to improve diabetic control with either insulin or oral agents [16–18]. There is intense burning pain that is difficult to manage. Objective signs of neuropathy are usually mild. Strength is preserved as are reflexes, aside from reduced or absent ankle jerks. In one case, the sural nerve biopsy showed loss of small caliber axons and signs of axonal regeneration [17]. Narcotics are often required for pain relief. Nutritional supplements may be necessary to achieve positive calorie balance, with the unwanted side effect of worsening diabetic control. The painful period generally improves after more than a year of follow-up [18], but the underlying polyneuropathy remains.

Neuropathology of DPN

Our understanding of the pathology of DPN is primarily based on studies of sensory nerve biopsies, a small number of autopsy studies using modern methods, and peripheral nerve specimens from animals with experimental or spontaneous diabetes. There is nonspecific diffuse axon loss that is more evident in distal than proximal axon segments. Myelinated and unmyelinated fiber populations are normal, reduced, or absent. However, an increase in unmyelinated fibers numbers may occur in the course in some cases [19, 20]. Endoneurial capillaries are thickened, but microvascular occlusions are unusual [21]. Infarct-like lesions were observed in proximal nerves of patients with diabetic polyneuropathy [22, 23]. This, and focal areas of axon loss in distal nerves, suggests that at least in some of the apparent length-related distal axon, loss may be the consequence of proximal axonal injury. Electron microscopy has shown increased glycogen in Schwann cells. Human axon-Schwann deformities at nodes of Ranvier have been observed but not by all investigators. Nodal changes have been suggested as a cause of nerve conduction slowing that is greater than predicted by changes in axonal diameter [24].

Nerve biopsy is now seldom done as part of the clinical evaluation for suspected DPN. Biopsy remains a useful tool when looking for other causes of neuropathy like amyloidosis, vasculitis, CIDP, or leprosy. Skin biopsies have low morbidity and provide a means for examining, staining, and counting intradermal nerve axons to confirm a small-fiber-type neuropathy. Material can be obtained from distal and proximal sites using skin punch biopsy or skin blister biopsy. Normal values are now available to take age-related axon loss and variable fiber densities from similar sites. Malik [25] and others have shown that corneal confocal microscopy can demonstrate changes in corneal axon morphology and density in a noninvasive way. This method is currently limited by the need for considerable technical expertise at the testing laboratory.

Clinical Neurophysiology of Diabetic Polyneuropathy

The peripheral nervous system is relatively accessible and thus allows the clinician to directly study nerve conduction from sensory, motor, and mixed nerves. Such nerve conduction studies (NCS) contribute to the measurement of axonal loss. NCS, along with quantitative sensory testing (QST) (see below), may detect neuropathy that is not yet clinically apparent. NCS may help determine if there are superimposed compression neuropathies, such as carpal tunnel syndrome or ulnar neuropathy at the elbow. Unmyelinated and small myelinated nerve fibers that subserve pain and autonomic function cannot be tested by standard nerve conduction studies. The function of these nerve fibers can be assessed by more limited, specialized techniques including autonomic function testing, QST, and intraepidermal nerve fiber (IENF) measures with skin punch biopsy.

The electrodiagnostic (EDX) evaluation of a patient with symptoms or signs of diabetic neuropathy usually is undertaken to confirm the presence of neuropathy, to determine its severity, and to look for another neuromuscular disorder that may produce such symptoms. This approach does not differ from that used to evaluate any patient with suspected polyneuropathy. A number of common disorders may mimic diabetic polyneuropathy and electrophysiologic studies may help differentiate the potential causes. For example, multiple lumbosacral radiculopathies due to lumbar canal stenosis may also produce distally predominant sensory and motor deficits with reflex loss. Patients with diabetes also may develop other neuromuscular causes of weakness, such as

motor neuron disease or chronic inflammatory demyelinating polyneuropathy (CIDP).

Electrophysiologic testing in diabetic neuropathy is primarily focused on nerve conduction velocities (CV) and evoked sensory and motor response amplitudes. Mean nerve CV values from populations of diabetics with symptomatic neuropathy are lower than those with normal matched individuals but only by 5–10 m/s [26–30]. Individual values may be normal in that they do not fall below the lower limit for normal controls. Asymptomatic diabetics also have mean CVs that are slower than matched controls [29, 31]. There is a positive correlation between the clinical severity of neuropathy and extent of CV slowing for type 1 and type 2 diabetics [32]. There is also a positive correlation between the degree of slowing and the duration of diabetes [30, 33]; F-wave and distal motor latencies in diabetic patients are prolonged in proportion to the slowing of leg or forearm CVs, indicating that conduction slowing is in general a diffuse process. However, slowing is more prominent in the lower extremities [34].

Nerve conduction slowing may on occasion be greater than one would expect from loss of large-fiber axons alone. Parallel biopsy studies have shown that this cannot be explained by segmental demyelination [24]. The basis for this additional slowing is not known. Metabolic factors are suspected. It is known that nerve conduction may slow shortly after induced hyperglycemia. Normalization of elevated blood glucose, or treatment with aldose reductase inhibitors and other compounds, may improve this slowing [35–37]. In experimental animals, these velocity changes occur without convincing alterations of Schwann cells or axons. Cool limb temperature slows conduction, and warming improves it. Transient biophysical alterations at nodes of Ranvier are likely to be responsible. These small changes in velocity are of uncertain clinical importance. They are not thought to result in sensory loss or weakness, but they may play a role in the development of fluctuating paresthesias during blood glucose fluctuations.

NCV is influenced by multiple factors, including the integrity of the largest diameter fibers, the presence of demyelination, and limb temperature. NCV can fall to 70–75 % of the lower limit of normal from large and medium axon loss alone. Once these myelinated axons are largely gone, there is no recordable distal response after nerve stimulation. Motor CVs below 70 % of the lower limit of normal, a sign of demyelination, are rarely seen with DPN when technical factors like low limb temperatures are corrected. In a study comparing the diagnostic accuracy of criteria used for the diagnosis of CIDP, Bromberg [38] included 63 patients with diabetic neuropathy. None of the diabetic patients met electrophysiologic criteria for CIDP. In a study looking for conduction block in diabetic neuropathy, only 6 of 76 nerve segments studied demonstrated block (defined as a >20 % peak-peak amplitude drop with a <15 % change in negative-peak duration), with a range of block from 21 to 41 % [39]. Likely none of these would meet current criteria for partial conduction block [40]. Thus, if there is electrophysiologic evidence of primary demyelination, with marked CV slowing or conduction block, then other causes of neuropathy should be sought.

Sensory nerve action potential (SNAP) and compound muscle action potential (CMAP) amplitudes are the result of potentials generated by functioning axons under recording electrodes. Loss of axons results in smaller response amplitudes. In DPN, SNAP amplitudes are more likely to decrease before CMAP amplitudes. The amplitude changes are most evident at distal sites [41]. A reduction of the sural SNAP is the most sensitive EDX abnormality in early DPN [26, 42]. Sural SNAP abnormalities have been recorded in up to 40 % of diabetics [24, 43]. Sural and superficial peroneal SNAPs are almost always reduced and may be absent from patients with a chronic DPN. In those with moderate or severe neuropathy, the distal lower extremity CMAPs are also reduced by 50 % and often both the SNAPs and CMAPs in the distal lower extremities are absent.

Needle electromyography (EMG) is helpful to document the extent of muscle denervation and reinnervation when present. This gives an additional measure of the extent of motor axon loss and a sense of the chronicity and activity of the neuropathy. Needle EMG also assists to confirm the length-related pattern of axon loss, where distal muscles are more denervated than proximal ones. Needle EMG may be helpful if there is reason to suspect another disorder, such as myopathy or motor neuron disease.

Other clinical electrophysiologic tests are available. Near-nerve sensory conduction studies can measure more slowly conducting potentials from the small myelinated fibers not assessed by standard clinical techniques [44]. In a study of 27 diabetic patients with mild clinical neuropathy, a correlation was seen between the slowly conducting nerve responses obtained by this technique and cool detection thresholds as measured by quantitative sensory testing [45]. Single-fiber EMG is a specialized technique that provides a sensitive measure of motor nerve reinnervation. Reinnervation is an early marker of motor axon loss. It is accompanied by abnormalities of fiber density and jitter and can be assessed by single-fiber EMG. Bril and coworkers [46] studied 90 diabetic patients with clinical neuropathy and found single-fiber abnormalities in all, even though 18 % had normal NCSs. These abnormalities also correlated well with poor diabetic control.

Clinical Autonomic Testing

Autonomic nervous system (ANS) testing consists of a variety of techniques aimed at assessing the small myelinated and unmyelinated nerve fibers that make up the peripheral

components of the autonomic nervous system. These nerve fibers cannot be studied directly, so it is necessary to use provocative tests. Currently available autonomic tests can provide measures of cardiovagal, adrenergic, and postganglionic sudomotor function (see Chap. 10). The complex nature of the tests and multiple confounding factors produce a considerable degree of variability. It is imperative that well-standardized techniques be employed to reduce the inherent variability [47, 48].

Cardiovascular heart rate (HR) tests are the most widely studied and best validated in diabetics with neuropathy [49–51]. These tests have about the same sensitivity to detect the presence of diabetic neuropathy as do NCS [31]. The most frequently used test is HR variability to deep breathing. This variation in HR (measured as the R-R variation) is produced by sinus arrhythmia, where the HR increases with inspiration and decreases with expiration. Slow and deep breathing at six times per minute maximizes this effect. A number of medications, aging, and other test factors can influence the results and must be taken into account. The other widely used test is the HR response to a standardized Valsalva maneuver. The sensitivities of the HR response to deep breathing and to the Valsalva maneuver are similar, and both are correlated with the duration of diabetes and severity of polyneuropathy. In a study of 261 patients with diabetic neuropathy, cardiovascular testing abnormalities were present in 0 % of normal controls, 13 % of diabetic patients without neuropathy, 34 % in those with subclinical neuropathy, 49 % with clinical neuropathy, and all of those with autonomic symptoms [52]. Abnormalities in these studies may be seen early, often at the time of diagnosis [53].

The most readily available quantitative measure of sudomotor function is the quantitative sudomotor axon reflex test (QSART). Sudomotor function can be quantitatively assessed by this method in which there is good normative data and the techniques can be rigidly standardized. Acetylcholine is iontophoresed into the skin and the resultant sweat response is measured using a sudorometer that quantifies the change in humidity over the skin [54, 55]. This device is commercially available and allows recordings to be made with less than a 20 % coefficient of variation. In a study of 73 patients with diabetic neuropathy, 58 % had an abnormal QSART response from the foot and this correlated with other cardiovascular measures of autonomic dysfunction [56]. Several studies have confirmed that QSART can detect distal sudomotor loss in patients with neuropathy with a high sensitivity and specificity [48].

The sympathetic skin response (SSR) is a transient reflex change in the electrical potential of the skin that can be elicited by stimuli that produce a central sympathetic discharge [56–58]. These include a painful electrical shock or an inspiratory gasp. SSR testing can be performed easily in an EMG laboratory. Limitations of the test include marked variability among normal individuals and it quickly habituates. Some have found this technique to be useful in measuring sudomotor involvement in diabetic neuropathy [59–62]. The SSR correlates with small-fiber involvement as determined from biopsied sural nerves [60] and with microneurographic evidence of abnormal autonomic physiology [59, 63]. Bril and colleagues [64] measured the SSR in 337 diabetics and found no correlation with symptoms of pain, autonomic dysfunction, or cool detection thresholds on quantitative sensory testing but did identify a relationship with sural SNAP amplitudes and vibration detection thresholds. They concluded that the SSR is not a reliable index of autonomic dysfunction in diabetic neuropathy.

Pathogenesis of Diabetic Polyneuropathy

Physicians have known about a relationship between diabetes and peripheral nerve symptoms, including foot ulcers, since the late nineteenth century [65]. In a landmark paper, Pirart [66] reported on 4,400 patients in his personal practice. He observed a correlation between the severity and duration of hyperglycemia and diabetic complications.

The pathogenic link between diabetic complications and hyperglycemia was strengthened by the results of the Diabetes Control and Complications Trial (DCCT) [67]. In this study, a cohort of 1,441 type 1 diabetics with no meaningful complications was followed for 5 or more years. The control group was treated with insulin to achieve standard good glycemic control. The intervention groups were managed the same way, except that intensive multi-dose insulin therapy was administered to achieve best-possible glycemic control. This resulted in Hgb A1c levels that were about 2 % lower than the control group. In the primary prevention group, the incidence of neuropathy was reduced from 10 to 3 % (69 % risk reduction). In a secondary intervention group, individuals with mild complications, the incidence of neuropathy was reduced from 16 to 7 % (57 % risk reduction). There were similar benefits for nephropathy and retinopathy. Individuals in the intensive treatment group maintained an advantage over the conventional treatment group years later if their Hgb A1c levels declined to that of the standard treatment group. This has been interpreted as evidence that a period of intensive glycemic treatment may confer a future advantage, even for individuals who cannot maintain that level of glycemic control. The mechanism for this memory effect remains obscure.

A similar benefit from glycemic control was found for type 2 diabetics. In the United Kingdom Prospective Diabetes Study [68], 3,867 of type 2 patients were treated with oral agents for an average of 10 years. The group with modest improvement of glycemic control (mean Hgb A1c of 7.0 %) had a 25 % risk reduction in microvascular complications when compared to a standard treatment group (mean Hgb A1c of 7.9 %).

Table 31.2 Mechanisms that have been implicated in the pathogenesis of DPN

Direct glucose toxicity
Insulin deficiency
Hyperglycemia-related metabolic derangements
Excess flux of sugar alcohols, accumulation of fructose and sorbitol, reduced nerve inositol
Reduced Na^+/K^+ ATPase at nodes of Ranvier
Slowed axonal transport
Deficiency of growth factors that support neurons
Oxidative stress with apoptosis, mitochondrial dysfunction
Nitrogen-based free radicals (nitrative stress)
Microvascular and circulatory abnormalities
Decreased nerve blood flow, endoneurial ischemia, depressed prostaglandins
Impaired vasodilation by nitric oxide
Abnormal nonenzymatic glycosylation of neural and other proteins
AGE deposition with alteration of RAGE receptors and other proteins
Altered nerve/endothelial protein functions
Autoimmune-mediated neurotoxicity
Abnormal signaling to neurons by circulating advanced glycosylated end products

Hyperglycemia and/or insulin deficiency are now considered central factors for determining diabetic complications. However, the variability of complications among seemingly similar patients indicates that there are coexisting modifying factors. These include hyperlipidemia, older age, male gender, smoking, and as yet unknown genetic factors. Although glucose is essential for the maintenance of neuronal function, elevated blood glucose may be toxic to peripheral nerves. Intravenous infusions of glucose can rapidly increase the intensity of neuropathic pain [69] and reducing hyperglycemia may relieve pain [70].

Animal models of type 1 and type 2 diabetes have been helpful. However, there is little axonal degeneration, an important feature of human DPN. Diabetic animals develop nerve CV slowing that may improve with blood glucose lowering or many other interventions. Studies of drug-induced or genetic diabetes in experimental animals have pointed to a number of ways that hyperglycemia can affect peripheral nerve function (Table 31.2). Hyperglycemia leads to reduced nerve blood flow and potentially toxic endoneurial hypoxia, which appears to be independent of hypoperfusion. Potentially toxic oxidative stress may occur in this setting [71]. In experimental animals, there is depressed Na/K ATPase at nodes of Ranvier and slowing of nerve conduction.

Glucose may bind nonenzymatically not only to fetal hemoglobin but also to proteins in nerves and vessels, with a potential toxic effect on nerve function. These "glycation products" may interfere with axon and endoneurial vessel function [72]. Nerve growth factors are suppressed after hyperglycemia, which may lead to complex derangements in nerve homeostasis and cell death [1, 73]. Autoimmunity is a possible cause of diabetic polyneuropathy and other diabetic neuropathies. Circulating anti-neuronal antibodies are reported in some diabetics, and inflammatory cells are observed in nerves of patients with diabetic neuropathy. Vascular mechanisms are appealing because the other late complications of diabetes, retinopathy, nephropathy, and large vessel ischemia also have a vascular basis. Microvascular disease has not yet been convincing liked to DPN.

Clinical Trials for Diabetic Polyneuropathy

Research Criteria for Diagnosing Diabetic Polyneuropathy

The clinical recognition and characterization of diabetic neuropathy can usually be readily accomplished by a focused history and neurologic examination. For the purposes of research studies, it is necessary to use standard techniques to detect, measure, and follow neuropathy [50, 74, 75]. An expert panel systematically reviewed the literature to develop a case definition of distal symmetric polyneuropathy in order to standardize and facilitate clinical research studies [76]. Diabetic neuropathy was the focus of most of the high-quality studies analyzed. The panel assessed the diagnostic accuracy of neuropathic symptoms, neurologic signs (decreased or absent ankle reflexes, decreased distal sensation, distal muscle weakness), and nerve conduction studies (NCS). They concluded that the highest likelihood of polyneuropathy (a definition useful for clinical trials) occurs with a combination of multiple symptoms, multiple signs, and abnormal NCS. Restrictive diagnostic criteria are best applied in the research setting where they can provide a more rigorous approach to the population under study but are not practical in the routine clinical setting [50, 75].

The diagnosis of subclinical diabetic neuropathy requires the presence of an objective abnormality of peripheral nerve dysfunction, preferably on nerve conduction studies, in the absence of symptoms or signs of neuropathy. In this cohort of patients, it is especially important to perform the NCS carefully with the appropriate control of testing conditions and techniques as well as the use of appropriate reference values [75, 77].

Measurement of Diabetic Neuropathy

There are several neuropathy composite scores that incorporate neurologic signs and have been well validated. These have been used as an outcome measure in clinical trials. These include the Michigan Diabetes Neuropathy Scale (MDNS) [78], the lower extremity portion of the Neuropathy Impairment Score (NIS-LL) [79, 80], and the Total Neuropathy Score (TNS) [81]. More recently, the Utah Early

Neuropathy Scale has been developed that includes more measures of small-fiber sensory function, a potential advantage in mild diabetic neuropathy [82].

Electrophysiologic testing in diabetic neuropathy is primarily focused on NCS. The issues relating to the electrodiagnostic confirmation of polyneuropathy are listed in the diagnosis section with regard to patients in clinical practice. In the setting of clinical trials, there is a trade-off between identifying patients with mild polyneuropathy with NCS criteria that may allow normal patients ("false positives") into the study who do not actually have neuropathy versus more rigorous criteria that have a higher specificity but may require the screening of a large number of patients to meet these stricter criteria. Dyck and colleagues [77] have carefully modeled eight different NCS criteria for the diagnosis of diabetic polyneuropathy. They concluded that the best criteria combined a composite score of normal deviates (from percentiles) of NCS.

When performing NCS as part of a longitudinal study, as is commonly done in clinical trials of new therapies, a special set of issues arises. Diabetic neuropathy is a slowly progressive disorder and thus small changes need to be detected over the usual study periods of less than 2 years. Over the 5-year DCCT study period, there was a 54 % mean risk of developing clinical neuropathy in the primary prevention cohort. This corresponded to a 0.8 m/s/year difference in the peroneal motor nerve CV between the experimental and control groups. The secondary prevention cohort showed a mean change in peroneal CV of 0.5 m/s/year, compared to the conventional treatment group [83]. Similar figures were obtained from smaller studies, such as the Oslo Study [84]. The goal of detecting a statistically significant difference of 0.5 m/s/year (e.g., 1.0 m/s over a 2-year study period) compared to untreated controls can be a daunting task.

NCS studies for clinical trials are usually performed at multiple centers that are widely distributed. The variability among sites can be reduced by requiring the use of the same techniques (electrode locations, measurements, skin preparation), standard equipment (particularly recording electrodes), and minimum limb temperatures. Training in the techniques used in the study should be provided in person in a centralized location and with a manual of the procedures to be followed. A central review of the data by experienced clinical neurophysiologists allows feedback and corrections to the sites as the study is in progress [85–87].

The test-to-test variability inherent in NCS needs to be considered as well. A 20 % change by chance alone at 1 year would obscure the true effects of an agent intended to result in a 20 % improvement. The reproducibility (coefficients of variation) of these measures in clinical trials has been reported to be 4–10 % for CVs, 15–75 % for amplitudes, and about 10 % for F-waves latencies [85, 87–90]. These studies may be performed in triplicate on different days to reduce this variability considerably [87].

Quantitative sensory testing (QST) allows more precise measurement of sensory function through the determination of the absolute sensory threshold to various stimulus modalities [91]. In these studies, the measured thresholds are the minimum vibratory or thermal (cold or warmth) stimuli that are detected using established psychophysical techniques. QST has advantages over the bedside sensory examination. The equipment provides precise control over the stimulus intensity in a graded fashion, there are validated testing algorithms, there is less subject or tester bias, and a numeric value is produced [92]. An individual's measured values can be compared with established normative data. This may be helpful in screening for mild neuropathy where there are few symptoms or signs. They may also provide information not readily assessed by NCSs, which provide information about the fastest conducting large diameter sensory nerves that primarily are associated with the modalities of vibration and proprioception. QST also measures the function of small-diameter nerve fibers that subserve pain and thermal sensation. These values may be assessed longitudinally or can be correlated with the development of other complication of diabetic neuropathy, such as foot ulcers.

QST abnormalities correlate well with the presence of neuropathy in diabetic populations [74] as well as individual patients. Vibratory detection threshold (VDT) testing at the standard frequencies (125 Hz) measures the function of Meissner and Pacinian corpuscles and their large diameter sensory nerve fibers. VDT abnormalities are associated with loss of the Achilles tendon reflexes and have been correlated with the development of diabetic foot ulcers [93]. VDT abnormalities have been shown to be related to longer duration of diabetes and sensory loss and areflexia on clinical examination, but not with neuropathic symptoms [94]. Thermal detection threshold reflects the integrity of the free nerve endings and their associated small-diameter myelinated and unmyelinated nerve fibers. Both warm and cold detection thresholds (CDT) can be assessed, have been validated, and correlate well with small nerve fiber dysfunction [95, 96]. In a large prospective study of 380 diabetic patients, abnormal VDT and CDT were strongly correlated with clinical examination deficits and abnormalities on NCSs [31]. Greater abnormalities in these QST attributes also were associated with increasingly severe degrees of clinical neuropathy. Heat-pain thresholds may also be measured as an additional attribute of small-fiber sensory function [97].

Since a relatively reproducible quantitative threshold value is measured, QST studies are well suited for use in longitudinal studies. As such, QST is an important endpoint in clinical trials of pharmacologic agents aimed at treating diabetic polyneuropathy. The reproducibility of QST studies depends on the equipment used, the patient population

studied, and whether they are done at multiple sites. In the Rochester Diabetic Neuropathy Study [98], the test-retest correlation coefficients were >0.9 for both VDT and CDT. Using standardized techniques, QST studies have excellent reproducibility even when performed in many centers as part of a clinical trial [87, 99].

Autonomic tests can provide quantitative measures of cardiovagal, adrenergic, and postganglionic sudomotor function. The complex nature of the tests and multiple confounding factors produce a considerable degree of variability. It is imperative that well-standardized techniques be employed to reduce the inherent variability [47, 48]. Ideally, a combination of cardiovagal and sudomotor studies should be performed to quantify the autonomic involvement in diabetic neuropathy.

There are other sensitive and quantitative techniques that are particularly suited to measuring small-fiber sensory nerves in diabetic neuropathy [100]. These surrogate markers are likely to be used as endpoints in future trials. These techniques include intraepidermal nerve fiber (IENF) measures with skin punch biopsy [48, 101] and corneal confocal microscopy [102, 103]. The latter technique has the advantage of being less invasive than skin biopsy but is less readily available at the current time.

Summary of Clinical Trial Results

There have been a number of agents designed to improve the underlying pathophysiology of the disorder rather than for symptomatic pain relief. Many of these are based on a reasonable scientific rationale [2, 104, 105], but none show convincing effectiveness. At this time, there are no agents approved in the United States for the treatment of diabetic polyneuropathy. This may be that the drugs are truly not effective. Alternatively, methodological difficulties inherent to the studies may have obscured a positive treatment effect.

Of the proposed mechanisms that underlie the diabetes-induced damage to peripheral nerve, two are linked to "oxidative stress." These include advanced glycosylation end products (AGEs) and the accumulation of sorbitol. There have been no clinical trials of AGE inhibitor in patients with diabetic neuropathy. Aldose reductase is the first enzyme of the polyol (sorbitol) pathway, which serves to convert glucose into sorbitol. Aldose reductase inhibitors (ARI) have been used in a number of trials over the past 30 years to alter the proposed metabolic insult from excess nerve sorbitol. There is considerable evidence in animal models that treatment with such agents might be beneficial [106, 107]. The first randomized, double-blind clinical trial of an ARI, sorbinil, demonstrated an improvement in sensory and motor CVs compared to placebo [37]. Subsequent studies suggested small improvements in other parameters. However, efficacy could not be established. Long-term trials were not performed as a result of the significant toxicity of this agent, which included rash, lymphadenopathy, and pancytopenia. Subsequent large, multicenter studies of other ARIs, including tolrestat, ponalrestat, epalrestat, zenarestat, and ranirestat, did not demonstrate a convincing, clinically meaningful effect as measured using standard trial design (NCSs, QST, autonomic testing, and clinical examination scales) [108]. Nonetheless, there were trends that suggested that these agents hold promise if a compound with adequate aldose reductase inhibition has an acceptable safety profile, and can be tested over a long enough period with clinically meaningful endpoints.

Recombinant human nerve growth factor (rhNGF) has been the subject of several trials. NGF is a neurotrophic factor that plays a role in the development, maintenance, and regeneration of neuronal tissue, particularly small sensory nerve fibers. There is some evidence that decreased availability of NGF contributes to the pathogenesis of diabetic polyneuropathy [109, 110]. A phase II trial of rhNGF over 6 months showed preliminary evidence of efficacy in patients with diabetic neuropathy. There was improvement compared to placebo in certain QST parameters (cooling detection threshold and perception of heat as pain) and trends toward an improved neurologic examination scale. However, larger phase III trials over a year period were not able to confirm any beneficial effects [111, 112].

Proinsulin C-peptide is deficient in patients with type 1, but not type 2, diabetes. C-peptide is a bioactive peptide with physiologic cellular effects that may play a role in the development of diabetic neuropathy [113]. C-peptide replacement therapy with short-term use (3 months) in a controlled trial of patient with type 1 disease had early beneficial effects on sensory nerve conduction studies and some measures of sensory function [114, 115].

Deficiency of myoinositol is reported in animal models of diabetic polyneuropathy. Dietary supplementation with myoinositol over 6 months improves NCSs in rats, but no definitive clinical or electrophysiologic benefits were seen in human trials [116, 117]. Other vitamin supplements, such as thiamine, vitamin B12, and pantothenic acid, were ineffective when performed as controlled clinical trials [2].

Evaluation of the Patient with Diabetic Polyneuropathy

All individuals with diabetes should be evaluated at least yearly for evidence of DPN, even if they do not report neuropathy symptoms. Patients without known diabetes but with symptoms consistent with neuropathy should be screened for diabetes if they are at high risk for developing type 2 diabetes. Risk factors include elevated BMI, hyperlipidemia, proteinuria, and a family history of diabetes.

There is an increased incidence of diabetes in association with seemingly unrelated genetic and acquired disorders. These include myotonic dystrophies, Friedreich ataxia, other spinocerebellar ataxias, mitochondrial disorders, and POEMS syndrome [4].

A challenging problem is determining whether a patient with neuropathy and known diabetes has diabetic neuropathy, another cause of neuropathy, or both. One step is to determine that the patient has an axonal polyneuropathy and that the severity of the neuropathy is consistent with the likely duration and severity of diabetes. DPN is more likely if there are other diabetic complications like retinopathy or retinopathy. Subsequent diagnostic testing should then be driven by the history. There should be an inquiry about possible other causes of an acquired or inherited neuropathy. For patients with painful small-fiber-type neuropathy, consider a prescribed or environmental neurotoxin, autoimmune vasculitis, sarcoidosis, Sjögren syndrome, HIV infection, amyloidosis, and uremia.

Vitamin B12 level should be tested, particularly if the patient with worsening diabetic neuropathy takes metformin [118]. If there is more weakness and greater reflex loss than expected for DPN, then serum protein electrophoresis with immunofixation and EDX studies are indicated. If there is intrinsic hand muscle weakness or more prominent sensory symptoms in the hands, upper extremities NCSs may detect median neuropathy at the wrist or ulnar neuropathy at the elbow. Needle EMG may be helpful to document the nature and severity of the neuropathy. Spine MRI imaging is helpful if there is a suspicion of cervical or lumbosacral radiculopathy, or a myelopathy. Diabetes and neuropathy may be the result of a shared underlying condition like mitochondrial disorders. It is helpful to rethink the diagnosis of DPN at follow-up visits if the patient's clinical course differs from that of typical DPN.

There may be clinical clues that a patient with neuropathy is unlikely to have diabetic neuropathy (Table 31.3). If present, these features should lead to further investigation. In one study of 100 consecutively evaluated diabetic patients with symptomatic neuropathy, one third had a neuropathy unrelated to diabetes [119]. Features that were more indicative of nondiabetic neuropathy included a short interval between diagnosis of diabetes and the onset of neuropathy, early motor deficits, markedly asymmetric deficit, and generalized areflexia.

Table 31.3 Clues that a diabetic patient's polyneuropathy may not be from diabetes alone

Late diabetic neuropathic complications are unlikely
Diabetes known to be of <5 years duration
No associated retinopathy or microalbuminuria
Onset or topography of polyneuropathy is unusual for diabetes
Painful rapid progression without weight loss or a change in glycemic control
Stepwise acute multifocal nerve involvement
Distribution of sensory loss is not length-related (stocking and glove)
Large fiber-type functions are selectively affected (ataxic neuropathy)
Weakness is present without sensory loss
Bulbar or proximal weakness when the distal findings are not advanced
Disproportionate loss of reflexes, suggesting demyelination
Shoulder girdle weakness
Electrodiagnostic features unusual for an axonal polyneuropathy
NCV < 70 % of low limit of normal with preserved CMAP amplitudes
Multifocal conduction slowing or block

Management of the Patient with Diabetic Polyneuropathy

General Considerations

Early assessment of the severity of a patient's DPN is helpful for establishing a neurologic baseline and determining prognosis and disability. The written history should include a relevant neurologic review of systems, including the autonomic systems. Resting pulse and blood pressure measurements should be documented. There should be a description of the feet, especially calluses and ulcers. The neurologic examination should include comments about possible hand and intrinsic foot muscle atrophy, foot and toe dorsiflexion strength, reflexes, and large and small-fiber sensory deficits, including arm and leg sensory levels.

There are excellent grading scales for the severity of DPN that use combinations of symptoms, signs, and nerve conduction studies. These include San Antonio criteria, the modified Toronto Clinical Neuropathy Score, the Utah Early Neuropathy Scale, the Michigan Neuropathy Scale, and Dyck/Mayo Clinic Neuropathy Impairment Score. The elements of these scales have been summarized [4].

The role of the neurologist in the care of a patient with DPN depends on the nature of the referral, the experience of the referring doctor, and the consultant's personal view about the limits of his or her responsibility. When possible the consultant should establish a diagnosis, recommend treatments, and make recommendations for the alleviation of pain. Consultants may consider it appropriate to verify that the patient is followed by a clinician or center with special expertise in the modern management of diabetes. There should be a plan to address treatable risk factors and diabetic complications including hyperlipidemia, cardiovascular disease, renal involvement including proteinuria, and diabetic retinopathy. Potentially reversible risk factors like obesity and smoking should be highlighted. If obesity is a factor, then the patient should be told about the importance of working with his or her caregivers to develop a plan for weight management and regular exercise.

Table 31.4 Medical therapies used or under evaluation to treat diabetic polyneuropathy

Proven effective
Intensive glucose control
Other therapies proven effective
None
Unproven in human trials but has scientific rationale
Aldose reductase inhibitors [ARIs] – normalize polyol metabolism
Nerve growth factor, other neurotrophic factors – replacement may restore axonal homeostasis; regeneration potential
C-peptide – lacking in type 1 diabetes; replacement binds with receptor and alters nerve metabolism
Alpha-lipoic acid [LA] – protect against oxidative stress
Gamma-linolenic acid [GLA, evening primrose oil] – increase nerve blood flow
Myoinositol [MI] – replace nerve inositol deficiency
Intravenous immunoglobulin (IVIG) – suppress autoimmune response

Therapy to Prevent Axon Loss

The neurologist should explain that there is currently no cure for DPN. The only proven treatment for diabetic neuropathy is best-possible glycemic control (Table 31.4). Evidence-based guidelines for managing diabetes and its complications are available [9]. Intravenous and oral 600 mg/day α-(alpha) lipoic acid has been shown to improve nerve conduction slowing and relieve sensory symptoms when given over short periods [120]. Trials of γ-(gamma) linolenic acid (evening primrose oil) reportedly improved NCSs but without evident clinical benefits. Many remedies with no proven value have been recommended to treat diabetic neuropathy. There is no scientific evidence that vitamin supplements containing thiamine, folic acid, pyridoxine, or cobalamin are of benefit unless the patient is deficient in that vitamin.

Neuropathic Pain

Although most patients referred to a neurologist with diabetic polyneuropathy have pain as a primary complaint, pain is also common in general diabetes clinics as well. Neuropathic pain effects 16 % of patients with diabetes [121] and is an important management problem. On the other hand, before embarking on medications that may ameliorate the pain, it is important to establish that the pain is due to diabetic polyneuropathy. The patient should have a history and examination consistent with polyneuropathy (see above). The quality of the pain should be consistent with painful diabetic polyneuropathy. This would include distal predominance (in the feet), the quality of the pain (burning, shock-like, or tingling), and the relation to rest and ambulation. Typically, diabetic neuropathic pain is more intense at rest, particularly in the evening or when trying to fall asleep, and less bothersome when walking. Pain that radiates down the legs with ambulation suggests lumbar stenosis. Foot pain that is largely limited to weight-bearing is likely mechanical or local at the foot and not due to neuropathic pain.

Table 31.5 Recommended treatments for painful diabetic polyneuropathy [122]

Recommended drugs	Recommended topical agents
Level A	
Pregabalin	
Level B	Level B
Other anticonvulsants	Capsaicin cream
Gabapentin	Isosorbide dinitrate spray
Sodium valproate	Percutaneous electrical nerve stimulation
Tricyclic antidepressants	
Amitriptyline	
Desipramine	
Nortriptyline	
Serotonin norepinephrine reuptake inhibitors	
Duloxetine	
Venlafaxine	
Opiod agonists[a]	
Tramadol	
Dextromethorphan	
Oxycodone CR	
Morphine sulfate	
Not recommended	
Other anticonvulsants – oxcarbazepine, carbamazepine, phenytoin, lemotrigine, lacosamide, topirimate	
Mexelitine	
Clonidine	
Magnetic field therapy	
Surgical nerve decompression	

Level A – established as effective; requires at least two class I studies
Level B – probably effective; requires at least one class I and two class II studies
[a]Some experts do not recommend these agents for chronic neuropathic pain

Drug treatment for neuropathic pain (Table 31.5) is considered in Chap. 80. A recent evidence-based guideline based on a systematic review of the literature on the treatment of painful diabetic neuropathy [122] concluded that pregabalin is established as effective (Level A). Other agents that are probably effective and should be considered (Level B) for treatment include other anticonvulsants (gabapentin and sodium valproate), tricyclic antidepressants (amitriptyline, desipramine, and nortriptyline), selective serotonin norepinephrine reuptake inhibitors (duloxetine and venlafaxine), and opiates (tramadol, dextromethorphan, morphine sulfate, and oxycodone). Topical agents that are probably effective and may also be considered included capsaicin cream, isosorbide dinitrate topical spray, and percutaneous electrical nerve stimulation.

Tricyclic antidepressants (TCAs) have been a mainstay for treatment of diabetic neuropathic pain [123]. Amitriptyline may be effective at a small dose, 10–25 mg at bedtime, and one can work up slowly to 75 or 150 mg if necessary. Somnolence is a common side effect, so these drugs are often

administered at bedtime. The associated sedation is helpful for pain-related insomnia. TCAs can cause prolongation of the QT interval and should be avoided for most patients with cardiac conduction defects, unstable angina, recent myocardial infarction, or ventricular arrhythmias. It should be used with caution in men with symptoms of an enlarged prostate. The universal dry mouth is a mild unwanted complication of these compounds. Desipramine and nortriptyline have less anticholinergic activity than amitriptyline.

The other antidepressant medications that have been demonstrated to be effective for diabetic neuropathic pain are those of the serotonin norepinephrine reuptake inhibitor class, duloxetine and venlafaxine. Common side effects include nausea, somnolence, and dizziness.

Pregabalin treatment resulted in a significant reduction in pain in a pooled analysis of seven randomized clinical trials involving 1,510 patients with painful diabetic neuropathy [124]. Adverse effects included weight gain, dizziness, somnolence, and peripheral edema. Gabapentin was effective in several randomized clinical trials [122]. The major side effects of gabapentin are dizziness, somnolence, and ataxia. A randomized trial of patients with painful neuropathy suggested that gabapentin combined with nortriptyline was more effective than either agent alone for reducing pain [125]. There are several small trials that suggest that sodium valproate is effective in reducing pain and diabetic neuropathy. Sodium valproate should not be used in women of childbearing potential because of teratogenic effects. Some of the other anticonvulsants, such as topiramate, phenytoin, carbamazepine, lacosamide, and lamotrigine, are not currently recommended due to lack of data supporting efficacy.

The antiarrhythmic mexiletine has been used for diabetic neuropathic pain based on favorable case series, but the only class one study of this agent suggested that it is ineffective [122]. Opioid agonists in the right circumstances should be considered for the treatment of pain from diabetic neuropathy. This is supported by clinical trial evidence of the effectiveness of tramadol, dextromethorphan, oxycodone controlled-release, and morphine sulfate. Adverse events are common and include sedation, nausea, constipation, and rebound headache. Chronic use of opiates may result in dependence, tolerance, and frequent escalation of dose. It is clear that they are effective for short-term pain management, but there are concerns regarding long-term opiate therapy for nonmalignant pain.

Various topical treatments are likely effective and can be considered for the treatment of painful diabetic neuropathy. Capsaicin cream includes a component of hot peppers and presumably causes pain relief through the completion of substance P in the skin. It may have modest benefit and may be useful in combination with an oral agent. Local burning and skin irritation are the major side effects. Many patients are unable to tolerate the burning pain that is prominent with initial use. That side effect decreases with continued use. Given the limited evidence from small trials, isosorbide dinitrate spray and percutaneous electrical nerve stimulation may be beneficial [122].

There are proposed algorithms for the treatment of painful diabetic polyneuropathy, based on the effectiveness of therapy and the side-effect profile. A common approach [126, 127] is to start with one of the three potential first-line agents: an anticonvulsant (pregabalin or gabapentin), a tricyclic antidepressant, or a SNRI (duloxetine). If pain control is ineffective or there are unacceptable side effects, substitute or add one of the other agents. For example, if gabapentin is used first and it is ineffective for pain relief, the next step would be to substitute or add a tricyclic antidepressant or duloxetine. If pain control is still inadequate, some experts would add an opioid agonist. Others, based on the special concerns regarding chronic opioid use, would not use this class of agents at all.

Surgical decompression of multiple peripheral nerves has been proposed as a potential method for treating painful diabetic neuropathy. The rationale for such an approach is dubious and there are no adequately designed clinical trials to support the use of invasive surgical decompression of multiple nerves as treatment for diabetic polyneuropathy. This treatment is not recommended.

Autonomic Symptoms

When autonomic neuropathy accompanies DPN, a wide spectrum of symptoms may occur. These symptoms may arise from the cardiovascular, gastrointestinal, genitourinary, pupillary, sudomotor, and neuroendocrine systems. Orthostatic hypotension is a common accompaniment of diabetic polyneuropathy, but symptoms usually are mild. A prescribed cardiovascular exercise program, elastic stockings, increased salt intake, and elevating the head of the bed are helpful. Fludrocortisone and midodrine [128] are effective but may cause unacceptable hypertension. Erectile dysfunction often responds to sildenafil, or other phosphodiesterase-5 inhibitors, in about half of treated patients. Bladder dysfunction should be confirmed by urodynamic testing. This is often effectively treated by scheduled urinations coupled with bethanechol. Chronic gastroparesis is treated by dietary modification (e.g., hydration and multiple, small low-fat meals) and adding agents, like metoclopamide or domperidone, to increase gastric motility.

Other Patterns of Polyneuropathy Associated with Diabetes

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an autoimmune polyneuropathy associated with demyelinating electrophysiology, elevated spinal fluid protein, and response to immunotherapy. Most often it is also

characterized by proximal and distal weakness, hyperreflexia or areflexia, and a subacute course. These features are quite distinct from diabetic polyneuropathy. However, there are patients with diabetes who develop CIDP.

Early reports suggested that CIDP is much more common in diabetics. There is speculation that diabetes is a risk factor for CIDP [129, 130]. Most of these reports were not population based and were likely subject to referral bias. It is likely that these disorders are coincidental. Laughlin and colleagues [131] detailed the prevalence of CIDP in a population-based cohort from Olmstead County, Minnesota. They found that diabetes was not a risk covariant for CIDP. The prevalence of diabetes in CIDP was 4 % compared to 12 % in the control population. The number of CIDP patient was relatively small, so the authors could not exclude a small association between diabetes and CIDP with certainty. It is likely that some patients with painless, symmetric radiculoplexopathy (proximal diabetic neuropathy) are mislabeled as having CIDP.

There have been several studies that have compared patients with diabetes and CIDP to CIDP patients who do not have diabetes [132–134]. These have found no significant differences between the two groups. The two CIDP cohorts, those with and without diabetes, have similar clinical features, electrophysiologic findings, and pathologic abnormalities. There was no identifiable difference in the response to immunotherapy in these nonrandomized comparison studies. One of the larger series [133] found minor differences between the two groups. The patients with diabetes and CIDP were older and the electrophysiology and pathologic findings on nerve biopsy showed more axonal loss in the idiopathic CIDP patients. Although the diabetic CIDP patients also responded to immunotherapy, the degree of improvement was less favorable. The authors speculated that these differences likely reflected the additive effects of diabetic polyneuropathy in patients who develop superimposed CIDP.

It is important to recognize CIDP in patients with diabetes so that it can be treated appropriately. Although mild forms of CIDP may be difficult to distinguish from diabetic polyneuropathy, there are clinical clues to the possibility of this superimposed autoimmune demyelinating neuropathy. Since the temporal progression of DPN is slow, a subacute progression or a relapsing-remitting course would not be consistent with DPN and should suggest the possibility of proximal diabetic neuropathy, CIDP, or another neuromuscular disorder. If the weakness is as prominent proximally as distally, or if there is disproportionate weakness in the absence of significant sensory loss, then CIDP would also be a consideration. Widespread areflexia or prominent ataxia would also suggest CIDP. There are also important electrodiagnostic findings that are not consistent with DPN. The NCS and needle EMG features of diabetic polyneuropathy are those of an axonal polyneuropathy and the EDX criteria for primary demyelination are usually not met [38, 135]. Patients with both diabetic polyneuropathy and uremic polyneuropathy may have nerve CVs sufficiently slowed to meet the criteria used by most authors to identify primary demyelination. Cerebrospinal fluid (CSF) examination and nerve biopsy are generally unhelpful. In most cases, the CSF examination is unlikely to be helpful because the protein is often elevated in patients with diabetic polyneuropathy, even to the degree seen in CIDP. Although not routinely performed, nerve biopsy findings also may not distinguish these two neuropathies [104].

Motor Neuropathy

When a patient develops a predominantly motor neuropathy in the setting of diabetes, it is most likely another less common form of diabetic neuropathy (i.e., proximal diabetic neuropathy) or an alternative neuromuscular disorder, such as CIDP. There is no convincing evidence that a predominantly motor form of diabetic polyneuropathy occurs. There are reports of a motor neuron disorder occurring in the setting of a chronic hypertensive anemic state and repeated periods of severe hypoglycemia. This is seen in the context of an insulinoma [136].

If the neuropathy is subacute, asymmetric, and with prominent pain and weakness, proximal motor neuropathy of diabetes (diabetic lumbosacral radiculoplexus neuropathy) should be considered. CIDP can also present as a subacute neuropathy that is predominantly motor. A painless, symmetric form of proximal motor neuropathy (diabetic lumbosacral radiculoplexus neuropathy) may be confused with CIDP. Other neuromuscular disorders can occur coincidentally with diabetes and also produce weakness, sometimes superimposed on a preexisting diabetic polyneuropathy. These include motor neuron disease, inflammatory myopathies, disorders of neuromuscular transmission (such as myasthenia gravis or Lambert-Eaton myasthenic syndrome), and other non-length-related patterns of neuropathy.

Proximal Motor Neuropathy (Diabetic Lumbosacral Radiculoplexus Neuropathy or Diabetic Amyotrophy)

This disorder is much less common than chronic diabetic polyneuropathy. It was first described by Bruns [137], but Garland and Traverner [138] emphasized it as a distinct clinical entity seen with diabetes and manifested by asymmetric pain and proximal leg weakness but little demonstrable sensory loss. Garland was uncertain of the underlying pathology and termed this entity diabetic amyotrophy [139].

Other designations have been proposed including the Bruns-Garland syndrome, diabetic femoral neuropathy, femoral-sciatic neuropathy, ischemic mononeuropathy multiplex, proximal diabetic neuropathy, diabetic polyradiculopathy, diabetic proximal amyotrophy, and diabetic lumbosacral radiculoplexus neuropathy [137–148]. These names emphasized different aspects of the clinical presentation and possible sites of peripheral nervous system involvement. There is a varying degree of importance ascribed to the pain and asymmetry, association with weight loss, and amount of sensory involvement. Due to these divergent views, it was proposed that diabetic amyotrophy be discarded in favor of the term proximal motor neuropathy (PMN) [144]. This term appropriately highlights the proximal leg weakness without implying a localization or pathogenesis. Others prefer the term diabetic lumbosacral radiculoplexus neuropathy (DLRPN), which emphasizes the complex localization of this disorder to the lumbosacral plexus, nerve roots, and peripheral nerves [147, 148].

There appears to be a spectrum of features between the painful, asymmetric cases of acute or subacute onset and the painless, more slowly progressive cases [144]. These features overlap in most patients (see below), with a rapidly evolving, asymmetric onset followed over several months by a slower progressive course frequently affecting both legs [137, 147, 148]. Although less common, progressive, painless proximal leg weakness can be seen as a sole manifestation of this disorder [146, 149–151].

Etiology and Pathogenesis

There is fairly strong evidence that this disorder is due to an inflammatory microvasculitis causing ischemic nerve injury [152, 153]. The clinical feature of acute or subacute onset with prominent pain favors an inflammatory or ischemic basis. The association with weight loss in many patients and the anecdotal reports that recovery is hastened by improved nutritional support suggest that some metabolic process may play a role.

Said and colleagues [154] performed nerve biopsies of the intermediate cutaneous nerve of the thigh, a sensory branch of the femoral nerve, in ten patients with PMN. All had an asymmetric disorder of subacute onset and signs of polyneuropathy. True vasculitis, inflammation and vasonecrosis, was seen in two and perivascular inflammatory infiltrates in four others. Nerve lesions felt consistent with ischemia were seen in three specimens. A subsequent by the same group [155] of four additional patients with proximal motor neuropathy demonstrated similar inflammatory lesions. The mean duration of symptoms prior to biopsy ranged from 4 to 18 months. The inflammatory lesions at that point were a mixture of B and T lymphocytes and macrophages. Inflammatory cell infiltrates or microvasculitis in this disorder has been reported by others [147, 156, 157].

A study by Kelkar and coworkers [157] examined nerve biopsy specimens, most from the intermediate nerve of the thigh, in 15 patients with PMN. These biopsies were performed relatively early after the onset of asymmetric, progressive, and painful proximal leg weakness. The duration of symptoms at the time of biopsy ranged from 5 weeks to 12 months, but several were done within six 6 weeks. Four patients had transmural infiltration of polymorphonuclear leukocytes into the small epineurial blood vessels. Six patients had "perivasculitis" with mononuclear cell infiltrates around small vessels without signs of true vasculitis (i.e., fibrinoid necrosis of the vessel walls or transmural inflammation). Activated complement was demonstrated in the endothelium of the small vessels and IgM in the endoneurium. They suggested that the primary event early in the course of PDN is a polymorphonuclear vasculitis secondary to immunoglobulin or immune complex deposition. This evolves, later in the disorder, into a perivasculitis involving primarily lymphocytes.

Dyck and colleagues [147, 148] prospectively studied 33 patients with proximal motor neuropathy, which they termed DLRPN. They performed an ipsilateral nerve biopsy and found strong evidence implicating an ischemic injury due to microvasculitis. There was increased inflammation in all nerves, with inflammatory cells in the vessel walls (suggestive of microvasculitis) and evidence of ischemic injury. The latter evidence included focal or multifocal fiber loss, perineurial thickening, and epineurial neovascularization. In two cases, there was evidence of necrotizing vasculitis. However, the overall pathologic changes were those of a microvasculitis involving small arterioles and venules without fibrinoid necrosis.

The link between diabetes and such localized inflammatory infiltrates is uncertain. Some have postulated that the primary event in PMN is an immune attack and microvasculitis within nerve [148]. Abnormal blood vessels or blood-nerve barrier secondary to diabetes might trigger a reactive vasculitis. IgM or immune complex deposition could set off a complement cascade which further disrupts the blood-nerve barrier and hastens the vasculitic process. The final result is epineurial and perineurial blood vessel occlusion that then produces nerve ischemia and infarction. There are no convincing data that a metabolic abnormality plays a primary role in the pathogenesis of PMN. It is possible that a metabolic insult triggers the events in some fashion, such as abruptly changing the small blood vessel endothelium with an alteration of the blood-nerve barrier. This could set the stage for the inflammatory processes.

Clinical Presentation

PMN (DLRPN) is primarily a disorder of older adults with type 2 diabetes. Men are more often affected than women. In general, patients with PMN are not known to be diabetic for a long period of time. Glycemic control is often not poor [148]. In some patients, this is the presenting feature, leading to the diagnosis of diabetes. This was seen in 7 of 33 patients in a recent series [147]. The mean age at diagnosis ranged from 57 to 65 years [147, 158–160], with very few patients younger than age 50. Anorexia and substantial weight loss occurred before or during the progressive phase of the neuropathy in most. Weight loss was usually modest, but Pascoe and colleagues [161] noted a mean weight loss of 18 kg in 31 of 38 patients. Dyck and coworkers [147] found that there was 10 lb or more of concomitant weight loss in 85 % of patients. Blood glucose may normalize following weight loss, confusing the diagnostician.

The characteristic presentation is abrupt, asymmetric severe thigh pain, followed within weeks by mild to severe hip and thigh muscle weakness. The pain is typically in the hip and thigh but may involve the leg or foot particularly later in the course. It less commonly involves the low back and buttock [147]. Pain is often severe, requiring treatment with long-acting oral narcotics. Weakness and atrophy of the affected muscles follows. The muscles most often affected early in the course are the iliopsoas, quadriceps, and thigh adductors. Hip extensors and hamstrings are often involved. The combination of thigh muscle weakness with sparing of distal muscles is a clinical pattern of weakness distinctive for PMN. Distal muscles also may be weak, particularly peroneal-nerve innervated. Proximal muscles are always more affected initially, which is the reverse of the usual pattern with axonal polyneuropathies. Over subsequent months, the unaffected segments of the limb are often affected and the contralateral side may be involved. In a large prospectively studied series [147], this syndrome began unilaterally in 88 % of patients but became bilateral in 97 %. The median time to bilateral disease was 3 months.

Sensory loss generally is minor in PMN, except distally from the commonly associated polyneuropathy. About two third of patients with PMN have clinical or EDX signs of a distal symmetric polyneuropathy [154, 162]. Cutaneous sensory loss or hyperesthesia over the thigh may be demonstrated in half of patients, but it is usually subtle [155, 158].

Recurrent episodes are uncommon [145, 158]. The progressive phase of weakness may develop over a few days or more slowly, over months. A relatively symmetric, slowly progressive disorder has been reported [146, 149, 151, 163] but is less common in practice. A large, well-characterized series of 23 patients with this disorder convincingly demonstrated that this is painless PMN and not a different entity [151]. The diabetic patients in this series had a similar median weight loss of 30 lb and the physiologic studies and nerve biopsy features were similar to painful PMN. These patients differed only in the lack of pain, more symmetrical involvement, and slower progression. Barohn and colleagues [137] suggested that two phases are seen in patients with PMN; a rapid phase associated with pain is followed by a slower phase of weakness that progresses over weeks or months. There also appears to be an apparent spectrum of PMN from an acute painful, asymmetric, and rapidly progressive form to a less common painless, more symmetric form with slower progression.

Spontaneous recovery was noted in early reports. Coppack and Watkins [158] followed 27 patients who had a mean time to pain recovery of 3 months which varied from 1 to 12 months. Pain was the first manifestation to improve, as early as a few weeks, but little beyond 12 months.

On occasion, patients develop a similar disorder affecting the upper extremity. Upper limb involvement was noted in 2 of 13 patients reported by Leedman and coworkers [164]. In a larger series of 60 patients with PMN, 9 patients had upper extremity involvement [165]. Seven of the nine patients had the onset of upper extremity involvement after the leg symptoms began, ranging from 3 weeks to 15 months later. The clinical and electrodiagnostic features showed multifocal, axonal loss in the cervical roots, brachial plexus, and upper limb peripheral nerves analogous to the pattern of involvement in the lower extremities.

Evaluation and Diagnosis

PMN is a consideration in any patient with proximal lower extremity weakness. It may be the presenting feature of late-onset type 2 diabetes. Alternatively, weight loss may normalize the serum glucose and the diagnosis of diabetes may be missed at the time of neurologic presentation. It may be necessary to search for distant blood work for clues that diabetes was a preexistent disorder, perhaps mild and overlooked. Pain and weight loss are most often present, although not invariably.

There are no laboratory, hematologic, or biochemical abnormalities that characterize PMN. The serum CK is often mildly elevated as observe in other denervating disorders. All patients have an elevated CSF protein. In one series of 26 patients, the mean CSF protein was 92.5 mg/dL [161]. In another large series [147], the mean CSF protein was 89 mg/dL with a range of 44–214. The CSF cellularity and other parameters are normal.

The typical clinical presentation and the EDX findings of PMN support the diagnosis. A focal lesion of the lumbar roots needs to be excluded by lumbar magnetic resonance imaging. If clinically appropriate, imaging of the pelvis and lumbosacral plexus may be warranted. On occasion, another

disorder may mimic PDN and present with proximal leg weakness in the setting of diabetes, such as chronic inflammatory demyelinating polyneuropathy, polymyositis, or motor neuron disease. In most cases, these can be distinguished from PMN by the EDX studies, serum CK, and the clinical course. If the course is atypical of PMN, repeat electrophysiologic studies are often helpful.

EDX evidence of a distal symmetric polyneuropathy is found in the majority of those patients who present with PMN [145, 161, 162]. Subramony and Wilbourn [162] found no convincing evidence on NCSs of distal polyneuropathy in 10 of 27 patients studied. The disorder is heterogeneous, not only with respect to the distal polyneuropathy, but also the extent and asymmetry of the EDX findings. In patients with a distal polyneuropathy associated with PMN, the NCS findings are those of axonal loss. Since NCSs of the lower extremities generally examine distal sensory and motor nerve function, conclusions about the nature of PMN cannot be drawn from studies of distal nerves and muscle.

Femoral motor NCSs with recording from the quadriceps muscles add little to the diagnostic efforts [159, 162, 166]. However, in patients with significant weakness and atrophy of the quadriceps muscle, the femoral compound muscle action potential (CMAP) of the affected limb is either low in amplitude or absent, reflecting the degree of axonal loss. The delayed distal latency, that may accompany reduced amplitude CMAP, reflects loss of the largest diameter conducting motor axons. The femoral CMAP should be compared to the other side, particularly when it is an asymmetric process, to get a better estimate of the amount of axonal loss. This may provide some prognostic information regarding the expected pace of recovery. When this study is performed early in the course of the disease, the reduction in CMAP amplitude accurately reflects the degree of axonal loss. However, later in the illness, after collateral sprouting has occurred, the CMAP amplitude may be relatively normal. The evidence of marked collateral sprouting and reinnervation would, however, be evident on the needle EMG examination.

The needle EMG abnormalities observed in affected muscles are a function of the timing of the study and the onset of illness. In the first few months, needle EMG signs of acute denervation (fibrillation potentials) are present. They are more abundant in more severely weak muscles but can be detected often in strong muscles. Initially, motor unit action potential (MUAP) morphology is normal, but neurogenic MUAP recruitment is evident in weak muscles. Several months later, after collateral sprouting has begun to reinnervate muscle fibers previously denervated, fibrillation potentials are less evident. At this time, normal amplitude, polyphasic MUAP morphology is a prominent finding and may be mistaken for myopathy. As time progresses, the MUAP configuration is characteristic of chronic denervation with large amplitude and long duration MUAPs.

The needle EMG examination is always abnormal but quite heterogeneous in the distribution of findings. The abnormalities are typically most severe in the quadriceps, iliopsoas, and thigh adductor muscles. Abnormalities may also be seen in the hamstrings and glutei, as well as lumbar paraspinal muscles. Distal muscles may be affected in several ways. There may be variable involvement of any of the foreleg muscles, most pronounced in the tibialis anterior and the anterior compartment muscles. In many, there is bilateral distal chronic denervation, as part of coexistent chronic diabetic polyneuropathy, even in those who clinically have only unilateral leg weakness.

In general, the EDX findings reflect involvement of nerve roots, plexus, and peripheral nerve in the limb, or limbs, affected. The electrophysiologic abnormalities are more widespread than the clinical deficits suggest [147].

Treatment and Management

There are anecdotal reports that patients who regain a portion of the lost weight and begin insulin therapy seem to improve faster than those who remain cachexic. Some physicians instruct their patients to refrain from caloric restriction and to try to regain their pre-morbid weight until they recover from this disorder. However, there have been no controlled trials, or large series, to support this approach.

Since pain is the most common symptom at the onset of PMN, and usually the most severe and limiting feature early on, it should be managed with narcotic analgesics. These generally can be tapered and discontinued after the pain begins to remit. Chronic pain may respond to the agents used in other forms of neuropathic pain, such as gabapentin and tricyclic antidepressants. Physical therapy is beneficial after the progressive phase of the illness [167]. As an inflammatory process may play a role in PMN, immunotherapy may be considered. No controlled trials have been published to support the efficacy of immunotherapy in PMN [168]. However, intravenous immunoglobulin (IVIG) therapy was reported as effective in several case series [129, 161]. Several case series also have documented improvement with corticosteroids, particularly with regard to pain relief [129, 161, 169]. Occasional patients respond to corticosteroids dramatically, although this greatly complicates the problem of glucose control. Since the natural history is one of spontaneous improvement, it is difficult to know if immunotherapy is beneficial.

Prognosis

Spontaneous recovery occurs in most patients, albeit to varying degrees. Coppack and Watkins [158] followed 27 patients

who had a mean time to the start of recovery of 3 months with a range of 1–12 months. Recovery was generally complete by 18 months. Pain was the first manifestation to improve, as early as a few weeks, but little beyond 12 months. Although a minority had residual weakness when reexamined at an average of 45 months, none had disabling weakness. Others found that improvement is seen in a majority but often incomplete. In a follow-up study of 21 patients at about 3 years after the onset of symptoms, Pascoe and coworkers [161] found 12 had resumed normal walking, 7 ambulated with an aid, and 2 were wheelchair bound. In the 33 patients followed prospectively by Dyck and colleagues [147], most of the patients required wheelchairs at the initial evaluation, but most had substantial improvement. Only 10 % still required a wheelchair after a median follow-up of 2 years.

Mononeuropathies and Radiculopathies Without Nerve Compression

Much like PMN, the mononeuropathies and radiculopathies that occur in association with diabetes have a very different onset and course than chronic diabetic polyneuropathy. Diabetic polyneuropathy tends to be insidious in onset and progression and develops usually in patients with longstanding disease. In contrast, diabetic mononeuropathies are usually acute or subacute in onset and are often associated with substantial pain. Many are associated with a recent weight loss or a change in glucose control. They run a defined course and then tend to remit, at least in part, in 6–12 months. They occur in middle or later life and may be an early manifestation of diabetes. All of these features imply a different pathogenesis underlying the focal neuropathic complications.

Cranial Neuropathies

Acute cranial mononeuropathies may coexist with chronic diabetic polyneuropathy. Watanabe and colleagues [170] compared the incidence of cranial nerve palsies in 1961 diabetic patients and 3,841 patients without diabetes. They found that cranial nerve palsies occurred more frequently in diabetics (1 %) compared to nondiabetic patients (0.1 %). The cranial nerves most frequently affected were the facial nerve (VII), followed by the oculomotor nerves (III, IV, and VI).

Since these mononeuropathies are uncommon, there are few population-based studies that give reliable figures for the incidence of *ocular motor mononeuropathies* due to diabetes. Many older individuals have other risk factors for the development of these so-called vasculopathic neuropathies. These risk factors include diabetes, hypertension, advanced age, smoking, atherosclerotic disease, and hypercholesterolemia. In a large study of 2,229 patients with oculomotor palsies, 306 (13.7 %) were associated with diabetes [171]. In the diabetic group, cranial nerve VI was most often affected (50.0 %), followed by III (43.3 %) and IV (6.7 %). In another large study of 4,278 patients with third, fourth, and sixth nerve palsies, the authors ascribed 103 cases (2.4 %) solely to diabetes [172].

Unilateral ocular motor neuropathies appear suddenly, over hours or a few days, and are usually painful. Symptoms begin with ocular pain or unilateral headache in more than half of patients, with pain and diplopia progressing over several days. With *third nerve palsies*, the pain is accompanied by diplopia and ptosis. There is ptosis and paresis of third nerve-supplied extraocular muscles, but pupillary function is typically spared. This is likely due to the fact that the disorder is thought to occur as a result of peripheral nerve infarction. Asbury and colleagues [173], in a postmortem histopathologic study of a patient with diabetic third nerve palsy, demonstrated centrofascicular fiber loss in the mid-cavernous portion of the nerve, findings supportive of nerve ischemia. Since pupillary fibers lie on the outside of the third nerve, they are less susceptible to ischemia. There may be minimal pupillary involvement (less than 2 mm anisocoria) in a minority of patients. Pupillary sparing helps to differentiate this from a compressive third nerve lesion, such as a cerebral aneurysm or tumor. However, pupillary function may be partially spared with a compressive lesion in up to 20 % of cases, particularly early in the course of the illness.

Patients with *sixth nerve palsies* develop binocular horizontal diplopia. As with other cranial mononeuropathies associated with diabetes, the onset is usually acute and painful. The examination demonstrates unilateral weakness of the lateral rectus muscle. An associated facial neuropathy on the same side or contralateral hemiparesis should suggest a pontine lesion as an alternative cause. Bilateral abduction deficits should suggest increased intracranial pressure ("false-localizing sign") or an infiltrative or inflammatory process in the subarachnoid space. Patients with *fourth nerve palsies* complain of binocular vertical diplopia. They have weakness of the superior oblique muscle and generally have an ipsilateral head tilt. Other associated neurologic signs, such as a Horner's syndrome or dysmetria, should suggest a brainstem lesion rather than diabetic mononeuropathy.

The diagnosis of an acute third, fourth, or sixth nerve palsy as a diabetic mononeuropathy is supported by the typical presentation with pain and acute diplopia. Some authors suggest that patients over age 50 with pupil-sparing, complete third nerve palsies should have neuroimaging performed with MRI and MRA or CT angiogram [174]. Even isolated, pupil-sparing third nerve palsies can be caused by small infarcts in the mesencephalon or by compressive lesions. In patients in this age group who have risk factors like diabetes, other authors suggest performing neuroimaging

if there has been no improvement after 12 weeks of close follow-up [175]. These patients should be examined frequently in the first 2 weeks for the possible development of delayed pupillary involvement. Patients with partial third nerve palsies that are also pupil sparing should have neuroimaging and be followed closely in the first 2 weeks for evidence of pupillary involvement that may not be evident on first examination. Pupillary involvement raises the possibility of a compressive lesion, and of most concern is an aneurysm of the posterior communicating artery. This generally requires brain neuroimaging, including cerebral angiography. Diabetic patients over 50 with isolated sixth or fourth nerve palsies should also have neuroimaging to exclude an intracranial process [174]. Others suggest performing neuroimaging if there has been no improvement after 4–12 weeks [175]. All patients under 50, even with a history of diabetes, should be thoroughly evaluated for alternative causes of cranial mononeuropathies.

There is no specific treatment for these ocular motor mononeuropathies. The prognosis for vasculopathic ocular motor mononeuropathies, including those due to diabetes, is excellent [175]. In one series, 72 % recovered completely or partially in 4–6 weeks [172]. In another series, the mean time to recovery was 2.5 months [176].

Idiopathic facial neuropathy (*Bell's palsy*) appears to be more common in older diabetics than nondiabetics. The incidence of diabetes in patients with Bell's palsy ranges from 6 to 10 % [177–179] and is higher if impaired glucose control, by glucose tolerance testing, is considered [178, 180, 181]. It is clearly more common in older diabetics, making up 17 % of those 30 or older but only 4 % of those under 30 in some series [179, 182]. However, some investigators have not found diabetes to be an independent risk factor for Bell's palsy [183].

The presentation is that of any other case of idiopathic facial palsy. There is an acute onset of facial weakness that may progress to maximal over several days. There is involvement of upper and lower facial muscles, often pain, and varying loss of taste and hyperacusis. The examination is notable only for unilateral peripheral facial weakness. Other neurologic signs, such as ophthalmoparesis or sensory loss, are not present. Pecket and Schattner [178] found a disturbance of taste in 14 % of those with diabetics compared to 83 % of those with no diabetes. This suggests that the lesion in diabetics is most often distal to the chorda tympani. Other features of the facial neuropathy are identical to those without diabetes.

The acute unilateral facial weakness should not be accompanied by other neurologic symptoms or signs. If it is, then an alternative diagnosis should be considered and investigated. The differential diagnosis of typical Bell's palsy in a diabetic includes idiopathic facial neuropathy, Lyme disease, varicella-zoster infection, and trauma.

The EDX findings in Bell's palsy associated with diabetes are similar to those seen with others with the idiopathic form. The facial CMAP amplitudes on NCSs 1 week or more after the onset are normal, low in amplitude, or absent, reflecting the variable amount of axonal loss. MRI imaging studies may show enhancement of the affected seventh nerve but need not to be done routinely.

Patients with incomplete facial weakness generally recover fully over weeks to months. Those with complete paralysis of facial muscles are more likely to have slower and incomplete recovery. The recovery depends on the degree of axonal loss which can be estimated by measuring the amplitude of the facial CMAP on NCSs done at least a week after the onset of weakness (after completion of Wallerian degeneration). In those patients who have a preserved distal CMAP (20 % lower limit of normal or better), the prognosis for recovery is good [184]. For those who have no elicitable motor response, there is a reasonable likelihood of incomplete recovery with persistent weakness and aberrant regeneration. This is also reflected in the amount of fibrillation potentials seen on needle EMG examination more than 3 weeks after the onset and also by a reduction in the MUAPs recruited with voluntary muscle contraction.

Truncal Radiculoneuropathies

This unusual disorder, also termed thoracic polyradiculopathy, truncal neuropathy, and diabetic thoracoabdominal neuropathy, is distinctive [185]. It occurs in older patients, more often in men with either type 1 or 2 diabetes, and the symptoms commonly appear during a fluctuation of diabetic control. It may occasionally be the presenting feature of diabetes. Like PDN, it often occurs in the setting of weight loss. Most of the five patients reported by Sun and Streib [186], as well as previous reports that they summarized, had substantial associated weight loss, as much as 19 kg. Four of the five patients detailed by Watkins and Thomas [187] had a weight loss of at least 10 kg. An occasional patient will have simultaneous onset of this disorder with diabetic proximal neuropathy [186, 188, 189].

Patients develop pain, cutaneous hypersensitivity, sensory loss, and sometime weakness in the distribution of one or more somatic nerves or roots. Pain is usually present at the onset and is the predominant symptom. It is typically aching or burning in quality and may be quite severe. The chest or abdomen may be involved. The affected segments usually are contiguous but do not necessarily follow classical root distribution territories, and involvement may be patchy. It is usually unilateral but can be bilateral. The examination may show only evidence of cutaneous hypersensitivity in the general distribution of the pain that is difficult to localize to a particular nerve or root level. When present, the pattern of

sensory loss may be quite variable. Stewart [190] carefully mapped out the topography of the sensory deficits in 17 episodes of truncal neuropathy. Some patients had a unilateral or bilateral dermatomal band of sensory deficit from the involvement of adjacent main spinal nerves. However, two thirds of patients had involvement restricted to the ventral or dorsal rami of the spinal nerves or a combination of these distributions. Focal muscle weakness may lead to local areas of abdominal wall weakness and a local bulge, simulating an abdominal hernia [191, 192].

The diagnosis of diabetic truncal radiculopathy is generally a clinical one. Most patients have abnormalities on the needle EMG examination that may help confirm this disorder. The pain intensity and location may incorrectly suggest a myocardial infarction, acute cholecystitis, or acute appendicitis [189]. The differential diagnosis should focus on mimicking medical, surgical, or orthopedic conditions. With weight loss, a search for cancer is often carried out before referral to a neurologist. Once the neuropathic nature of the pain and sensory loss is clear, the evaluation should include consideration of herpes zoster, a central cord syndrome, and a length-related polyneuropathy, with the associated shield of anesthesia on the chest and anterior abdomen. A slowly developing truncal sensory loss in a patient with a length-related pattern of sensory loss due to diabetic polyneuropathy is called diabetic truncal polyneuropathy [193]. It should not be confused with the very different acute, painful focal radiculoneuropathy detailed above.

The subacute onset, associated pain and weight loss, and course suggest a similar pathogenesis to diabetic proximal neuropathy (PMN, DLRPN, diabetic amyotrophy). This is supported by the observation that these disorders may develop together [186, 188]. The anatomic site of the lesions has not been established. EDX studies indicate a multisegmental disorder at the root or proximal intercostal and abdominal nerve levels, or both. This is generally manifest by fibrillation potentials in paraspinal, intercostal, and abdominal muscles in varying combinations [186, 194]. Stewart found patterns of paraspinal sparing that were more suggestive of multiple proximal neuropathies than radiculopathies [190]. Lauria and coworkers [195] showed that cutaneous skin biopsies in three patients with diabetic truncal radiculoneuropathy had loss of intraepidermal nerve fibers. There was return of the intraepidermal nerve fibers after clinical recovery suggesting a lesion distal to the dorsal root ganglion. It is likely that this disorder is at the level of the thoracic roots, or posterior primary rami, and the intercostal or abdominal nerve in varying combinations. Until the site of the lesion is firmly established, its heterogeneous involvement is best characterized by the term radiculoneuropathy.

The progressive phase is generally short, days or weeks. Pain control may be difficult in the early months of the disorder, but pain usually subsides within 4–10 months. Cutaneous sensory loss in the same distribution may persist lifelong. The role of corticosteroids or intravenous immunoglobulin for treatment is uncertain. More potent immunosuppression or long-term use of corticosteroids is not warranted. The focus of treatment is symptomatic management of the neuropathic pain. Protein-calorie supplements may be useful if there has been appreciable recent weight loss.

Limb Mononeuropathies

Cervical and lumbosacral radiculopathies and other focal neuropathies can occur coincidentally with diabetes, and it may be difficult to distinguish the etiology. Other common causes should be considered and investigated. Diabetic focal limb mononeuropathies not at the common sites of local nerve compression do occur but are rare. Despite frequent statements to the contrary, isolated femoral neuropathies are rarely due to diabetes. The distribution of weakness, after careful examination, is more widespread and is usually due to proximal diabetic neuropathy (DLRPN).

Acute mononeuropathies that result from nerve infarction are quite different from the compression/entrapment neuropathies that occur with diabetes (see below). Most of the compression neuropathies, other than peroneal neuropathy, are slowly progressive. Nerve infarction is acute and painful. When the localization of the lesion can be identified clinically or electrophysiologically, it is not at a common site of compression (e.g., radial nerve in the forearm). It is characterized by axonal loss, so conduction block or focal slowing across the lesion is not seen on nerve conduction studies. Recovery is slow and determined by the site and extent of axonal loss. A lesion with severe axonal loss (reflected in absent motor responses on the NCS) that is very distant from the weak muscle, such as proximal sciatic neuropathy producing foot drop, may not have any improvement at all. In contrast, a lesion with partial axonal loss only a few inches from the weak muscles would be expected to recover completely over a few months time.

Multiple noncompressive mononeuropathies in the same patient are known as mononeuropathy multiplex. Mononeuropathy multiplex is not a complication of diabetes, although the coexistence of focal compressive neuropathies and polyneuropathy in the same patient may superficially resemble such a disorder. An acute, or subacute, mononeuropathy multiplex should raise a concern for vasculitis.

Mononeuropathies with Focal Nerve Compression

Diabetic patients and others with chronic polyneuropathy are considered more susceptible to focal compression neuropathies than those without polyneuropathy. The sites

of compression are the conventional ones, including the median nerve at the wrist, the ulnar nerve at the elbow, and possibly the peroneal nerve at the knee [29, 196]. These compressive, or entrapment, neuropathies are clinically and electrophysiologically similar to those that develop in the absence of diabetes. However, the frequent coexistence of diabetic polyneuropathy results in manifestations and EDX abnormalities that also need to be considered in this context. For milder compression neuropathies, the EDX features are that of focal slowing of motor and sensory conduction and/or conduction block across the usual sites of compression. With more severe lesions, the SNAPs are absent, the CMAP amplitudes are reduced, and there is denervation on needle EMG examination of the affected muscles. However, these latter changes do not necessarily reflect focal compressive lesions, as do focal slowing or conduction block. They may also represent coexistent polyneuropathy. It is necessary to study other sensory and motor nerves of the limb to assess how much of the involvement is secondary to polyneuropathy or whether the abnormality is limited to the nerve and likely due primarily to the compressive neuropathy. This differentiation has important treatment and prognostic implications, as discussed below.

It is unclear why diabetics, particularly those with polyneuropathy, have an increased likelihood of developing compressive neuropathies. A number of possible mechanisms are proposed. Obesity may be a factor rather than diabetes itself.

The best evidence for increased susceptibility for the development of compressive neuropathy exists for *carpal tunnel syndrome* (*CTS*). The development of CTS seems to be related to the body mass index in diabetic patients [197], and increased nerve tissue vulnerability may also play a role [198]. Population studies of diabetics have unequivocally demonstrated an increased incidence of CTS. A large case–control study compared 3,391 patients with CTS to 13,564 matched controls [199]. The presence of diabetes was identified as a risk factor with an OR of 1.51. Stevens and colleagues [200] reviewed the records of 1,016 patients with CTS and found a standardized morbidity ratio of 2.3 for diabetes. The relative risk of CTS is also about 1.6 in patients with prediabetes [201]. Most studies show that CTS is about threefold more common in diabetic patients than matched controls [202, 203]. EDX evidence of CTS may be found in about a quarter of diabetic patients including those with mild diabetic neuropathy [197], but only a third of those are symptomatic. The occurrence of median neuropathy at the wrist increases with longer duration of diabetes. Most often the patient presents with numbness and paresthesias in the hand, particularly the thumb, index, and middle fingers, but symptomatically all the digits may be involved. These sensory symptoms are often worse at night and accompanied by pain. They may note a tendency to drop objects from the hand. Other than the nocturnal symptoms, the other manifestations are similar to what may be seen with diabetic polyneuropathy with hand involvement. Late in the course of CTS with severe axonal loss present, thenar weakness and atrophy is present. If there is also ulnar-innervated hand weakness and atrophy, such as in the interosseous muscles, then polyneuropathy should be considered as an alternative cause.

The diagnosis of CTS is best made electrophysiologically using the same criteria as for other patients [204]. However, in those with polyneuropathy and upper extremity involvement, the diagnostic challenges are greater [205]. Electromyographers have difficulty distinguishing CTS in the presence of advanced polyneuropathy with severe axon loss. Other nerves not subject to compression must be assessed to understand the severity of the polyneuropathy. Diabetic focal compression neuropathies may improve after surgical decompression, and diabetics with compressive neuropathy should be managed like others [206]. Patients with CTS and diabetes have the same beneficial outcome after carpal tunnel release as nondiabetic patients [207, 208]. Patients must be reminded that their underlying polyneuropathic symptoms will not change after successful CTS surgery. For example, nocturnal pain and paresthesias, undoubtedly due to CTS, would be expected to improve, but the hand numbness may not, if it is due in part to the polyneuropathy [209].

Ulnar neuropathy at the elbow, although much less common than CTS, also occurs more frequently in diabetics. Ulnar neuropathy has been found in 1.2–4.9 % of diabetic patients in most series [29, 210]. In the large population-based cohort study by Dyck and colleagues [74], 2 % of patients with type 1 and type 2 diabetes had ulnar neuropathy at the elbow. In a large series of 414 patients with ulnar neuropathy, identified postoperatively after procedures for unrelated disorders, 11 % had diabetes compared to 3 % of controls [211]. The incidence of diabetes in the setting of ulnar neuropathy at the elbow ranges from 5 to 17 % [212, 213].

Clinically, ulnar neuropathy presents with numbness and sensory loss in the ring and small digits of the hand, usually intermittent initially. This may be followed by progressive weakness and atrophy in ulnar-innervated hand muscles. This needs to be differentiated from the distal hand weakness that may occur from a coexistent polyneuropathy where median-innervated thenar hand muscles would also be involved [214]. Sudden onset of a significant sensory and motor deficit should suggest nerve infarction rather than compression. The EDX features should reflect the effects of compression at the elbow. As discussed with CTS, other nerves in the limb need to be examined by NCSs to determine the extent of coexistent polyneuropathy.

There is no generally accepted therapeutic approach for ulnar neuropathy at the elbow, and the same issues exist in the setting of diabetes. Conservative treatment with avoidance of positions that cause compression and the use of an

elbow pads is generally the first step. In those with a progressive deficit and clear electrophysiologic evidence of focal compression, surgical decompression is an option. Surgical decompression with or without nerve transposition may be performed, with no evidence to date that one is superior to the other. Compared with CTS surgery, successful outcome after these procedures is less common.

Peroneal neuropathy at the fibular head is infrequent enough that it may be a coincidental occurrence with diabetic polyneuropathy [29]. It was seen in only one of the 380 diabetics studied by Dyck and coworkers [74]. In a series of 103 patients with peroneal neuropathy at the fibular head, 8 % had diabetes [215]. The presentation is like that seen in nondiabetics, manifest by unilateral acute, painless foot drop. The EDX features demonstrate a variable combination of peroneal nerve conduction block and axonal loss. Usually, focal CV slowing cannot be demonstrated [215, 216]. The needle EMG may show evidence of acute denervation in peroneal-innervated muscles distal to the knee with sparing of the shorthead of biceps femoris muscle confirming that the lesions is at the level of the knee. The painless onset and demonstration of focal conduction block at an otherwise common site of compression in nondiabetics suggests that this is a compression neuropathy rather than nerve infarction.

Weakness is limited to peroneal-innervated muscles, as opposed to the more widespread, proximally predominant and painful course of diabetic amyotrophy. This needs to be differentiated from the more slowly developing symmetric weakness of severe polyneuropathy. The latter develops insidiously and is accompanied by severe distal sensory loss and areflexia. The natural history in diabetics is not different from those without diabetes and largely is dependent on the amount of axonal loss that has occurred. A lesion that is predominantly caused by conduction block due to segmental demyelination recovers quickly over weeks, in contrast to one with severe axonal loss that requires nerve regeneration for improvement to begin. The latter often takes 9–12 months for any recovery to be evident. Most are treated conservatively since recovery occurs spontaneously in most, if not all. This reflects the nature of the injury, acute external compression rather than chronic entrapment.

Lateral femoral cutaneous neuropathy (*meralgia paresthetica*) occurs in about 1 % of diabetics [74]. In a recent population study from Olmstead County, Minnesota, meralgia paresthetica was significantly associated with diabetes with an incidence rate in the diabetic population being 7 ½ times the general population [217]. Although obesity may be an alternative explanation for this occurrence in diabetic populations, patients with meralgia paresthetica were twice more likely to have diabetes than age-, gender-, and body mass index controls [217]. Meralgia paresthetica presents with burning and numbness over the anterolateral thigh in the distribution of the lateral femoral cutaneous nerve distribution. Most often it is unilateral but may occur bilaterally. Most resolve spontaneously after several months.

Other compression neuropathies, such as radial neuropathy at the spiral groove and tarsal tunnel syndrome, have rarely been described in patients with diabetes.

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Nutritional and Alcoholic Neuropathies

32

Robert W. Shields Jr.

Introduction

Polyneuropathy due to dietary nutritional deficiency is relatively uncommon in developed countries except in the setting of the nutritional deficiency that occurs in association with chronic alcoholism [1–4]. Nevertheless, polyneuropathy due to dietary nutritional deficiency may still occur in underdeveloped countries particularly in the setting of famines [5]. More often, polyneuropathies due to nutritional deficiency are caused by specific disorders such as pernicious anemia, sprue, and following gastrectomy that result in malabsorption of single or multiple vitamins. It has been suggested that the nutritionally related polyneuropathies are more likely caused by an imbalance of nutrition than a complete deficiency that may occur in starvation [6]. In addition, these polyneuropathies are more often associated with a deficiency of multiple vitamins rather than an isolated deficiency of a single vitamin [6]. This is particularly true regarding the etiology of alcoholic polyneuropathy.

Neuropathic Beriberi

Introduction

Since the 1600s, neuropathic beriberi or dry beriberi was recognized as a condition that caused pain, paresthesias, and paralysis of the limbs [6]. When cardiac manifestations including tachycardia, dyspnea, and edema predominated the clinical picture, the term "wet beriberi" was used. By the mid- to late 1800s, numerous detailed clinical descriptions of wet and dry beriberi were recorded [6, 7] and it became evident that both forms of beriberi represented different manifestations of the same disease [6, 8]. Beriberi was a relatively uncommon disorder until the latter part of the nineteenth century when it reached epidemic proportions, particularly in areas of the world in which rice was the mainstay of the diet. This epidemic was the result of a new method of processing rice utilizing steam-powered rice mills. This process resulted in separating the pericarp and germ from the rice shaft rendering this "polished" rice deficient in thiamine and other nutrients [9]. Although beriberi was initially believed to be caused by an intoxication or an infection [7], evidence of a nutritional etiology was observed by Van Leent, a Dutch naval physician [6, 7], and Admiral Kanehiro Takaki of the Japanese Navy [6, 7, 10]. These naval physicians were able to reduce the incidence of beriberi among sailors by providing them with diets that were similar to that of officers [6, 7, 10]. Admiral Takaki incorrectly presumed that the cause of beriberi was a protein deficiency. In 1897, Christiaan Eijkman, a Dutch military surgeon, discovered that a disease similar to beriberi occurred in birds that were fed a diet of steamed cooked polished rice as opposed to crude rice [6, 7, 9, 10]. Initially, Eijkman speculated that the rice husks countered a toxin in the polished rice, but subsequently he and others postulated theories suggesting that certain foods may contain protective substances which are essential for health [7, 9]. Casimir Funk, working in the Lister Institute in London, was successful in isolating a water-soluble substance from rice polishings that appeared to be an essential neurotrophic factor [7, 10–12]. Funk demonstrated that polyneuritis similar to beriberi could be produced in pigeons fed a diet deficient in this water-soluble substance [7, 12]. He named this substance "vitamine" to indicate that it was a "vital amine" and suggested that other diseases including scurvy, pellagra, and rickets may also be due to a deficiency of this particular vitamin or other vitamins yet to be discovered [6, 7, 12, 13]. Subsequently, it was discovered that not all vitamins are amines and the term "vitamine" was changed to "vitamin." Jansen and Donath in

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1926 isolated the "antineuritic vitamin" and, subsequently, it was synthesized and named thiamine by Williams in 1936 [14].

The discovery of thiamine had a dramatic impact on the management of wet beriberi as administration of thiamine quickly and effectively reversed the cardiac manifestations of the disease. However, the effect of thiamine on peripheral neuropathy was more difficult to demonstrate and led some to speculate that thiamine deficiency was not the specific cause of polyneuropathy occurring in neuropathic beriberi [6]. This concern was also fostered by the difficulty in developing an animal model of neuropathic beriberi due to isolated thiamine deficiency [6]. Nevertheless, animal models were eventually developed and demonstrated that isolated thiamine deficiency may result in polyneuropathy [6, 15, 16]. Thus, the discovery of thiamine deficiency as a cause of beriberi was instrumental in developing the concept of disease due to nutritional deficiency.

Etiology and Pathogenesis

Thiamine or vitamin B1 is a pyrimidyl-substituted thiazole that is found in most animal and plant tissues but it is abundantly present in unrefined cereal grains, wheat germ, yeast, soybean flour, and pork [17]. The recommended daily allowance for thiamine ranges from 1.0 mg/day for older women up to 1.5 mg/day for young men [17]. Thiamine is absorbed in the small intestine by passive diffusion and an active transport process [17]. In the jejunum, thiamine is phosphorylated to thiamine pyrophosphate (TPP), the principal coenzyme form of thiamine [17]. Thiamine and TPP are primarily involved in carbohydrate metabolism. The two primary biochemical reactions in man utilizing thiamine and TPP are the oxidative decarboxylation of alpha-keto acids and the formation of alpha-ketols catalyzed by transketolase [17]. Although the precise biochemical mechanism of nerve injury in neuropathic beriberi has not been defined, it is likely that thiamine's role in carbohydrate metabolism may be the mechanism by which peripheral nerves are affected [18]. Neuropathic beriberi is rarely encountered in developed countries as a result of dietary nutritional deficiency except in the context of the general nutritional deficiency seen in chronic alcoholics [6]. However, wet and dry forms of beriberi may still be observed in the context of total parenteral nutrition and in other situations in which alternative methods of nutritional support are provided to patients [19–21]. Thiamine deficiency has also been reported in patients following various bariatric surgical procedures [22, 23] and has been termed bariatric beriberi [24]. Gestational polyneuropathy due to thiamine deficiency may occur, usually triggered by hyperemesis gravidarum and is often associated with encephalopathy and other signs of Wernicke's disease [25].

Clinical Presentation

The very best clinical and pathologic descriptions of beriberi are found in the writings of Pekelharing and Winkler who traveled to the Dutch East Indies during the beriberi epidemic in order to study this disease and determine its etiology [6, 7]. The neuropathic features include a rather nonspecific clinical syndrome often characterized by painful paresthesias, muscular aches and pains, and limb weakness all conforming to a generalized sensorimotor polyneuropathy [7, 8]. The symptoms are typically symmetrical and are distributed in a distal to proximal gradient. The polyneuropathy usually evolves rather slowly over weeks or months, but occasionally it may develop rapidly over a period of several days [6]. On occasion, pain may dominate the clinical picture resulting in the syndrome of a painful small-fiber neuropathy. Cranial nerve involvement, including tongue and facial weakness, is occasionally observed. However, involvement of the recurrent laryngeal nerve is a relatively common clinical feature that manifests as hoarseness and weakness of the voice [6]. Rarely, amblyopia manifested by central and centrocecal scotomas presumably due to retrobulbar optic neuropathy has been attributed to beriberi [6]. However, it was suggested that the occurrence of optic neuropathy is more likely due to Strachan's syndrome, especially when there is orogenital dermatitis accompanying a predominately sensory polyneuropathy [26]. Other features that have been attributed to beriberi, including ocular motor weakness and nystagmus, are more likely related to coexistent Wernicke's disease. The clinical features of beriberi tend to progress in a slow chronic fashion until the nutritional deficiency is corrected.

Differential Diagnosis

Because neuropathic beriberi produces a relatively nonspecific clinical syndrome of a symmetric and generalized sensorimotor polyneuropathy, a wide variety of other disorders causing similar clinical syndromes need to be considered in the differential diagnosis (see Table 32.1). The clinical features of recurrent laryngeal nerve involvement, facial weakness, and tongue involvement are not often encountered in other common causes of generalized polyneuropathy and may provide important clues to the presence of beriberi. In developed countries, neuropathic beriberi is likely to occur due to an iatrogenic mechanism, especially total parenteral nutrition [19–21]. Thus, this diagnosis should be considered in all patients with the typical clinical features of beriberi who are at risk for nutritional deficiency. Many authors have commented on the striking similarities between neuropathic beriberi and alcoholic polyneuropathy and have suggested that alcoholic polyneuropathy is in fact

Table 32.1 Generalized chronic sensorimotor polyneuropathies

1. Diabetic polyneuropathy
2. Alcoholic polyneuropathy
3. Uremic polyneuropathy
4. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
5. Paraneoplastic polyneuropathies
6. Myeloma and dysproteinemic polyneuropathies
7. Drug and toxin induced polyneuropathies
8. Amyloid neuropathies
9. Endocrine polyneuropathies
10. Infectious polyneuropathies
11. Polyneuropathies associated with HIV infection
12. Vasculitic polyneuropathies
13. Polyneuropathy associated with sarcoidosis
14. Hereditary polyneuropathies

a manifestation of neuropathic beriberi or thiamine deficiency [6, 27–29]. Certainly both wet and dry forms of beriberi can be seen in the setting of the general malnutrition associated with chronic alcoholism. These issues are discussed later in the section on alcoholic polyneuropathy (see below).

Evaluation and Diagnosis

The electrodiagnostic (EDX) features of neuropathic beriberi are those of an axon loss generalized sensorimotor polyneuropathy [30–33]. Pathologic features also conform to axonal degeneration [6, 33, 34]. Thus, these aspects of the evaluation may characterize the nature of the underlying polyneuropathy as an axonal degenerative process, but do not provide specific diagnostic criteria for neuropathic beriberi. The specific diagnosis of neuropathic beriberi centers on the documentation of thiamine deficiency. Historically, attempts to directly measure thiamine in the blood and urine have failed to provide consistent and reliable results [6, 17, 18, 35]. A more accurate and reliable indicator of thiamine deficiency is the assay of red blood cell transketolase activity [36–39]. Transketolase, a thiamine diphosphate-dependent enzyme, discloses reduced activity in the setting of chronic thiamine deficiency [39]. Although this test has been utilized as an indicator of thiamine deficiency, it has not been sufficiently studied to establish its precise sensitivity and specificity [18]. Furthermore, transketolase activity may normalize rapidly following dietary supplementation [36, 37, 40]. Although elevated levels of blood lactate and pyruvate are observed in thiamine deficiency, these findings are nonspecific for diagnostic purposes [18, 41, 42]. More recently, new methods utilizing high-performance liquid chromatography have provided more reliable assays for thiamine deficiency [43–45]. These methods, which quantitate the amount of thiamin diphosphate in whole blood and erythrocytes, compare favorably to results via transketolase activity and provide clear technical advantages regarding sensitivity, specificity, precision, and robustness [43, 44].

Treatment, Management, and Prognosis

Once a diagnosis of neuropathic beriberi is made or considered, thiamine replacement therapy should be initiated and maintained until proper balanced nutrition is restored. Typically, thiamine is administered intravenously or intramuscularly at a dose of 50–100 mg daily. In contrast to the dramatic response thiamine has on wet beriberi [46], it has been more difficult to demonstrate a beneficial effect on neuropathic beriberi [6]. Some clinical improvement is expected in most patients but improvement tends to develop slowly, and in patients with rather severe deficits there may be permanent residual deficits [32].

Alcoholic Polyneuropathy

Introduction

The association between chronic alcoholism and polyneuropathy was first documented in the reports of Lettsom in 1787 [47] and by Jackson in 1822 [48]. These early descriptions were subsequently followed by numerous similar reports such that by the late 1800s, the clinical features of alcoholic polyneuropathy were well described and widely known [6]. During that time, it was believed that the polyneuropathy encountered in chronic alcoholism was due to a direct toxic effect of alcohol on peripheral nerves. This concept went unchallenged until 1928 when Shattuck first suggested that the polyneuropathy seen in chronic alcoholism was caused by a nutritional deficiency of vitamin B and thus should be regarded as a manifestation of beriberi [28]. Since Shattuck's proposal, considerable evidence has been gathered which documents that nutritional deficiency caused by alcohol displacing essential nutrients from the diet is the principal pathogenic mechanism of alcoholic polyneuropathy [1–3, 6, 27, 29, 42, 49–52]. However, controversy still remains as to whether alcohol may also act as a toxin to peripheral nerve and in some alcoholic patients may be the primary cause or contributing factor to their polyneuropathy [53–59].

Chronic alcoholism associated with malnutrition is a relatively common cause of generalized sensorimotor polyneuropathy. Although the precise incidence of alcoholic polyneuropathy is unknown, it occurs in approximately 9 % of alcoholic patients admitted to hospital for alcohol-related disorders [1, 60]. The magnitude of the problem of alcoholic polyneuropathy is underscored by the high prevalence of

asymptomatic alcoholic patients with physical signs of polyneuropathy [6, 60], abnormalities of nerve conduction studies [61–65], or alterations on autonomic nervous system testing indicating autonomic neuropathy [58, 66, 67].

Etiology and Pathogenesis

The proposal that alcoholic polyneuropathy is, in fact, a nutritional disorder stems from the observation that the clinical features of alcoholic polyneuropathy are essentially identical to those of neuropathic beriberi [6, 28]. Furthermore, it is well documented that alcoholic patients may develop both wet and dry forms of beriberi [6, 27, 68, 69]. More compelling evidence regarding the nutritional etiology of alcoholic polyneuropathy comes from the writings of Victor and Adams who methodically studied hundreds of alcoholic patients with various neurological complications including polyneuropathy [1–3, 6]. These authors documented that a history of poor nutrition was invariably present in every patient with alcoholic polyneuropathy in whom an accurate nutritional history could be obtained [1–3, 6]. In addition, these authors emphasized that it is often difficult to obtain an accurate history of nutritional deficiency in alcoholic patients. Thus, the nutritional history should be pursued and confirmed with family or friends. Direct clinical evidence supporting a nutritional etiology of alcoholic polyneuropathy is provided by an experiment performed by Strauss in 1935 [52]. He allowed ten hospitalized alcoholic patients with polyneuropathy to continue drinking alcohol according to their current habit (between one pint and one quart of whiskey per day) providing that they ate an adequately balanced nutritious diet. These subjects were under observation between 14 and 129 days with a mean duration of 64 days. Despite the continued alcohol intake, the clinical features of alcoholic polyneuropathy improved in all ten subjects. In another experiment, Victor and Adams studied ten alcoholic patients admitted to hospital who were given diets deficient in thiamine for 5 days while ceasing alcohol consumption upon admission [2]. None of the ten patients improved until thiamine was subsequently added to their diet.

The clinical evidence citing that alcohol may indeed act as a neurotoxin in the genesis of alcoholic polyneuropathy comes from reports of polyneuropathy occurring in alcoholic patients who do not appear malnourished [53, 55, 58]. However, in most of these reports, the assessment of nutritional status and the criteria used to define nutritional deficiency may not be sufficient to completely exclude the possibility of malnutrition as a pathogenic factor. One of the most widely cited studies that supports the toxic etiology for alcoholic polyneuropathy was reported by Behse and Buchthal [53]. They studied 37 alcoholic patients with alcoholic polyneuropathy. Twenty-three of the patients had no clinical evidence of nutritional deficiency by virtue of a history of adequate dietary intake and the absence of weight loss, whereas 14 patients had overt evidence of nutritional deficiency on the basis of a marked weight loss. The clinical, EDX, and pathologic features of polyneuropathy in the alcoholic patients were identical in both groups leading Behse and Buchthal to conclude that malnutrition was not a requirement for polyneuropathy in alcoholic patients and that alcohol may act as a toxin on peripheral nerve [53]. However, the issue of nutritional status in their patients is somewhat complex. Most of the subjects were beer drinkers and thus weight was not a reliable indicator of malnutrition in this setting. Furthermore, details regarding the nutritional status of their patients were not documented by outside sources other than the patient's own history.

A study by Monforte et al. has been widely cited as evidence that alcoholic polyneuropathy is due to the cumulative toxic effect of the total lifetime dose of alcohol [58]. These authors studied 107 alcoholic patients and 61 controls with clinical surveys, careful examinations, EDX studies, and autonomic tests to assess somatic and autonomic neuropathy related to alcoholism. A detailed history of alcohol intake, dietary habits, and nutritional status was assessed by a standard structured questionnaire and was confirmed with family members. However, the details of the nutritional history extended only 2 months prior to hospital admission. Only 15 of the 107 patients met their criteria for malnutrition, although the alcoholic patients had a smaller arm circumference, a thinner tricipital skin fold, and a significantly lower mean percentage of ideal body weight than the control group. Despite these findings, a multivariate analysis showed that the only independent variable that was related to peripheral neuropathy was the total lifetime dose of alcohol. However, this study failed to take into account the fact that alcoholic polyneuropathy is often a chronic disorder and that the nutritional deficiency that may be associated with chronic alcoholism may evolve intermittently over many months or years. Thus, the assessment of a lifetime exposure to alcohol without a similar measure of nutritional status does not permit a direct comparison of these two potential mechanisms in the genesis of polyneuropathy in these patients.

A more recent study supporting the contention that alcoholic polyneuropathy is due to a direct toxic effect of alcohol rather than nutritional deficiency provided evidence that alcoholic polyneuropathy is clinicopathologically distinct from nonalcoholic thiamine-deficient polyneuropathy [70]. These authors used the thiamine level at presentation as the indicator of the influence of the thiamine status during the evolution of the clinical features. Although thiamine status at presentation is likely to correlate well with acute or subacute presentations of thiamine-deficient polyneuropathy, it may not correlate well with the more typical chronic course of alcoholic polyneuropathy. Alcoholic polyneuropathy often evolves over many months or years and may be influenced

by intermittent fluctuations in the amount of alcohol consumed and the nutritional status of the patient. Furthermore, the authors did not report on other indicators of poor general nutrition, such as diet or weight loss, that may reflect a high risk for other nutritional deficiencies that may contribute to the polyneuropathy.

Animal studies have also been utilized to investigate the pathogenesis of alcoholic polyneuropathy. Although numerous animal models appear to indicate that alcohol may act as a toxin on peripheral nerve, in nearly all of these studies, the animals often sustained a coexistent nutritional insult which may certainly have contributed to the development of peripheral nerve damage [54–57]. In a carefully performed study utilizing a rat model of alcoholism, Windebank and colleagues were unable to demonstrate a toxic effect of alcohol on peripheral nerves [18]. In this study, nutrition was carefully controlled in eight rats who were given 16.8 g of alcohol per kg of body weight per day and in eight control rats. No weight loss occurred in either group. When the nerves were analyzed at 3 and 9 months into the study, there was no evidence of polyneuropathy on 1 μm thin section or on teased fiber analysis. In a primate model of alcoholic polyneuropathy reported by Hallett et al., five male monkeys who were given a diet in which 50 % of their calories were derived from alcohol were compared to four control monkeys [50]. The duration of this experiment spanned 5 years. At the conclusion, there was no histological or electrophysiological evidence of polyneuropathy in either group. In a similar study of 19 female monkeys, 9 monkeys derived 30 % of their calories from alcohol and were compared with ten controls over a 3-year span [50]. Again, there was no evidence histologically or electrophysiologically of polyneuropathy in either group.

Clearly, the precise etiology of alcoholic polyneuropathy remains controversial. There is abundant evidence that many alcoholic patients suffer from nutritional deficiency and that poor nutritional status is associated with the development of polyneuropathy in these patients [1–3, 6]. Thiamine deficiency has been regarded as the most likely nutritional factor involved in the genesis of alcoholic polyneuropathy. Clinical studies arguing that alcohol acts as a toxin in the development of alcoholic polyneuropathy have not been convincing as most of these studies have difficulty in separating the influence of poor nutrition from the consumption of alcohol, factors which are nearly always intertwined in the alcoholic patient. In addition, both nutritional status and the amount of alcohol consumed are difficult to measure, especially in the typical patients with chronic alcoholism who have a slowly evolving polyneuropathy. When alcohol consumption and nutrition can be controlled, as in the animal studies involving both rats and primates that insured stable general nutrition during the consumption of alcohol, no pathological or electrophysiological evidence of polyneuropathy was found [18, 43]. This provides additional evidence supporting the role of nutrition in the development of alcoholic polyneuropathy. More study in this area is needed to better define this complex issue.

Clinical Presentation

The best clinical descriptions of alcoholic polyneuropathy are found in the writings of Victor and colleagues who have carefully and methodically studied hundreds of alcoholic patients with polyneuropathy and other alcoholic-nutritional disorders [1–3, 6]. Alcoholic polyneuropathy occurs in the setting of serious, chronic, persistent alcoholism and prominent nutritional deficiency [1, 3, 6]. In many patients, there may be a substantial and profound weight loss often in the range of 30–40 lb or at least 10 % of body weight. However, weight loss is not uniformly present and, in fact, obesity is sometimes observed in alcoholics who consume large quantities of beer [6]. However, careful nutritional histories can usually document malnutrition in nearly all alcoholic patients with polyneuropathy [6]. It should be emphasized that the nutritional deficiency that results from alcohol displacing essential nutrients from the diet does not occur in the spree or periodic drinker, but only in alcoholics with sustained and persistent alcohol intake and poor nutrition. Although most of the non-nutritional complications of alcoholism occur predominantly in men, alcoholic polyneuropathy occurs equally in men and women [1], a curious observation for which no adequate explanation has been provided.

The clinical manifestations of alcoholic polyneuropathy conform to those of a generalized, sensorimotor polyneuropathy. The symptoms are usually symmetrical and often encompass complaints of weakness as well as sensory disturbance. In approximately 25 % of patients, severe dysesthetic burning pain may dominate the clinical picture suggesting a small-fiber neuropathy [1, 6]. The severity of the polyneuropathy may vary from subclinical involvement detected only upon neurological or EDX examinations to severe and profound polyneuropathy that may prevent the patient from standing and walking. Autonomic fiber involvement is frequently documented on autonomic nervous system testing [58, 66], but overt symptoms or signs of autonomic dysfunction are relatively uncommon [67, 71, 72]. In most patients, alcoholic polyneuropathy represents a chronic disorder that evolves slowly over weeks, months, or even years. However, patients with chronic polyneuropathy may experience subacute or acute worsening that may be so profound that it mimics the Guillain-Barré syndrome [73].

The neurological examination discloses a generalized sensorimotor polyneuropathy [6]. Sensory impairment is typically noted in the lower extremities in a distal to proximal gradient. All sensory modalities are usually involved,

although in some patients more prominent involvement of superficial sensation or deep modalities may occur. Hyperpathia or allodynia may be observed in some patients, while in others, tenderness of muscles in the feet and legs to light pressure may be noted [6, 28, 49]. Muscle weakness is also distributed in a relatively symmetric fashion with a distal to proximal gradient and is often accompanied by reduction or absence of tendon reflexes. On occasion, proximal lower extremity muscles may also be involved giving the false impression of a chronic alcoholic myopathy [6, 74, 75]. In some patients, clinical findings of other alcoholic-nutritional disorders may be observed including cerebellar degeneration and Wernicke-Korsakoff syndrome [1, 3, 6]. In addition to the neurologic findings, many patients with alcoholic polyneuropathy will demonstrate physical findings indicative of their chronic alcoholism and poor nutrition including rhinophyma, abnormal pigmentation of the skin, acne vulgaris, and dry scaly skin [6]. In addition, signs of chronic liver disease may also be observed [6, 76].

Differential Diagnosis

The diagnosis of alcoholic polyneuropathy rests on the recognition of the characteristic clinical syndrome occurring in the setting of chronic sustained and serious alcoholism with malnutrition. Because alcoholic polyneuropathy produces a relatively nonspecific clinical syndrome, a wide variety of other chronic sensorimotor polyneuropathies need to be excluded (see Table 32.1).

Evaluation and Diagnosis

The EDX features of alcoholic polyneuropathy are nonspecific and conform to those of a generalized axon loss sensorimotor polyneuropathy [53, 63, 77–80]. Typical findings on the nerve conduction studies include low or absent sensory nerve action potentials (SNAPs) in the lower extremities [53, 63, 65], mild slowing of motor conduction velocities [53, 65, 78], prolongation of distal sensory and motor latencies [53, 65, 78], and, in more advanced disease, a reduction in amplitude or absence of compound muscle action potentials (CMAPs). These findings are first observed in the lower extremities but in more severe cases, similar alterations may be observed in the upper extremities. F-waves and H-reflexes latencies may also be increased or these late responses may be absent [63, 65, 78]. Needle electromyography (EMG) often discloses changes consistent with a distal to proximal gradient of motor fiber loss manifested by fibrillation potentials and chronic neurogenic motor unit potential alterations of increased duration, amplitude, and polyphasia [80]. Special quantitative methods including single-fiber EMG may also disclose changes consistent with axonal degeneration including an increased fiber density and jitter [81]. The pathologic features of alcoholic polyneuropathy reported on nerve biopsy are relatively nonspecific and tend to conform to changes seen in axonal polyneuropathies [6, 18, 53, 82]. There is usually a reduction in myelinated axons of all sizes [53, 82] and inflammatory changes are not observed [18]. Involvement of the autonomic nervous system was reported in autopsies [6, 83].

General laboratory studies may disclose findings consistent with liver disease and chronic malnutrition including macrocytic anemia and altered liver function tests [6, 18, 76]. Cerebrospinal fluid examination is usually normal, although modest elevations of protein may be observed [6]. Because alcoholic polyneuropathy is regarded as a nutritional disorder, predominantly due to thiamine deficiency, efforts have been made to document a deficiency of thiamine in these patients. As noted previously, the direct measurement of thiamine in the blood and urine is problematic [18, 35]. Although measuring red cell transketolase activity has been the preferred method for assessing thiamine status [36–38], this method has been largely replaced by more modern methods using high-performance liquid chromatography assessing thiamin diphosphate in whole blood or erythrocytes [43–45].

Treatment, Management, and Prognosis

The treatment of alcoholic polyneuropathy consists of stopping the consumption of alcohol and restoring proper nutrition. In this context, it is essential that multivitamins be administered parenterally until adequate balanced nutritional intake can be achieved. Patients with relatively mild or modest polyneuropathy will experience definite improvement over the weeks and months that follow restoration of balanced nutrition. However, patients with more serious or severe polyneuropathies have a less favorable prognosis. Ultimately, prognosis resides in the management of the chronic alcoholism. Thus, detoxification and persistent abstinence are the keys to a long-term recovery.

Vitamin E Deficiency

Introduction

The first observation that vitamin E deficiency could result in a neurological disorder is credited to Evans and Burr who published a report in 1928 documenting paralysis in the suckling offspring of mother rats deficient in vitamin E [84]. Subsequently, other observations were made in various animal models that vitamin E deficiency could result in

neurologic and neuromuscular disorders [85]. However, it was not until 1965 that Kayden et al. proposed that vitamin E deficiency was the pathogenic mechanism of the neurological disorder associated with abetalipoproteinemia [86]. Since then, numerous other observations were made documenting that vitamin E deficiency plays an important role in the neurological disorders associated with chronic lipid malabsorption states [87–92].

Etiology and Pathogenesis

Vitamin E typically refers to alpha-tocopherol, the most active of the major four forms of vitamin E. Gamma-, beta-, and delta-tocopherol have less bioactivity [85]. Dietary vitamin E is predominantly in the form of alpha- and gamma-tocopherol and is found abundantly in wheat germ and vegetable oils [85]. Vitamin E is a lipid-soluble molecule that is absorbed in the small intestine after it is acted upon by bile acids. The bile acids solubilize vitamin E into mixed micelles that also contain other dietary lipids including free fatty acids and cholesterol [85]. Vitamin E is then absorbed by the intestinal mucosa by a noncarrier-mediated passive diffusion process. Once inside the enterocyte of the small intestine, vitamin E is incorporated with other dietary lipids into chylomicrons that are transported via the mesenteric lymphatics into the systemic circulation [85]. Vitamin E is then processed in the liver and resecreted as a component of very low-density lipoproteins (VLDL) which are later converted to low-density lipoproteins (LDL). Vitamin E appears to play an important role as a scavenger of free radicals and may also have an important role in maintaining the structure of cell membranes [93].

In developed countries, vitamin E deficiency is rarely related to a true dietary deficiency as vitamin E is widely distributed in animal fat, vegetable oils, and various grains [85]. More often, vitamin E deficiency is observed in disorders in which lipid malabsorption may occur [85, 87, 89, 90, 92, 94–97] and in rare selective vitamin E deficiency syndromes [98–102]. A wide variety of inherited and acquired disorders results in vitamin E deficiency and the accompanying neurologic syndromes [103]. Inherited or familial disorders include abetalipoproteinemia, a relatively rare autosomal recessive disorder characterized by steatorrhea, pigmentary retinopathy, acanthocytosis, and progressive ataxia [86, 90]. In fact, it was in this disorder that vitamin E deficiency was first proposed as the mechanism of the neurologic disease [86]. Cystic fibrosis is another autosomal recessive disorder associated with steatorrhea and vitamin E malabsorption [94, 104]. Familial syndromes of isolated vitamin E deficiency without evidence of lipid malabsorption have conformed to autosomal recessive [98], X-linked, or autosomal dominant inheritance [101]. In some patients with selective malabsorption of vitamin E, a mutation occurs on the alpha-tocopherol transfer protein gene on chromosome 8q13 [105, 106]. The resulting defect in the alpha-tocopherol transfer protein results in decreased incorporation of vitamin E into plasma VLDL. Vitamin E deficiency may also occur as a result of numerous chronic cholestatic and hepatobiliary disorders [87, 89, 91, 92, 95, 96, 107, 108] as well as in the short bowel syndrome that may follow small bowel resections for treatment of various intestinal disorders [96, 97, 109].

The principal pathologic features of vitamin E deficiency include axonal spheroids in the cuneate and gracile nuclei of the brain stem as well as axonal dystrophy in the posterior columns of the spinal cord, Clarke's column, and the dorsal and ventral spinocerebellar tracts [91, 94, 108, 110–112]. In addition, loss of large-caliber myelinated axons in peripheral sensory nerves is a prominent finding [91, 92, 94, 110, 113, 114] and tends to correlate with the observation that the dorsal root ganglion cell may be a principal target for vitamin E deficiency [18].

Clinical Features

Vitamin E deficiency is associated with a wide array of neurological manifestations [85]. The clinical features of vitamin E deficiency may not be apparent until several years after the onset of deficiency and progression tends to be slow and insidious. In adults it may take up to 5–10 years of vitamin E depletion for neurologic symptoms to develop, although in children the symptoms may occur after shorter intervals of time. The principal clinical features are those referable to a spinocerebellar ataxia associated with a polyneuropathy [85]. The syndrome is usually manifested by progressive gait and limb ataxia and signs of posterior column dysfunction including vibratory and joint position sense loss and hyporeflexia [85, 91, 95–97, 99, 102, 107, 112, 115, 116]. Other neurologic manifestations which may be present include visual loss from pigmented retinopathy [85, 97, 109, 116], ophthalmoplegia [85, 91, 95, 112, 115, 116], ptosis [116], dysarthria [99, 100, 102, 116], dystonia and bradykinesia [100], and generalized or proximal weakness attributable to a myopathic mechanism [113, 117]. Rarely, vitamin E deficiency may present as an isolated polyneuropathy [87, 118].

Differential Diagnosis

Although the constellation of a spinocerebellar degeneration with chronic fat malabsorption makes a diagnosis of vitamin E deficiency relatively straightforward, there are other disorders that may present with similar neurologic features. Certainly, all of the spinocerebellar degenerations should be

considered in the differential diagnosis, particularly when evidence of malabsorption may not be apparent [119]. These disorders include, but are not limited to, Friedreich's ataxia and other inherited spinocerebellar ataxias, as well as adult-onset hexosaminidase A deficiency (late-onset Tay-Sachs disease). The ataxias that manifest predominantly with cerebellar signs without evidence of a polyneuropathy or posterior column involvement may usually be distinguished readily from the spinocerebellar features of vitamin E deficiency. The polyneuropathy of vitamin E deficiency is relatively nonspecific. Thus, when vitamin E deficiency presents as a polyneuropathy, a wide array of other etiologies need to be considered in the differential diagnosis (see Table 32.1).

Evaluation and Diagnosis

The occurrence of a slowly progressive spinocerebellar degeneration in the context of a chronic disorder of lipid absorption provides the essential diagnostic criteria to suspect a vitamin E deficiency syndrome. Documenting vitamin E deficiency is achieved by direct measurement of alpha-tocopherol in the serum, usually by high-performance liquid chromatography [85]. The lower normal limit for children 12 years of age and older and adults is 5 ug/ml, but for children aged 6 months to 12 years the lower limit is in the range of 3–4 ug/ml [120]. Because vitamin E appears in the plasma lipoproteins, the vitamin E concentration may appear normal in hyperlipidemic states despite a true deficiency [121]. For this reason, the ratio of the total serum vitamin E to the total serum lipid concentration has been advocated as a better assessment of vitamin E status [121]. Normal values for children age 1–12 years is >0.6 mg of total tocopherol/g of total lipid and for older children and adults the normal limit of the ratio is >0.8 mg/g [120]. In patients with chronic vitamin E deficiency, the alpha-tocopherol level is typically undetectable [92].

EDX studies often reveal reduced or absent SNAPs with normal motor nerve conduction studies and needle EMG [95, 100, 109, 114, 122]. H-reflexes are usually absent or prolonged but F-responses are normal [122]. These findings are consistent with a pure sensory neuropathy or sensory neuronopathy in which the dorsal root ganglion cells are preferentially involved [18]. On occasion, motor nerve conduction responses may be involved to a mild degree and signs of active and chronic denervation may be noted on needle EMG [107, 122]. In some adult-onset cases, EDX studies may be normal [98, 102]. Somatosensory evoked potentials typically demonstrate a delay in central conduction or failure to conduct beyond the cervical segments [96–98, 100, 102, 109, 112, 122]. The electroretinogram (ERG) may be abnormal in patients with pigmented retinopathy [122] and visual evoked potentials may be abnormal in those patients with abnormal ERGs [122]. Auditory evoked potentials are usually normal [122].

Treatment, Management, and Prognosis

The primary goal of treatment for the neurologic disorders associated with vitamin E deficiency is to prevent further progression of the neurologic deficits. This is usually accomplished by rather high doses of oral vitamin E supplementation. Treatment guidelines have been created for the specific disorders that cause the vitamin E deficiency. For patients with isolated vitamin E deficiency, treatment usually consists of 1–4 g (1,500–6,000 IU) of oral vitamin E per day in divided doses [85]. In the setting of chronic cholestasis, treatment may begin with 50 IU/kg/day of oral vitamin E. The dose may be increased in 50 IU/kg increments up to a dose of 200 IU/kg/day pending normalization of the tocopherol/lipid ratio in the blood [85]. In cystic fibrosis patients who are receiving oral pancreatic enzyme therapy, good responses are usually achieved with doses of 5–10 IU/kg/day of oral vitamin E [85]. However, in cystic fibrosis patients with cholestasis, treatment should conform to guidelines for patients with chronic cholestasis. In patients with short bowel syndrome, good responses are achieved with 200–3,600 mg/day (300–5,400 IU/day) of oral vitamin E [85, 96, 109, 112, 123]. In abetalipoproteinemic patients, treatment usually begins with 100–200 mg/kg/day (150–300 IU/kg/day) of oral vitamin E in divided doses [85]. Because vitamin E levels do not typically improve following successful therapy in this condition, methods other than blood levels are used to assess adequate vitamin E replacement. These methods include peroxide hemolysis testing [116], serial needle aspirate biopsies of adipose tissue for vitamin E stores [124], and serial electrophysiological studies, particularly somatosensory evoked potentials. Concomitant treatment with 15–20,000 IU/day of vitamin A is also recommended along with monitoring the vitamin A concentrations. With this regimen begun early in life, the neurological features of vitamin E deficiency may be averted or stabilized in older patients [85].

Vitamin B12 Deficiency

Introduction

The neurological disorder associated with vitamin B12 (cobalamin) deficiency was first reported in the 1880s [125]. Subsequent reports documented that the principal pathologic alterations were found in the cervical and upper thoracic spinal cord and consisted of a vacuolar myelopathy primarily

involving the posterior columns and the corticospinal tracts [125–127]. This pathological pattern prompted the term subacute combined degeneration of the cord (SCDC) [128]. Although there is clear evidence that peripheral nerves may be involved in vitamin B12 deficiency [6, 129–133], it is often difficult to delineate the clinical features of a polyneuropathy from the sensory and motor features of the spinal cord involvement [6, 134].

Etiology and Pathogenesis

Vitamin B12 is a complex corrinoid compound with four pyrrole rings and a central cobalt atom [135, 136]. Cobalamin, which is active in two coenzyme forms, methylcobalamin and adenosylcobalamin, is required for two enzymatic reactions in man. Methylcobalamin is essential for methionine synthase, the enzyme that catalyzes the reaction between homocysteine and methyltetrahydrofolate, which results in the formation of methionine and tetrahydrofolate [136, 137]. Adenosylcobalamin is an essential cofactor for methylmalonyl-CoA mutase, the enzyme that converts methylmalonic coenzyme A to succinyl coenzyme A, which ultimately enters the Krebs cycle [136, 137]. In the setting of cobalamin deficiency, both methylmalonic acid and homocysteine will accumulate in the blood. Detection of increased levels of these metabolites in the plasma and urine is a sensitive test for the metabolic consequences of cobalamin deficiency [137].

Because cobalamin is found only in cobalamin-producing microorganisms, animal products are the sole dietary source for mammals [138]. The recommended daily requirement is approximately 1 mcg/day [139]. Cobalamin is bound to R proteins in the saliva and gastric juice but is liberated from the R protein by pancreatic proteases in the duodenum. Intrinsic factor, a glycoprotein secreted by gastric parietal cells, binds the cobalamin and the cobalamin-intrinsic factor complex is then absorbed in the jejunum by active transport. An acidic environment in the stomach is necessary for cobalamin to be released from its protein-bound state [138]. Cobalamin is bound to transcobalamin II in the blood and is transported to various tissues where it is absorbed by endocytosis and converted into its coenzyme forms, adenosylcobalamin and methylcobalamin.

The most common cause of vitamin B12 deficiency is pernicious anemia, an autoimmune disorder often associated with antibodies to intrinsic factor. In this disorder, there is a selective defect in vitamin B12 absorption due to failure of gastric parietal cell secretion of intrinsic factor, a substance that is essential for vitamin B12 absorption [138, 140]. Less common causes of vitamin B12 deficiency include ileal or gastric resection [141, 142], bariatric surgery [22, 143], strict vegetarian diet, severe steatorrhea [144], and infection with the fish tapeworm *Diphyllobothrium latum* [145]. The neurological syndrome of SCDC may also result from nitrous oxide use [146, 147] or abuse [148, 149] and rare genetic disorders involving methionine synthase [150] and the binding protein for vitamin B12 transport [151]. The mechanism by which vitamin B12 deficiency causes SCDC and its other neurologic manifestations is unknown. Inhibition of the vitamin B12-dependent enzyme methionine synthase may have a role in pathogenesis [152–154]. The pathological features in the spinal cord consist of demyelination as well as axon loss of the posterior columns of the lower cervical and upper thoracic segments with extension up and down the cord as well as extension into the lateral and anterior columns [126]. Although many of the pathological studies of peripheral nerve in pernicious anemia were incomplete or inconclusive [6, 18], peripheral nerves usually show modest demyelination or axonal degeneration [126, 133].

Clinical Presentation

Vitamin B12 deficiency typically produces prominent sensory disturbances including paresthesias that begin in the feet and legs but which may evolve into the upper extremities [127, 155]. As the disorder progresses, weakness in the lower extremities may develop along with spasticity, hyperreflexia, ataxia, and extensor plantar signs. Sensory signs usually reflect abnormalities of the posterior columns including loss of vibratory sense and joint position sense [127, 155]. However, it is conceivable that an underlying peripheral neuropathy may also contribute to the sensory manifestations to some extent. The absence of Achilles tendon reflexes that may be observed in some patients may represent the most significant clinical evidence for peripheral nerve involvement [18].

Differential Diagnosis

The diagnosis of the neurologic syndromes associated with vitamin B12 deficiency is usually considered in the clinical setting of a myelopathy in which there is a progressive syndrome of corticospinal tract and posterior column dysfunction, conforming to the syndrome of SCDC. Thus, a wide array of disorders causing spinal cord disease needs to be considered in the differential diagnosis including spinal cord compression from spondylosis, abscess or tumor, various forms of myelitis, vascular malformations, intraspinal tumors, multiple sclerosis, and copper deficiency [156]. Vitamin B12 deficiency should also be considered in the differential diagnosis of chronic generalized sensorimotor polyneuropathies, especially when sensory features predominate (see Table 32.1). Clearly, when clinical features of a

generalized sensorimotor polyneuropathy occur in combination with signs of myelopathy, the diagnosis of vitamin B12 deficiency should be considered.

Evaluation and Diagnosis

Vitamin B12 deficiency may be diagnosed by a direct blood assay of vitamin B12 [152, 157]. However, even in patients with apparently normal or low normal vitamin B12 levels, performing assays for serum homocysteine and, in particular, methylmalonic acid adds greater sensitivity to the detection of a vitamin B12 deficiency state [137, 152, 157]. Megaloblastic anemia may occur in B12 deficiency, but it is not invariably present even in the setting of neurologic manifestations [127, 132, 158]. A diagnosis of pernicious anemia may be made on the basis of gastric atrophy and achlorhydria on gastroscopy, as well as the presence of antibodies to parietal cells and/or intrinsic factor. In patients with a history of gastrectomy, malabsorption, or other obvious cause of vitamin B12 deficiency, it is rarely necessary to pursue more formal evaluation for the etiology of the deficiency. In patients without an apparent cause of the vitamin B12 deficiency, a Schilling test should be done. If the Schilling test documents malabsorption of vitamin B12 that is corrected by coadministration of intrinsic factor, then a diagnosis of pernicious anemia can be made. If intrinsic factor does not correct the malabsorption, then the Schilling test should be repeated after an interval of antibiotic or vitamin B12 therapy. Further investigations should also be pursued to look for an occult cause of the malabsorption.

A wide array of neurophysiologic methods is utilized to study vitamin B12 deficiency. EDX tests disclose features of an axon loss sensorimotor polyneuropathy [129–131, 133, 148, 155, 159]. Typical findings on nerve conduction studies include mild slowing of motor or sensory conduction velocity [129, 130, 132], and reduced or absent sensory responses [130, 131, 133]. The needle EMG may disclose signs of denervation, particularly in distal lower extremity muscles [131]. Somatosensory evoked potential studies are typically abnormal, particularly when testing the lower extremity nerves, and are indicative of spinal cord involvement [131, 160]. Visual evoked potentials may be mildly abnormal [131] but auditory evoked potentials are often preserved [131].

Treatment, Management, and Prognosis

Treatment guidelines for vitamin B12 deficiency vary considerably [161, 162]. A typical plan begins with intramuscular injections of 1,000 ug of cobalamin per day for 5 consecutive days [163]. This 1,000 ug dose may be repeated weekly for an additional month and then monthly for the remainder of the patient's life depending upon the specific etiology of the B12 deficiency state. Because approximately 1 % of ingested cobalamin may be absorbed by passive diffusion, some patients may be treated with high doses of oral cobalamin at 1,000 ug/day [164, 165]. If treatment is initiated relatively early in the course of the neurological disorder, prognosis may be excellent [155, 166]. However, symptoms and signs present for 6 months or longer may persist despite replenishment of the B12 stores [155].

Vitamin B6 Deficiency and Toxicity

Vitamin B6 (pyridoxine) may cause a polyneuropathy due to a deficiency state [167] and as a result of a direct toxic effect [168, 169]. Pyridoxine deficiency is most often observed in patients treated with the antituberculosis drug isoniazid or the chemically related antihypertensive drug hydralazine [170–172]. Vitamin B6 deficiency may also be observed in the setting of general malnutrition that accompanies chronic alcoholism [173] and in patients receiving hemodialysis [174]. The polyneuropathy of vitamin B6 deficiency conforms to a chronic axon loss sensorimotor polyneuropathy [170, 171], with a wide differential diagnosis (see Table 32.1). The diagnosis of vitamin B6 deficiency can be confirmed by a direct assay of vitamin B6 in the blood [17]. Vitamin B6 supplementation at a dosage of 50–100 mg of vitamin B6 per day is recommended in patients treated with isoniazid and hydralazine [18] and is a reasonable dosage for dietary deficiency. In alcoholic patients with vitamin B6 deficiency, it is likely that other vitamins and nutrients are also deficient. Thus, treatment in this group should address general nutritional therapy along with abstinence from alcohol.

The neuropathy that results from excessive dietary intake of vitamin B6 produces a syndrome of sensory neuronopathy with profound deafferentation and ataxia dominating the clinical picture (see Chap. 35) [168]. However, EDX studies have documented some element of motor axon loss as well [168]. The toxic sensory neuronopathy of vitamin B6 may result from as little as 200 mg of pyridoxine per day [175, 176]. Unfortunately, the prognosis of the sensory neuronopathy is relatively poor, although modest improvement of the EDX findings of motor fiber involvement was reported [177].

Pellagra

Pellagra is a nutritional disorder of niacin deficiency. Although rare in developed countries, pellagra continues to occur in certain underdeveloped parts of the world, particularly in Africa and Asia, where corn remains the principal source of carbohydrate in the diet. More recently, pellagra

was observed in India and Egypt where it is associated with diets based upon jowar, a type of sorghum [178]. Although pellagra is occasionally encountered in malnourished patients, especially alcoholics [4, 179, 180], it has essentially been eradicated in many Western countries by the practice of enriching bread with niacin.

Pellagra is a disorder characterized by the classic triad of dermatitis, diarrhea, and dementia [6, 179, 180]. The skin lesions are hyperkeratotic and reddish brown in coloration with a somewhat typical distribution over the face, neck, and dorsal surfaces of the limbs [180, 181], sometimes resembling a sunburn indicating photosensitivity [180]. Diarrhea and the other associated gastrointestinal symptoms usually contribute to general weight loss and fatigue. The neurological manifestations are rather diverse and may correlate with involvement of the brain, spinal cord, and peripheral nerves. Because of the rather protean neurologic manifestations, there is a controversy as to how often the neurological symptoms of pellagra are indeed related to peripheral nerve involvement [6]. It appears that when peripheral nerves are involved, the disorder is relatively mild and shares many features with beriberi [6, 182]. Pathologic findings in peripheral nerves disclose signs of axonal degeneration. Despite the discovery of niacin and the demonstration that it is the principal vitamin deficient in pellagra, it has been observed that supplementation with niacin may not resolve the peripheral nerve symptoms [46, 182–184]. Furthermore, there is evidence that some of the neurological manifestations of pellagra may indeed be due to other coexisting vitamin deficiencies including thiamine and pyridoxine [6]. Niacin supplementation at doses of 40–250 mg daily is usually adequate to reverse most of the non-neuropathic symptoms and signs of pellagra [6].

Strachan's Syndrome

The syndrome of painful polyneuropathy with associated features of amblyopia, and orogenital dermatitis was first described by Strachan in 1888 [185] and later in 1897 [186]. Strachan observed this clinical syndrome in Jamaican sugarcane workers and subsequently the disorder was termed peripheral neuritis of Jamaica. A similar clinical syndrome was later described by Scott in 1918 [187]. Although Strachan initially proposed that this disorder was caused by malaria, it was subsequently regarded as a nutritional deficiency disorder [6]. Numerous reports of similar clinical syndromes appeared in the literature in the 1930s and 1940s in which the central clinical features were polyneuropathy and optic neuropathy [6, 188].

The principal clinical features of Strachan's syndrome are those of a painful, predominantly sensory polyneuropathy accompanied by visual loss secondary to central or centrocecal scotomas [6]. The orogenital dermatitis may be expressed to variable degrees and may include excoriation of the corners of the mouth, prepuce, anus, and vulva [6]. In addition, corneal degeneration and stomatoglossitis may be observed [6].

The typical pathologic features of Strachan's syndrome were carefully studied by Fisher in Canadians held as prisoners during World War II [189]. Prominent findings included demyelination and axon loss in the posterior columns of the spinal cord and the columns of Goll as well as degeneration of fibers in the optic nerves referable to the papillomacular bundle [189]. There was no obvious abnormality of peripheral nerves but comprehensive study of peripheral nerves was not undertaken. Furthermore, definitive pathologic studies on peripheral nerves have not been reported [6, 18].

In 1992 and 1993, there was an epidemic in Cuba of a clinical syndrome resembling Strachan's syndrome which included polyneuropathy, sensorineural deafness, optic neuropathy, and dorsolateral myeloneuropathy [5]. These clinical features clearly overlap those attributed to Strachan's syndrome. In this disorder, sural nerve biopsies showed an axonal neuropathy predominantly affecting large-diameter myelinated axons [190]. The myeloneuropathy was manifested by clinical deficits reflecting posterior column involvement as well as sensory ataxia and mild corticospinal tract signs [5]. Bilateral high-frequency sensorineural hearing loss was accompanied by tinnitus. Many patients displayed isolated optic neuropathy or combinations of optic neuropathy and myeloneuropathy, as well as other variations [5]. Although overt malnutrition was not present in most of the patients, a deficiency of micronutrients, including thiamine, cobalamin, folate, and sulfur amino acids, appears to have been the primary mechanism of this disorder [5]. The vast majority of patients improved with treatment of B group vitamins and folate. Thus, it is likely that this syndrome as well as the classical Strachan's syndrome represent disorders of multiple deficiencies especially thiamine, niacin, riboflavin, pyridoxine, and cobalamin. An epidemic of optic neuropathy and polyneuropathy resembling Strachan's syndrome occurred in coastal Tanzania in 1988. This epidemic was also attributed to micronutrient deficiency [191]. In classical Strachan's syndrome, treatment with riboflavin (vitamin B2) rapidly reverses the orogenital dermatitis, but does not appear to have a substantial benefit regarding the optic neuropathy and myeloneuropathy [18].

Copper Deficiency

Copper is an essential trace element that is present in all living cells and involved in electron transport and oxidative reactions [192]. It serves as a cofactor for oxidative enzymes such as cytochrome c oxidase, a key enzyme in oxidative

metabolism, and superoxide dismutase, an important scavenger of superoxide radicals. Copper influences functions in many organs and, in particular, is important in maintaining bone marrow function and maintenance of the central nervous system [192]. Copper is absorbed primarily via active transport from the duodenum and to a lesser extent the stomach. Copper is bound to albumin and transported to the liver where it is complexed to ceruloplasmin, albumin, and transcuprien and ultimately released into the blood where it is transported to the tissues [192]. Dietary deficiency of copper is rare as it is ubiquitous in many foods and the dietary requirement of copper is low, 1.0 mg/day for adults with lower requirements for children and higher requirements for pregnant and/or lactating women [193]. Nevertheless, copper deficiency disorders have been recognized in both man and animals. In veterinary medicine, copper deficiency was documented in 1937 to cause a condition in ruminants called enzootic ataxia or swayback as well as anemia [194]. The hematological disorders in humans related to copper deficiency, primarily anemia and leukopenia often resembling a myelodysplastic syndrome, are also well established [195]. However, the appreciation that copper deficiency in humans may cause a myeloneuropathy is relatively recent.

The first report of copper deficiency causing a myelopathy in humans is attributed to Schleper and Stuerenburg in 2001 [196]. They reported a 46-year-old woman with progressive myelopathic symptoms for the preceding 18 months. The patient had undergone two gastric resection surgeries for peptic ulcer disease 18 and 3 years prior to presentation. Copper level in the blood was markedly reduced as was the ceruloplasmin level. The patient also had microcytic anemia and neutropenia. MRI scan revealed hyperintense signal on T2 images in the dorsal and medial region of the spinal cord from C1 to C7. Electrodiagnostic testing did not disclose evidence of polyneuropathy. After parenteral copper infusion, the sensory symptoms improved and the copper and ceruloplasmin levels returned to normal. However, the spastic tetraparesis persisted. Since then, numerous cases of copper deficiency have been reported in the literature [156, 197–203]. These cases resembled that of Schleper and Stuerenburg but in most of the cases in which careful electrodiagnostic testing was done, there was evidence of an axon loss polyneuropathy [156, 197–203].

The most common causes of the copper deficiency in these cases have included disorders resulting in malabsorption [156, 200], gastric surgery [156, 198, 199, 202, 204], bariatric surgery [143, 156, 205, 206], and excessive zinc ingestion [156, 197], including zinc ingestion from denture creams [203]. The mechanism of excessive zinc consumption causing copper deficiency is accounted for by the competitive absorption of copper and zinc in the stomach and duodenum [207]. In many patients, no specific etiology for the copper deficiency is noted [156, 201]. In a retrospective survey of 51 patients with copper deficiency, the most common causes were bariatric surgery, celiac disease, liver disease, surgery for Crohn's disease, and total parenteral nutrition [208]. In approximately 25 % of patients, no etiology for the low copper level was noted.

The clinical syndrome of copper deficiency shares many features with that of vitamin B12 deficiency [156]. Typically, patients present with paresthesias in the lower limbs and problems with gait. Neurological examination typically discloses spasticity in the lower extremities with hyperreflexia and Babinski signs. Sensory exam reveals prominent posterior column dysfunction with loss of vibratory and joint position sense. Sensory ataxia is common. In addition, in some patients, Achilles reflexes are absent and a distal to proximal loss of light touch and pin perception is noted, consistent with a polyneuropathy. Laboratory testing typically discloses a low copper level in the blood and reduced serum ceruloplasmin. In one series, copper levels ranged from undetectable to a 45 % reduction from the lower limit of normal and ceruloplasmin levels were reduced by 85 % from lower limit of normal [156]. Serum zinc was elevated in approximately half of patients but 24-h urine zinc excretion was elevated in 80 %. Cerebrospinal fluid was normal except for a modest elevation of protein in less than half of the patients [156]. Electrodiagnostic testing typically discloses findings of an axon loss length-dependent sensorimotor polyneuropathy [156]. Anemia and leukopenia may be seen in half of patients presenting with neurological symptoms [156]. Neuroimaging of the spine with MRI may disclose increased T2 signal in the paramedian dorsal cervical cord extending variably into the thoracic cord [156, 199, 201]. In some cases, the spine MRI may be normal [199, 200, 202]. Treatment with copper supplementation, either oral or parenteral, or both, will normalize the copper and ceruloplasmin levels and further progression of the myeloneuropathy should cease [156]. Clinical response regarding the neurological symptoms and signs is variable with some patients noting improvement, typically in the paresthesias [198, 200, 201], but most will have permanent neurologic residuals [156, 200, 201].

Nutritional Deficiency Polyneuropathy Associated with Bariatric Surgery

The worldwide epidemic of obesity is substantial with estimates of overweight or obesity affecting nearly 68 % of the US adult population [209]. Although the awareness of the serious medical consequences of obesity [210] has prompted more aggressive medical management for this condition [211], most medical interventions have not provided consistent results [212–214]. On the other hand, surgical treatments for obesity have demonstrated excellent efficacy with low morbidity and mortality [215, 216]. A variety of surgical

procedures have been employed for weight reduction in obese patients. These methods include laparoscopic adjustable gastric banding, laparoscopic sleeve gastrectomy, and gastric bypass, typically the Roux-en-Y procedure [216]. The most commonly performed procedure in the USA is the Roux-en-Y gastric bypass and approximately 90 % of all procedures are done laparoscopically [216].

The advent and the increased availability of bariatric surgery for the treatment of obesity have been accompanied by increased awareness of its neurological complications [22, 147, 217, 218]. Neurologic complications from these surgeries are not uncommon and are diverse, and many have been attributed to nutritional deficiency [22, 143, 217–220]. The most common neurological complications include encephalopathy, often Wernicke encephalopathy, a myelopathy conforming to a posterolateral syndrome, ataxia, polyneuropathy, and mononeuropathies [22, 143, 217–220]. Wernicke encephalopathy is often associated with polyneuropathy and is clearly related to thiamine deficiency, often in the setting of severe and persistent vomiting in the postoperative setting [22, 23, 143, 218–221]. This has been referred to as bariatric beriberi [24]. However, other micronutrients have also been documented to be deficient in bariatric surgery patients with neurological complications, including vitamin B12 and copper, either of which may be responsible for a posterolateral myelopathy and polyneuropathy [22, 143, 205, 206]. These nutritional complications most often occur within 6–18 weeks of the surgery but in some cases the onset may be delayed for many years [143].

Approximately, two thirds of the neurological complications following bariatric surgery conform to a generalized polyneuropathy [22]. In one large retrospective series of 435 bariatric surgery patients, 16 % of patients experienced a peripheral nerve complication following the surgery [217]. Peripheral polyneuropathy was noted in 6 %, radiculoplexus neuropathy in 1 %, and a mononeuropathy in 10 %. In the majority of patients with polyneuropathy, the disorder had features of a symmetrical sensory-predominant disorder that was insidious in onset and chronic in evolution. In approximately 20 % of patients, the polyneuropathy was subacute or acute in evolution. Pain and autonomic symptoms were noted in about half of the patients. Electrodiagnostic testing disclosed changes of a large-fiber axon loss polyneuropathy in approximately 80 % of patients. In the remaining 20 % of patients with normal electrodiagnostic testing, the clinical features conformed to a small-fiber neuropathy. Risk factors for the development of polyneuropathy included the amount of weight lost, the rapidity of the weight loss, lower post-surgery BMI, lower serum albumin and transferrin, prolonged postoperative gastrointestinal symptoms, less vitamin and calcium supplementation, and lack of attendance at nutritional clinics postoperatively. These authors concluded that malnutrition was the most likely cause for the polyneuropathy [217]. In some patients, the polyneuropathy conforms to an acute or subacute polyradiculoneuropathy, superficially resembling Guillain-Barré syndrome [143]. This form of polyneuropathy has axon loss features on electrodiagnostic testing and has often been associated with thiamine deficiency [23, 218, 221].

Comprehensive preoperative medical assessments emphasizing nutritional status are very important in the bariatric patient as micronutrient deficiencies in these patients are not uncommon [222]. In addition, careful postoperative follow-up designed to assess and provide optimal nutrition in bariatric surgery patients is essential as this may reduce the incidence of these neurological complications [222–224].

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Metabolic and Endocrine Neuropathies

33

Beth B. Murinson and Vinay Chaudhry

Introduction

Peripheral neuropathy occurs with variable frequency due to metabolic abnormalities associated with renal and hepatic failure and endocrine dysfunction of the thyroid and pituitary glands (Table 33.1) [1–3]. Even in the absence of overt symptoms, clinical examination and electrophysiological testing may reveal measureable neuropathy in patients with these disorders. Although nerve conduction studies show a length-dependent reduction of sensory and motor amplitudes suggesting an axonal process, reduction in velocities and prolongation of the distal and F-wave latencies may also be seen suggesting a mixture axonal and demyelinating picture. The severity of neuropathy generally correlates to the severity of the underlying metabolic or endocrine disease. In terms of clinical management, it is important to recognize that clinical reversal of metabolic or endocrine dysfunction may arrest the progression of neuropathy and may even result in meaningful improvements. While substantive peripheral neuropathy is typically observed only in association with advanced or end-stage liver or renal disease, it is important to note that carpal tunnel syndrome may be the first manifestation of underlying endocrine disease suggesting that thoughtful clinical appraisal is appropriate.

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Uremic Neuropathy

Incidence

Peripheral neuropathy is the most common neurological complication of chronic uremia, with prevalence estimates ranging to over 80 % of patients with end-stage renal disease [4–6]. In as many as 50 % of patients, this neuropathy is asymptomatic but demonstrable by nerve conduction abnormalities [5].

Uremic neuropathy is typically a progressive symmetrical sensory and motor axonopathy that is length dependent. Although features of uremic neuropathy were recognized by Charcot and Osler in the nineteenth century, it was not well characterized before 1960 [5]. With the advent of hemodialysis, the support of patients with renal failure permitted the study of uremic neuropathy. Early reports of progressive neuropathy supported the conclusion that frequent dialysis decreased the likelihood that peripheral neuropathy would worsen. Asbury, Victor, and Adams provided the first detailed description of uremic polyneuropathy [7].

Clinical Features

Clinically, uremic neuropathy presents as predominantly large-fiber neuropathy with distal, symmetrical, and "painless" paresthesias [8]. However recent work has highlighted the effects of renal failure on the small nerve fibers [9]. The tempo of progression is chronic and progressive in most cases, although an accelerated, acute neuropathy mimicking Guillain-Barré syndrome has been described [10]. The typical symptoms are tingling paresthesias, restless legs, and distal weakness. Tingling paresthesias may be a prominent first symptom but in some cases weakness precedes sensory symptoms. Muscle cramps are often described. Restless leg syndrome is commonly experienced at night and is characterized by the sensation of needing to move the legs to restore comfort [7, 11]. On physical examination, distal leg reflexes

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Table 33.1 Characteristics of metabolic neuropathies

	Uremic	Hepatic	Hypothyroid	Hyperthyroid	Acromegaly
Incidence	80 %	70 %	40 %	20 %	CTS 35 %
Fiber types	S(LF>SF)>M>A	S (SF>LF), M, A	S (SF>LF), M, CTS	M>S	CTS; rare SM neuropathy
Distribution	Length dependent, also CTS, ischemic monomelic neuropathy related to fistula	Length dependent, also CTS	Length-dependent sensory	Proximal-distal weakness	Entrapment neuropathy more common
Physiology	Reduced SNAP and CMAP; prolonged F-wave and reduced velocities	Length- dependent reduction of SNAP and CMAP amplitudes; mild reduction in CV	SNAP amplitudes reduced; reduced velocities; dispersion	Decreased CMAP amplitude and distal denervation	Mixed axonal and demyelination plus entrapments
Pathology	Axonal degeneration, segmental demyelination, decreased epidermal nerve fiber density	Thinly myelinated fibers; short internodes	Segmental demyelination	Acute denervation on muscle biopsy; no nerve biopsy available	Increased connective tissue in the perineurium and endoneurium; onion bulb
Severity	Asymptomatic 19 % Nondisabling 48 % Disabling 14 %	Mild	Mild	Severe	Varies
Treatment	Renal transplant reversal; dialysis stabilization; erythropoietin	Liver transplant	Hormone replacement	Treatment of thyrotoxicosis	Surgery or radiation of the pituitary; CTS release
Time course	Chronic progressive, rarely acute GBS-like	Progressive	Indolent	Acute to subacute	Chronic
Correlation	GFR <12 ml/min	Related to severity of liver disease	Severity of hypothyroidism	Other signs of hyperthyroidism	Visible enlargement of the hands
Mechanism	K^+ transients, middle molecule, PTH	Portosystemic shunt	Axonal transport; CTS; mucopolysaccharides and edema	Direct effect of thyroxine on muscle	Proliferation of cartilage, bone, connective tissue

S sensory, *M* motor, *A* autonomic, *SF* small fiber, *LF* large fiber, *PTH* parathyroid hormone, *GBS* guillain-barré syndrome, *GFR* glomerular filtration rate, *CTS* carpal tunnel syndrome, *SNAP* sensory nerve action potential, *CMAP* compound muscle action potential

are reduced or absent; decreased vibration sense may be the earliest objective evidence of uremic neuropathy. Other sensory alterations include loss of touch and position sense. Motor findings include weakness of foot dorsiflexion and eversion; mild atrophy may be found.

Abnormalities of the autonomic nervous system are seen in 45–59 % of uremic patients. Orthostatic hypotension, impotence, and constipation are associated with uremic peripheral neuropathy [12]. Tests of autonomic function including beat-to-beat (R-R) variability, tilt table, and galvanic skin response are often abnormal [13]. In a battery of tests, parasympathetic functions were much more frequently abnormal (14 of 16 patients) than were sympathetic functions (3 of 16) suggesting that myelinated parasympathetic nerve fibers are more affected by terminal uremia than are unmyelinated sympathetic fibers [13]. Parasympathetic responses normalize after renal transplant, whereas during dialysis they remain persistently abnormal [14–16].

In addition to the generalized symmetric polyneuropathy, median neuropathy at the wrist is common and mononeuropathies associated with fistula placement in the forearm are well established [17, 18]. The placement of an arteriovenous shunt in the limbs for hemodialysis may result in "stealing" of blood flow from the limb distal to the fistula and cause an ischemic monomelic neuropathy affecting radial, median, and/or ulnar nerves [17–19]. Distal ischemia and edema are also thought to be the mechanism for carpal tunnel syndrome in this setting. Another mechanism for carpal tunnel syndrome in persistent uremia is the deposition of amyloid protein, beta-2 microglobulin, as a manifestation of generalized amyloidosis in long-term renal failure. Uremic patients who are bedridden and cachectic may develop compressive neuropathies including the ulnar nerve at the elbow or peroneal nerve at the fibular head.

The development of uremic neuropathy appears to correlate with the degree of renal failure appearing after glomerular filtration rate falls below 12 ml/min [20, 21]. Laaksonen and colleagues studied 21 patients who were on chronic maintenance hemodialysis treatment and noted only four with no neuropathy; four were asymptomatic but had abnormal electrophysiology; ten had nondisabling symptoms with abnormal nerve conduction studies; and three had disabling symptoms and abnormal nerve conduction studies [21].

Electrophysiology

Abnormalities in nerve conduction studies generally precede clinical manifestations of the neuropathy and are consistent with axonal loss as the dominant pathology [22]. The most marked abnormality on nerve conduction studies is a progressive reduction in the amplitude of sensory and motor action potentials. In addition, prolonged distal and F-wave latency, reduced velocities, and dispersed morphology have been reported suggesting a mixed physiology as also seen with diabetic neuropathy. The number of motor units is decreased in patients on chronic hemodialysis [23]. This is consistent with a decrease in muscle action potential amplitude resulting from fewer large myelinated fibers. In several studies, a progressive reduction in nerve conduction velocities correlated with declining renal function measured by creatinine clearance [24]. In fact among patients with creatinine clearance of <10 ml/min, 50 % showed reduced nerve conduction velocity [24]. EMG demonstrates denervation-reinnervation in distal musculature.

Abnormalities of beat-to-beat variation (R-R interval) generally correlate with a loss of sensory and motor amplitudes. Autonomic neuropathy in renal failure has been the subject of recent studies [13]. For example, the assessment of autonomic, large-fiber, and small-fiber function in 42 dialyzed patients with ESRD excluding those with diabetes and amyloidosis showed that large-fiber peripheral neuropathy was the most prevalent peripheral nerve disorder (60 %), followed by parasympathetic dysfunction (50 %), sympathetic dysfunction (28 %), and small-fiber (thermal) dysfunction. About half of the patients with sympathetic dysfunction also manifested parasympathetic dysfunction. The patients in this study were relatively young with an average age of 46, with an average time on dialysis of 5 years [25]. The assessment of small-fiber structure as well as autonomic and large-fiber function in 40 dialyzed patients with ESRD excluding those with diabetes and other neuropathy-associated conditions found that epidermal nerve fiber density was reduced in these patients and that autonomic dysfunction was very prevalent with abnormal sympathetic skin responses measured in 63 % and heart rate variability reduced (parasympathetic function) in 54 %. Intriguingly, only 38 % of the patients in this study were found to have evidence of large-fiber dysfunction, an estimate that is lower than that reported elsewhere [21, 26]. This is especially noteworthy as the patients in this study were relatively old with an average age of 61 and an average time on dialysis of 7 years [9].

Pathology

Histopathologically, uremic neuropathy shares many features of toxic neuropathy. Axonal degeneration is the hallmark of uremic neuropathy; large myelinated fibers are decreased, there is axonal shrinkage, and nerve fiber loss is frequent. Nerve biopsies in uremic neuropathies demonstrate both chronic and active axonal degeneration as well as some segmental demyelination and remyelination and paranodal demyelination [6]. Some early studies emphasized changes in myelin but have been subsequently interpreted as representing alterations in segmental myelination secondary to

distal axonopathy [4, 5, 27]. There is a gradient of pathological alteration so that distal sites are more severely affected. The assessment of small-fiber structure as well as autonomic and large-fiber function in 40 dialyzed patients with ESRD excluding those with diabetes and other neuropathy-associated conditions found that epidermal nerve fiber density was reduced in these patients in the aggregate but that in 68 % of these patients the lower leg was completely devoid of epidermal nerve fibers [9].

Mechanism

The mechanism of uremic neuropathy is not known but accumulating evidence supports a role for persistent elevations in potassium as a pathogenic mechanism. And although recent work has highlighted the importance of ionic shifts associated with renal failure and dialysis, see below, the marked improvement of patients after renal transplantation led to the middle molecule hypothesis [28]. Essentially, the middle molecule hypothesis proposed that some molecule or molecules of size 1,350–5,000 Da are not efficiently filtered in routine hemodialysis and produce a toxic effect on axons [29]. The middle molecule theory however was not strongly supported by dialysis experience [4].

A series of studies by Krishan, Kiernan, and colleagues collaborating with Bostock has led to a new appreciation for the role of elevated potassium as a cause of peripheral neuropathy in renal failure [30–34]. In one study, 12 patients were studied using an experimental method of electrophysiological function of peripheral sensory nerves called "threshold tracking." This method uses a series of pre-pulses and graded stimulation pulses to assess the basal electrophysiological state of the peripheral nerve (electrotonus). The findings of this group of patients pre-dialysis showed a leftward shift in the stimulus response curve consistent with axonal depolarization, and there was an increase in refractoriness. When these same patients were restudied 1 h after dialysis, there was a dramatic correction in most but not all parameters. Correlation analysis of excitability parameters with serum potassium demonstrated a significant association, suggesting to the authors that hyperkalemia could account for many of the changes observed. There was also some correlation with urea levels; however, this co-correlated also with potassium. The authors comment that rebound hyperkalemia occurring in the hours after dialysis would produce changes likely to contribute to axonal degeneration [31]. A subsequent study of motor nerve excitability before and immediately after dialysis also demonstrates largely reversible changes in electrophysiological parameters consistent with axonal depolarization. This study includes a more extensive analysis of other potential toxins, including calcium, urea, uric acid, parathyroid hormone, and beta-2 microglobulin, and more conclusively demonstrates that potassium has a uniquely strong association with reversible electrophysiological dysfunction [32]. More recent studies supported the conclusion that dysfunction of the sodium-potassium pump (Na+-K+=ATPase) did not play a major role in neuropathy associated with renal failure [34].

There is clinical and experimental evidence to support a role for parathyroid hormone (PTH) in uremic neuropathy. Renal dysfunction produces impaired phosphate excretion, and the resulting hypocalcemia leads to excess secretion of PTH. Serum PTH was negatively correlated with motor nerve conduction velocity in humans [35, 36]. Experimental studies show that acutely uremic animals developed slowed motor NCV which was reversible upon withdrawal of PTH; however, slowed motor nerve conduction was not seen in animals that underwent parathyroidectomy prior to renal failure [37].

Differential Diagnosis

In the differential diagnosis of uremic neuropathy, it is important to consider other causes of progressive distal symmetrical neuropathy. Diabetes mellitus is a common cause of uremia and can independently cause peripheral neuropathy. Cranial neuropathies, autonomic neuropathies, and compressive mononeuropathies are much more frequent in diabetic neuropathies than in uremic neuropathies. Toxic and nutritional neuropathies may mimic the clinical picture of uremic neuropathy. Certainly, patients with suspected uremic neuropathy must demonstrate evidence of substantive renal failure and laboratory values consistent with the diagnosis. CSF is characteristically acellular although increased protein may be found in some patients. Cyto-albumenemic dissociation, typical of GBS, has been observed in the rare acutely progressive form of uremic peripheral neuropathy making the distinction difficult [10].

Treatment

The treatment of uremic neuropathy depends on management of the underlying renal disease. Renal transplant is particularly effective in reversing symptoms and signs and is often associated with subjective and objective improvement [22, 38, 39]. A regimen on frequent dialysis is viewed as beneficial [32]. Some early reports indicated that peritoneal dialysis had an advantage over hemodialysis; further studies have revealed no clear advantage [8, 40]. In either case, dialysis is less likely to produce reversal of progression than renal transplantation [40]. Dialysis is associated with halting the clinical progression of uremic neuropathy and

symptomatic improvement although electrophysiological abnormalities persist. Symptomatic improvement of paresthesias occurs quickly with transplantation and occurs often with dialysis [8, 38]. Strength returns more slowly, some patients on dialysis do not experience improvements in strength. The loss of vibration, proprioception, and light touch sensation are the clinical signs of disease most resistant to treatment. The prognosis for improvement without treatment of renal disease is poor; progression tends to be slowly relentless and may result in disability. The prospects for recovery are better when renal transplantation is performed early in the course of neuropathy. Renal transplantation is the best treatment of uremic neuropathy. Patients with mild early neuropathy may be fully treated and nerve conduction values may return to normal.

There has been some anecdotal evident to indicate that erythropoietin has an ameliorating effect on the neuropathy of end-stage renal disease. The role of erythropoietin in correcting anemia associated with end-stage renal disease has been recognized for some time [41], but evidence regarding the effects of erythropoietin on peripheral nerve function has been limited. There is strong support for the beneficial effects of erythropoietin on peripheral nerve function in preclinical models [42, 43]. A study of patients with pre-dialytic end-stage renal disease indicated that improvements in motor nerve amplitudes were observed and trends to improvements in motor nerve conduction velocities were observed following treatment with erythropoietin, and sensory nerve conduction parameters were not significantly improved although the conduction velocity and amplitudes values were higher after treatment [44]. Further study is needed in this area.

Hepatic Neuropathy

Incidence

Peripheral neuropathy has been reported in patients with liver disease with a frequency ranging from 19 to 100 % [45–52]. A study of 58 patients with end-stage liver disease reported peripheral neuropathy in 71 % of these patients [53].

Clinical Features

In most patients, the neuropathy is subclinical or associated with minimal symptoms. Examination shows distal sensory loss and loss of distal reflexes consistent with a length-dependent neuropathy. Small-fiber function (cooling threshold) is generally more affected than large-fiber function (vibration threshold) [53]. Besides distal symmetric polyneuropathy, autonomic neuropathy also occurs in chronic liver disease [53–60]. Abnormalities of heart rate variation with deep breathing and with the Valsalva maneuver are more likely to be present than orthostatic drop in blood pressure suggesting a predominance of parasympathetic dysfunction. The severity of autonomic dysfunction appears to correlate with severity of hepatic dysfunction [60]. A majority of patients with autonomic dysfunction have additional evidence of sensorimotor polyneuropathy [53].

Electrophysiology

Electrodiagnostic studies reveal a length-dependent reduction of sensory and motor amplitudes with preservation of conduction velocities confirming an axonal physiology. Although some reports of a demyelinating physiology exist in the literature [46–48], careful analysis of these reports shows that the conduction velocities are rarely in the demyelinating range and the findings are alternatively explained as reflective of large-fiber axonal loss. Furthermore, in these studies, entrapment neuropathies were not excluded as possible explanations for the reduced conduction velocities. Carpal tunnel entrapment of the median nerve occurs in one-third of patients with hepatic disease [53].

Pathology

A few pathology reports have interpreted the presence of thinly myelinated fibers and short internodes to suggest that hepatic neuropathy may be demyelinating [45–47, 61]. Active demyelination or inflammatory cells have not been reported and it remains possible that thinly myelinated fibers and small internodes may reflect axonal degeneration followed by regeneration [27, 62, 63].

Mechanism

The mechanisms of peripheral neuropathy associated with end-stage liver disease are not well defined and there are persistent questions regarding the extent of a causal relationship between liver disease and neuropathy as many systemic illnesses that cause liver dysfunction also are independent causes of peripheral nerve dysfunction [64, 65]. Alcohol-induced cirrhosis, porphyria, polyarteritis nodosa, certain intoxications, primary biliary cirrhosis, hepatitis C, and amyloidosis are examples of disorders that may cause neuropathy and hepatic disease independently [64–68]. Nonetheless, patients with cryptogenic liver disease also develop peripheral neuropathy of varying severity [53]. Furthermore, there is a correlation of the severity of neuropathy to the severity

of liver disease suggesting that the peripheral neuropathy is caused by metabolic dysfunction resulting from liver disease [53]. A study suggested portosystemic shunting to be the causative factor in the genesis of hepatic neuropathy. However, two other studies found no differences in the presence or severity of neuropathy in patients with or without portocaval shunt [48, 61]. An experimental study of portocaval anastomosis in rats also favored hepatocellular failure as the principal pathophysiologic mechanism in hepatic neuropathy [69]. Patients with chronic liver disease secondary to primary biliary cirrhosis appear to form a separate group as these patients present with pure sensory neuropathy with or without xanthomatous infiltration of the nerves [70, 71]. A recent study of 83 patients awaiting liver transplantation showed that sensory and sensorimotor neuropathies predominated. A length-dependent pattern was found, and the prevalence of neuropathy significantly correlated with disease severity. The authors also observed that the diagnosis of hepatitis C was associated with peripheral neuropathy independent of the severity of liver failure [52]. Unfortunately, the methodological approach of these authors makes direct comparison to their results difficult.

A series of 11 patients with end-stage liver disease were studied prior to liver transplantation, using the experimental method of threshold tracking developed by Bostock and colleagues. This method has the capacity to assess relative but not absolute states of polarization in peripheral nerves as well as refractoriness, subexcitability, and superexcitability. The study of patients with ESLD, which also includes standard approaches to peripheral nerve assessment, demonstrated prominent small-fiber involvement with a minority of patients having abnormal nerve conduction results indicative of large-fiber dysfunction. The evaluation of dynamic electrophysiological function showed evidence of axonal depolarization although these changes were mild in comparison to the changes demonstrated in studies of patients with end-stage renal disease. The authors did not observe a correlation between changes in these electrophysiological measures and putative toxins associated with ESLD [72].

Treatment

Liver transplantation may have a beneficial effect for patients with neuropathy related to end-stage liver disease, although the evidence for this is mixed. Lee and colleagues studied 25 patients before and 6 months after liver transplantation. Their study found that end-stage liver disease patients demonstrated sensory neuropathy (11 patients) and motor neuropathy (seven patients) prior to transplantation. Assessed 6 months after transplantation, there was an improvement in motor and sensory function with three patients demonstrating persistent abnormal nerve function study results [73]. McDougall and colleagues examine 42 patients with ESLD, 13 of who underwent liver transplantation subsequently. This study included assessment of autonomic, sensory, and motor nerve function. Their findings indicate that sensory nerve conduction abnormalities were widely prevalent (39 or 42) and persisted after transplantation (12 of 13). Parasympathetic measures were abnormal in about 60 %, motor nerve conduction studies were abnormal in half, and sympathetic measures were abnormal in about 20 %. Repeat testing performed between 4 and 27 months after transplantation did not demonstrate substantial improvement although a trend for improved responses to Valsalva was noted [74].

Hypothyroidism

Incidence

Sensorimotor axonal neuropathy occurs in 42 % and entrapment of the median nerve at the carpal tunnel occurs in 29 % of patients with hypothyroidism [75, 76].

Clinical Features

The symptoms of distal sensory polyneuropathies include paresthesias of the feet and muscle cramps in the legs along with severe burning distal pain and lancinating pains. Sensory involvement of the hands should raise the clinical suspicion for carpal tunnel syndrome. Progression may include motor symptoms but examination usually shows no more than mild distal leg weakness. Signs include decreased touch, position, and vibration sense; absent leg reflexes; and less commonly distal leg weakness [77, 78]. The findings on physical examination may be confounded by coexistent muscle disease, which should be considered if proximal weakness is observed [79]. Hypothyroid myopathy is much more common than the distal sensory neuropathy of hypothyroidism described here. Prolongation of the relaxation phase of the ankle jerks is a classical sign of hypothyroid state, although it is not directly related to neuropathy. The symptoms of entrapment neuropathy are no different in hypothyroid state than those seen with carpal tunnel syndrome of other etiologies and include paresthesias at the fingertips.

The diagnosis is suggested by observable symptoms and signs of hypothyroidism that include dry skin, fatigue, constipation, hair loss, muscle aches, and cold intolerance. The hearing loss associated with hypothyroidism is sensorineural but the relationship to distal sensory neuropathy is unclear; the hoarseness associated with hypothyroidism is probably not neurogenic in origin. A decreased thyroxine (T_4) level is

central to the diagnosis of hypothyroidism and thyroid function studies should be assessed. TSH is elevated in primary hypothyroidism. Long-standing hypothyroidism may be undetected because symptom onset is insidious.

Electrodiagnosis

Electrodiagnostic studies are important to characterize the neuropathy in question. There is no consensus regarding the findings of electrophysiological studies, which may show axonal, demyelinating, or mixed results. As a rule, the distal sensory polyneuropathy of hypothyroidism produces a mild-moderate decrease in conduction velocity and decreased amplitude of sensory nerve action potentials. There may be increased distal latency and dispersion of compound muscle action potentials [78–80].

Pathology

The mild chronic sensory polyneuropathy of hypothyroidism is histologically indolent. There are frequent regenerative clusters and an increased number of Pi granules are found in nerve biopsy [76, 77, 81]. Also seen, although not diagnostic of hypothyroidism, is the deposition of glycogen. Glycogen is observed ultrastructurally in most cells of the nerve fascicle including the Schwann cell, myelinated and unmyelinated axons, endothelial cells, and perineurial cells. Nerve biopsy studies have shown segmental demyelination and myelinated fiber loss. Large myelinated fibers are particularly affected. These findings suggest a process of axonal degeneration; however, in other studies, demyelination and remyelination was a prominent feature [77, 78, 81].

Mechanism

The mechanism of the distal sensory neuropathy of hypothyroidism is not known. It has been proposed that defective slow axonal transport produces this entity. The mechanism of carpal tunnel syndrome in hypothyroid state is related to collection of mucopolysaccharides and edema in the extracellular connective tissue within the nerve, in the tendon sheaths, and in the synovial membranes.

Treatment

Correction of thyroid insufficiency is the cornerstone of treatment. Improvement is likely; however, if axonal loss is severe, recovery may be incomplete. The prognosis of symptomatic and objective improvement may be anticipated with hormone replacement.

Hyperthyroid Neuropathy

Incidence

Polyneuropathy can be one manifestation of severe hyperthyroidism, reported in up to 19 % of patients [79].

Clinical Features

Basedow's paraparesis is a term used to describe subacute onset of proximal and distal weakness of the lower limbs with areflexia, sparing sensations, and sphincters, occurring as a complication of hyperthyroidism. It was described by Charcot in 1888. There is marked proximal and distal leg weakness, severe hypotonia, and areflexia in legs. Sensory signs and symptoms are mild; proprioceptive loss may be seen. The diagnosis is usually immediately evident given the other clinical manifestations of hyperthyroidism including exophthalmos, goiter, tachycardia, diaphoresis, tremor, and agitation [82]. The presentation of hyperthyroidism can be highly variable. Thyroid storm, which is rare, presents with fever, marked tachycardia, diarrhea, hypotension, and agitation. Evaluation of thyroid function studies is necessary.

Electrophysiology

The electrodiagnostic findings of hyperthyroid paraparesis are decreased CMAP amplitude and denervation of distal musculature [83]. There are descriptions of postexercise augmentation and fatigue of CMAP amplitudes [84].

Pathology

A published report with muscle biopsy evidence of acute denervation was suggestive of nerve involvement but nerve biopsy has not been studied in this disorder [81].

Mechanism

The precise mechanism of the Basedow's paraplegia is however not known; however, a direct effect of thyroxine on muscle cells has been proposed [83].

Treatment

Treatment of hyperthyroidism may produce clinical improvement that paradoxically may be accompanied by worsening nerve conduction findings. Treatment of the underlying hyperthyroidism is necessary. Supportive care and rehabilitation of motor deficits is important. With appropriate treatment of hyperthyroidism, improvement may be anticipated; however, return of motor function may require weeks to months.

Acromegaly

Incidence

Acromegaly is usually caused by excessive growth hormone secretion from an eosinophilic adenoma of the pituitary gland. Entrapment neuropathies, particularly carpal tunnel syndrome (30–50 %), are far more common than distal symmetric polyneuropathy in acromegaly [2, 85–89].

Clinical Features

Carpal tunnel entrapment of the median nerve occurs in more than one-third and may be the presenting complaint of acromegaly. The distal symmetrical polyneuropathy associated with acromegaly is rare relative to entrapment neuropathy. The initial symptom of the distal symmetrical polyneuropathy of acromegaly is distal paresthesias. Progression leads to weakness more prominent distally. Examination findings include decreased light touch, vibration, and proprioception sense in the lower extremities. Reflexes are absent in the legs and decreased in the arms. There is mild distal weakness of the legs. The symptoms and signs of carpal tunnel syndrome associated with acromegaly are essentially similar with median nerve dysfunction at the level of the wrist due to any cause and are discussed above with carpal tunnel of hypothyroidism. However, the visible enlargement of hands and fingers is a key clinical feature of acromegaly. Carpal tunnel syndrome in acromegaly may precede the obvious stigmata. Glucose intolerance is frequently associated with acromegaly and it is important to determine if diabetic neuropathy may account for confounding findings. Growth hormone levels vary diurnally and with fasting. As the measurement of elevated growth hormone may be insufficiently sensitive in mild cases, the measurement of IGF-1 (insulin-like growth factor) when reliably performed may be more informative and the diagnostic criteria incorporate this biochemical data as well as the results of MRI studies looking for pituitary adenoma. As discussed above, serum glucose may be elevated; assessment should include thyroid function studies as well. CSF is normal.

Electrophysiology

Electrodiagnostic studies may show decreased amplitude of sensory and mixed nerve action potentials and mild slowing of motor conduction velocity. Evidence of reduced velocity across compression sites (carpal tunnel and across elbow) as occurs with typical median neuropathy at the wrist and ulnar neuropathy at the elbow is commonly seen.

Pathology

Nerve biopsies from patients with the distal symmetrical polyneuropathy of acromegaly display increased connective tissue in the perineurium and endoneurium. Although there are a decreased number of myelinated and unmyelinated axons, there is no active degeneration and supporting a mixed axonal/demyelinating process is the observation of onion bulb formation [87].

Mechanism

The mechanism by which acromegaly leads to distal symmetrical polyneuropathy is not known. Carpal tunnel syndrome occurs as a result of proliferation of cartilage, bone, connective tissue, and synovial membranes in the area of the carpal tunnel.

Treatment

Treatment of acromegaly is carried out by an endocrinologist and may include irradiation of the pituitary or transsphenoidal extirpation. Even though resolution of acromegaly can be slow and may require years, removal of the growth hormone-secreting tumor is typically followed by resolution of carpal tunnel symptoms. For this reason, carpal tunnel symptoms are considered useful indicators of disease activity [88]. However, in some patients, surgical release of the carpal tunnel is necessary.

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Environmental Toxic Neuropathies

34

Michael T. Pulley and Alan R. Berger

Introduction

Toxic neuropathies can be caused by exposure to substances including chemicals or heavy metals. These exposures may be accidental (in the workplace or through drinking water) or intentional (homicide or suicide). Most toxic neuropathies produce symmetric deficits, but the symptoms and signs may vary, even when the intensity or duration of exposure to the substance is changed. Most heavy metal exposures produce other organ involvement such as skin, hair, or gastrointestinal symptoms and rarely cause an isolated peripheral neuropathy. Some toxins, particularly chemicals, produce damage to the distal ends of both central and peripheral axons and, in some cases, produce morphological changes such as giant axonal swellings. Diagnosing a toxic neuropathy requires suspicion and recognition of associated signs. Also, there are principles of toxin-induced disease that should be present such as consistency of disease in individuals with similar exposures. Treatment of toxic neuropathy involves removing the patient from exposure and, in the case of heavy metals, increasing the excretion of the toxin using chelating agents. Most toxic neuropathies have a good prognosis, but the ultimate outcome depends on the degree of impairment at the time exposure ceases.

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Identification of Toxic Neuropathies

Toxic neuropathies have received significant attention due to a few well-publicized clusters of cases [1]. However, epidemics of toxic peripheral neuropathies are rare, particularly in North America. Most toxic neuropathies are sporadic occurrences due to either intentional exposures (suicide or homicide) or accidental (individual or small group) occupational exposures.

The first step in identifying a neuropathy as toxic is a high degree of suspicion. The usual pattern of toxic neuropathy involves distal, symmetric sensory greater than motor abnormalities. As this presentation is similar to that of many other polyneuropathies, a good history of potential exposure usually is needed to raise suspicion. Toxic exposure must often be specifically inquired about, as many patients are unaware of the potential harmful effects of many compounds. Certain key principles of toxin exposure help to establish a cause and effect relationship [2]. First, there should be a consistent pattern of disease, commensurate with the dose and duration of exposure. Second, individuals with similar exposures should experience similar symptoms and signs. Third, the latency of symptom onset following presumed exposure should be short. Finally, removal of the individual from continued exposure should result in improvement or at least stabilization of the disease process. There are a few exceptions to the last rule that involve "coasting," which is the continued worsening of neuropathy after cessation of exposure, seen with certain toxins. Coasting may continue for weeks to months, but not indefinitely.

Another problem in diagnosing toxic neuropathies is the frequent absence of reliable laboratory tests for many of the compounds that cause neuropathies. Even when available, the person may have been removed from exposure before the responsible toxin could be measured and it may no longer be present. The diagnosis of neuropathy from an

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environmental toxin is a challenging and often difficult process that may require a visit to the patient's home or workplace to investigate potential sources of exposure. This chapter describes some of the more common environmental causes of toxic neuropathy.

Lead

Introduction

Lead toxicity is a well-known cause of neurologic dysfunction. Exposure to lead was previously common given its use as solder for drinking water pipes and metal food containers. Lead oxide was added to house paints, ceramic tableware, and toys; tetraethyl lead was added to gasoline [3]. The frequency of lead intoxication has been significantly reduced by the elimination of lead-based paints and other environmental sources. Nonetheless, potential for exposure to lead still exists, especially in the industrial setting. Inorganic lead exposure may occur in lead miners, plumbers, solderers, cable makers, automobile factory workers, lead glass blowers, and pottery glazers. Those employed in battery manufacturing, smelting plants, demolition, and automobile radiator repair [4] are also at risk. Using a torch or other heat source can vaporize lead paint producing intoxication via inhalation of lead. Other potential sources of exposure include drinking "moonshine" whiskey [5], working in indoor gun firing ranges [6], and burning batteries for heat. Exposure to organic lead is less common and is primarily through leaded gasoline products.

Pathogenesis

Lead gains access to the tissues via ingestion, inhalation, or dermal contact. Once in the body, lead interacts with sulfhydryl, amino, phosphate, and carboxyl groups [3]. The interaction with the sulfhydryl groups of enzymes in the heme biosynthetic pathway contributes to anemia. Detoxification of harmful free radicals is also hindered because of deficient activity of cytochromes that contain heme. High levels of inorganic lead may promote cell death by accumulation of intracellular calcium. Calcium levels are increased due to displacement of calcium ions, disruption of ion transport through calcium channels, and inhibition of calcium adenosine triphosphatase [7, 8].

Clinical Presentation

Lead intoxication in children is most commonly associated with central nervous system (CNS) dysfunction. This may lead to chronic cognitive dysfunction (developmental delay or loss of milestones) or acute encephalopathy. High-level acute exposure in adults can also lead to encephalopathy. The encephalopathy may progress to seizures, coma, or death in patients of any age [5, 9]. Ataxia, tremulousness, and choreiform movements are other potential manifestations of acute high-level exposure. CNS disturbances including hallucinations may occur with high-level intoxication and correlates with blood lead levels [10]. Chronic, low-level lead exposure may also have deleterious effects on cognitive or behavioral function.

Peripheral neuropathy resulting from chronic lead exposure may occur in children but is more often seen in adults. Other systemic features of lead toxicity are usually present at the time of presentation, including gastrointestinal (GI) disturbance (abdominal pain might include that the abdominal pain seen with acute lead toxicity can resemble that seen with acute cholecystitis and constipation), anemia (hypochromic, microcytic), weight loss, fatigue, renal dysfunction, bluish discoloration of the gums ("lead lines") and occasional gout. Due to the presence of GI manifestations, anemia, and peripheral neuropathy along with CNS disturbance, lead toxicity needs to be differentiated from porphyria, which lead exposure may precipitate [11].

Lead neuropathy develops insidiously with chronic exposure. Sensory symptoms and signs are minimal or absent while motor complaints predominate. Distal symmetric weakness with reflex loss and atrophy that may initially involve the arms is the usual pattern. Focal deficits such as finger drop are noted in the literature, but these may be due to secondary compression neuropathies [12]. Although lead exposure is associated with some lower motor neuron damage, the development of idiopathic motor neuron syndromes such as amyotrophic lateral sclerosis has not been linked to lead exposure [13]. Some recent reports have challenged the notion that sensory complaints due to lead exposure are unusual, particularly in those with chronic occupational exposure [14, 15].

Evaluation and Diagnosis

Laboratory evaluation reveals a microcytic, hypochromic anemia with basophilic stippling of erythrocytes. Urinary and blood lead levels can be measured. Chelating agents that draw lead from the tissues and allow for its excretion increase the diagnostic yield and may be beneficial therapeutically. The ratio of the micrograms of lead excreted to milligrams of calcium ethylenediamine tetraacetic acid (CaEDTA) administered should not exceed 0.6, and the 24 h urinary lead level after chelation therapy (usually with CaEDTA) should not be greater than 1 mg [16]. A blood lead level greater than 40 ug/100 ml of whole blood is considered abnormal. Although recent exposure causes an elevation of blood lead levels, this does not reflect the total body lead burden.

Axonal and demyelinating features are reported in different electrodiagnostic (EDX) studies. Nerve conduction

studies (NCS) clearly show evidence of sensory axon loss although sensory symptoms or signs are unusual. Asymptomatic individuals and those exposed to "safe" lead levels may have abnormal nerve conductions [17]. The amount of lead in the body predicts the degree of electrophysiologic abnormality [17]. Axonal degeneration leads to electromyographic (EMG) evidence of active denervation and chronic motor unit reinnervation. Somatosensory-evoked potential amplitudes are correlated with blood lead levels in exposed workers. Abnormalities of attention, visuospatial functioning, and memory are detected by neuropsychologic testing.

Treatment and Management

The presence of lead paint in older buildings makes children at risk for ingestion. Eradication efforts have significantly reduced the prevalence of children with elevated blood levels. Measures that may help to decrease the potential for lead exposure in the environment and workplace include enforcement of regulations regarding industrial lead emissions and occupational exposure levels, education of those at high risk regarding the potential long-term effects, promoting good hygiene, regular monitoring of exposure levels, and use of protective clothing and respirators. Urinary lead level monitoring may identify those with excessive exposure prior to symptom onset. Subclinical neuropathy may be detected by nerve conduction studies before it becomes severe [17].

The initial step in the treatment of lead toxicity is preventing further exposure. Chelating agents are then used to promote lead excretion. Penicillamine, succimer, CaEDTA, and British anti-Lewisite (BAL) administered in a short course are all effective chelating agents. Improvement usually begins within 2 weeks. Succimer and penicillamine are usually adequate for milder cases while combination therapy with both CaEDTA and BAL is recommended for more severe intoxication that includes encephalopathy. Diazepam should be tried for treatment of seizures associated with lead toxicity, although they are often refractory. In patients with brain edema, mannitol, hyperventilation, and fluid restriction should all be utilized to lower intracranial pressure. The mortality rate is high in patients presenting with seizures and encephalopathy. The neuropathy has a good prognosis for full recovery except in the most severely affected.

Arsenic

Introduction

Arsenic is famous as a poison used for suicide or homicide. This usually results from a massive, acute ingestion, although toxicity can also result from chronic low-grade exposure. Exposure may also occur in the occupational setting (smelting of lead and copper ore, mining, manufacture of integrated circuits or microchips [18]), through contaminated well water [19, 20], due to tainted illicit drugs, and with the burning of preserved wood [21] or arsenic-contaminated fossil fuels.

Pathogenesis

Absorption of arsenic occurs by inhalation (particulate arsenic and arsine gas), from the GI tract and via dermal contact. The underlying pathophysiology of arsenic neuropathy may be related to the affinity of this compound for thiol groups [22]. This affinity leads to binding with lipoic acid, which interferes with the conversion of pyruvate to acetyl CoA and, thus, energy metabolism. The accumulation of arsenic in hair and skin is also related to the thiol affinity in keratin molecules.

Clinical Presentation

The manifestations of arsenic exposure are dependent on the level of exposure [10]. High-level acute exposure causes severe GI disturbance (abdominal pain, vomiting, and diarrhea), tachycardia, hypotension, and vasomotor collapse with possible death [10]. Exposure to high levels of arsenic may also cause transient (organic psychosis, somnolence, or stupor [23]) or prolonged CNS dysfunction (behavioral and cognitive problems). The peripheral polyneuropathy manifests within weeks and may continue to worsen for a period of weeks after removal from exposure (coasting). Positive sensory symptoms (painful paresthesias, burning, aching, and tingling) occur in the toes and feet first and later in the fingers. Weakness is also dependent on nerve length, manifesting first in the distal lower extremities and later in the hands. There is early depression or loss of reflexes. Respiratory muscle weakness may occur with acute high-dose exposure or inadequate treatment, mimicking Guillain-Barré syndrome. Although the rapid presentation of the neuropathy may mimic Guillain-Barré syndrome, the associated GI symptoms, absence of demyelination on physiologic testing, and normal spinal fluid protein allow differentiation from Guillain-Barré syndrome. With high exposure levels, skin changes and bone marrow suppression are often present in addition to the nervous system manifestations.

Exposure to lower levels of arsenic for longer periods causes dermatologic abnormalities before neuropathy becomes apparent. Nonspecific symptoms develop including malaise, generalized weakness, vomiting, and anorexia. White transverse lines in the nails (Mee's lines), hyperkeratosis, hyperpigmentation of the skin, and irritation of the mucous membranes occur. The neuropathy is usually

subclinical at this time but may be detected by careful examination and electrodiagnostic testing. With continued exposure, clinical polyneuropathy develops that typically involves burning and numbness of the feet followed by the hands. Small- and large-fiber sensory modalities are affected causing abnormality of joint position sense in addition to dysesthesias. Weakness is usually not very severe, limited to the most distal muscles.

Evaluation and Diagnosis

Arsenic levels in the urine may remain elevated even when measured weeks after exposure [18]. Urinary levels greater than 25 ug per 24 h specimen are abnormal unless there was recent seafood ingestion, a source of pentavalent arsenic. Blood levels are not reliable even with very large exposure, as arsenic is cleared within 24 h. Testing of hair and nails may be necessary in chronic exposure or exposure that has since ceased. The electrodiagnostic findings are typical of a distal sensorimotor axonopathy [24]. There is mild slowing of motor conduction velocities with low-amplitude sensor nerve action potentials (SNAPs). Some active denervation is usually detected acutely on needle EMG with reduced motor unit action potential recruitment. Acute high-dose arsenic poisoning may initially produce EDX changes typical of acquired demyelinating polyradiculoneuropathy, as in Guillain-Barré syndrome [25]. However, serial electrodiagnostic testing confirms the progression to a distal dying back axonal loss polyneuropathy.

Treatment and Management

Prevention of arsenic toxicity involves limiting exposure and education of those at risk. Employees likely to be exposed to high levels of arsine gas or arsenic trioxide should be provided with respirators. Excessive exposure may be detected prior to development of symptoms by monitoring urinary levels [26]. Treatment with chelating agents is usually beneficial, but complete recovery may not occur, especially in advanced cases [27]. The CNS effects of arsenic poisoning may also be persistent after treatment [28]. Due to the life-threatening nature of acute arsenic intoxication, the patient should be treated in an intensive care unit with aggressive fluid and electrolyte resuscitation. Chelation therapy with penicillamine and dimercaptopropanol (British anti-Lewisite – BAL) promotes arsenic elimination. Treatment should be initiated as early as possible after exposure with several months of continued therapy often required. The fully developed neuropathy is unlikely to respond significantly to therapy, but milder cases recover completely.

Thallium

Introduction

Thallous salts were previously used as rodenticides and pesticides but are rarely used currently. Thallium ingestion continues to occur either accidentally by children or intentionally by homicide or suicide. Chronic low-level exposure in industrial occupations is much more common than acute high-level toxicity [29]. Another potential source of thallium toxicity is consumption of contaminated food and water [30].

Pathogenesis

Absorption of thallium takes place through the GI tract, dermal contact, or by inhalation. Thallium enters cells through potassium channels, substitutes for it in reactions, and can compete with potassium for sodium potassium ATPase [31, 32]. The substitution for potassium, however, may not be the mechanism of its toxicity.

Clinical Presentation

Thallium intoxication causes a distal, symmetric peripheral polyneuropathy. The pathology is predominately axonal loss with large fibers most affected. Sensory symptoms including pain are much more prominent than motor complaints. The distal portions of the longest axons undergo degeneration initially while the proximal segments are spared. Small unmyelinated fibers may also be involved as indicated by the appearance of delayed autonomic dysfunction [33].

Depending on the duration and intensity of exposure, there are three distinct syndromes of thallium neuropathy [10]. After acute high-level exposure, symptoms begin in 1–2 days. Abdominal pain, diarrhea, and vomiting usually begin within hours, but may not appear for up to a day. Within 2–5 days, distal burning paresthesias in the legs and intense joint pains develop. Both large- and small-fiber sensory systems are affected. The sensory disturbance occasionally involves the hands and trunk. Although not a prominent complaint, weakness is usually detected on examination. Massive ingestion may result in severe respiratory or cardiac failure. Declining mental status leading to lethargy, coma, or even death may result. The classic sign of thallium intoxication is alopecia, which appears after 15–39 days. However, alopecia is not specific for thallium intoxication, is not always present, and is not helpful in the acute setting.

Subacute thallium toxicity occurs following a smaller initial ingestion. The neuropathy begins more than a week after exposure and evolves more slowly. Sensory deficits in pin,

light touch and position sense are prominent. Weakness is frequently detected in distal muscles but tends to be mild in comparison to the degree of sensory dysfunction. Reflexes are also relatively preserved. Painful paresthesias in the feet may interfere with walking early in the course. Autonomic dysfunction resulting in hypertension or tachycardia may occur. Associated dermatologic abnormalities including Mee's lines (white striae of the nails), alopecia, and hyperkeratosis are often present. Chorea, ataxia, and cranial neuropathies may also occur in the subacute syndrome [34].

Chronic thallium toxicity due to prolonged low-level exposure is rare. The neuropathy is the primary finding and is identical to that described above.

The differential diagnosis of thallium neuropathy includes arsenic intoxication. Both cause alopecia and other dermatologic manifestations along with painful neuropathy and autonomic dysfunction. The rapid development of neuropathy with acute thallium intoxication may initially suggest Guillain-Barré syndrome. However, GI symptoms are much more prominent with thallium toxicity.

Evaluation and Diagnosis

Thallium levels can be measured in blood, urine, or tissue (hair and nails). Microgram quantities can be detected by the methods available. Although standard blood levels are available that indicate toxicity, this does not reflect the total body burden, as it does not measure the thallium in tissue. In cases where the baseline level of thallium in blood and urine is normal, but thallium toxicity is suspected, giving a challenge of potassium chloride will cause the urinary excretion of thallium to rise. The cerebrospinal fluid (CSF) protein is normal in thallium neuropathy. Mild slowing of motor conduction velocities and reduced SNAP amplitudes are seen on NCS. Needle EMG reveals evidence for motor axon degeneration. The severity of peripheral nerve damage may be monitored serially with EDX testing [35].

Treatment and Management

Prevention of thallium toxicity involves avoidance of exposure. Enforcement of established workplace exposure levels along with good personal hygiene and protective clothing helps to accomplish this goal. If no measures are taken to promote thallium excretion, the elimination half-life is 30 days. Elimination of thallium from the GI tract may be enhanced by treatment with activated charcoal, Prussian blue, and laxatives [36]. Urinary excretion is aided by administration of potassium chloride and forced diuresis.

Recovery from acute thallium intoxication is frequently incomplete. Anoxic injury often causes residual CNS dysfunction. Residual sensory loss usually remains after a slow recovery from the acute neuropathy. The prognosis for complete return of function is much better in subacute thallium neuropathy. Hair growth usually begins within 10 weeks of discontinuing exposure, and the neuropathy is fully recovered in most patients within 6 months.

Mercury

Introduction

Elemental mercury is a silver-colored liquid at room temperature that was used in thermometers [I do not believe that mercury is used in home thermometers any longer], barometers, and other gauges. Organic mercurial compounds are found in latex paints as a preservative, in various disinfectants, and are also used as industrial catalysts [37]. Inorganic mercurial salts and elemental mercury are used in the manufacture of chlorine, in dental amalgam, and in the natural gas industry. Outbreaks of mercury intoxication include the Minamata Bay incident in Japan with ingestion of contaminated seafood [1] and an episode of poisoning in Iraq through an organic mercury-containing fungicide applied to grain [38].

Pathogenesis

Elemental mercury vapor is absorbed by inhalation. Mercury salts are absorbed through the skin and GI tract and organic mercury is usually absorbed through the GI tract. There is some evidence of inhalation of mercury vapor in individuals with mercury amalgam dental fillings [39, 40], and several reports have linked mercury amalgam dental fillings to various diseases [41, 42]. However, after careful review, no clear relationship has been established between the presence of mercury amalgam dental fillings and any disease or toxicity [43].

Clinical Presentation

Intoxication with mercury results in predominantly CNS dysfunction, while there are some reports of peripheral nervous system (PNS) effects. The form of mercury determines the pattern of nervous system involvement and whether there are associated systemic symptoms.

Elemental mercury is very lipid soluble and tends to cause predominantly CNS involvement with little or no systemic signs. Micromercurialism refers to low-level toxicity caused by elemental mercury. Symptoms include anorexia, fatigue, GI dysfunction, tremor, and weight loss. With further

exposure, personality change, hyperexcitability, insomnia, and much more prominent tremor that may involve the head, face, and even the eyelids may occur. Systemic toxicity associated with mercury salts includes GI symptoms and nephrotic syndrome. The classic phrase "mad as a hatter" refers to the mental impairment that may occur with excessive exposure to mercury salts from the felt of hats. [Unless mistaken the mercury was used to treat the felt so that it became stiff – to enable a "top hat" to hold its shape (note the depiction of the hat worn by the mad hatter in Alice in Wonderland and subsequent works).]

Organic mercury compounds have varying effects depending on their structure. Short-chain compounds such as methyl mercury cause tremor, hearing loss, constriction of visual fields, mental impairment, and dysarthria with prolonged exposure. The other prominent symptom seen more often with organic mercury toxicity is sensory ataxia due to damage of dorsal root ganglion neurons. The earliest sign of sensory neuron damage may be paresthesias, which begin distally and progress to involve more proximal areas including the tongue. Complex organic mercurials are associated with nephrotoxicity.

PNS involvement has been reported with exposure to all forms of mercury. The relationship is better established with elemental or mercuric salt exposure than with organic mercury compounds. Mercury vapor exposure is associated with an acute neuropathy that may be confused with Guillain-Barré syndrome. There is usually a preceding irritation of the upper respiratory tract that may be mistaken for an infection [44]. As with other forms of mercury exposure, mercury vapor tends to cause prominent neuropsychologic dysfunction [44]. Some reports of mercury intoxication describe presentations mimicking motor neuron disease [45].

Evaluation and Diagnosis

Diagnosis of mercury intoxication is based on eliciting the appropriate exposure history in the setting of a neurologic syndrome as described above. Mercury levels can be measured in urine, blood, and hair. Blood mercury level is a good indicator of recent exposure [37] while serial urine measurements (especially with penicillamine administration) or hair samples are better for chronic exposure [38]. NCS may reveal evidence of a developing neuropathy in exposed workers prior to symptom onset [46]. Electrodiagnostic testing shows a motor greater than sensory axonal loss polyneuropathy [47].

Treatment and Management

Prevention is the ultimate goal in any form of toxin exposure. In the case of mercury, this includes education, protective equipment, and monitoring air levels. Treatment of mercury intoxication is primarily by removal from exposure. Although chelation with agents such as dimercaprol [48] or penicillamine increases excretion of mercury in the urine, it is not clear that this speeds recovery from the toxic effects. The prognosis for complete recovery in most patients is good.

Carbon Disulfide

Introduction

Carbon disulfide (CS_2) is a clear liquid that vaporizes at room temperature and is readily absorbed by inhalation. It is also a major metabolite in the breakdown of the drug disulfiram (Antabuse ®) which is used as a deterrent for alcohol abuse [49]. It is used in the production of cellophane films [50] and viscose rayon fibers [51].

Pathogenesis

CS_2 is most commonly absorbed by dermal contact or inhalation but can also be absorbed through the GI tract if swallowed [52]. The reactivity of CS_2 with amine, sulfhydryl, and hydroxyl groups in biologic systems is most likely responsible for its toxicity. Reactive sulfur atoms are formed which bind with and suppress the activity of the cytochrome P-450 enzymes. Inactivation of metalloenzymes such as dopamine B-hydroxylase (which is vital to norepinephrine production) may occur when di- and trithiocarbamates lead to chelation of copper. These compounds are also metabolized to isothiocyanates which covalently bind to and cross-link cytoskeletal proteins such as neurofilaments. This process may cause the formation of giant axonal swellings seen in experimental studies performed in rats.

Clinical Presentation

Acute or subacute exposure to high levels of CS_2 causes primarily CNS dysfunction including memory impairment, confusion, hallucinations, and emotional lability [53]. Low-level chronic exposure results in a combination of peripheral neuropathy and CNS abnormalities. The neuropathy can be subclinical when exposure is low and detected only by EDX testing. Higher exposure leads to a progressive sensorimotor distal polyneuropathy. Headache, dizziness, depression, memory impairment, and impaired sexual arousal are often signs of prolonged exposure [52]. Extrapyramidal signs of tremor, bradykinesia, and cogwheel rigidity, as well as hemiparesis or spasticity, may also be seen.

Evaluation and Diagnosis

Urinary levels of the CS_2 metabolite, 2-triothiazolidine-4-carboxylic acid are a sensitive measure of exposure. NCS reveal slowing of conduction velocities and prolongation of motor and sensory latencies [54, 55]. Acute and chronic denervation changes are seen in distal leg muscles on needle EMG due to axonal degeneration and chronic motor unit reinnervation. The CSF protein is normal.

Treatment and Management

Occupational exposure is usually via the respiratory route. Thus, sufficient ventilation, fume hoods or respirators, and periodic air sampling [52] are all helpful for prevention. The severity of the CNS and PNS dysfunction at the time of removal from exposure determines the degree of recovery. Nearly complete recovery from neuropathy and most of the CNS dysfunction can be expected in mild cases. Residual spinal cord damage may prevent complete recovery. Also, recovery is often incomplete in the case of severe neuropathy. In one series, symptoms and signs of neuropathy were present after 10 years of follow-up in more than one third of patients with severe CS_2 neuropathy [55]. Pyridoxine may have a role in treatment, as there is some reactivity of CS_2 with pyridoxine [52].

Acrylamide

Introduction

Acrylamide is a chemical compound used in grouting agents and in research laboratories; polyacrylamide is a flocculator used in wastewater treatment plants [56]. Acrylamide is absorbed by dermal, GI, or respiratory contact. It appears to interfere with axonal transport [57, 58] resulting in axonal swelling [59] due to accumulation of neurofilaments in the paranodal region [60]. The monomer is the toxic form while the polymer is innocuous. Both the parent compound and its metabolite, glycidamide, are neurotoxic [61].

Clinical Presentation

The duration and extent of exposure determine the manifestations of acrylamide toxicity [10]. As skin exposure is the usual route of entry, contact dermatitis is usually present prior to the symptoms of neuropathy. Low to moderate acute exposure leads to headache, malaise, dizziness, and anorexia. As the level of exposure increases, the neurologic picture may include encephalopathy, with seizures and truncal ataxia followed by peripheral neuropathy [10]. Family members or coworkers may report behavioral changes, as the patient may not be aware of them early on. With more chronic, low-level exposure, the dermatitis and neuropathy persist, but the CNS effects are not as prominent.

Acrylamide toxicity causes a specific pattern of neuropathy known as central-peripheral distal axonopathy [62]. Exposure first causes damage to the distal portion of the longest peripheral axons, but with continued exposure, subsequent damage to the distal segments of corticospinal, spinocerebellar, and dorsal column axons may occur [63]. Initial clinical manifestations include toe numbness and widespread hyporeflexia. Large-fiber sensory dysfunction with loss of vibration and proprioception is common while pain and paresthesia are rare [10]. Although sensory complaints dominate, motor and cerebellar deficits may be evident on physical examination. Acute, high-level exposure often results in widespread autonomic dysfunction including impairment of reflex changes in heart rate and blood pressure, vasomotor changes in fingers and toes, and excessive sweating. Overt autonomic dysfunction is less common in chronic exposure and may be limited to excessive sweating of the hands and feet.

Evaluation and Diagnosis

Electrodiagnostic testing reveals reduced SNAP amplitudes with preservation of motor amplitudes and conduction velocities [64]. In some instances, the electrophysiologic abnormalities may precede the development of symptoms. Sural nerve biopsy demonstrates reduced numbers of large-diameter, thickly myelinated fibers [64].

Treatment and Management

Education of those handling acrylamide regarding its potential toxic effects is the first step in preventing disease. As dermal absorption is a potential source of exposure, protective clothing and gloves should be worn. Good personal hygiene such as washing hands prior to eating should be stressed. Adequate ventilation can help prevent respiratory exposure, and respirators should be used in areas with high acrylamide levels in the air. Removal from exposure usually results in recovery if the neuropathy is mild. Some residual loss of vibratory sensation may be apparent. However, in the case of severe neuropathy, spasticity, ataxia, more profound sensory dysfunction, and memory problems may remain. CNS dysfunction, such as spasticity and upper motor neuron weakness, may be obscured initially by the peripheral nerve dysfunction. Coasting, the worsening of symptoms after termination of exposure, may occur [60]. Acute ingestion should prompt gastric lavage to reduce levels of intoxication.

Liver and renal failure may necessitate blood transfusions or hemodialysis.

Organophosphates

Introduction

Organophosphorous (OP) compounds are used as insecticides, antioxidants, petroleum additives, flame retardants, lubricants, and plastic modifiers. Although these compounds have a variety of industrial uses, group exposure in the occupational setting is rare. Accidental exposure from agricultural spraying is the most common cause of individual intoxication. Estimates of the annual incidence of pesticide-induced toxicity range from 150,000 to 300,000 cases, but less than 2 % of cases are actually reported to public health officials [65]. Individuals mixing or applying the pesticide may become intoxicated. Those working in the fields after spraying may be affected by dermal contact [66]. Most OP esters are quickly degraded in the environment. OP esters are occasionally ingested intentionally in suicide attempts.

Pathogenesis

In addition to dermal exposure, OPs are absorbed through the GI and respiratory tracts. OP causes irreversible inhibition by phosphorylation of the enzyme acetylcholinesterase (AChE) in erythrocytes and nervous tissue. This prevents degradation of acetylcholine resulting in excessive stimulation of both muscarinic and nicotinic receptors (see Chap. 52). There are acute (type I) and intermediate (type II) cholinergic syndromes depending on which receptor is preferentially affected. A delayed central-peripheral axonopathy may develop with exposure to some OPs, independent of the development of the type I or type II syndromes. The neuropathy is not related to the inhibition of AChE.

Clinical Presentation

The acute or type I OP syndrome [67] results from excessive stimulation of muscarinic cholinergic receptors. The acute syndrome frequently begins hours after exposure and always within 1 day. Symptoms include diarrhea, salivation, nausea and vomiting, micturition, sweating, and tachy- or bradycardia. CNS involvement including emotional lability, decreased alertness, fatigue, cognitive impairment, nervousness, convulsions, and coma may occur in extreme cases. These behavioral changes are the only manifestations on rare occasion. Susceptibility to the acute syndrome may be increased by previous OP exposure due to a decrease in functional AChE.

The type II or intermediate OP syndrome [68] occurs within 12–96 h of exposure and is due to nicotinic ACh receptor activation in skeletal muscle. The term intermediate indicates that it precedes the delayed peripheral neuropathy but follows the early muscarinic symptoms. The patient may seem to recover after the acute syndrome only to have onset of the intermediate syndrome after an interval of 1–4 days. Although the neuropathy is discussed more frequently, it probably occurs less often than the type II syndrome. The initial feature is usually respiratory insufficiency followed by weakness of the neck flexors and proximal muscles. The cranial muscles including extraocular muscles may be involved, but strength in the distal extremities typically is normal. Dystonic posturing may be seen. Sensory function is unaffected. Recovery begins 5–15 days after exposure, proceeding from the cranial muscles to the respiratory muscles, proximal muscles, and lastly the neck flexors. As atropine is specific for muscarinic receptors, it does not prevent or treat the intermediate syndrome [67].

The neuropathy has been labeled the organophosphate-induced delayed polyneuropathy (OPIDP), since there is an interval of 7–21 days after exposure. Although less common than the cholinergic syndromes, OPIDP causes significant morbidity. Fortunately, most OPs applied as pesticides are not associated with development of the OPIDP. The most severe cases of neuropathy seem to be caused by compounds that cause very mild cholinergic symptoms. OPIDP is more likely to occur in the setting of chronic low-level exposure. In contrast to most toxic central-peripheral axonopathies which are chronic, the onset of OPIDP is subacute. The maximal deficit occurs by 2 weeks or less after onset. Cramping pain in the calves and painful paresthesias in the feet are the initial manifestations. Although sensory loss is detected by examination, motor symptoms and signs dominate the clinical picture. Leg muscle weakness with foot drop occurs early. Later, the intrinsic hand muscles are affected. The proximal muscles are spared until late in the course. Gait ataxia is more profound than expected based on the sensory loss. Although ankle reflexes are invariably lost, the activity of the other reflexes reflects the degree of CNS impairment. Involvement of the cranial nerves or autonomic nervous system is unusual.

Differential Diagnosis

The acute syndrome (type I) may have prominent mental status abnormalities, and other drug or toxin ingestion needs to be excluded. The intermediate syndrome (type II) with prominent muscular weakness that may present in a fulminant fashion can mimic Guillain-Barré syndrome, periodic

paralysis, or a severe attack of myasthenia gravis. The delayed neuropathy needs to be distinguished from other central-peripheral distal axonopathies caused primarily by other toxins. It may also present in an earlier stage as a simple distal axonopathy, which has a very broad differential diagnosis.

Evaluation and Diagnosis

Electrodiagnostic testing in OPIDP reveals a sensorimotor axonal loss polyneuropathy. Although motor symptoms are most prevalent, sensory conduction abnormalities are more dramatic and appear earlier. SNAPs are reduced in amplitude or absent while motor conduction studies are either normal or reveal minimal slowing of conduction velocity. Needle EMG reveals evidence of acute and chronic denervation in the distal and, occasionally, proximal limb muscles in OPIDP but is normal in the intermediate syndrome [69]. Shortly after OP exposure, spontaneous repetitive motor action potentials (SRMAPs) following the initial compound motor action potential are elicited by a single stimulus [69]. The ability to elicit SRMAPs is a sensitive indicator of OP exposure, but does not reflect the degree of intoxication. With the onset of weakness, a decremental response to repetitive nerve stimulation is seen. In the case of mild intoxication, rapid stimulation rates may be required to demonstrate a decremental response. Decrements may be followed by increments when SRMAPs are present. With more severe exposure, decrements are evident even with slow rates of stimulation and SRMAPs may be absent [70].

Standard laboratory testing is usually normal. Recent exposure to OP causes reduced AChE levels in erythrocytes. Levels below 20 % of normal are associated with severe weakness. Serial measurements documenting a progressive decline in AChE activity is the best indicator of toxicity as there is significant variability of normal erythrocyte AChE levels. The AChE level cannot be used to reliably predict which patients will eventually develop OPIDP. Because regeneration occurs at the rate of 1 % per day, AChE levels may have recovered to normal values prior to testing. Pseudocholinesterase levels are not helpful. There may be slight elevation of the CSF protein level, but there is typically no CSF pleocytosis.

Treatment and Management

Prevention involves education regarding potential toxicity, use of protective clothing, good hygiene, and monitoring for toxicity. As noted above, after emergence of the acute syndrome, administration of atropine has no effect on the later development of the intermediate syndrome or OPIDP. However, NCS may reveal evidence of early, reversible neuropathy in exposed individuals [71].

Organophosphate poisoning carries a significant risk of respiratory failure, and even when respiratory function is not compromised, intubation may be necessary due to excessive secretions or vomiting in the setting of depressed level of consciousness. In acute intoxication, contaminated clothing should be removed and the skin cleansed to prevent further dermal absorption. Cathartics and gastric lavage are indicated in the case of ingestion. Reactivation of AChE may be accelerated by the administration of pralidoxime. This is most effective if given early in the course. Pralidoxime may prevent the emergence of the intermediate syndrome [72]. Fortunately, the muscarinic symptoms are typically relieved with atropine. However, as the duration of action is short, it must be continued, to prevent the recurrence of symptoms that may still be fatal. As there is some evidence that administration of atropine to patients with respiratory insufficiency may be associated with increased risk of ventricular arrhythmias, patients need to be adequately ventilated and cardiac monitors in place, before it is given. Atropine is specific for muscarinic receptors and has no effect on depolarizing neuromuscular blockade due to overstimulation of nicotinic receptors.

With good supportive care, there is usually complete recovery from the acute and intermediate syndromes. Although only 40–60 % of AChE content is regenerated by 1 week after exposure, this is usually sufficient for functional recovery. If CNS damage occurs, this may persist after recovery from the acute syndrome. Patients with mild OPIDP usually have a good outcome. Residual foot drop, claw hand deformity, or atrophy is sometime seen in cases of severe neuropathy. The damage to distal dorsal column and corticospinal axons may only become apparent after recovery from the peripheral neuropathy and is more likely to persist.

Hexacarbons

Introduction

Both n-hexane and methyl n-butyl ketone (MnBK) are clear, colorless, volatile liquids. They are metabolized to the toxic compound 2,5 hexanedione [73]. Methyl ethyl ketone (MEK) is not neurotoxic by itself, but is present in many solvent mixtures and may potentiate the neurotoxicity of n-hexane and MnBK. Hexacarbons are components of glues and lacquers and are used as solvents. Hexacarbon exposure occurs in the production and refining of petroleum products. The cabinet-making and shoe industries use these compounds in lacquers and glues [74, 75]. The sandal and shoemaking industries of Japan [76] and cabinet-finishing plants in the USA [75] have been responsible for reports of

hexacarbon neuropathy. An epidemic of peripheral neuropathy resulted from the substitution of MnBK for MEK and methyl isobutyl ketone in the manufacturing of plastic-coated and color-coated fabrics [77]. High-level exposure also occurs with intentional inhalation (glue sniffing [78]). Hexacarbon-related neuropathy is less common at present with the removal of hexacarbons from many industrial and commercial products. However, recreational abuse usually via glue sniffing remains a substantial epidemiologic problem.

Pathogenesis

Hexacarbons gain entry to the body via inhalation, dermal contact, and, rarely, ingestion. The peripheral nerves of patients with hexacarbon toxicity have a very characteristic morphological abnormality that involves the formation of giant axonal swellings. These occur due to the accumulation of neurofilaments but are also seen with exposure to carbon disulfide or acrylamide [79] and in the genetic neuropathy, giant axonal neuropathy [80]. The paranodal regions are the focus of neurofilament accumulation [60]. Cross-linking and disruption of axonal transport cause the accumulation of neurofilaments. This leads to a distal-central dying back neuropathy.

Clinical Presentation

High-level acute exposure causes CNS depression and narcosis. Repeated massive exposure (i.e., glue sniffing) leads to a subacute, predominately motor neuropathy with cranial nerve dysfunction [81]. Autonomic dysfunction including impotence, hyper- or anhidrosis, and vasomotor instability may sometimes occur with this neuropathy, leading to a mistaken diagnosis of Guillain-Barré syndrome. In contrast to that seen with chronic high-level exposure, chronic low-level exposure results in a slowly developing, length-dependent, central-peripheral axonopathy. This refers to a process whereby distal portions of peripheral axons degenerate first, but continued exposure leads to damage of distal dorsal column, corticospinal, and other central pathways. Pinprick, temperature, and vibratory sensations are initially impaired in the feet with proximal progression if exposure continues. Ankle reflexes are lost early in the course, but relative to the degree of sensory loss, the other reflexes may be preserved. Weakness of distal arm and leg muscles may be present. Atrophy and weakness may become the prominent complaint if the neuropathy becomes advanced. Weight loss, abdominal pain, malaise, and leg cramps may be present in severe cases. Symptoms frequently continue to worsen after removal from exposure (coasting).

Evaluation and Diagnosis

Electrodiagnostic studies characteristically show prominent slowing of distal latencies and motor conduction velocities [79]. This is an unusual finding in toxic neuropathies in general, but not in subacute hexacarbon neuropathy. Asymptomatic workers employed in factories with documented cases of solvent polyneuropathy may also have slowed conduction velocities. CSF protein may be elevated if the nerve roots are involved.

Treatment and Management

The toxic effects of solvents containing n-hexane or MnBK need to be discussed with those who will come in contact. Gloves and other protective clothing help to reduce dermal contact [82]. Adequate ventilation is essential and ventilators should be provided in areas with high concentrations. The risk of exposure can be gauged by monitoring ambient air levels [83]. Urinary measurement of 2,5 hexanedione may allow detection of exposure prior to the appearance of significant toxicity [84]. The only available treatment is cessation of hexacarbon exposure. Complete recovery usually occurs in cases of mild neuropathy. Severe neuropathies frequently leave residual sensory loss, atrophy, and distal weakness. Hexacarbon neuropathy is well known for the "coasting" phenomenon, which refers to the progression of clinical manifestations despite removal from exposure. Central damage (spasticity, long-tract weakness) may only become apparent after resolution of the peripheral neuropathy.

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Drug-Induced Toxic Neuropathies

35

Kevin R. Hargrave, Gregory J. Ferenz,
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Introduction

Drug-induced toxic neuropathies can be grouped either by their clinical pattern or by their underlying pathology. Clinically, drug-induced peripheral neuropathies may present with sensorimotor, primary sensory, or primary motor patterns (Table 35.1). Pathologically, the site of damage may be the cell body (neuronopathy), the axon (axonopathies), or the myelin sheath (myelinopathies) (Table 35.2). Most drug-induced toxic neuropathies are axonal, sensorimotor polyneuropathies with a typical "dying back" pattern (Fig. 35.1).

Chemotherapeutic Agents

Chemotherapeutic agents often result in peripheral neuropathies. *Vincristine* sulfate (Oncovin®, part of the common "CHOP" regimen) is an antineoplastic agent derived from the periwinkle plant, Vinca rosea. Like its predecessor, *vinblastine*, and its lesser-used relative vindesine, it inhibits microtubule polymerization and interferes with axonal transport. Peripheral nerve toxicity occurs in most patients treated with vincristine. It is a dose-dependent phenomenon which leads to a dose reduction or discontinuation of the drug in many patients [2–5]. Patients complain of numbness and tingling of the hands and feet, with the hands being symptomatic first in some. Weakness is often prominent and may be of sudden onset; it predominantly affects the upper extremity extensors and distal lower extremity muscles, often leading to foot drop and gait dysfunction [6]. Some patients become totally areflexic [7], whereas others lose their ankle jerks only [2, 8]. Loss of ankle reflexes is usually the first objective finding and is often permanent [4]. In some cases, autonomic dysfunction may result in constipation, ileus, and orthostatic hypotension [9].

Table 35.1 Clinical presentations of drug-induced toxic neuropathies

Sensorimotor	Primarily sensory	Primarily motor
Allopurinol	Acetazolamide	Chloroquine
Amiodarone	Almitrine	Cimetidine
Amitryptiline	Ara-C	Dapsone
Atorvastatin	Bortezomib	Imipramine
Captopril	Chlorambucil	Methimazole
Chloroquine	Chloramphenicol	Zimeldine
Colchicine	Cis-platinum	
Cyclosporine	Clioquinol	
Disulfiram	Colistin	
Docetaxel	ddC	
Ethambutol	ddI	
FK506	Ethionamide	
Gold	Etretinate	
Hexamethylmelamine	Flecainide	
Indomethacin	Glutethimide	
Interferon alpha	Hydralazine	
Isoniazid	Mercury	
Leflunomide	Methimazole	
Linezolid	Ixabepilone	
Lithium	Metronidazole	
Lovastatin	Niacin	
Methaqualone	Nitrous oxide	
Nitrofurantoin	Oxaliplatin	
Paclitaxel	Paclitaxel	
Perhexiline	Procarbazine	
Phenytoin	Propylthiouracil	
Podophylin	Pyridoxine	
Pravastatin	Stavudine	
Sodium cyanate	Streptomycin	
Suramin	Thalidomide	
Thalidomide		
TNF alpha		
Vincristine		

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Table 35.2 Pathophysiology of drug-induced peripheral neuropathies

Axonal	Ganglio/neuronopathy	Demyelinating
Allopurinol	Cis-platinum	Amiodarone
Almitrine	Paclitaxel	Cytarabine (Ara-C)
Amiodarone	Pyridoxine	Chloroquine
Bortezomib	Simvastatin	FK506
Chloroquine	Thalidomide	Gold
Cis-platinum		Misonidazole
Clioquinol		Perhexiline
Colchicine		Suramin
Cytarabine		TNF alpha
Dapsone		
ddC		
Disulfiram		
Docetaxel		
Ethambutol		
Ethionamide		
Etretinate		
Flecainide		
Glutethimide		
Gold		
Hmg CoA inhibitors		
Hydralazine		
Isoniazid		
Ixabepilone		
Leflunomide		
Linezolid		
Lithium		
L-tryptophan		
Metronidazole		
Misomidazole		
Nitrofurantoin		
Nitrous oxide		
Oxaliplatin		
Paclitaxel		
Perazine		
Perhexiline		
Phenytoin		
Podophyllin		
Pyridoxine		
Sodium cyanate		
Suramin		
Thalidomide		
Vincristine		

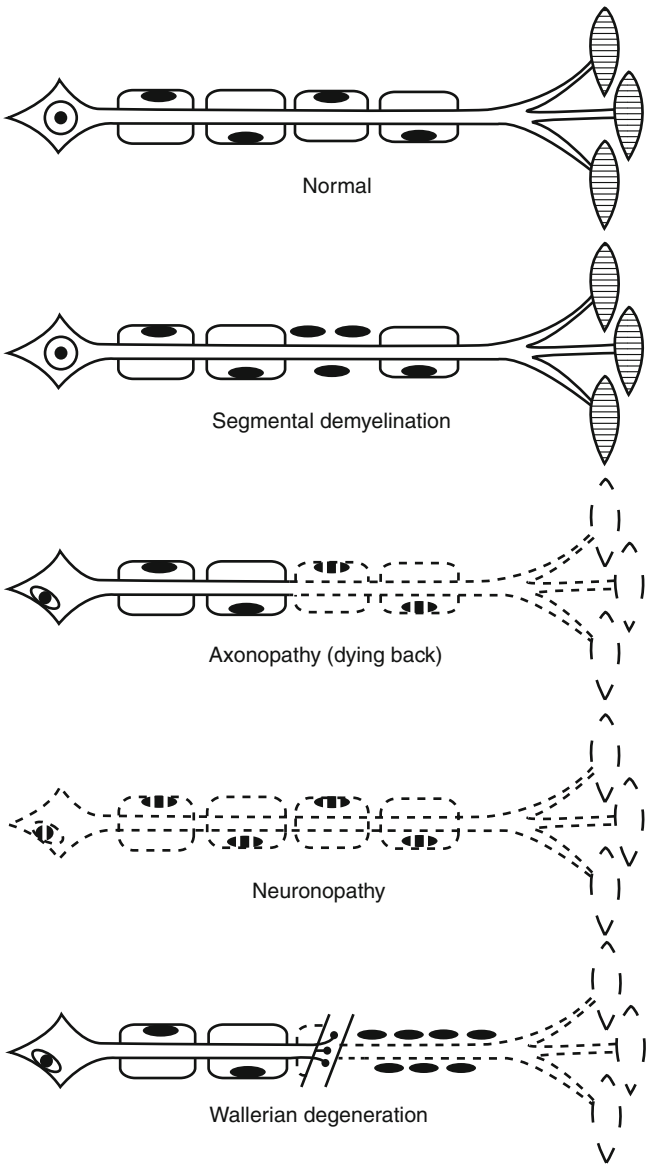

Fig. 35.1 Schematic showing the main sites of damage in the four principal types of polyneuropathy. The cell body of the neuron is shown at the *left*. Note that muscle fiber degeneration due to denervation occurs only when the axon or motor neuron is affected (Reproduced with permission from Guberman [1])

Electrodiagnostic studies (EDX) show low-amplitude sensory nerve action potentials (SNAPs) and compound motor nerve action potentials (CMAPs) and mild slowing of conduction velocities [2, 4]. Denervation and reinnervation are evident on needle electromyography (EMG), usually more prominent distally [4, 8, 10]. Nerve biopsy shows primarily axonal degeneration of both large and small fibers [2]. Teased fiber preparations typically show evidence of wallerian degeneration with a minority of fibers showing secondary demyelination [2]. Increased intra-axonal filaments/tangles may be present [6] (Fig. 35.2).

Patients often improve after discontinuation of the drug but may be left with permanent deficits [3, 8]. Some patients may worsen for several months after discontinuation of the drug before recovering [2]. SNAPs often remain abnormal despite disappearance of sensory signs and symptoms [4].

The chemotherapeutic agent *cis-platinum* causes a dose-dependent large fiber sensory polyneuropathy [11, 12]. As nephrotoxicity has been reduced with use of hyperhydration, peripheral neuropathy remains the major dose-limiting toxicity, often occurring after a total dose of >200–500 mg/m^2

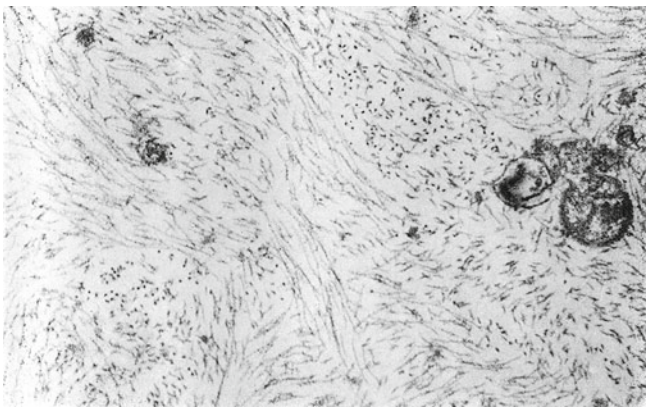

Fig. 35.2 Vincristine-induced neurofibrillary tangle. Filaments measure 90–100 Å in diameter (×41,700) (Reproduced with permission from Shelanski and Wisniewski [6])

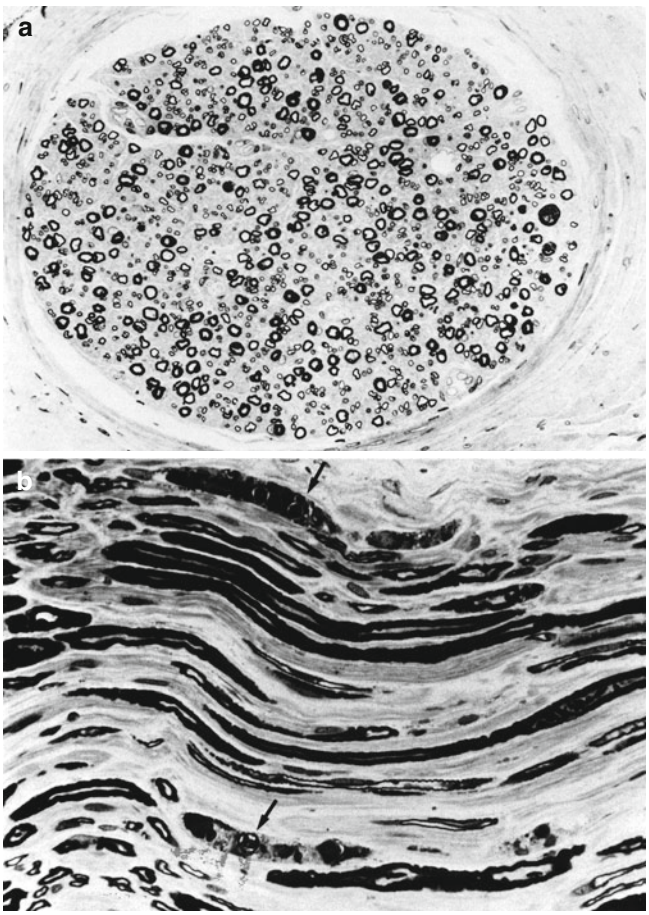

Fig. 35.3 Cisplatin neuropathy – cross section of sural nerve (*top*). The fascicle shows a marked loss of large myelinated fibers. Few degenerating fibers are present. Longitudinal section of sural nerve (*bottom*). Axonal degeneration is apparent in two myelinated fibers (*arrows*) (Reproduced with permission from Thompson et al. [12])

[3, 11, 13]. In general, patients develop numbness of the hands and feet, which may progress to a sensory ataxia. A Lhermitte's sign and lancinating pains are often present [14, 15]. Physical exam shows loss of reflexes and vibratory loss distally, sometimes before symptoms develop [16]. Later, light touch and pinprick loss may be seen in the lower extremities [3]. Weakness is observed only in the most severe cases [8]. One series showed that all patients receiving five daily doses of 40 mg/m^2 developed neuropathy [16]. In another series, 10 of 11 patients developed neuropathy, but only one discontinued therapy because of neuropathy [12].

Intra-arterial administration of cis-platinum may cause plexopathies. In addition, cranial neuropathies and ototoxicity have been reported [17–19]. Experimental studies have shown that the dorsal root ganglion may be the primary site of damage [20].

EDX may be normal early but later show low-amplitude SNAPs with prolonged distal latencies and slowed conduction velocities. Motor conduction studies are normal [12, 21]. Needle EMG may show denervation or may be normal [3, 16]. Biopsy shows axonal degeneration, especially of large myelinated fibers, but segmental demyelination may also be present in association with disintegrated axons [12] (Fig. 35.3). Recovery is often incomplete and protracted, continuing for up to 1 year or more [5]. *Glutathione* (*GSH*), a nucleophilic sulfur containing compound/tripeptide thiol, has shown promise in protecting against various toxicities of cis-platinum toxicity, including nephrotoxicity, hematologic toxicity, and peripheral neuropathy [22].

Combination chemotherapy with cis-platinum and either *doxorubicin* [12, 16] or *docetaxel* [23] may be more neurotoxic than with cis-platinum alone. *Carboplatin* causes much milder peripheral nervous system disease and usually only occurs at markedly high doses [5].

Oxaliplatin is a third-generation platinum derivative that has a unique structure from cisplatin in that it contains, 2-diaminocyclohexane [24]. It is used in combination with other drugs in the treatment of advanced colorectal cancer, and its combination with fluorouracil/leucovorin as adjuvant therapy in stage III colon cancer is currently the standard of care [25]. Though chronic therapy produces a predominantly sensory neuropathy similar to cisplatin, the drug causes an idiosyncratic acute neuropathy not found in other chemotherapeutics [26].

The drug frequently causes an acute neuropathy consisting of jaw tightness, perioral paresthesias, dysphagia, shortness of breath, or cramps that develop with 2 days of the infusion. A unique feature is paresthesias precipitated by cold exposure [26, 27]. The incidence is reported between 85 and 95 % [28]. NCS shows reduced CMAPs, and needle EMG shows neuromyotonic discharges consistent with peripheral nerve hyperexcitability [26]. The pathophysiology is not yet fully described but may be related to voltage-gated sodium channels [29]. These symptoms invariably transient and do not require dose modification [26, 28, 29].

Though the incidence of oxaliplatin-induced chronic neuropathy is less common than the acute neuropathy, its role as being a common adverse effect to lead to dose modification makes it potentially more serious. The chronic neuropathy is predominantly sensory, axonal, and distal greater than central [30].

Paclitaxel (Taxol®) produces a dose-dependent, axonal, sensorimotor neuropathy at cumulative doses usually above 200–250 mg/m^2 [31, 32]. Large and small fibers are affected. A reversible axonal neuropathy with distal deficits is most common, although a sensory neuronopathy affecting the upper extremities and face may occur with higher doses [32–34]. The incidence of neuropathy is more common with concurrent cis-platinum therapy or ethanol abuse [32]. Symptoms may begin as early as 1–3 days after initiating therapy [33]. Mild paresthesias have been reported in 50 % of patients treated for ovarian cancer [12]. Motor involvement has been reported in 17 % of cases; autonomic involvement is infrequent [31, 35]. Paresthesias of the hands and face may occur before the feet and trunk which may become involved later. Dysesthesias are common with narcotics often needed to treat acute pain [3, 32, 36]. Improvement usually occurs but may require several months [5].

The neurologic exam shows a stocking-glove loss of most sensory modalities and decreased or absent reflexes [3, 32, 37]. EDX shows low-amplitude SNAPs and slowed conduction velocities [33, 37, 38]. Similar findings are seen in motor nerves in severe cases [33]. Paclitaxel causes polymerization of microtubules and blocks depolymerization [12]. On biopsy, aggregates of microtubules are found in axons, Schwann cells, and dorsal root ganglia [33, 39] (Fig. 35.4). However, the pathophysiology may be multifactorial [35], with other biopsy studies showing axonal atrophy, nerve fiber loss, and secondary demyelination, suggesting a primary ganglionopathy [40].

The semisynthetic derivative of Taxol known as *docetaxel* (Taxotere®) is derived from the needles of Taxus baccata, a European yew tree. It is much more abundant and easier to extract than its predecessor Taxol, which is derived from the bark of the Pacific yew, Taxus brevifolia, and requires the sacrificing of whole trees [36]. This antineoplastic is more potent than its predecessor [23] and is primarily used in breast, ovarian, and lung cancers. Neuropathy has been seen with doses of as little as 50 mg/m^2 (but usually >400 mg/m^2) of docetaxel [32]. One series showed an 11 % frequency of peripheral neuropathy with docetaxel [37]. Another study of 55 patients undergoing combination therapy with docetaxel and cis-platinum showed a 53 % frequency of neuropathy [41].

Clinically, some patients appear to have a small fiber neuropathy with prominent pain [23], but nerve biopsies have shown large myelinated fiber loss and axonal degeneration [37]. EDX shows denervation and reinnervation in distal leg muscles [37]. Muscle biopsy shows neurogenic atrophy [37]. Nearly all patients improve after withdrawal of the drug [37].

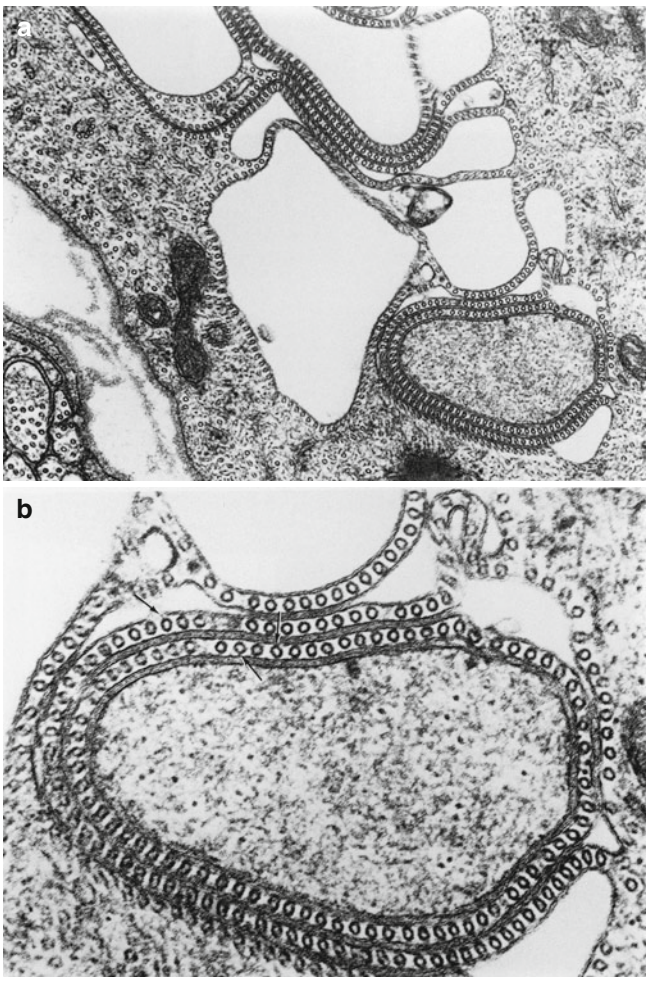

Fig. 35.4 Taxol-induced neuropathy. A multinucleated, large Schwann cell that is devoid of axons and contains complex stacks of membranes and microtubules. (*Top*) Note the regular alignment of microtubules along the membranes forming the walls of the intracellular cisternae. Narrow channels of cytoplasm traverse these cisternae and contain regularly spaced microtubules. The basal lamina of the Schwann cell lies to the left and the plasmalemma is not affected by the microtubule anomaly (×40,000). (*Bottom*) Detail of the circular stack of cytoplasmic bridges containing microtubules. Some microtubules appear to be attached to the membranes by stalks (*arrows*). Note how the outer leaflets of the affected membranes become closely apposed to form a structure similar to the intraperiod line of the myelin sheath (×115,000) (Reproduced with permission from Roytta and Raine [39])

The semisynthetic alkaloid *vinorelbine* (Navelbine®) is used to treat solid tumors. In combination therapy with paclitaxel, vinorelbine is associated with a mild neuropathy in 44 % of patients [42] and a severe sensory neuropathy in 28 % of patients [39].

The widely used chemotherapeutic agent *cytarabine* (Cytosine arabinoside, Ara-C®) most often causes prominent

CNS dysfunction but rarely leads to peripheral neuropathy (0.6 %) [43]. The neuropathy is often associated with painful paresthesias [7], usually occurring with doses greater than 200 mg/m²/day [44]. Clinical presentations in these cases range from pure sensory neuropathies to Guillain-Barré-like syndromes requiring ventilator assistance for life support [43, 45]. The onset may occur within hours after the first dose [44]. Recovery is often incomplete [44]. Sural nerve biopsies have shown axonal loss and demyelination [46].

Chemically similar to metronidazole, *misonidazole* is a radiosensitizer used in cancer therapies. It is associated with a dose-limiting painful peripheral neuropathy at cumulative doses greater than 18 g [47]. Sural nerve biopsies have shown axonal degeneration and demyelination [48, 49]. Partial recovery occurs after discontinuation [21].

The agent *suramin*, used as an antiparasitic since the 1920s and later an antiretroviral, has recently been used to treat refractory neoplasms. In one series, the drug resulted in a severe sensorimotor neuropathy in 4 of 38 patients after 5–8 weeks of therapy [50]. Toxicity is associated with high serum drug levels and is not necessarily related to cumulative dose. The risk of developing neuropathy was 40 % in patients with drug levels greater than 350 mcg/ml. Patients experienced paresthesias followed by weakness. A Guillain-Barré-like syndrome occurred in two patients with bulbar, respiratory, and autonomic involvement, requiring mechanical ventilation. EDX showed conduction block and decreased nerve conduction velocities. The primary pathology in these two patients appears to be demyelinating [50].

Bortezomib is a boronic acid dipeptide which reversibly inhibits the chymotryptic site of the 26S proteasome interfering with cancer cell-signaling cascades. It has been approved by the FDA for the treatment of patients with multiple myeloma and for patients with mantle cell lymphoma who have received at least one prior therapy. Neuropathic symptoms are typically small fiber, length dependent, and accompanied with significant neuropathic pain [51]. Motor neuropathy can occur in a minority of patients [52]. Neuropathy is a dose-limiting complication in 5–10 % of patients and typically occurs within the first few courses of treatment [53]. The prevalence increases with cumulative dose, reaching a plateau at the fifth cycle [54]. The incidence of mild neuropathy has been reported in two large trials to occur in 35 % of all patients with severe neuropathic symptoms in 14 % [55, 56]. However, other studies have shown a higher incidence, particularly in patients with baseline neuropathy or recurrent disease [57]. The mechanism of neuropathy from bortezomib is as yet not well understood [58]; however, risk factors for the development of symptoms may include preexisting neuropathy, age, and impaired renal function [59–61].

EDX testing may show decreased amplitudes of SNAPs and CMAPs and denervation changes in more distal muscles of the lower limbs [52]. However, this is complicated by evidence of peripheral neuropathy in up to 54 % of patients with multiple myeloma before treatment with bortezomib [62]. With dose modification or discontinuation, the majority of patients have improvement or resolution of their symptoms within 3 months [54, 62]. Dose modification guidelines have been shown to reduce the severity of symptoms [63].

Ixabepilone is a semisynthetic epithilone analog used in the treatment of breast cancer. It was approved by the FDA in 2007 for the treatment of metastatic or locally advanced breast cancer in combination with capecitabine in which the cancer is resistant to anthracycline or a taxane. It is additionally approved for monotherapy in the treatment of metastatic or locally advanced breast cancer resistant or refractory to treatment with anthracyclines, taxanes, and capecitabine [64]. The mechanism of action includes microtubule stabilization, alteration of mitotic spindle formation, and induction of apoptosis [65]. The incidence of peripheral neuropathy is reported to range from 20 to 63 % with increased risk ascribed to advanced disease and prior treatments [66]. The neuropathy is predominantly sensory with 9 % reported to have a motor component [67]. Sensory findings are often mild and length dependent occurring in a stocking-glove pattern. Less than 20 % of patients have been reported to develop a severe neuropathy, and when this does occur, it is typically after the fourth treatment cycle [68]. More than 75 % of patients with neuropathy will have improvement in their symptoms with dose reduction in 4–5 weeks [67, 69]. Guidelines for dose reduction have been published [64].

Thalidomide, once touted as a sedative hypnotic, and used as an immunosuppressant in rheumatoid arthritis and autoimmune skin conditions, is now FDA approved for use in multiple myeloma. A sensorimotor neuropathy appears in persons taking the drug after 1–18 months at daily doses of 50–400 mg [70]. Patients develop numbness and paresthesias which begin in the feet and later ascend along with proximal weakness. Reflexes may be decreased, absent, or increased with Babinski signs in some patients. CSF exam may show elevated protein [70]. EDX shows decreased to absent SNAPs [71]. Sural nerve biopsy shows selective loss of large diameter fibers [72]. Recovery is often very slow and deficits are sometimes permanent [70].

Other chemotherapeutic agents have been associated with neuropathies. Sensory neuropathies have occurred with *chlorambucil* [73]. Mild peripheral neuropathy may be seen with repeated courses of high-dose therapy with *etoposide* (VP-16) [5]. The alkylating agent *ifosfamide* rarely causes peripheral neuropathy [5]. The chemotherapeutic agent *procarbazine*, structurally similar to INH, has been associated with a mild peripheral sensory neuropathy at high doses [5, 74]; whether pyridoxine (vitamin B6) ameliorates or prevents this neuropathy is uncertain [5]. Isolated limb perfusion with *interferon*, *tumor necrosis factor*, and *melphalan* in

melanoma patients has caused a dose-dependent local sensory neuropathy [75].

Antituberculous Agents

Isoniazid (isonicotinic acid hydrazide/INH®), the most commonly used antituberculous agent, may result in an axonal sensorimotor polyneuropathy that is in part preventable by concurrent administration of vitamin B6. Before the recognition of B6 deficiency with INH therapy, the incidence of neuropathy was quite high, with 17 % of patients receiving a dose of 400 mg/day developing neuropathy [76, 77]. With supplemental vitamin B6, one study showed only one of 62 INH-treated patients developed neuropathy [78].

Excretion of vitamin B6 is increased with INH administration [79–81]. Poor nutritional status, alcohol abuse, liver disease, thyroid dysfunction, and pregnancy are risk factors for INH neuropathy [3]. Slow acetylators are more commonly affected [3, 12].

Symptoms usually begin with numbness and paresthesias of the hands and feet. If the drug is discontinued after the first symptoms begin, recovery is rapid [8]. Myalgias, muscle cramps, ataxia, and weakness may be seen as well [3, 8, 78, 82]. Examination shows distal sensory loss, weakness, absent reflexes, and ataxia [3]. Late in the course, atrophy and fasciculations may be seen [83]. EDX shows a sensorimotor axonal polyneuropathy [3]. Nerve biopsies show axonal degeneration and loss of myelinated and unmyelinated fibers [12, 84].

The recommended prophylactic dose of pyridoxine is 25–50 mg/day [78]. If much higher doses are used, a separate pyridoxine-induced sensory neuronopathy may occur [85]. Some studies suggest that even 10 mg/day is effective [81]. Recovery from the neuropathy is often slow and ranges from incomplete to good. Whether B6 deficiency is the only cause of INH neuropathy remains unsettled [3, 79, 85, 86]. Experimentally, INH may result in multifocal axonal lesions in animals after a single oral dose [87].

Ethambutol, a common additional antituberculous drug, causes a sensorimotor polyneuropathy [88]. An optic neuropathy is more commonly seen [21]. Distal paresthesias and a reversible neuropathy have been reported with *ethionamide* [86, 89]. Improvement occurs slowly after the drug's discontinuation [89].

Antiretroviral Agents

A dose-limiting painful, dysesthetic sensory neuropathy occurs with *Zalcitabine*® (2′3′dideoxycytidine or ddC) in approximately one-third of patients treated with 2.25 mg/day [90]. The neuropathy may be confused with distal sensory neuropathy associated with HIV [91] but can be differentiated by its more rapid progression (weeks vs. months) with a median onset at 16 weeks of therapy [3, 90]. Patients complain of numbness, tingling, and pain. Examination shows decreased pinprick sensation, hyperpathic pain, and ankle areflexia; vibratory loss occurs in only a third of patients [90]. Patients may or may not improve after discontinuation of the drug [90, 92]. Risk factors for neuropathy include coexistent diabetes, weight loss, advanced HIV disease, preexisting peripheral nerve problems, alcohol abuse, and nutritional deficiency [90, 93].

In one study of 44 patients treated with *didanosine* (ddI), neuropathy occurred in nine and a preexisting neuropathy worsened in one [94]. The neuropathy seen with ddI is similar to that seen with ddC [94]. Biopsies may show intramyelin edema and myelin infolding (Fig. 35.5) [84].

Peripheral neuropathy is the major dose-limiting toxicity of the antiretroviral *stavudine*. The neuropathy limits the maximum tolerated dose to 4 mg/kg/day, at which dose 60 % of patients develop neuropathy. At a dose of 2 mg/kg/day, less than 40 % of patients develop neuropathy; current doses approved for use are approximately 1 mg/kg/day [95]. The neuropathy is similar to that seen with ddI and ddC [95].

Other Antimicrobial Agents

The antimicrobial drug *metronidazole* (Flagyl®) may cause a predominantly axonal sensory polyneuropathy, more common after a cumulative dose of 50 g [81]. Patients complain of distal dysesthesias. Examination shows distal sensory loss, weakness, and decreased reflexes [78]. EDX shows reduced SNAP amplitudes with normal latencies; less frequently, motor fibers are affected [21]. Sural nerve biopsy shows axonal degeneration of myelinated and unmyelinated fibers and segmental demyelination [10, 86, 96]. Recovery may be slow but is usually good [3, 81].

Nitrofurantoin, a commonly prescribed agent for urinary tract infections, may result in an axonal sensorimotor polyneuropathy and rarely a fulminant radiculoneuropathy. Total toxic doses are usually greater than 20 g but can be less in patients with compromised renal function [97]. When polyneuropathy occurs, it usually does so within 6 weeks of starting the medication [86]. Patients complain of paresthesias and numbness followed by weakness [3, 86]. Severe weakness and loss of reflexes, similar to the Guillain-Barré syndrome have been reported [98]. In addition, patients have been reported with pure motor neuropathies [7, 99, 100]. EDX have demonstrated decreased conduction velocities and distal denervation even in some asymptomatic patients [101]. Nerve biopsies and autopsies have shown wallerian degeneration [102]. Renal failure and volume depletion predispose patients to nitrofurantoin's neurotoxic effects [102].

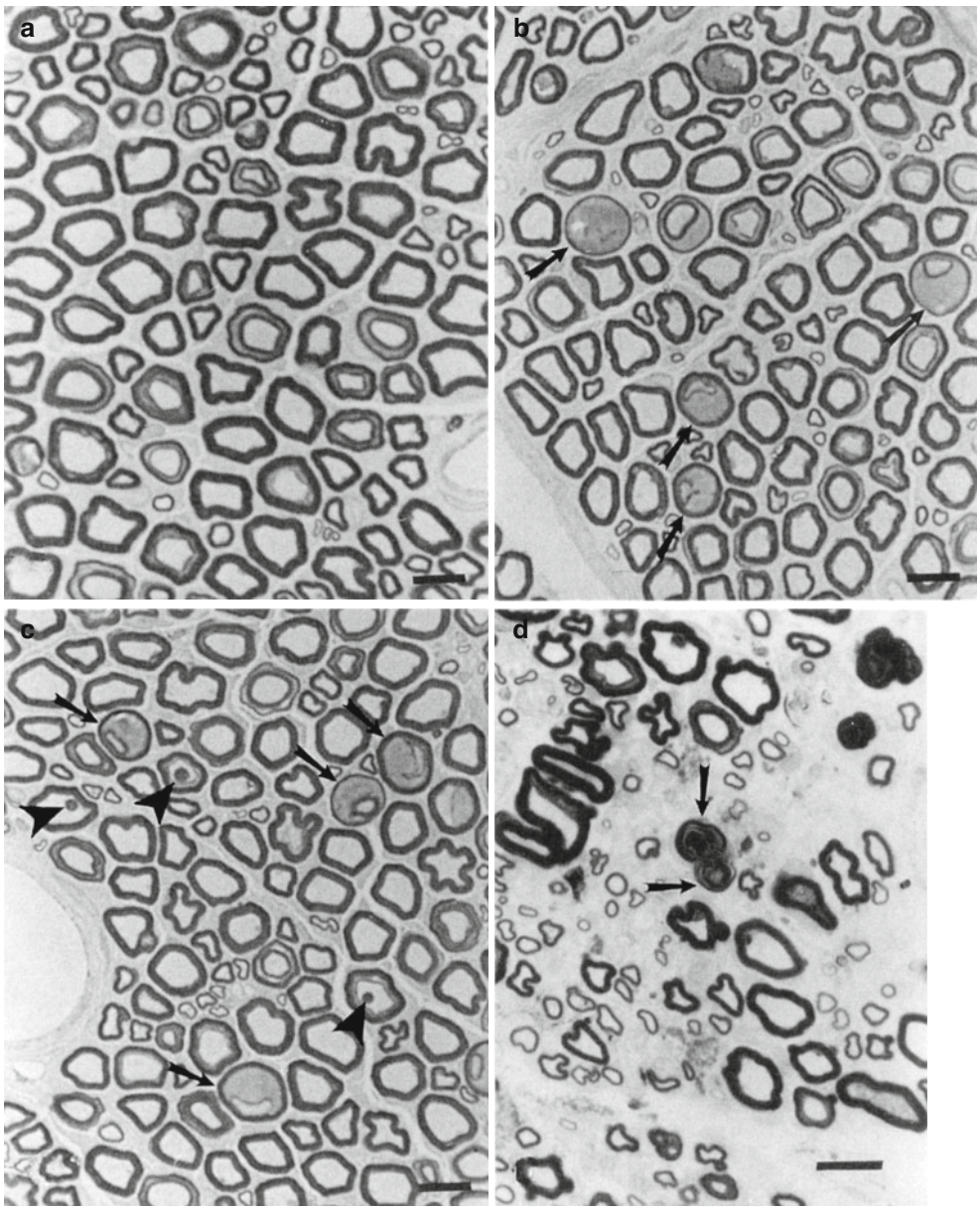

Fig. 35.5 ddI neuropathy. Brightfield photomicrographs of semithin plastic-embedded sciatic nerve stained with toluidine blue and basic fuchsin. (**a**) Reveals mostly normal morphology of nerve tissue from animals dosed with the vehicle control. (**b**, **c**) Myelin pathologies frequently seen following chronic ddI dosing. *Solid arrows* indicate examples of intramyelin edema, whereas *arrowheads* indicate myelin infolding. Neuropathies resulting from chronic isoniazid administration (**d**) include a decrease in axonal volume, an increase in extracellular debris, and an increase in the appearance of whorls (*arrows*). Scale bars equal 10 um (Reproduced with permission from Schumued et al. [84])

Partial recovery sometimes occurs after discontinuation of the drug [21].

Linezolid is the first in a new class of oxazolidinone antibiotics effective against multidrug-resistant gram positive infections. It is indicated in the treatment of drug-resistant streptococcus pneumonia, complicated skin and soft tissue infections including methicillin-resistant *Staphylococcus aureus*, and osteitis [103]. It is an attractive antimicrobial agent due to its effectiveness, general tolerability, and bioavailability making oral preparations available [104]. Neurologic adverse effects include peripheral neuropathy, optic neuropathy, and seizures. Additionally, one case of auditory neuropathy has been reported [105]. Peripheral neuropathy has been reported to be the second leading cause for treatment discontinuation occurring in 9.1 % of patients with osteomyelitis treated for more than 4 weeks [106], though the incidence has been reported as low as 0.36 % [107]. In a 2007 survey of the Infectious Diseases Society of America Emerging Infections Network, 17 % of the physicians who responded as having prescribed linezolid reported having observed at least one case of peripheral neuropathy while on the drug [108]. Although reported as predominantly length-dependent axonal sensorimotor polyneuropathy by EDX studies [109, 110], frequent complaints of neuropathic pain and demonstration of decreased epidermal nerve density indicate small-fiber sensory nerve denervation as well [111]. The most significant risk factor for development of peripheral neuropathy is chronic use with symptoms usually developing after the recommended maximal dose of 28 days and often after 3 months [112]. The etiology is unknown but may

be associated with mitochondrial protein synthesis [113]. Despite discontinuation of the drug, most symptoms of peripheral neuropathy do not resolve [106, 110, 114]. However, cases of neuropathic pain have been reported to improve over time [111].

Chloramphenicol causes a painful sensory neuropathy, more commonly in the pediatric population. It usually occurs after large doses administered for extended periods; renal failure increases the risk. It may occur before, concomitantly with, or after an associated optic neuropathy. Patients complain of distal paresthesias with a stocking-glove distribution of sensory loss on examination [3, 86]. Decreased ankle and patellar reflexes may also be seen [115]. Complete recovery is possible after discontinuation of the drug [10]. The pathophysiology may be related to interference with vitamin B12 activity [116], but the efficacy of using vitamin B12 supplementation as preventive therapy is not established [3].

The antimalarial *chloroquine* (Plaquenil®) is also widely used as an anti-inflammatory agent. Although more commonly associated with a vacuolar myopathy, neuropathy can also occur. Dose and duration of treatment vary but the neuropathy usually occurs after several months to a few years of therapy [86]. In some patients, motor fibers are predominantly affected [117], whereas others have a sensorimotor polyneuropathy with both axonal and demyelinating features [118, 119]. Examination shows weakness and reduced or absent reflexes. Needle EMG may show fibrillation potentials, myotonic discharges, and complex repetitive discharges, along with neurogenic motor unit action potential (MUAP) recruitment [118]. Nerve biopsy shows segmental demyelination and remyelination [118, 119]. Electron microscopy shows abnormal Schwann cell inclusions similar to those seen in amiodarone neurotoxicity [118]. Improvement is seen with discontinuation of the drug [21, 118], but the extent of improvement depends on the severity of the neuropathy at the time of drug discontinuation [86].

Cardiovascular Agents

Amiodarone, a di-iodinated benzofuran derivative, is notable for several toxic effects, but its efficacy as an antiarrhythmic has disallowed its retirement. Neuropathy occurs in 6 % of patients [120, 121] and is a dose-dependent phenomenon. Patients receiving greater than 400 mg a day are at increased risk. More often, distal sensorimotor findings develop, but proximal weakness can occur as well, resulting in marked gait disturbance [10, 120, 122]. In addition, a predominantly motor neuropathy has been described [121].

Amiodarone-associated peripheral neuropathy affects both myelinated and unmyelinated fibers. EDX shows both demyelinating and axonal features [121–123]. Serum amiodarone levels of 2.4 mg/l have been associated with peripheral neuropathy, with sural nerve specimens showing high levels of the drug [124]. One study showed that the sural SNAP was inversely related to serum concentration [125].

Electron microscopy of sural nerve biopsies have shown lysosomal inclusion bodies (Figs. 35.6 and 35.7) in Schwann cells, muscle fibers, and capillary endothelial cells, similar to chloroquine and perhexiline [12, 126], along with loss of myelinated fibers [121, 122] (Fig. 35.7). The pathophysiology is likely related to inhibition of lysosomal phospholipases [12, 126]. A reversible tremor and ataxia are more common than polyneuropathy [127] and occur in about 70 % of patients taking 800 mg/day [21, 120]. An optic neuropathy also occurs [128].

Hydralazine (Apresoline®) results in distal paresthesias in a minority of patients and rarely causes an axonal polyneuropathy that is primarily sensory in nature. Chemically, the drug resembles INH, and thus some speculate that its pathophysiology may be related to vitamin B6 depletion; the neuropathy does often improve after the drug's discontinuation or B6 supplementation [10, 129].

Reversible neuropathies with prolonged motor and sensory latencies and decreased conduction velocities have been associated with *captopril* (Capoten®) [130]. A temporal association of captopril with a Guillain-Barré-like syndrome has been reported in two cases [131, 132]. Whether this represents cause-and-effect relationship or a chance occurrence remains not settled. In a similar manner, the thrombolytic agent, *streptokinase*, derived from group C streptococci, has been associated with Guillain-Barré syndrome in at least nine cases of since 1983 [133, 134]. Streptokinase may also cause permanent median and ulnar neuropathies after post-injection extravasation [135].

Lipid-Lowering Agents

The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors are widely known to cause symptomatic myopathies, but most of these agents have also been implicated in drug-induced neuropathies, with most patients recovering fully after discontinuing the drug.

Lovastatin (*Mevacor*®) has been shown to cause neuropathies affecting peripheral and cranial nerves [12, 136]. When lovastatin is used with *gemfibrozil* (Lopid®), toxic effects, particularly myopathy, can be up to 5 % [137], and with cyclosporine A, up to 30 % [138]. *Simvastatin* (*Zocor*®) has caused axonal sensorimotor polyneuropathies [139]. Manifestations range from mostly sensory to sensorimotor neuropathy to profound and disabling weakness [139]. EDX shows widespread chronic denervation along with mild slowing of conduction velocity. Sural nerve biopsy shows axonal degeneration with reduced numbers of small and large myelinated fibers [139]. Some patients may develop symptoms abruptly after the first dose, while others require months to years of therapy.

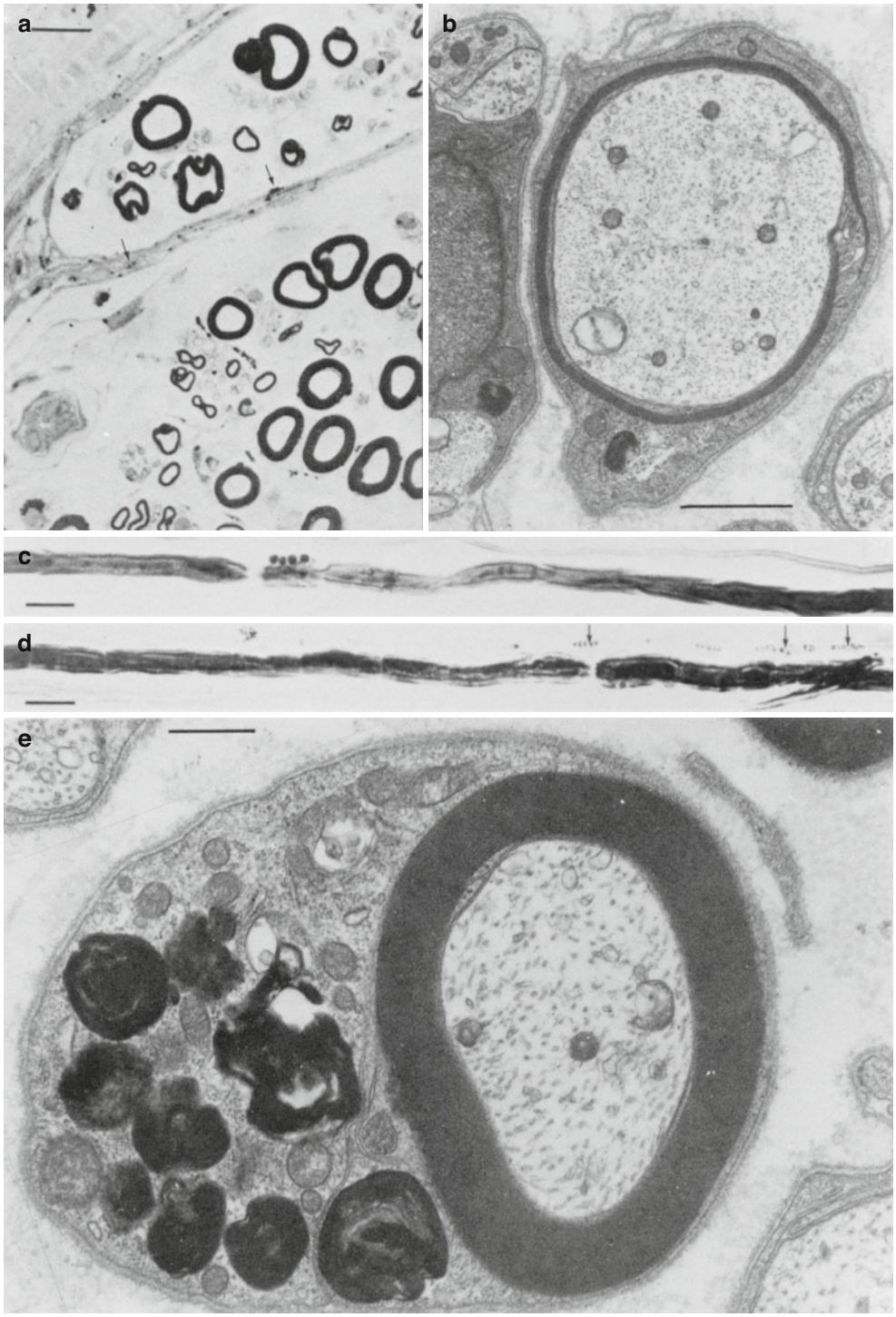

Fig. 35.6 Amiodarone neuropathy. Pathological changes with amiodarone. (**a**) Small granular lipid inclusions in Schwann cells and perineural sheath (*arrows*), PPD staining, bar = 10 µm. (**b**) Remyelinating axon, bar = 1 µm. (**c**) Teased fibers, lipid inclusions in a large myelinated fiber, bar = 20 µm. (**d**) Teased fibers, lipid inclusions in an unmyelinated fiber, bar = 20 µm. (**e**) Membranous lamellar lipid inclusions in Schwann cell of a myelinated fiber, bar = 0.5 µm (Reproduced with permission from Pellessier et al. [122])

Immunosuppressants

The immunosuppressant agents in the class of tumor necrosis factor alpha antagonists (*infliximab*, *etanercept*, and *adalimumab*) are used in the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriasis, and Crohn's disease. In the peripheral nervous system, rare case reports have associated their use with Guillain-Barré syndrome [140, 141], Miller Fisher syndrome [140], chronic inflammatory demyelinating polyneuropathy [142–144], multifocal motor neuropathy with conduction block [145–148], mononeuritis multiplex [149], and axonal sensorimotor polyneuropathy [144, 148, 150]. In a review of these case reports, most peripheral neuropathies improve over months with drug discontinuation. However, recent studies suggest that symptom resolution with drug discontinuation may not be as favorable as previously described and chronic immunosuppressive and immunomodulating therapy may be necessary [143, 151].

There are reports of *cyclosporine A* (Neoral®, Sandimmune®) associated with reversible neuropathies [152]. Later studies suggest that a solvent used in IV cyclosporine preparations containing Cremophor EL may be neurotoxic, as it interferes with axonal transport in vitro [153]. However, animal studies, which used Cremophor injections as a control, have not confirmed this finding [34].

A demyelinating neuropathy have been reported weeks after starting therapy with *FK506* (tacrolimus/Prograf®) and manifesting with dysesthesias and progressive weakness. CSF protein was elevated and EDX showed demyelination, similar to Guillain-Barré syndrome or chronic inflammatory demyelinating polyneuropathy. Some patients improve after dosage reduction. Others improve with intravenous gamma globulin (IVIG) or plasmapheresis, implying a probably coincidental development of Guillain-Barré syndrome or chronic inflammatory demyelinating polyneuropathy [154–156].

Interferon alpha, an immunomodulating agent used in cancer and other fields of medicine, has been reported to cause a mild sensorimotor neuropathy [5, 157]. *Interleukin 2*, an immunomodulator, has been associated with carpal tunnel syndrome and brachial plexopathies [158, 159]. The pathophysiology is possibly from increased vascular permeability and perineural tissue swelling.

Neurologic/Psychiatric Agents

The peripheral nervous system complications of *lithium* may be underdiagnosed, secondary to the prominent CNS toxic manifestations [160]. There is an inverse linear correlation between motor and sensory nerve conduction velocities and lithium levels [161]. Objective deficits may be seen on EDX after only 1 week of treatment in normal volunteers with therapeutic levels [162, 163]. Patients may develop sensory complaints, decreased or absent reflexes, and varying degrees of weakness [3, 160, 164]. EDX shows reduced CMAPs and SNAPs, slowing of conduction velocities, and distal denervation on needle EMG [162, 163]. Sural nerve biopsy shows axonal degeneration and loss of myelinated fibers [164]. Partial improvement may occur after discontinuation of the drug [164], but the degree of recovery is highly variable [160]. Since lithium therapy mainly causes subclinical peripheral neuropathy, perhaps more clinically relevant is its potential to exacerbate other comorbid neuropathies, such as with peripheral neuropathies related to alcohol or diabetes [162].

Amitriptyline (Elavil®), an antidepressant drug well known for its use in treating pain and dysesthesias of peripheral neuropathies, has been rarely reported to cause acute polyradiculoneuropathies [3, 7, 165]. Only five cases are reported prior to 1987. A case report of a patient who overdosed on amitriptyline developed quadriplegia, areflexia, bulbar dysfunction, and respiratory compromise requiring ventilatory assistance [165]. The CSF protein was initially normal but became remarkably elevated to 1,500 mg/dl 1 week after the ingestion and remained high for 1 month. EDX showed decreased conduction velocity of motor nerves and denervation on needle EMG. CMAP amplitudes were decreased and F waves prolonged. No evidence of conduction block was seen.

Approximately 50 % of patients on anticonvulsants have either peripheral nerve symptoms or abnormalities on EDX [166]. *Phenytoin* (Dilantin®) often causes asymptomatic loss of reflexes in 50 % of patients on the drug for 15 years or more [167]. Some patients develop lower extremity sensory and vibratory loss with EDX demonstrating an axonal sensorimotor neuropathy [168]. Sural nerve biopsies show axonal degeneration with segmental demyelination [169] and increased numbers of small myelinated fibers suggesting axonal atrophy [12]. Prolonged administration and elevated serum levels predispose patients to the development of neuropathy [168]. Improvement in the physical examination and electrophysiologic parameters occurs after drug discontinuation [169].

Methysergide (Sansert®), well known for its complication of retroperitoneal fibrosis, has rarely been associated with ischemic neuropathies [170, 171]. The sedative agent *methaqualone* has been implicated in some cases of sensorimotor neuropathies [7].

Rheumatologic Agents

Allopurinol (Zyloric®) used to treat hyperuricemia and gout may rarely result in a delayed axonal sensorimotor polyneuropathy characterized by distal weakness and dysesthesias [172, 173]. Examination shows stocking-glove sensory loss and, often, absent reflexes. Sural nerve biopsies have shown axonal degeneration and segmental demyelination [173]. Improvement may follow discontinuation of the drug [173].

Colchicine is associated with a distal axonal polyneuropathy and a vacuolar myopathy. The mechanism of colchicine-induced neuropathy is inhibition of polymerization of tubulin and blocking of axonal transport. The incidence of neuropathy is higher in patients with renal insufficiency and in patients with cyclosporine-induced gout [174]. Along with the neuropathy, a vacuolar myopathy is the more common neurologic sequela of colchicine therapy, most frequent in patients with hepatic and/or renal failure [8, 10, 12, 174–176].

Leflunomide is a disease-modifying drug approved for use in the treatment of rheumatoid arthritis [177]. Though peripheral neuropathy was not reported in phase II and III clinical trials [178, 179], several case reports after its approval

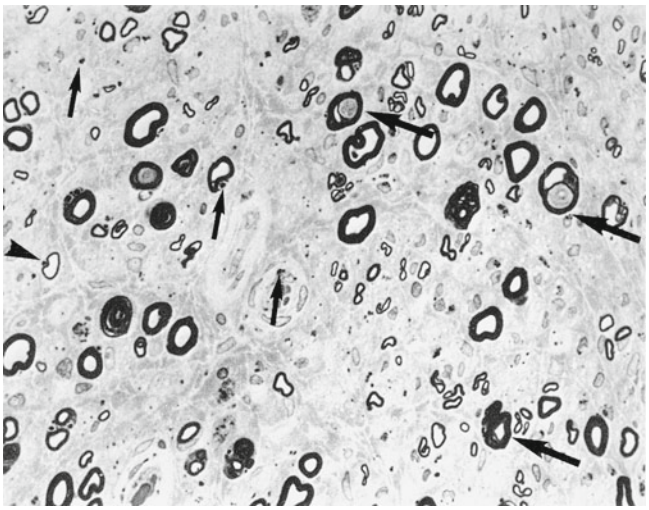

Fig. 35.7 Amiodarone neuropathy. One micrometer section of sural nerve showing a reduced density of myelinated fibers. A few degenerating fibers are seen; others show myelin abnormalities (*large arrows*). The *arrowhead* indicates an axon with an inappropriately thin myelin sheath. Some small regenerating clusters are seen. *Small arrows* point to some of the many inclusions in Schwann cells and endothelial cells. Toluidine blue ×720 (Reproduced with permission from Jacobs and Costa-Jussa [121])

suggested a causal relationship [180–182]. The incidence of peripheral neuropathy in leflunomide is unknown. In a retrospective study of 785 patients treated with leflunomide, 1.4 % were found to possibly have drug-related neuropathy by both clinical and EDX findings [183]. A prospective cohort study of 32 patients found that although 54 % of those treated with leflunomide reported symptoms of peripheral neuropathy, only 1 of the 16 in the leflunomide-treated group had an abnormal EDX study [184]. The neuropathy is predominantly a sensorimotor axonal type which usually begins between 3 and 6 months of treatment [181, 185], though it has been reported as early as 2 weeks after exposure [180]. A review of 80 cases of peripheral neuropathy in patients treated with leflunomide reported to the FDA between 1998 and 2004 found no association between age, sex, or dose of leflunomide and the time of onset of neuropathy [185]. However, a cohort study found an increased association of neuropathy in patients who were older, had concurrent diabetes, or were previously treated with neurotoxic drugs [186]. Treatment is with discontinuation of the drug. One study found that patients who stopped taking leflunomide within 30 days of symptom onset were 86-fold more likely to have symptom improvement than those who discontinued treatment after 30 days of symptom onset [185]. Furthermore, if stopped within 30 days of symptom onset, the median time to improvement or recovery was [135] days compared to 755 days if stopped after 30 days [185].

Peripheral neuropathy is a rare side effect of *gold* therapy but is usually not dose dependent. It is often difficult to determine if the gold salts or the underlying rheumatologic condition were responsible for the peripheral neuropathy [187]. Gold-induced neuropathy is associated with sensory symptoms initially, more often loss of pain and temperature sense than vibration. Distal weakness and areflexia develop later, followed by lower extremity or diffuse myokymia which can be a distinguishing feature [188–190]. Weakness is usually acute and may be profound and asymmetric [189, 191]. A Guillain-Barré-like syndrome with demyelinating polyneuropathy can occur but is uncommon [7].

EDX studies may show prolonged distal latencies and slowed conduction velocities on nerve conduction studies. On needle EMG, denervation potentials and myokymic discharges may be present [188–190]. Changes on nerve biopsy are mixed, with both axonal and segmental demyelination. Discontinuation of the drug often brings about improvement, but severely affected patients may not fully recover [189]. Cranial polyneuropathies, encephalopathy, and stroke have been reported as other neurologic complications [188].

Indomethacin (Indocin®), an anti-inflammatory/analgesic, has been implicated in sensorimotor neuropathies with the primary clinical manifestation being weakness. Paresthesias and ataxia may be seen. EDX studies show decreased motor nerve conduction velocities and normal sensory latencies. Recovery is often complete after discontinuation of the drug [192].

Miscellaneous Agents

Disulfiram (Antabuse®), used in alcoholic rehabilitation, is known to cause a sensorimotor distal axonopathy in patients taking more than 250 mg/day. Sensory symptoms are seen first in the feet [8]. Sensory loss occurs before weakness, and burning dysesthesias are common. Examination shows absent distal reflexes, a stocking-glove sensory loss, and distal weakness [3]. Axonal degeneration and loss of myelinated fibers are seen on sural nerve biopsy. In some cases, segmental demyelination [193] and neurofilament accumulations are seen [194, 195]. There is usually slow recovery after discontinuation of the drug. Optic neuropathy has been shown to occur as well [10]. The pathophysiology of the polyneuropathy is thought to involve carbon disulfide, one of disulfiram's metabolites, a known neurotoxin [196].

Nitrous oxide (N_2O) used as an anesthetic in dentistry has been shown to cause peripheral neuropathy and myelopathy, mostly commonly in vitamin B12-deficient persons [197]. Methionine synthetase inhibition may be the pathophysiologic mechanism; supplementation with methionine and folic acid has been shown to protect against the neuropathy associated with N_2O [198, 199].

Perazine, a phenothiazine derivative, has been reported to cause a "sunbath polyneuritis," in which sun exposure

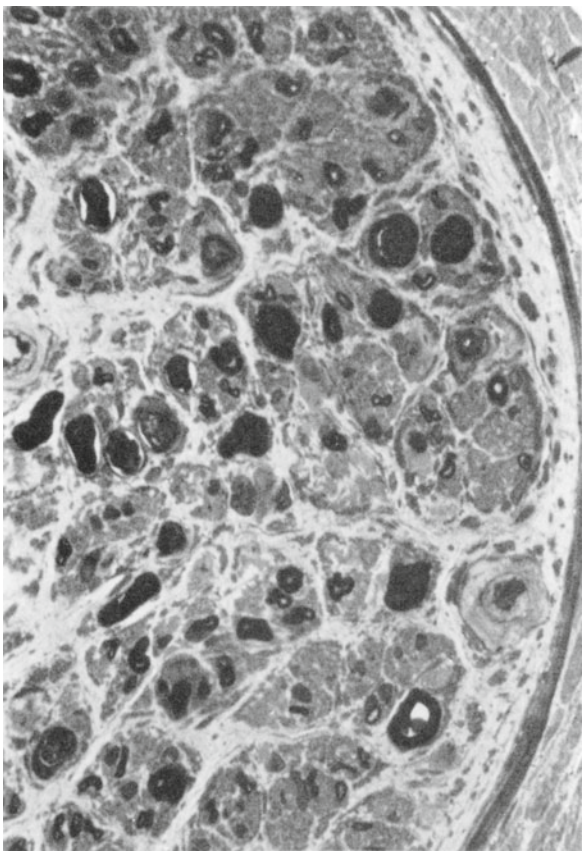

Fig. 35.8 Cross section of a sural nerve in a patient taking pyridoxine for 9 months (2 g/day). There is severe fiber loss and some myelinated fibers are undergoing degeneration (×720) (Reproduced with permission from Schaumburg et al. [202])

puts patients at risk for a sensory neuropathy. This is presumably caused by photoproduct-related cell damage via a lipid peroxidation mechanism. Three of the seven patients in one report had bilateral facial nerve palsies. Needle EMG of facial muscles showed denervation potentials [200]. Sural nerve conduction velocities are reduced, but motor nerve conduction velocities are normal [200]. All patients had a monophasic illness and near complete recovery [201].

Ironically, *pyridoxine* (vitamin B6), used to prevent INH-induced neuropathy, causes a neuropathy. This usually occurs at large doses (2–6 g/day) but may occur with as little as 50 mg/day (human requirement being 2–4 mg/day) [202, 203]. The entity is often heralded by unsteady gait and numb feet, with patients reporting difficulty using their hands; perioral numbness sometimes follows [202]. Examination shows stocking-glove sensory loss with vibration and proprioception loss, often leading to ataxia and choreoathetosis [8, 202]. Reflexes are decreased or absent. Strength is preserved. EDX shows absent SNAPs but normal motor nerve conductions and needle EMG, consistent with a sensory neuronopathy [202]. Sural nerve biopsy shows loss of large and small fibers [202, 204] (Fig. 35.8). CSF is normal [202]. Patients may improve within a few months of discontinuing the vitamin or may be left with permanent deficits [3, 202, 204].

Amphetamines can cause a necrotizing hypersensitivity angiitis with multiple mononeuropathies [10]. *Intravenous heroin* has been shown to cause nontraumatic plexopathies which are very painful and may recur in those who resume its use after a period of abstinence [10].

Dapsone, used for malaria prophylaxis, leprosy, and various skin conditions, causes predominantly a motor neuropathy when used in high doses (200–500 mg/day) for greater than 6 weeks [8, 205]. Patients treated at lower doses, as is commonly employed in leprosy, rarely develop neuropathy [86]. There may be paresthesias, but objective sensory loss is not demonstrable [21]. There is usually severe muscle atrophy, especially of the hands, and hyporeflexia or areflexia [21, 206]. Biopsy shows axonal degeneration of both sensory and motor nerves [86, 205]. Recovery is sometimes prompt [78] but is usually slow after discontinuing the drug [10]. A severe optic neuropathy can also be seen [10].

This psoriatic therapy *etretinate* (Tegison®) has been shown to cause a reversible axonal sensory polyneuropathy which on sural nerve biopsy shows axonal degeneration of small and large myelinated fibers [207].

Topical *ammoniated mercury* has resulted in a primarily axonal polyneuropathy with secondary demyelinating pathology [208, 209]. Burning dysesthesias are prominent. Examination shows decreased lower extremity reflexes and a stocking-glove sensory loss.

Podophyllin, used for topical treatment of condyloma acuminata, causes an axonal sensorimotor polyneuropathy when significant systemic absorption occurs [210]. Central nervous system depression, hallucinations, seizures, ataxia, autonomic instability, pancytopenia, and multiorgan failure have also occurred [3, 210]. Examination shows distal weakness, loss of ankle jerks, and sensory loss in a stocking-glove distribution which may persist for several months [210]. EDX study shows decreased SNAP and CMAP amplitudes, increased distal latencies, and denervation on needle EMG [210]. CSF may show elevated protein suggesting root involvement [3, 210].

Acetazolamide (Diamox®) has been reported to cause painful paresthesias and distal sensory loss, which can sometimes be disabling [7]. *Sodium cyanate*, used to prevent sickle cell crisis, causes a sensorimotor neuropathy [211]. *Stilbamidine* is known to cause facial paresthesias and other unpleasant sensations [7, 212]. *L-tryptophan*-induced eosinophilia-myalgia syndrome can be associated with a severe axonal sensorimotor polyneuropathy as a prominent feature in some patients.

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Vasculitic Neuropathies and Neuropathies of Connective Tissue Diseases

36

Michael P. Collins and John T. Kissel

Introduction

The connective tissue diseases (CTDs) are a complex group of systemic autoimmune disorders linked by their propensity to involve the musculoskeletal system [1–3]. The primary CTDs (also called collagen vascular diseases) are listed in Table 36.1. While these diseases are all assumed to be autoimmune, their etiologies and mechanisms are poorly understood. They are generally felt to arise from complex interactions among heterogeneous genetic, environmental, immunologic, and endocrinologic influences.

The CTD-related neuropathies are challenging to diagnose and treat for several reasons. First, the underlying rheumatologic condition is often difficult to precisely identify. Second, most of the neuropathic phenotypes are nonspecific and can occur in all of the CTDs. Third, manifestations of treatable neuropathies, such as vasculitis, overlap with those of non-treatable neuropathies. Finally, the pathogenesis of most non-vasculitic neuropathies is obscure.

Etiopathogenic Mechanisms of Neuropathies in Connective Tissue Diseases

Neuropathies occurring in the course of a CTD may arise from several mechanisms, some independent of the immunologic disturbances of the disease. Understanding these mechanisms is of fundamental importance to managing these patients.

Vasculitis

The term vasculitis refers both to the pathologic finding of inflammatory destruction of vessel walls and to a large group of clinical conditions resulting from that process (Fig. 36.1) [1, 4]. In addition to the primary vasculitides, where vasculitis is the defining feature of the condition, essentially all CTDs can produce a secondary vasculitis that occurs as part of the disease process or is triggered by an exogenous antigen, such as an infection or drug.

Neuropathy from Organ System Failure

Organ system failure is an important but infrequent cause of neuropathy in CTDs. Most common are neuropathies resulting from renal failure in the vasculitides, systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and occasionally rheumatoid arthritis (RA). The pathogenesis of uremic neuropathy is uncertain, but its improvement following transplantation suggests that a neurotoxin resulting from renal compromise is operative [5].

Entrapment Neuropathies

Clinical and animal studies indicate that most generalized neuropathies predispose patients to entrapment neuropathies [6]. Disorders like RA and SSc, which are associated with chronic inflammation and proliferation of connective tissues, may further compromise the anatomic pathways of nerves, especially the median nerve in the carpal tunnel [7]. In these conditions, the combination of mechanical pressure and ischemia results in focal demyelination, followed by axonal degeneration if the compression persists.

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Neuropathy from Inflammatory Demyelination

Neuropathies clinically and electrodiagnostically identical to Guillain-Barre syndrome (GBS) [8] and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) [9] can occur in the setting of CTDs, most commonly SLE [10]. Whether the immunopathogenic mechanisms underlying these neuropathies are distinct from or identical to those occurring in patients with similar neuropathies but no CTD is unclear.

Table 36.1 Classification of the principal connective tissue disorders

Primary vasculitic syndromes
Predominantly small-vessel vasculitides
Wegener's granulomatosis (granulomatosis with polyangiitis)
Microscopic polyangiitis
Churg-Strauss syndrome (eosinophilic granulomatosis with polyangiitis)
Henoch-Schönlein purpura (IgA vasculitis)
Essential mixed cryoglobulinemia
Predominantly medium-vessel vasculitides
Polyarteritis nodosa
Kawasaki disease
Predominantly large-vessel vasculitides
Giant cell (temporal) arteritis
Takayasu arteritis
Other vasculitides (e.g., Behçet's disease)
Nonsystemic/localized vasculitides
Connective tissue diseases[a]
Rheumatoid arthritis
Primary Sjögren's syndrome
Systemic lupus erythematosus
Systemic sclerosis
Mixed connective tissue disease
Relapsing polychondritis
Seronegative spondyloarthropathies

[a]Each of these conditions may themselves predispose to an associated vasculitis

Neuropathy Due to Ganglionitis

One neuropathy with a unique immunopathogenesis is the dorsal root ganglionitis associated most closely with primary Sjögren's syndrome (pSS) [11]. This neuropathy is probably mediated in part by cytotoxic T lymphocytes (CTLs), but many pathogenic questions remain unanswered, including its etiology, antigenic triggers, and basis for targeting the sensory ganglia.

Cryoglobulinemia

Cryoglobulins occur as secondary phenomena in many CTDs [12, 13]. They are circulating immunoglobulins that precipitate at temperatures below 37 °C. Type I cryoglobulins consist of monoclonal immunoglobulins and usually occur in lymphoproliferative diseases. Type II are composed of monoclonal immunoglobulin (usually IgMκ) rheumatoid factors (anti-IgG activity) and polyclonal IgG, while type III are a mixture of polyclonal IgM rheumatoid factors (RFs) and polyclonal IgG. Types II and III are termed mixed cryoglobulins, which can be *essential* – without known cause – or *secondary* to pSS, RA, SLE, SSc, lymphoproliferative

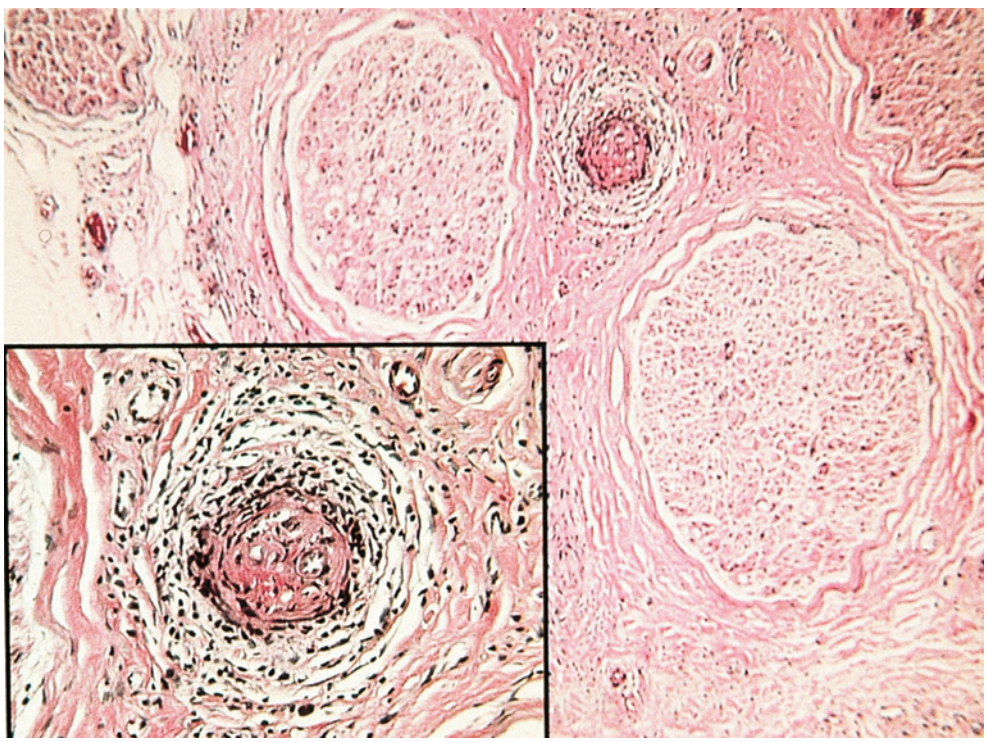

Fig. 36.1 Superficial peroneal nerve biopsy in patient with nonsystemic vasculitic neuropathy. One epineurial vessel is surrounded by perivascular inflammatory cells. Higher power view (*inset*) shows that the inflammatory cells infiltrate and disrupt the vessel wall and are associated with a recanalized thrombus (hematoxylin and eosin)

Table 36.2 Immunosuppressive drugs used for connective tissue diseases that may cause neuropathy

Drug	Rheumatic disease uses	Type(s) of neuropathy	Frequency
Chloroquine and hydroxychloroquine	RA, SLE, cutaneous lupus, SSc, pSS, dermatomyositis	Distal, axonal/demyelinating, sensorimotor; concurrent proximal vacuolar myopathy; occasional myotonic discharges; abducens palsies	Uncommon
Colchicine	Behçet's, leukocytoclastic vasculitis, morphea, SSc	Distal, axonal, sensorimotor; concurrent proximal vacuolar myopathy; occasional myotonic discharges	Uncommon
Cyclosporine	RA, SLE, SSc, polymyositis dermatomyositis, vasculitides	1. Acute, motor predominant, axonal or mixed axonal/demyelinating (GBS-like) 2. Brachial plexopathy 3. Distal paresthesias 4. Optic neuropathy	Rare, except tingling ~25 %
Dapsone	Relapsing polychondritis, RA, cutaneous lupus, Behçet's, cutaneous vasculitides	Axonal, motor-predominant, distal; occasionally upper limb predominant	Uncommon at usual doses
Gold salts	RA, psoriatic arthritis	Axonal or mixed axonal/demyelinating, sensorimotor; usually distal symmetric but can mimic GBS; often with myokymia; cranial neuropathies	Rare
Interferon-α	Essential and HCV-associated mixed cryoglobulinemia; HBV-related PAN; Behçet's; refractory CSS	1. Anterior ischemic optic neuropathy (AION) 2. Vasculitic or multifocal, sensorimotor axonal 3. Distal, symmetric, axonal, sensory/sensorimotor 4. Symmetric CIDP-like 5. Rare reports of many other phenotypes	Rare, except AION
Leflunomide	RA, maintenance of remission in ANCA-associated vasculitis	Distal, symmetric, axonal, sensory or sensorimotor Biopsy evidence of vasculitis in some cases	Uncommon
D-penicillamine	SSc, RA (rarely used anymore)	1. Motor or sensorimotor, acute or chronic demyelinating (CIDP, GBS) 2. Distal axonal with oculomotor palsies and ANAs 3. Neuromyotonia 4. Optic neuropathy	Rare
Tacrolimus (FK 506)	RA, SLE, Behçet's disease	1. Chronic demyelinating, sensorimotor, multifocal or symmetric (CIDP, LSS) 2. Acute, axonal, motor-predominant 3. Bilateral optic neuropathies 4. Distal paresthesias	Rare, except tingling ~25 %
Thalidomide	RA, SLE, cutaneous lupus, Behçet's disease	Distal, axonal, sensory	Common
TNF-α inhibitors	RA, spondyloarthropathies	1. Acute or chronic, symmetric demyelinating (GBS, CIDP) 2. Chronic, asymmetric demyelinating (MMN, LSS) 3. Vasculitic or multifocal, sensorimotor axonal 4. Distal, symmetric, axonal, sensory/sensorimotor	Rare

AION anterior ischemic optic neuropathy, *ANAs* antinuclear antibodies, *ANCAs* antineutrophil cytoplasmic antibodies, *CIDP* chronic inflammatory demyelinating polyradiculoneuropathy, *CSS* Churg-Strauss syndrome, *GBS* Guillain-Barre syndrome, *LSS* Lewis-Sumner syndrome, *MMN* multifocal motor neuropathy, *PAN* polyarteritis nodosa, *pSS* primary Sjögren's syndrome, *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus, *SSc* systemic sclerosis, *TNF-α* tumor necrosis factor-alpha

diseases, glomerulonephritis, and chronic infections. Chronic infection with hepatitis C virus underlies 80–90 % of essential mixed cryoglobulinemia [14]. Patients with mixed cryoglobulinemia may develop a neuropathy mediated by (1) immune complex-induced vasculitis [15]; (2) intravascular deposition of cryoglobulins causing an endoneurial microangiopathy [16]; (3) IgM binding to myelin, producing demyelination [17]; or (4) T cell-mediated vascular damage [18].

Neuropathy Due to Drug Toxicity

Several drugs used to treat CTDs can themselves produce a neuropathy (Table 36.2), a situation destined to create diagnostic confusion, as there is nothing distinctive about the clinical, electrodiagnostic, or pathologic features of these drug-induced neuropathies. Drugs most commonly cause a distal symmetric polyneuropathy, but more atypical patterns can be seen [19–24].

Thrombotic Vasculopathy

In vasculitides and CTDs associated with antiphospholipid antibodies, microvascular thrombosis may lead to neuropathy [25]. In the vasculitides, inflammatory damage to vascular endothelium results in the release of cytokines and other mediators that promote vasospasm, myointimal cell proliferation, and activation of clotting factors and platelets, all of which contribute to thrombotic occlusion of vessels [26].

Autoantibodies

CTDs are often associated with multiple autoantibodies, some of which may be directed against peripheral nerve antigens. Candidates include anti-ganglioside or anti-sulfatide antibodies, which can be found in patients with SLE and other CTDs and have been associated with neuropathy [27, 28].

Vasculitis

The vasculitides are diseases in which inflammatory infiltrates target and destroy vessel walls, resulting in ischemic and inflammatory injury to the involved tissues [3, 4]. Triggers include infections, drugs, and cancers, but in most patients, the inciting antigen is unknown. Vasculitis usually affects many tissues simultaneously but may be confined to a single organ, e.g., the peripheral nervous system (PNS).

Classification of Vasculitides with Neuropathy

Derivation of a uniform classification scheme for the vasculitides has always been problematic. Many classification systems have been proposed [29]. Most have distinguished the *primary* vasculitides (without known cause) from the *secondary* vasculitides (with an accepted etiology or predisposing disease). The most widely used *classification criteria* for the primary systemic vasculitides were derived by the American College of Rheumatology (ACR) in 1990 for polyarteritis nodosa (PAN), Churg-Strauss syndrome (CSS), Wegener's granulomatosis, hypersensitivity vasculitis, Henoch-Schönlein purpura (HSP), giant cell arteritis (GCA), and Takayasu arteritis [30]. In 1994, the Chapel Hill Consensus Conference (CHCC) proposed a new *nomenclature* that has also been widely accepted [31]. In the CHCC definitions, GCA and Takayasu arteritis primarily involve large vessels; PAN and Kawasaki disease affect small- to medium-sized arteries; and microscopic polyangiitis (MPA), Wegener's granulomatosis, CSS, HSP, cutaneous leukocytoclastic angiitis, and cryoglobulinemic vasculitis all predominantly involve the microvasculature, although small- to medium-sized arteries are also sometimes affected. For PAN, microvascular involvement was deemed exclusionary; as a result, it has become a rare disease in recent studies. Hypersensitivity vasculitis was excluded as a diagnostic entity. Further refinements followed in 2007, with a new consensus classification of CSS, MPA, PAN, and Wegener's granulomatosis [32].

The CHCC nomenclature was revised in 2012 [33]. Eponyms were eliminated except for disorders with ill-defined pathogeneses. Wegener's granulomatosis was renamed granulomatosis with polyangiitis (GPA), CSS was labeled eosinophilic granulomatosis with polyangitis, and HSP was recast as IgA vasculitis. In the revised nomenclature, small-vessel vasculitides are divided into those associated with sparse versus prominent vascular wall deposits of immunoglobulin and complement. The "pauci-immune" disorder are the ANCA-associated vasculitides: GPA, MPA, and CSS. The "immune complex small-vessel vasculitides" include anti-glomerular basement disease (Goodpasture syndrome), cryoglobulinemic vasculitis, IgA vasculitis (HSP), and hyopcomplementemic urticarial vasculitis. Additional entities are also incorporated into the revised nomenclature. "Variable-vessel vasculitides," which affect vessels of all sizes and types, include Behçet disease and Cogan syndrome. "Single-organ vasculitis" (also referred to as nonsystemic or localized vasculitis) affects vessels of any type in a single organ or tissue [34, 35]. Localized vasculitis has been described in almost all organs. Of greatest import, nonsystemic vasculitic neuropathy (NSVN) was identified as a unique, PNS-confined form of vasculitis by Dyck et al. in 1987 [36]. The many secondary causes of vasculitis are categorized as "vasculitis associated with systemic disease" (e.g., a CTD) or "vasculitis associated with a probable etiology" (e.g., drug- or infection-associated vasculitis).

The PNS is most commonly involved in vasculitides affecting small- to medium-sized vessels. Of the *primary* systemic vasculitides, neuropathies occur most frequently (50–70 % of patients) in CSS, PAN, and MPA [37–39]. For the *secondary* vasculitides, peripheral nerves are routinely affected in hepatitis B-associated PAN (80 % of patients) [38], hepatitis C-related mixed cryoglobulinemia (~60 %) [14, 40], and rheumatoid vasculitis (RV) (45–50 %; see below). In contrast, vasculitic neuropathies are unreported in Kawasaki disease, Takayasu arteritis and anti-glomerular basement membrane disease and very uncommon in GCA, Behçet disease, Cogan syndrome, and HSP. A consensus classification of vasculitides associated with neuropathy has been proposed by the Peripheral Nerve Society guideline group on NSVN (Table 36.3) [41].

Epidemiology of Primary Systemic Vasculitides and Vasculitic Neuropathy

Epidemiological studies have demonstrated that GCA and the primarily cutaneous vasculitides have the highest incidence rates, followed by RV, GPA, and MPA [42–45]. PAN is rare as defined by CHCC criteria. The frequency of the

Table 36.3 Classification of vasculitides associated with neuropathy [41]

I. Primary systemic vasculitides
1. Predominantly small-vessel vasculitis
(a) Microscopic polyangiitis[a]
(b) Churg-Strauss syndrome (eosinophilic granulomatosis and polyangiitis)[a]
(c) Granulomatosis with polyangiitis (Wegener's)[a]
(d) Essential mixed cryoglobulinemia (non-HCV)
(e) Henoch-Schönlein purpura (IgA vasculitis)
2. Predominantly medium-vessel vasculitis
(a) Polyarteritis nodosa (PAN)
3. Predominantly large-vessel vasculitis
(a) Giant cell arteritis
II. Secondary systemic vasculitides associated with one of the following
1. Connective tissue diseases
(a) Rheumatoid arthritis
(b) Systemic lupus erythematosus
(c) Sjögren's syndrome
(d) Systemic sclerosis
(e) Dermatomyositis
(f) Mixed connective tissue disease
2. Sarcoidosis
3. Behçet's disease
4. Infection (such as HBV, HCV, HIV, CMV, leprosy, Lyme disease, HTLV-I)
5. Drugs
6. Malignancy
7. Inflammatory bowel disease
8. Hypocomplementemic urticarial vasculitis syndrome
III. Nonsystemic/localized vasculitis
1. Nonsystemic vasculitic neuropathy (includes nondiabetic radiculoplexus neuropathy and some cases of Wartenberg's migrant sensory neuritis)
2. Diabetic radiculoplexus neuropathy
3. Localized cutaneous/neuropathic vasculitis
(a) Cutaneous PAN
(b) Others

CMV cytomegalovirus, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *HTLV* human T-lymphotropic virus
[a]Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides

vasculitic *neuropathies* is somewhat different due to the variable prevalence of neuropathy in these conditions and the fact that vasculitic neuropathy not infrequently occurs in isolation (i.e., NSVN). No study has determined the incidence or prevalence of any vasculitic neuropathy, but based on the best available data, the most common vasculitic neuropathies are NSVN (26 %) and those associated with MPA/PAN (25 %), RV (12 %), and CSS (10 %) [46]. Vasculitic neuropathy can develop at any age but most commonly occurs in the sixth through eighth decades [47–55]. For NSVN, the age at diagnosis ranges from 13 to 88 years, with a mean of 59.5 years [46]. Men are more frequently affected than women in PAN, MPA, RV, and HSP, while women are preferentially affected in GCA, SLE-related vasculitis, cryoglobulinemic vasculitis, and NSVN. Men and women are afflicted with roughly equal frequency in GPA and CSS [3, 45, 46].

Pathogenesis of Primary Systemic Vasculitides

Most vasculitides are assumed to result from autoimmune mechanisms, although the specific immunologic events are incompletely understood [3, 56–59]. Vasculitis begins with activation of the innate immune system by environmental or internal triggers, with subsequent self-antigen recognition by naïve autoreactive T and B lymphocytes, triggering both humoral and cellular immune responses. These processes, in turn, prime circulating leukocytes, activate endothelial cells, and upregulate antigen-presenting cells (APCs) in and around vessel walls. The primary mediators of endothelial cell activation are the pro-inflammatory cytokines TNF-α, IL-1, and IL-17. The endothelium responds by production and expression of cell adhesion molecules, tissue factors, cytokines, chemokines, inflammatory peptides, and angiogenic factors. Leukocytes then adhere to the endothelial surface, become activated, and migrate through the endothelium, an interaction that depends on a complex array of cellular adhesion molecules, cytokines, chemotactic agents, and other inflammatory regulators [60–62]. Additional effector cells are then recruited, including neutrophils, eosinophils, monocytes/macrophages, T cells, and NK cells, which damage vessel walls via various cellular and biochemical mechanisms [63–66]. The involved cells continue to release cytokines and tissue factors that stimulate coagulation, intimal cell proliferation, vessel wall fibrosis, and neovascularization [67]. Regulatory T cells and cytokines eventually downregulate the inflammatory response, leaving a fibrotic and often thrombosed or occluded vessel [58].

Cytokines are a diverse group of soluble polypeptides produced by multiple cell types that function as growth factors and hormones of the immune and hematopoietic systems [68, 69]. The term encompasses the interleukins, chemokines, interferons (INFs), and colony-stimulating factors. Subsets of CD4+ T helper (Th) lymphocytes can be distinguished by their cytokine profiles [70, 71]. The signature cytokines produced by these subsets are INF-γ for Th1 cells; IL-4, IL-5, and IL-13 for Th2 cells; and IL-17 for Th17 cells. Th1 cells activate macrophages, induce T cell proliferation, and increase production of opsonizing and complement-fixing IgG antibodies, promoting phagocyte-mediated defense against infections, granuloma formation, and T cell-mediated autoimmune diseases. Th2 cells promote IgE- and eosinophil-mediated immune responses, including allergic reactions. Th17 cells induce pro-inflammatory cytokines, chemokines, inflammatory mediators, and antimicrobial peptides; mediate recruitment of neutrophil-rich inflammatory reactions; and activate macrophages and T cells [71, 72]. They are required

Table 36.4 Pathogenic mechanisms in vasculitides

Mechanism	Implicated diseases
Circulating immune complexes	Henoch-Schönlein purpura (IgA)
	Hepatitis B-associated polyarteritis nodosa
	Mixed cryoglobulinemic vasculitis
	Other infectious vasculitides
	Some drug-induced and paraneoplastic vasculitides
	Connective tissue disease-associated vasculitides
Anti-endothelial cell antibodies	? Antineutrophil cytoplasmic antibody-associated vasculitides
	? Polyarteritis nodosa
	? Takayasu arteritis
	? Rheumatoid vasculitis
	? Lupus vasculitis
	? Kawasaki disease
	? Behçet's disease
Antineutrophil cytoplasmic antibodies	Granulomatosis with polyangiitis (Wegener's)
	Microscopic polyangiitis
	Churg-Strauss syndrome
Cytotoxic T lymphocytes	Allograft rejection
	? Vasculitic neuropathies
Delayed-type hypersensitivity	Giant cell arteritis
	? Granulomatosis with polyangiitis (Wegener's)
	? Churg-Strauss syndrome
Eosinophils	Churg-Strauss syndrome

? = mechanism proposed for this disease but not established

for host defense against bacterial infections but are also implicated in many autoimmune diseases [73].

Within this basic framework, several distinct immunopathogenic mechanisms have been proposed to produce vessel injury in the vasculitides (Table 36.4).

Circulating Immune Complexes

In this model, antibodies interact with circulating antigens to form antigen-antibody complexes, activate complement, and prime circulating leukocytes [56, 74–77]. Pathogenic deposition of immune complexes in vessel walls is promoted by turbulent flow, impaired clearance mechanisms, immune complexes with certain physical properties (intermediate sized and cationic), and abnormally permeable vessel walls. Deposited immune complexes activate more complement, generating chemoattractants (C3a and C5a) and C5b-9 membrane attack complex (MAC) that mediates endothelial cell lysis. The immune complexes also activate resident macrophages and mast cells via the Fc gamma receptor ($Fc_{\gamma}R$) pathway to release platelet-activating factor (PAF), eicosanoids, cytokines, bradykinin, and other inflammatory mediators. Neutrophils are recruited to the site within 24–48 h and release proteolytic enzymes and reactive oxygen species that further damage the vessel wall.

Antineutrophil Cytoplasmic Autoantibodies (ANCAs)

ANCAs are directed against cytoplasmic proteins in neutrophils and monocytes [78, 79]. They are classified as cytoplasmic cANCAs or perinuclear pANCAs based on their immunofluorescence (IF) staining pattern. In vasculitis, cANCAs usually target proteinase 3 (PR3), while pANCAs target myeloperoxidase (MPO). The three ANCA-associated vasculitides are GPA, MPA, and CSS [80–82]. ANCAs are present in 80–90 % of patients with active, generalized GPA and MPA but only 40 % of those with CSS [3, 4, 83]. PR3-cANCAs are most strongly associated with GPA, while MPO-pANCAs occur most commonly in MPA and CSS. A meta-analysis provided a weighted pooled sensitivity of 85 % and specificity of 99 % in the diagnosis of MPA, GPA, or CSS [84].

Multiple pathogenic mechanisms for ANCAs have been proposed [57, 58, 80–82]. The first involves interactions of ANCAs with primed (pre-activated) neutrophils. ANCA-activated neutrophils adhere to the endothelium, degranulate, undergo respiratory burst, and damage endothelial cells through release of reactive oxygen species, nitric oxide, serine proteases (including MPO and PR3), neutrophil extracellular traps, factors activating complement via the alternate pathway, and inflammatory mediators [57, 80, 81, 85, 86]. Released PR3 can, in turn, induce endothelial cell activation, lysis, and apoptosis. ANCAs also directly activate endothelial cells [87]. In addition, PR3 and MPO are transferred to the surface of apoptotic neutrophils, permitting interactions with their respective ANCAs [85, 88]. Although ANCAs do not activate apoptotic neutrophils, they do serve as opsonins, enhancing the recognition of these cells by phagocytic macrophages. Phagocytosis of ANCA-opsonized apoptotic neutrophils triggers production of pro-inflammatory molecules, amplifying and perpetuating the inflammatory response [85, 88, 89]. Defective clearance of PR3 and MPO on apoptotic neutrophils may be the initiating mechanism for ANCA production and subsequent development of vasculitis [85, 90].

Anti-endothelial Cell Antibodies

Anti-endothelial cell antibodies (AECAs) interact with endothelial cell antigens to form immune complexes that have the potential to produce damage via complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), or induction of endothelial cell apoptosis [91–95]. Target antigens could be constitutive components of the vessel wall, cryptic-induced antigens, foreign antigens, or adherent "planted" antigens. AECAs have been detected with varying prevalence in ANCA-associated vasculitides, PAN, GCA, Takayasu arteritis, RV, Kawasaki disease, Behçet's disease, HSP, and lupus vasculitis, but there is still no convincing evidence to support a causal relationship in these disorders [91, 92, 95–98]. AECAs are not unique to vasculitis, occurring in many other conditions. Studies assessing the ability of AECAs to mediate CDC or ADCC

have produced contradictory results [99–102]. There is more compelling in vitro evidence that AECAs can trigger apoptosis of endothelial cells [97].

Cytotoxic T Lymphocytes

Cellular immunity may play a pathogenic role in some vasculitides by promoting delayed-type hypersensitivity (DTH) or directly killing target cells [58, 59, 103, 104]. CTLs are activated after MHC-restricted binding to APCs such as dendritic cells and activated macrophages [66, 105]. They destroy antigen-bearing target cells by various secretory and nonsecretory pathways [66, 106–111].

Delayed-Type Hypersensitivity

Chronic DTH is an immune reaction in which T cell-dependent macrophage activation and cytokine-mediated inflammation cause tissue injury, a mechanism important in the pathogenesis of GCA. Activation of adventitial dendritic cells is an early event in GCA [112, 113]. Activated dendritic cells initiate a CD4+ Th1 cell response against an unknown antigen in the perivascular space. A separate population of dendritic cells activates a second pathogenic pathway mediated by Th17 cells [59]. Th1 and Th17 cells produce INF-γ, IL-17, and IL-32, which, in turn, induce macrophage activation [59, 114]. Activated macrophages migrate to the media and form granulomas. Macrophages, giant cells, activated T cells, and vascular smooth muscle cells produce pro-inflammatory cytokines, chemokines, matrix metalloproteinases, reactive oxygen species, nitric oxide, vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) that damage the vessel wall and promote neovascularization. In other granulomatous vasculitides, such as GPA and CSS, similar mechanisms may be active [115].

Eosinophils

CSS is characterized by persistent eosinophilia and allergic phenomena resulting from a foreign or autoantigen triggering a Th2 response in genetically predisposed individuals [116, 117]. The most commonly reported association is with leukotriene antagonist use [118]. IL-5 plays the key role in inducing eosinophil maturation and activation and prolonging eosinophil survival [119]. Infiltrating eosinophils damage vessels by the release of multiple cytotoxic enzymes [120].

Pathogenesis of Vasculitic Neuropathies

The preponderance of evidence supports the view that NSVN and most systemic vasculitic neuropathies (SVNs) are mediated by direct cellular cytotoxicity and chronic DTH [121, 122]. One gene expression profiling analysis and other more directed investigations of cytokine/chemokine expression in vasculitic neuropathy revealed increased pro-inflammatory cytokines and upregulated cytokines, chemokines, and chemokine receptors active in T cell and macrophage inflammatory responses [123–128]. Pathologic studies demonstrate a marked predominance of CD4+ and CD8+ T cells and macrophages in epineurial infiltrates in sural nerve biopsies of patients with vasculitic neuropathy [54, 121, 122, 129], and many of the T cells are activated and express markers characteristic of CTLs [122, 129]. Markers of APCs are upregulated in the epineurium and endoneurium [121, 130–133]. Costimulatory molecule CD86, which interacts with CD28 on naïve T cells, is upregulated on endothelial cells in NSVN [133]. Costimulatory molecule ICOS (inducible costimulator), which is expressed preferentially by effector memory CD4+ and CD8+ cells, is upregulated on epineurial T cells, while ICOS ligand is upregulated on macrophages in areas where ICOS-expressing T cells are found, suggesting that macrophages act as APCs to restimulate activated T cells [134].

These observations support a pathogenic model wherein disease-specific, autoreactive T cells are recruited to the PNS; undergo activation by self-glycolipid or peptide antigens presented by macrophages, Schwann cells, and/or endothelial cells; and then mature into CTLs that damage target cells in epineurial vessels. However, arguing *against* this model, one investigation of T cell receptor (TCR) Vβ gene utilization in epineurial infiltrates in sural nerve biopsies of patients with NSVN revealed no clonally expanded T cells, suggesting that T cells had been nonspecifically recruited to the PNS [135].

In addition to mononuclear cells, epineurial vessel walls in vasculitic neuropathy often contain deposits of IgM, IgG, C3, and complement terminal MAC [121, 136]. Moreover, a DNA microarray analysis of nerve biopsies in vasculitic neuropathy showed immunoglobulin genes relevant to B cell selection and antigen recognition to exhibit maximally upregulated transcription [128]. Thus, immune complex deposition with subsequent activation of complement and recruitment of phagocytic cells might represent another mechanism of vascular damage. However, pointing away from immune complexes as a key mechanism, B cells and polymorphonuclear leukocytes are rarely identified [54, 121, 122].

The final common pathway of tissue damage is regional ischemia due to occlusion of the involved epineurial or nutrient vessels. In experimental models of small-vessel occlusion, the central regions of larger fascicles in proximal nerve trunks degenerate most consistently [137]. Autopsy studies of peripheral nerves in patients with vasculitic neuropathy have demonstrated that while vasculitis is diffusely distributed in the epineurium throughout the proximal and distal segments of the nerves, marked myelinated fiber loss and Wallerian-like degeneration begin in the middle segments (corresponding to the distal arm and distal thigh) [138, 139]. Likewise, the ischemic pattern of centrofascicular degeneration occurs only in proximal and middle nerve segments, while diffuse nerve loss predominates in distal sections. The spinal

cord, dorsal root and sympathetic ganglia, and ventral and dorsal roots are spared. These findings indicate that vasculitis affects peripheral nerves diffusely but produces maximal damage in a border zone vulnerable to ischemia in the proximal/midportion of the upper and lower limb nerves.

Clinical and Laboratory Features of Systemic Vasculitides Associated with Neuropathy

Small- and Medium-Vessel Primary Systemic Vasculitides

The small- and medium-vessel primary systemic vasculitides are a diverse group of potentially life-threatening diseases characterized by vasculitic involvement of multiple organs. They include PAN, MPA, CSS, GPA, and HSP. Each disorder has distinguishing anatomic, pathologic, laboratory, and clinical features (Table 36.5). The ANCA-associated vasculitides – GPA, MPA, and CSS – share a predilection for small vessels, paucity of immune deposits in vascular lesions, and potential for rapidly progressive glomerulonephritis and pulmonary capillaritis [140]. Neuropathies occur in 60–70 % of patients with PAN [38]. The incidence of neuropathy in MPA is less well defined but appears to occur in ~50 % of patients [37, 141–145]. For CSS, neuropathy develops in 2/3 of patients [142, 144, 146–152]. In GPA, neuropathies are less common than in PAN, MPA, and CSS, occurring in 15–20 % of patients [141, 142, 144, 153–157], but cranial neuropathies are more common and develop in about 15 % [144, 145, 153]. HSP is only rarely associated with neuropathy.

Predominant Large-Vessel Primary Systemic Vasculitides

GCA is a granulomatous vasculitis involving large- and medium-sized arteries, especially branches of the aortic arch and extracranial carotid arteries (Table 36.5) [158, 159]. Typical symptoms are headache, weight loss, fever, jaw claudication, and polymyalgia rheumatica (PMR), a synovitis that produces pain and stiffness in the neck, shoulders, and proximal extremities. Almost 90 % have vestibular dysfunction and 60 % report hearing loss [160]. There is a 15–20 % risk of permanent visual loss from acute ischemic optic neuropathy. Symptoms of large-vessel disease (claudication and ischemic necrosis/ulceration) affect the upper limbs in 6–8 % of patients and lower limbs in 2–7 % [161–163]. ESR and CRP are almost always elevated [164–167]. Superficial temporal artery biopsy showing granulomatous inflammation, infiltration of macrophages and T cells, and disruption of the internal elastic lamina remains the gold standard for diagnosis. In a large, population-based series of 166 GCA patients, focal/multifocal neuropathies suspicious for vasculitis were identified in 6 % of patients [168]. Over 100 cases of GCA-related, corticosteroid (CS)-responsive neuropathy have been described, to include diffuse polyneuropathies in ~40 %, focal or multifocal neuropathies (most commonly involving the distal median nerve) in ~40 %, and C5/6 radiculopathies or upper trunk plexopathies in ~20 % [169–175].

Secondary Systemic Vasculitides Associated with Neuropathy

The secondary systemic vasculitides occur in the context of an underlying systemic disease predisposing to autoimmune phenomena or a specific etiologic trigger, such as an infection, drug, or malignancy. In addition to the autoimmune CTDs (see below), systemic diseases sometimes accompanied by vasculitic neuropathies include mixed cryoglobulinemia (see Table 36.5), infections, sarcoidosis, inflammatory bowel diseases, and cancers.

Localized Vasculitides

Nonsystemic Vasculitic Neuropathy

Many patients with vasculitic neuropathy exhibit no systemic involvement despite long-term follow-up, i.e., NSVN [36]. Although initially considered rare, NSVN is the most commonly reported vasculitic neuropathy [36, 48, 54, 55, 176–178]. A Peripheral Nerve Society guideline group derived consensus diagnostic criteria for NSVN [41]. Patients are first required to have pathologically definite or clinicopathologically probable vasculitic neuropathy. The diagnosis is excluded by such systemic features as clinical evidence of other organ involvement, angiogram-revealed visceral aneurysm, ANCAs, ESR ≥100 mm/h, cryoglobulins, pathologic evidence of vasculitis in non-neuromuscular tissues, infection underlying the vasculitis, or medical condition/drug predisposing to vasculitis. Constitutional symptoms, diabetes mellitus, and muscle vasculitis are still compatible with NSVN.

NSVN Variants/Subtypes

Several syndromes described by other names represent variants of NSVN. The first is vasculitis restricted to nerves and skin [179]. The best characterized entity is cutaneous PAN, a disorder that affects small- to medium-sized arteries in the dermis and panniculus [180–184]. The disease is mediated by immune complex deposition with complement activation via the classical pathway. The salient skin lesions are recurrent, painful nodules in the lower legs that often ulcerate; other manifestations include livedo racemosa, gangrene, urticaria, and bullae. The disease is characterized by multiple episodes of reactivation and resolution. Constitutional symptoms are common. Approximately 45 % of patients develop a multifocal or distal symmetric neuropathy in the lower limbs [46, 183, 185, 186].

A second variant is diabetic radiculoplexus neuropathy (DRPN), a distinct syndrome that occurs in 1 % of diabetics, especially older men with type 2 diabetes [187–195]. Most patients first develop pain in their hip/thigh, with weakness

Table 36.5 Clinical and pathologic features of primary vasculitides associated with neuropathy

Disorder	Histopathology	Vessels affected	Other clinically involved organs (%)	Laboratory studies (%)	PNS, CNS changes
Classic polyarteritis nodosa (post CHCC)	Necrotizing vasculitis; mixed infiltrate	Small and medium arteries	Skin 55–60 Joints ~50 Kidneys 40–50 GI ~30 Testes 2–29 Heart 10–15 ENT – rare Lungs – rare	↑ESR ~85 ↑WBC ~70 ↓Hgb ~60 ↑Platelets ~60 RF ~30 Hep B 20–30 ↓Comp ~25 ANA ~15 Hep C 5–10 ANCA <10 Angio 70 (aneurysm)	PNS 65–70 CNS ~5
Microscopic polyangiitis	Necrotizing vasculitis; mixed infiltrate[a]	Arterioles, capillaries, venules, veins > small and medium arteries	GN 75–90 Joints 40–60 Skin 30–60 Lungs 35–50 GI 30–40 ENT 20–30 Heart 10–20 Testes – rare	↑ESR >90 ANCA 75–85 (MPO > PR3) RF 25–50 ANA 20–30 ↓comp – rare Hep B/C (–) Angio – rare	PNS 50 CNS 10–15
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)	Necrotizing vasculitis; eosinophils; granulomas[a]	Small and medium arteries, arterioles, capillaries, venules, veins	Lungs 100 (asthma) 40–75 (infiltrates) ENT (sinusitis, rhinitis) 60–80 Skin 50–70 GI 35–50 Joints 30–50 Heart 30–50 (60 by MRI) GN 15–30	↑Eos 100 ↑ESR ~85 ↑IgE ~75 ANCA 40 (MPO > PR3) RF 40–50 ANA ~10 ↓comp – rare Hep B/C (–) Angio + 30	PNS 65–70 CNS 10–15
Granulomatosis with polyangiitis (Wegener's)	Necrotizing vasculitis; palisading; granulomas; collagen necrosis[a]	Small and medium arteries, arterioles, capillaries, venules, veins	ENT 90–95 Lungs 65–85 GN 60–75 Eyes 50–60 Skin 25–50 Joints 65–75 Heart 5–20 GI 5–10	ANCA 80–90 (PR3 > MPO) ↑ESR ~85 ↓Hgb ~75 ↑ Platelets 55 RF 50–60 ↑WBC ~35 ANA ~25	PNS 15–20 CNS 5–10 CrN 15

(continued)

Table 36.5 (continued)

Disorder	Histopathology	Vessels affected	Other clinically involved organs (%)	Laboratory studies (%)	PNS, CNS changes
IgA vasculitis (Henoch-Schönlein purpura)	LCV in skin; IgA vascular deposits	Arterioles, capillaries, venules	Skin 100 Joints 65–70 GI ~60 GN ~40 children ~70 adults Testes ~15 Lungs – rare	↑ESR 50–60 ↑IgA ~50 ↑WBC ~50 ↑ASO 20–50 Cryos 20–25 ↓Comp 10–20 ↓Hgb 5–15 RF ~5 ANA ~5 ANCA <5	PNS – rare CNS – rare
Cryoglobulinemic vasculitis	Necrotizing vasculitis; occlusive microangiopathy; LCV in skin	Small arteries, arterioles, capillaries, venules	Skin ~95 Joints 70–90 GN ~30 Salivary glands (sicca) ~30 Raynaud's 25–50 GI (pain) 10–20	Hep C 80–90 ↓Comp 80–90 RF ~70–80 ↑ESR ~70 ↓Hgb ~70 ANA ~55 Hep B ~5 ANCA <5 Angio – infreq	PNS ~60 CNS – rare
Giant cell arteritis	Necrotizing vasculitis; granulomas and giant cells ~50 %	Medium-large arteries	PMR ~50 Liver ~30 (abnormal LFTs) Subclavian-axillary-brachial 6–8 Aorta 15–20 Superficial femoral-popliteal 2–7 GN ~10	↑CRP 98–100 ↑ESR 85–100 ↓Hgb 55–60 ↑WBC 20–30 ANCA – rare RF (–) ANA (–) Angio – infreq	Otologic 60–90 Optic nerve 15–20 PNS ~5 CNS ~5
Nonsystemic vasculitic neuropathy	Necrotizing vasculitis: epineurial >> endoneurial	Small arteries, arterioles	Muscle 15	↑ESR ~50 Anemia ~25 ANA ~25 ↑WBC ~15 RF ~10 ↓Comp ~5	PNS 100 CNS 0

ANCAs antineutrophil cytoplasmic autoantibodies, *angio* abdominal angiographically demonstrated microaneurysms, *CHCC* Chapel Hill Consensus Conference nomenclature, *CNS* central nervous system, *comp* circulating complement factors, *CrN* cranial nerve involvement, *cryos* cryoglobulins, *ENT* upper respiratory tract involvement, *GN* glomerulonephritis, *Hep B* hepatitis B surface antigenemia, *Hep C* hepatitis C antibodies or RNA, *Hgb* hemoglobin, *LCV* leukocytoclastic vasculitis, *LFTs* liver function tests, *PMR* polymyalgia rheumatica, *PNS* peripheral nervous system, *RF* rheumatoid factor, *WBC* white blood cell count

[a]All may be associated with leukocytoclastic vasculitis in skin

emerging days to weeks later. Proximal muscles are more commonly affected than distal muscles, but weakness routinely spreads to other segments of the same limb, involving more than nerve. Pain and weakness usually begin unilaterally and spread contralaterally in 80–90 %. Most patients lose weight. Upper limb involvement occurs in ~10 %. Laboratory workup reveals mildly elevated ESR in ~20 % and elevated CSF protein in 85 %. Symptoms typically worsen over several weeks to months (median 4 months) and then slowly improve over many months (median 15 months), but 10–15 % of patients relapse. Nerve biopsies reveal T cell-predominant perivascular/vascular inflammation involving epineurial and, to a lesser extent, endoneurial microvessels, accompanied by changes suggestive of vasculitis, including asymmetric fiber loss, neovascularization, hemosiderin deposition, focal perineural thickening, injury neuroma, and complement deposition in vessel walls [189, 191–195]. *Necrotizing* vasculitis is rare. These findings suggest that DRPN is a PNS microvasculitis, characterized by proximal lower limb involvement and self-limited course. A painless form of DRPN has also been described with slower progression, increased symmetry, greater upper limb involvement (75 %), and distal (rather than proximal) predominance (55 %) [196]. An analogous syndrome is "non-diabetic lumbosacral radiculoplexus neuropathy," an entity considered a subtype of NSVN [197, 198].

Wartenberg's migrant sensory neuritis features episodic, migratory attacks of purely sensory symptoms in the distribution of individual cutaneous nerves [199–204]. Transient stabbing, tingling, or burning pain is followed by persistent sensory loss. Limb nerves are routinely affected, but in 30–40 % of patients, the trigeminal or truncal nerves are also involved [204]. Symptoms typically remit after 6 weeks to several months, but infrequently, numbness persists indefinitely. The clinical course is benign but can extend over years. Cutaneous nerve biopsy findings suggest that some patients with this phenotype have a benign, purely sensory form of NSVN [200, 201, 203, 205].

Clinical Features of Vasculitic Neuropathy (NSVN and SVN)

The clinical presentation of peripheral nerve vasculitis depends on the distribution of affected neural vessels, severity of the vasculitic process, and spectrum of extra-neurologic involvement [36, 47–55, 126–128, 142, 145, 198, 206–218]. Multiorgan involvement is indicative of a systemic vasculitis or underlying CTD (Table 36.5). The most commonly affected organs with systemic vasculitides involving the PNS are the skin, mucous membranes, and ENT tissues [145]. Patients with NSVN, by definition, have no extra-PNS involvement. Constitutional symptoms such as fever, weight loss, fatigue, myalgias, and arthralgias occur in 70 % of patients with a SVN and 30–40 % of patients with NSVN.

Vasculitic neuropathy has a characteristic clinical picture whether occurring alone or as part of a systemic vasculitis. Symptoms typically evolve over weeks to months, with delay from symptom onset to diagnosis ranging from 2 to 8 months in most series [49, 52, 54, 55, 176, 177, 198, 210, 215]. Some patients present fulminantly, mimicking GBS [219], while others follow an indolent course and are not diagnosed for several years [55, 177, 220]. Most patients experience at least one acute attack, but one-third have a slowly progressive course [36, 55, 177]. The most distinctive presentation is a *multifocal neuropathy* or *multiple mononeuropathy*, resulting from ischemic insults to individual nerves. Patients develop pain, weakness, and sensory loss in a stepwise fashion in the distribution of individual nerves. In other patients, individual mononeuropathies overlap, creating an *asymmetric polyneuropathy*. The distribution most difficult to recognize as vasculitic is a *distal*, *symmetric polyneuropathy*, a statistically improbable outcome for a pathologically multifocal process. The reported relative prevalence of these patterns is 45 % multifocal neuropathy, 35 % asymmetric polyneuropathy, and 20 % distal symmetric polyneuropathy [41].

In practice, the most commonly affected nerves are a diffuse mixture of lower limb nerves derived from the lumbosacral plexus [177]. The most frequently affected individual nerve is the common peroneal or peroneal division of the distal sciatic nerve [36, 40, 55, 177]. In the arms, the ulnar nerve is most commonly involved. Neurologic deficits are almost always distally accentuated, but proximal involvement is not uncommon. Cranial neuropathies occur in 10 % of patients [54, 55, 177].

Vasculitis generally affects mixed or purely sensory nerves rather than anterior horn cells or sensory/autonomic ganglia [139]. Most patients develop mixed sensory and motor deficits, but 10 % have predominantly sensory findings [36, 49, 52, 54, 55, 145, 177, 207, 214, 216, 218]. Sensory dysfunction usually involves all modalities, but exceptional patients have small-fiber predominance [55]. Pure motor or autonomic presentations are rare. Eighty percent of vasculitic neuropathies are painful [41].

Differential Diagnosis of Multifocal /Asymmetric Neuropathy

Although vasculitic neuropathy is not common, the differential diagnosis includes other multifocal neuropathies (Table 36.6) that are generally even more uncommon, such as multifocal, acquired, demyelinating sensory and motor (MADSAM) neuropathy (Lewis-Sumner syndrome); DRPN; neuralgic amyotrophy; sarcoidosis; Lyme disease; leprosy; hereditary neuropathy with liability to pressure palsies

Table 36.6 Differential diagnosis of multifocal/asymmetric neuropathy

A. Ischemic neuropathies
1. Peripheral nerve vasculitis (see Table 36.3)
2. Livedoid vasculopathy
3. Sickle cell anemia
4. Cholesterol emboli syndrome
5. Atrial myxoma
6. Diffuse intravascular coagulation
7. Essential thrombocythemia
8. Antiphospholipid antibody syndrome

B. Inflammatory/immune-mediated neuropathies
1. Sarcoidosis[a]
2. Multifocal acquired demyelinating sensory and motor neuropathy (Lewis-Sumner syndrome)
3. Multifocal motor neuropathy
   (a) Idiopathic
   (b) Associated with tumor necrosis factor-alpha inhibitors
   (c) Paraneoplastic (lymphomas)
4. Multifocal acquired motor axonopathy
5. Multifocal variants of Guillain-Barre syndrome
6. Idiopathic brachial or lumbosacral plexopathy (neuralgic amyotrophy)[a]
7. Neuropathy with eosinophilia[a]
   (a) Idiopathic hypereosinophilic syndrome
   (b) Eosinophilic fasciitis
   (c) Eosinophilia-myalgia syndrome
   (d) Kimura disease
8. Neuropathy with gastrointestinal conditions (Crohn disease, ulcerative colitis, celiac sprue)[a]
9. Chronic graft-versus-host disease
10. Wartenberg's migrant sensory neuritis (inflammatory cases)[a]
11. Disialosyl antibody-related neuropathy (e.g., CANOMAD)
12. Sensory perineuritis
13. Hashimoto thyroiditis
14. Toxic oil syndrome
15. Multiple sclerosis with multifocal demyelinating neuropathy

C. Infectious/toxic neuropathies[a]
1. Leprosy
2. Lyme disease
3. Viral (human immunodeficiency virus, human T cell lymphotropic virus type I, varicella zoster virus, cytomegalovirus, Epstein-Barr virus, parvovirus B19, West Nile virus, measles)
4. Diffuse infiltrative lymphocytosis syndrome
5. Infective endocarditis
6. Tuberculosis
7. Sporotrichosis
8. Meningococcemia
9. Other (Group A β-hemolytic streptococcus, leptospirosis, hepatitis A, Mycoplasma pneumoniae, Salmonella typhi, Pseudomonas aeruginosa, trichinosis, ascaris, Plasmodium falciparum, scrub typhus, Coxiella burnetii, relapsing fever)

D. Drug-induced neuropathies[a]
1. Antibiotics (penicillin, sulfonamides, minocycline, vancomycin, macrolides)
2. Cromolyn
3. Thiouracil
4. Allopurinol
5. Amantadine
6. Interferon-α
7. Naproxen
8. Montelukast and other leukotriene receptor antagonists
9. Tumor necrosis factor-alpha inhibitors
10. Valacyclovir
11. Leflunomide
12. Gasoline sniffing (? n-hexane)
13. Drugs of abuse (amphetamines, cocaine, heroin)
14. Statins (?)

E. Genetic neuropathies
1. Hereditary neuropathy with liability to pressure palsies
2. Hereditary neuralgic amyotrophy
3. Porphyria
4. Familial amyloid polyneuropathy (transthyretin)
5. Tangier disease
6. Krabbe disease
7. Mitochondrial disorders

F. Mechanical neuropathies
1. Multiple peripheral nerve injuries
2. Multifocal entrapments not related to a genetic disorder
3. Postoperative neuropathies
4. Compartment syndromes
5. Intermittent pneumatic compression (bilateral common peroneal)
6. Gluteal lipoaugmentation (bilateral sciatic)
7. Burns
8. Wartenberg's migrant sensory neuritis (mechanical cases)
9. Heterotopic ossification

G. Neuropathies related to neoplastic diseases
1. Direct infiltration of nerves by tumor
   (a) Lymphoma (neurolymphomatosis)
   (b) Leukemia
   (c) Multiple myeloma
   (d) Intraneural metastases
2. Paraneoplastic (vasculitic and non-vasculitic)[a]
3. Multifocal peripheral nerve mass lesions with external/internal compression (e.g., neurofibroma, Schwannoma, intraneural perineurioma)
4. Neurofibromatosis type 2 (Schwann cell proliferation/dysfunction)
5. Lymphomatoid granulomatosis[a]
6. Intravascular lymphoma
7. Neoplastic meningitis
8. Primary systemic AL amyloidosis
9. Non-amyloid light chain or IgM deposition
   (a) Waldenström's macroglobulinemia
   (b) IgM monoclonal gammopathy of undetermined significance

H. Intraneural hemorrhage
1. Idiopathic thrombocytopenic purpura
2. Acute leukemia
3. Hemophilia
4. Vasculitic neuropathy

[a]Conditions occasionally or routinely associated with vasculitis

Table 36.7 Recommendations for laboratory investigation of suspected vasculitic neuropathy [41]

A. Routinely indicated studies: Complete blood count, eosinophil count, chemistry panel, urinalysis, glycosylated hemoglobin and/or 2-h glucose tolerance test, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibodies, rheumatoid factor, antineutrophil cytoplasmic antibodies, serum protein immunofixation electrophoresis, complement (C3, C4, total), cryoglobulins, hepatitis B surface antigen, hepatitis C antibodies, and chest X-ray
B. Occasionally indicated studies: SSA/SSB antibodies, other antibodies against extractable nuclear antigens, double-stranded DNA antibodies, cyclic citrullinated peptide antibodies, angiotensin-converting enzyme, lysozyme, vascular endothelial growth factor, beta2-microglobulin, human immunodeficiency virus antibodies, Lyme antibodies, hepatitis C RNA, cytomegalovirus antigen or DNA, paraneoplastic autoantibodies, lactate dehydrogenase, high-density lipoprotein cholesterol, porphyria screen, DNA for PMP22 deletion associated with hereditary neuropathy with liability to pressure palsies, DNA for transthyretin gene, chest CT, gallium-67 scan, visceral angiography, salivary gland biopsy, lumbar puncture, and other body imaging for malignancy

(HNPP); amyloidosis; paraneoplastic or pSS-related sensory neuronopathy; neoplastic meningitis or neural infiltration; and porphyria. Electrodiagnostic testing permits differentiation of the demyelinating features of Lewis-Sumner syndrome, HNPP, and leprosy from the axonal pattern of vasculitic neuropathy. Laboratory studies and nerve biopsy are also often required for accurate diagnosis of these patients.

For patients with pathologic evidence of vasculitic neuropathy, the differential diagnosis includes all conditions associated with PNS vasculitis, including the primary systemic vasculitides, CTDs, hepatitis B, HIV infection, hepatitis C, cryoglobulinemia, sarcoidosis, cancers, and–rarely–other infections or drugs. For the primary systemic vasculitides, consideration of the non-neurologic features and laboratory findings usually permits an accurate diagnosis.

Electrodiagnostic and Laboratory Features of NSVN and SVN

Laboratory evaluation of a patient with suspected vasculitis should assess for systemic organ involvement, markers of inflammation, autoantibodies, and specific causes of multifocal or vasculitic neuropathy. In the guideline on NSVN, consensus was reached on laboratory tests to be considered in a patient with an unexplained neuropathy suspicious for vasculitis (Table 36.7) [41]. Laboratory studies predictive of biopsy-confirmed vasculitic neuropathy include elevated ESR, CRP, RF, β2-microglobulin, MPO-ANCAs, and plasma VEGF [41].

In NSVN, an elevated ESR is found in 50 % of patients; other laboratory markers of inflammation or immune activation (e.g., ANA, RF, anemia, leukocytosis, and hypocomplementemia) are abnormal in less than 25 % of patients [46]. ANCAs occur in only 3 % of patients [55, 221]. For patients with neuropathies caused by a *systemic* vasculitis, laboratory abnormalities are more common: elevated ESR in 85 %, leukocytosis in 75 %, anemia in 45–50 %, RFs in 45 %, decreased complement in 30 %, and ANAs in 30 % [47, 49, 50, 52, 54, 55, 206, 208–214, 216, 218]. Spinal fluid examination is not helpful because CSF pleocytosis is uncommon (~5 %) and mild-to-moderate CSF protein elevation occurs in 30 % of patients with both NSVN and SVN [36, 49, 50, 52, 54, 55, 177, 208, 211, 212]. The best laboratory predictors of an underlying systemic vasculitis are ANCAs and ESR ≥100 mm/h [41].

Electrodiagnostic studies are useful for documenting non-length-dependent features of the neuropathy, excluding a primary demyelinating process, and identifying which nerve to biopsy [222–225]. Findings reflect multifocal axonal damage to motor and sensory fibers. Nerve conduction studies reveal low-amplitude or non-reproducible sensory nerve action potentials (SNAPs) and compound muscle action potentials (CMAPs), while conduction velocities are normal or mildly reduced and distal latencies normal or mildly prolonged. H reflexes and F waves are often impersistent or unevocable with normal or mildly prolonged latencies. "Pseudo" or "axon non-continuity" conduction blocks occur in 10–25 % of patients, resulting from acute Wallerian-like degeneration [36, 226]. If nerve conductions are repeated in 2 weeks, pseudo-conduction blocks disappear due to degeneration of the distal stumps [227, 228]. True demyelinating partial motor conduction blocks are rarely seen [229, 230], possibly caused by due to axonal swelling and attenuation with secondary segmental demyelination, structural changes at the nodes of Ranvier, reperfusion-induced segmental demyelination, and inactivation of nodal voltage-gated sodium channels [231–234].

Needle EMG examination reveals fibrillation potentials in ~70 % of patients and decreased recruitment of motor unit potentials (MUPs) in clinically weak muscles [41]. Long-duration MUPs are found in 20–50 % of patients (those with long-standing disease or preexisting conditions) [41, 226]. Short-duration MUPs suggestive of concomitant myopathy occur in 10–15 % of patients with systemic disease [47, 55, 211, 212] but not in those with NSVN [55, 212, 226]. Sufficiently extensive electrodiagnostic studies usually show evidence of a multifocal or asymmetric neuropathy.

Pathologic Features of VN

Since axons are more vulnerable to ischemia than Schwann cells, perineurial cells, and fibroblasts, nerve biopsies in SVN and NSVN usually reveal changes indicative of a

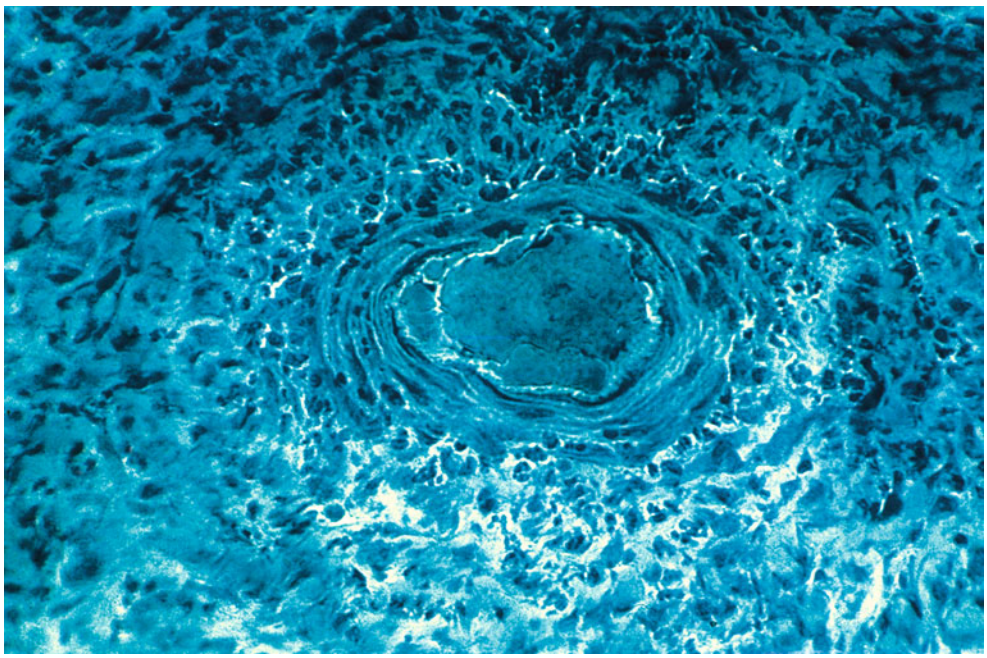

Fig. 36.2 This superficial peroneal nerve biopsy in a patient with nonsystemic vasculitic neuropathy shows an epineurial arteriole infiltrated and surrounded by an inflammatory infiltrate. The vessel is occluded by an acute thrombus (Modified Gomori trichrome)

primary axonal process [49, 51, 53, 54, 176, 235, 236]. Affected fascicles show decreased myelinated nerve fiber density, abundant Wallerian-like degeneration, regenerating axonal clusters, and inconspicuous demyelinating/remyelinating changes. In fulminant vasculitis, all cellular elements are lost. Axon loss tends to be centrofascicular in proximal watershed areas but becomes multifocal in distal parts of the nerve due to intermingling of descending fibers [137–139, 235]. Cellular infiltrates in vasculitic neuropathy are perivascular and predominate in the epineurium [36, 54, 124, 135]. They are composed primarily of T cells and macrophages. B cells are uncommon and NK cells and polymorphonuclear leukocytes rare [54, 121, 122]. Peripheral nerve vasculitis has a predilection for epineurial vessels with diameters of 50–300 μm [36, 48, 49, 54, 235, 237, 238]. NSVN tends to involve smaller vessels (<100 μm) within this range but is not limited to microvessels [54, 178]. Direct IF (DIF) shows deposits of IgM, fibrinogen, C3, and/or C5b9 in epineurial vessel walls in 55–80 % of patients [49, 121, 136, 176].

Diagnostic Criteria: Pathologically Definite and Pathologically Probable

The pathologic diagnosis of *definite active* vasculitic neuropathy requires inflammation within the vessel wall *and* signs of vascular damage such as fibrinoid necrosis, endothelial disruption, fragmentation or loss of the internal elastic lamina, degeneration or loss of smooth muscle cells in the media, hemorrhage, or acute thrombosis [41, 235] (Fig. 36.2). Perivascular or mural inflammation alone, without associated structural damage, is nonspecific. A diagnosis of *definite chronic* vasculitis requires vascular inflammation and signs of healing/repair, such as intimal hyperplasia, fibrosis of the media or adventitia, or chronic thrombosis with recanalization [41, 224] (Fig. 36.1).

Many investigators have attempted to increase pathologic sensitivity by defining alterations "suggestive" or "suspicious" for "probable" vasculitic neuropathy in specimens lacking definite vasculitis [52, 55, 176, 194, 224, 235, 238]. Most of these criteria require perivascular or vascular inflammation and one or more changes predictive of definite vasculitis, e.g., active Wallerian-like degeneration [177], asymmetric nerve fiber loss [177, 239, 240], hemosiderin deposits [239–241] (Fig. 36.3), myofiber necrosis/regeneration in peroneus brevis muscle biopsy [177], and DIF for vascular immune deposits of IgM, complement, or fibrinogen [136, 242]. Endoneurial hemorrhage, epineurial neovascularization, focal perineurial degeneration/thickening, and injury neuroma might also be supportive features, but their specificity for vasculitis is not established [194, 238].

Nerve Biopsy: Indications, Sensitivity, and Specificity

Because the differential diagnosis of a multifocal/asymmetric neuropathy is broad (Table 36.6), most patients with suspected vasculitic neuropathy should undergo nerve biopsy, usually of the sural or superficial peroneal nerve (SPN). SPN biopsy is combined with a peroneus brevis muscle (PBM) biopsy through a single incision in the lower leg [48, 52]. For patients in whom the sural nerve and SPN are not clinically involved, the superficial radial, lateral

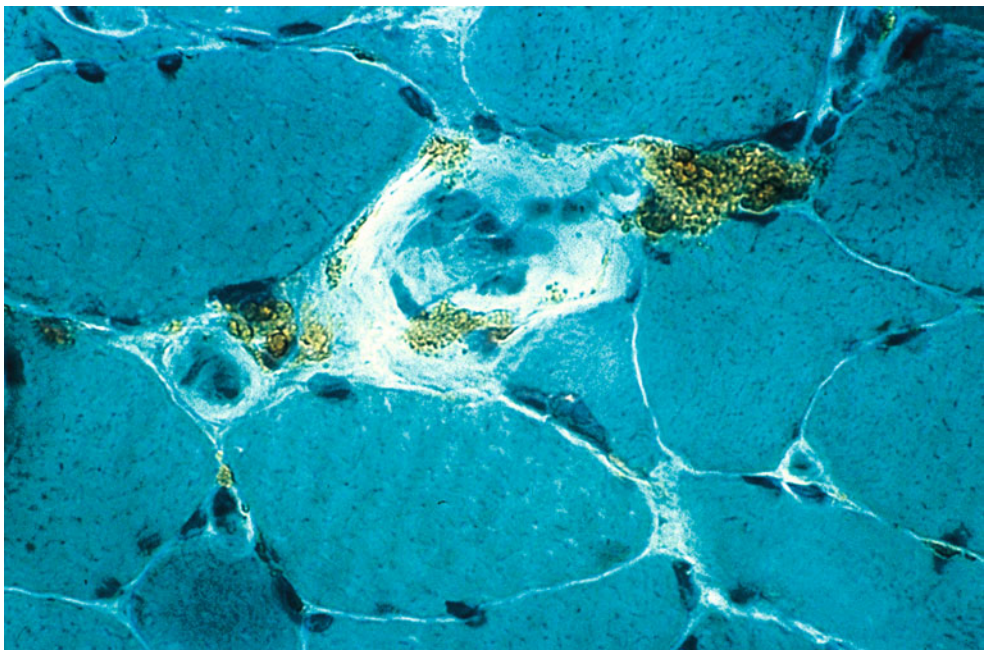

Fig. 36.3 Peroneus brevis muscle biopsy from a patient with nonsystemic vasculitic neuropathy. Hemosiderin deposits are seen surrounding a single endomysial vessel. This finding is suggestive but not diagnostic of vasculitis (Modified Gomori trichrome)

antebrachial cutaneous, intermediate femoral cutaneous, or saphenous nerves are alternatives. Although nerve is more commonly diagnostic than muscle in cases of suspected vasculitic neuropathy, concomitant muscle biopsy increases the yield by 15 % [243].

Not all patients with a cryptogenic neuropathy require nerve biopsy for vasculitis. In patients with an unexplained distal symmetric polyneuropathy, the yield of nerve biopsy for vasculitis is <5 % [214, 244, 245]. This yield is enhanced if the patient has an asymmetric/multifocal pattern [124, 225, 244, 246], pain [240], acute-onset [246], progressive clinical course [240], ANCAs [247], elevated ESR/CRP [240, 246], elevated beta2-microglobulin [246], or increased VEGF [248]. In the absence of an independent gold standard, the true sensitivity of nerve biopsy for vasculitic neuropathy is unclear. However, in patients who lack nerve biopsy evidence of definite vasculitis, clinically probable vasculitic neuropathy can be diagnosed by clinical and pathologic criteria [41]. Assuming these clinically probable cases truly have vasculitic neuropathy, the estimated sensitivity for definite vasculitis is 55–60 % with sural nerve [36, 53, 55, 176, 177, 224] and 60–65 % with SPN/PBM [41, 52, 214, 225] or sural nerve/gastrocnemius muscle biopsy [217].

Treatment

Although many randomized controlled treatment trials (RCTs) have been conducted in the vasculitides over the past 20 years, there is still little data relevant to treatment of any type of vasculitic *neuropathy*. For all vasculitides, treatment begins with a search for precipitating factors, such as drugs, infections, or neoplasms. If present, the triggering condition should be eliminated or treated. Examples of this approach include the use of pegylated INF-α or oral antiretroviral drugs (e.g., lamivudine, adefovir, entecavir, tenofovir, telbivudine) in patients with chronic hepatitis B-associated PAN [249], pegylated INF-α plus ribavirin in hepatitis C-associated vasculitic neuropathy [250], antiretroviral therapy in HIV-related vasculitis [251], and ceftriaxone in Lyme disease-induced vasculitic neuropathy [252], sometimes accompanied by plasma exchange. However, no inciting or perpetuating antigen can be identified in most vasculitides (including NSVN), necessitating immunosuppressive therapy (Table 36.8).

Immunosuppressive Therapy of Primary Small- to Medium-Vessel Vasculitis

The traditional immunosuppressive regimen for the primary small- and medium-vessel systemic vasculitides – PAN, MPA, CSS, and GPA – involves a combination of CS and cyclophosphamide (CYC), a regimen that has never been validated in a RCT [253]. Prednisone is started at 1 mg/kg/day for 2–4 weeks, tapered to 60 mg every other day over 1–2 months, and then more gradually tapered over 12 months. The CYC dose is 2 mg/kg/day continued for 1 year after complete remission and then tapered by 25 mg every 2–3 months. While effective in controlling most vasculitides, long-term follow-up studies have revealed standard therapy-treated GPA and NSVN to be chronic, relapsing diseases with a high incidence of drug-related morbidity [177, 254, 255]. For example, in one cohort of 158 GPA patients,

Table 36.8 Immunosuppressive medications used in treating vasculitis

Agent	Route	Typical dose	Side effects	Monitor
Prednisone	Oral	1.0 mg/kg/day	Infections, osteoporosis, hyperglycemia, hypertension, cataracts, glaucoma, mood changes, insomnia, confusion, aseptic joint necrosis, weight gain, edema, fat redistribution, myopathy, delayed wound healing, gastric ulcers, hypokalemia, skin atrophy	Glucose, electrolytes, blood pressure, eyes, bone density
Methotrexate	Oral or IV	15–25 mg/week	Hepatotoxicity, leukopenia, infections, alopecia, mucositis, nausea, abdominal pain, pneumonitis, nodulosis, neoplasia	CBC, LFTs, creatinine
Cyclophosphamide	Oral IV	1.5–2.0 mg/kg/day 600–700 mg/m^2 or 15/mg/kg every 2–3 weeks	Leukopenia, infections, hemorrhagic cystitis, pneumonitis, alopecia, neoplasia, nausea, vomiting, diarrhea, SIADH, infertility, rash	CBC, UA
Azathioprine	Oral	1.5–2.5 mg/kg/day	Leukopenia, infections, hepatotoxicity, nausea, diarrhea, drug fever, pancreatitis, mucositis, alopecia, neoplasia	CBC, LFTs
IVIg	IV	2.0 g/kg	Fevers, chills, headache, aseptic meningitis, myalgias, back pain, chest pain, nausea, acute renal failure, rash, anaphylaxis with IgA deficiency, leukopenia, hemolytic anemia, thromboembolic events, blood-borne infections	Blood pressure, pulse, CBC, creatinine
Mycophenolate mofetil	Oral	2–3 g daily	Leukopenia, infections, diarrhea, nausea, abdominal pain, GI hemorrhage, PML	CBC
Rituximab	IV	375 mg/m^2/week ×4 weeks	Immune hypersensitivity reaction, infections, leukopenia, lymphopenia, anemia, rash, nausea, diarrhea, abdominal pain, edema, headache, arthralgia, myalgia, dysrhythmia, PML	CBC, blood pressure, pulse, cardiac rhythm

CBC complete blood count, *GI* gastrointestinal, *IV* intravenous, *IVIg* intravenous immunoglobulin, *LFTs* liver function tests, *PML* progressive multifocal leukoencephalopathy, *UA* urinalysis

treatment-associated side effects included ovarian failure (57 %), serious infections (46 %), hemorrhagic cystitis (43 %), cataracts (21 %), fractures (11 %), diabetes mellitus (8 %), avascular hip necrosis (3 %), bladder cancer (3 %), and myelodysplasia (2 %) [254]. Compared to the general population, there was a 2.4-fold increase in malignancies, with a 33-fold increase in bladder cancers and 11-fold increase in lymphomas. Other studies have confirmed an increased risk of bladder, skin, and hematologic malignancies in GPA patients treated with CYC [256, 257]. These findings have provided a strong impetus to (1) reduce patient exposure to CYC and (2) more rapidly taper CS.

Over the past 20 years, treatment has evolved to a more individualized approach tailored to the patient's age, extent and severity of disease, and prognostic factors. Current strategies minimize exposure to CYC by use of non-CYC-based maintenance regimens or by replacement of CYC in the induction phase for patients with less severe disease. As outlined in consensus guidelines, patients with localized or mild, generalized ("early systemic") disease characterized by normal or mildly abnormal renal function and no other organ-threatening manifestations are treated with high-dose CS and methotrexate (MTX) 15–25 mg/week [258, 259]. The guidelines recommend starting prednisone at 1.0 mg/kg/day for 1 month and tapering to 10 mg/day by 6 months. It is then stopped or continued at low doses (5.0–7.5 mg daily) to reduce relapses [260]. MTX is discontinued after 18–24 months. Patients with moderate-to-severe, generalized disease (including progressive neuropathies) are treated with CYC and prednisone. CYC can be administered orally at 2.0 mg/kg/day or in the form of IV pulses, e.g., 15 mg/kg or 0.60–0.70 g/m^2 every 2–3 weeks [261, 262]. The dose needs to be reduced in the elderly and those with chronic kidney disease. CYC is stopped once the patient remits, generally in 3–6 months, replaced by an agent to maintain remission, usually azathioprine (AZA) 1.5–2.0 mg/kg/day or MTX 20–25 mg/week. Leflunomide 20 mg/day is a second-line option. Mycophenolate mofetil (MMF) has also been used for maintenance of remission, but in one open-label RCT, it was inferior to AZA in preventing relapses in ANCA-associated vasculitis [263]. Remission maintenance therapy is continued for at least 18–24 months. In patients with severe renal disease (creatinine >5.6 mg/dl) or alveolar hemorrhage, CS/CYC is augmented with plasma exchanges [264]. Based on the results of two recent RCTs, rituximab is now a first-line alternative to CYC for induction of remission in newly diagnosed MPA or GPA [265–268].

Immunosuppressive Treatment of SVN and NSVN

There are no RCTs of treatment for vasculitic neuropathy associated with any type of vasculitis. In the absence of evidence, vasculitic neuropathies occurring in the primary small- to medium-vessel systemic vasculitides are generally managed in the same manner as the underlying systemic

vasculitis. While none of the controlled trials in these vasculitides had *primary* neuropathic endpoints, the implication from published studies is that vasculitic neuropathies generally improve hand in hand with the non-neurologic manifestations [41, 269].

Treatment trials in patients with primary small- to medium-vessel systemic vasculitides cannot be directly extrapolated to NSVN. Several studies have suggested that NSVN is clinically and pathologically milder than a SVN, suggesting that less aggressive therapy may be indicated [54, 55, 238]. Although no RCTs of therapy in NSVN have been performed, two class III retrospective cohort surveys involving 73 patients have provided limited evidence, suggesting that combination therapy is more effective than CS monotherapy in inducing sustained remission and improving disability in NSVN [176, 177].

A Peripheral Nerve Society guideline on NSVN offers several consensus-driven good practice points on treatment of NSVN [41]. CS monotherapy is considered first line. Prednisone is started at 1.0 mg/kg/day, tapered to 10 mg/day at 6 months, and continued at low doses for another 6–18 months. Combination therapy is recommended for rapidly progressive NSVN and patients progressing on CS alone. First-line immunosuppressive options are CYC, MTX, or AZA, with CYC preferred for severe neuropathies. CYC is generally administrated in IV pulses (as above) to decrease the cumulative dose and side effects. MTX is started at 15 mg/week and titrated to 25 mg/week over 1–2 months. AZA dose is 2.0–2.5 mg/kg/day. Once remission is achieved, maintenance therapy for 18–24 months is recommended to reduce relapses. First-line options are AZA 1.0–2.0 mg/kg/day or MTX 20–25 mg/week. In patients refractory to the initial regimen, CYC should be used if not already done. In patients refractory to CYC, unproven treatment options based on extrapolation from RCTs in the small- to medium-vessel primary systemic vasculitides include IVIg, plasma exchange, and rituximab [264–266, 270].

Supportive Care

Effective management of vasculitic neuropathy also incorporates aggressive supportive care, including pain management, rehabilitation, counseling, and education. For most patients, pain control is a fundamental issue, mandating the use of tricyclic antidepressants, gabapentin, pregabalin, serotonin-norepinephrine reuptake inhibitors, carbamazepine, valproate, tramadol, topical lidocaine, topical capsaicin, and scheduled narcotics [271]. With rare exceptions, pain control alone is *not* an indication to continue high-dose CS. Physical therapy helps maintain strength and range of motion, prevent contractures, limit osteoporosis, and counteract CS myopathy. Occupational therapy helps to maximize function, especially for activities of daily living (ADLs), sometimes facilitated by appropriate bracing. Walking aids (e.g., cane, wheeled walker, or crutches) or a wheelchair may be required to maintain mobility. The value of psychological support cannot be overemphasized. Because of physical limitations, chronic pain, exposure to high doses of CS, prolonged recovery, and uncertain prognosis, patients with vasculitic neuropathy are at high risk for depression and other psychological reactions [272, 273]. The treating physician must maintain a high index of suspicion and be prepared to provide pharmacologic support or psychiatric referral for patients who become depressed.

Prognosis of SVN and NSVN

The prognosis of untreated vasculitic neuropathy associated with the primary systemic vasculitides is variable and unpredictable [206, 274, 275]. Similarly, the natural history of NSVN is unknown because nearly all reported patients have received immunosuppressive agents. However, based on rare reports of untreated patients and reported patients' clinical courses prior to treatment, NSVN may follow a monophasic course with complete or near-complete recovery, slowly progress for as many as 40 years, slowly progress for several years prior to stabilizing or subacutely worsening, progress in a fulminant fashion to quadriparesis or death in weeks to months, or spontaneously relapse and remit [41].

Treated NSVN appears to have a better prognosis than treated SVN. Five-year survival rates in two studies of NSVN were 85 and 87 %, contrasting with ~75 % in modern systemic vasculitis cohorts [48, 177, 276, 277]. NSVN has low risk for systemic dissemination, provided no symptoms, signs, or serologic features of a systemic vasculitis are identified, and immunosuppressive therapy is implemented. In the largest NSVN cohort, only 6 % of patients developed signs of vasculitic involvement in non-neuromuscular tissues during median follow-up of 63 months, and in these patients, spread was limited to the skin [177]. More common than systemic spread is the appearance of relapsed neuropathy symptoms following a sustained treatment response in one-third of patients [46]. Relapses tend to occur in patients whose therapy has been stopped or reduced to low doses of CS, suggesting the need for more extended maintenance therapy. In long-term survivors of NSVN, 60 % of patients have no or mild symptoms, ~20 % have mild-to-moderate impairment with independent ambulation, and ~20 % are dependent in some ADLs (e.g., requiring assistance with ambulation) or nonambulatory [176, 177]. This compares favorably to neurologic morbidity in surviving patients with SVN: 40 % no or mild symptoms, ~35 % mildly to moderately impaired, and ~25 % dependent in walking or ADLs [49, 52, 207, 216]. While most NSVN patients have mild or no neurologic deficits at end of follow-up, chronic pain ensues in 60 % [177].

Connective Tissue Diseases

Rheumatoid Arthritis

Definition/Epidemiology

RA is a chronic disorder characterized by inflammation of the synovium and secondary damage to articular cartilage and underlying bone in peripheral joints in a symmetric distribution [278, 279]. It is the most common CTD, affecting 0.2–1.1 % of adults [280]. Annual incidence ranges from 10 to 50 new cases per 100,000 and increases with age. Women are affected three times more commonly than men [278]. Most patients develop symptoms between the ages of 35 and 50 years.

Etiology/Pathogenesis

The cause of RA is unknown [278, 279, 281–284]. One hypothesis holds that the disease occurs in genetically susceptible individuals as an exaggerated immune response against an infectious agent, but no convincing etiologic link with any organism has been established [279, 281]. Smoking is the main environmental risk factor [279]. Alternatively, repeated inflammatory insults mediated through Toll-like receptors (TLRs) and other specialized receptors that recognize microbial products in a genetically susceptible individual might contribute to the breakdown of immune tolerance [281]. Genetic factors explain up to 60 % of disease susceptibility [285, 286]. Genome-wide association studies have identified more than 30 genetic loci associated with RA, most in genes encoding proteins implicated in regulation of the immune response [285, 287]. The so-called shared epitope in the third hypervariable region of the HLA-DRB1 gene is the major genetic risk factor. With aging, defects in homeostatic control of the T cell population may lead to the loss of tolerance to neoantigens, such as citrullinated peptides. Citrullination refers to the posttranslational conversion of arginine to citrulline [288, 289]. In RA, citrullination occurs in the inflamed synovium. The specifically citrullinated proteins vary but include many normal constituents, such as vimentin, fibrinogen, fibronectin, and collagen. Immunoglobulins targeting these proteins are then produced, the anti-cyclic citrullinated peptide (CCP) antibodies [283, 290].

The earliest pathologic changes in the synovium are microvascular injury and hyperplasia of synovial lining cells, followed by perivascular inflammatory cell infiltration and angiogenesis [281, 291]. The predominant infiltrating cells are CD4+ memory T lymphocytes, most of which differentiate into Th1 cells, but IL-17 is the chief T cell-derived cytokine in the synovium [292]. Polyclonal immunoglobulins, RFs, and anti-CCP antibodies are produced within the synovium, resulting in immune complex deposition and complement activation [281, 293]. Products of complement activation and chemokines attract neutrophils to the synovial fluid. Synoviocytes (fibroblast-like and macrophage-like), chondrocytes, osteoclasts, and mesenchymal stromal cells are then activated. Macrophages and fibroblast-like synoviocytes are the primary sources of pro-inflammatory cytokines, such as TNF-α [281, 294]. The synovial membrane enlarges to from a pannus that invades cartilage and bone, resulting in bone erosions and periarticular osteoporosis [295]. In RV, AECAs and deposition of immune complexes produced within the synovium and entering the circulation may participate in the pathogenic cascade [296, 297].

Clinical Presentation

RA presents with the insidious onset of pain, stiffness, and swelling in multiple joints over weeks to months, often accompanied by fatigue, myalgias, anorexia, and weight loss [2, 279, 298, 299]. Commonly affected joints are the wrists, hands, feet, knees, ankles, elbows, and shoulders. Joint involvement is classically symmetric. Morning stiffness lasting more than 1 h is a nearly constant feature. As the disorder progresses, a chronic erosive synovitis develops with compromise of joint space integrity and secondary joint deformities and contractures (Fig. 36.4). Extra-articular involvement occurs in up to 40 % of patients, especially those with advanced disease and high RF titers [279, 299, 300]. Manifestations are vasculitis, rheumatoid nodules, serositis, pulmonary nodules, interstitial lung disease, keratoconjunctivitis sicca, lymphadenopathy, Felty syndrome (RA, splenomegaly, neutropenia), amyloidosis, neuropathy, two- to fourfold increased risk of lymphoma, and accelerated atherosclerosis [301, 302].

Vasculitis

RV develops most commonly in patients with long-standing disease, history of smoking, high RF levels, decreased circulating C3, joint erosions, subcutaneous nodules, cryoglobulins, Felty syndrome, and HLA-DRB1 *shared epitope* genotypes [299, 303–306]. Autopsy series have revealed vasculitis in 20 % of patients [307–311], most of which was subclinical. In prospective clinical studies, vasculitis develops in 4–5 %. The incidence of RV has decreased over the past two decades, possibly due to more aggressive treatment of RA [312–314]. Skin involvement is the most frequent (75 % of cases) and often initial feature [304, 306]. Neuropathies are next most prevalent, occurring in 45–50 % of patients [303, 307, 311, 315–317]. Clinical involvement of other organs is uncommon. Laboratory findings are similar to those in the primary systemic vasculitides, but CCP antibodies are a distinguishing feature [318].

Evaluation and Diagnostic Criteria

The diagnosis of established RA depends on a characteristic clinical picture, radiographic findings of periarticular osteopenia and bony erosions, inflammatory synovial fluid,

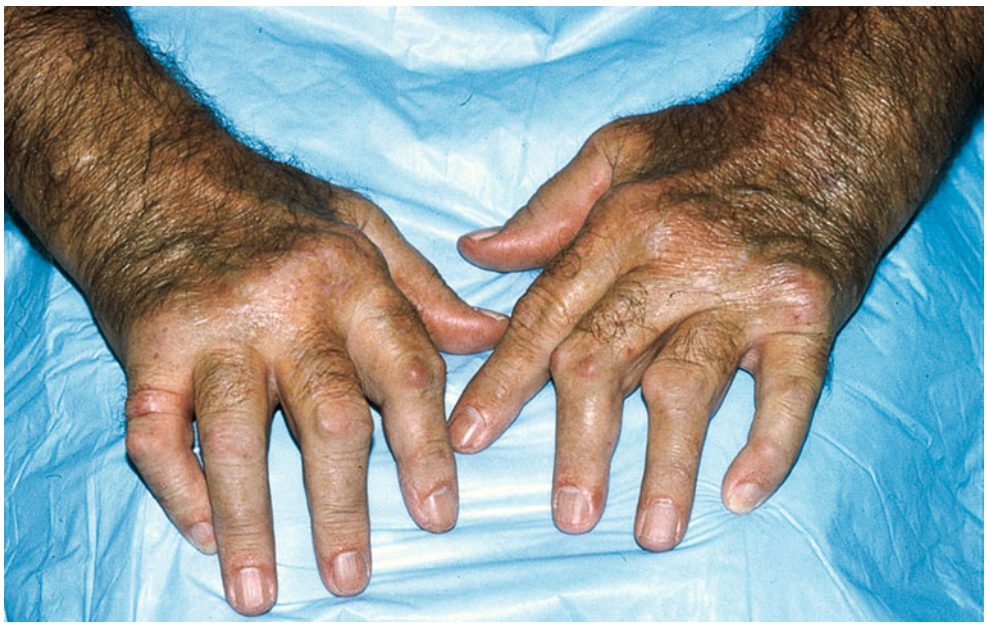

Fig. 36.4 Hands from a 56-year-old man with a 20-year history of rheumatoid arthritis who presented with a right foot drop and symmetric distal sensory loss. There is severe joint involvement of the wrist, metacarpophalangeal, and proximal interphalangeal joints producing swelling and joint deformity with slight radial deviation at the wrist and ulnar deviation of the digits. Note the relative sparing of the distal interphalangeal joints

and abnormal serologic studies. The 1987 ACR revised classification criteria for RA are 91–94 % sensitive and 89 % specific for RA in a control population consisting of other types of CTDs, but they do not discriminate new-onset RA from other inflammatory arthropathies [319]. New classification criteria devised in 2010 focused on early features of the disease predictive of persistent or erosive RA (Table 36.9) [320].

ESR and CRP are elevated in almost all patients with active disease [298]. About 25 % of patients develop normocytic anemia secondary to chronic inflammation. ANAs are present in 20–30 % of patients. Complement levels are normal or increased. ANCAs occur in 20–50 % of patients, but they are not consistently associated with RV [321, 322]. RFs have only moderate sensitivity (70 %) and specificity (79 %) for RA [323]; they can be detected in many other conditions (including all CTDs), 1–5 % of the general population, and 10 % of elderly individuals [324, 325]. High titers of RFs are predictive of a more severe clinical course with erosive disease and extra-articular manifestations. Anti-CCP antibodies are more specific (96 %) and equally sensitive (67 %) [323]. They are found in 1–2 % of normal individuals, 5–10 % of patients with other chronic inflammatory diseases, and 34 % of patients with tuberculosis [326, 327]. Titers of RF and anti-CCP antibodies are not useful in monitoring disease activity.

Treatment/Prognosis

In decades past, patients with indolent disease were managed with nonsteroidal anti-inflammatory drugs (NSAIDs) alone, while those with more aggressive disease received CS or one of the disease-modifying antirheumatic drugs (DMARDs), such as MTX, sulfasalazine, or hydroxychloroquine [279, 328, 329]. Because early treatment with DMARDs improves clinical/radiographic outcomes compared to delayed treatment, initiation of DMARD therapy within 3 months of diagnosis has been the established best practice since the 1990s [279, 328–334]. Most patients are initially treated with MTX rapidly escalated from 7.5–15 to 20–25 mg/week. When MTX is contraindicated, sulfasalazine and leflunomide are alternatives. Patients with persistent disease activity despite use of MTX are treated with a TNF-α inhibitor (etanercept, infliximab, adalimumab, golimumab, or certolizumab pegol) [335]. Combination therapy with MTX and a TNF-α inhibitor yields better clinical outcomes and reduced radiographic progression than MTX or TNF-α monotherapy in patients with early RA. Those who fail MTX combined with a TNF-α inhibitor can be treated with another TNF-α inhibitor, rituximab (CD20 monoclonal antibody), tocilizumab (IL-6 receptor antagonist), or abatacept (CTLA-4 fusion protein) [336]. In patients with high disease activity and poor prognostic factors, initial treatment with both MTX and a TNF-α inhibitor is recommended [332, 333]. The addition of low-dose CS to DMARDs in RA also retards radiographic progression [337]. The optimal treatment approach for systemic RV is unknown, but in practice, combined CS and CYC is the mainstay of treatment [338–340]. Patients with milder disease are often managed with CS combined with AZA or MTX [306]. For patients refractory to or intolerant of CYC, class IV evidence suggests a role for the TNF-α inhibitors and rituximab [341, 342]. There are also case reports of efficacy for abatacept and tocilizumab [343, 344].

Although about 10 % of patients with early RA undergo spontaneous remission without residual disability, most patients have progressive disease [278, 279]. About 65 % of

Table 36.9 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis (RA) [320]

Target population: Patients with:	
(1) at least 1 joint with definite clinical synovitis (swelling)[a]	
(2) synovitis not better explained by another disease	
Classification criteria for RA (add score of categories A–D; score of ≥6/10 needed for definite RA)	
Category	**Score**
A. Joint involvement	
1 large joint[b]	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints)[c]	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result needed for classification)	
Negative RF and negative ACPA	0
Low-positive RF or low-positive APCA (≤3 x ULN)	2
High-positive RF or high-positive APCA (>3 x ULN)	3
C. Acute-phase reactants (at least 1 test result needed for classification)	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	
<6 weeks	0
≥6 weeks	1

ACPA anti-citrullinated protein antibody, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *RF* rheumatoid factor, *ULN* upper limit of normal

[a]The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of RA with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA. Patients with long-standing disease, including those whose disease is inactive (with or without treatment), who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA

[b]Large joints refer to shoulders, elbows, hips, knees, and ankles

[c]Small joints refer to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists

patients have radiographic evidence of erosive arthritis within 3 years of disease onset [345]. Disability increases by an average of 0.6 % per year and joint damage by 2.0 % per year [346]. Mortality rates in patients with RA are 1.5–1.6-fold higher than in the general population [347, 348].

Neuropathies

Polyneuropathies have been identified in ~15 % of patients with RA in prospective studies employing clinical criteria and ~30 % in electrodiagnostic investigations (data from 17 clinical and 10 EMG studies) [349–354]. Approximately 45 % of these neuropathies are asymmetric or multifocal. About 50 % of RA-related neuropathies are "sensory" in clinical series, but most involve both sensory and motor fibers in electrodiagnostic studies [354, 355].

Vasculitic Neuropathy

As previously noted, neuropathies evolve in 45–50 % of patients with RV, suggesting that up to 10 % of all patients with RA will eventually develop a vasculitic neuropathy. Vasculitic neuropathy usually occurs in patients with long-standing, seropositive, nodular disease but can be a heralding feature of the illness. Signs and symptoms are similar to those of other vasculitic neuropathies, except for a larger proportion (~50 %) of predominantly sensory neuropathies [42, 51, 303, 317, 356–359]. The laboratory and electrodiagnostic features have already been discussed above.

Distal Sensory or Sensory-Motor Polyneuropathy

About 10 % of patients with RA develop a distal sensory or sensory-motor polyneuropathy. Patients present with slowly progressive distal paresthesias, numbness, and sometimes pain; typically minor motor involvement; and modest pan-modality sensory loss [360, 361]. Electrodiagnostic studies usually reveal axonal motor involvement, even when clinical findings are primarily sensory [354, 355]. Asymmetries should prompt consideration of an overlapping vasculitic neuropathy. Information on nerve pathology is sparse and conflicting, but some biopsies or postmortem examinations have revealed vasculitis, healed arteritis, or findings predictive of vasculitis [51, 349, 352, 360, 362–365].

Entrapments

Carpal tunnel syndrome and ulnar neuropathy at the elbow develop in 15–20 % of patients with RA based on clinical, nerve conduction, or sonographic criteria [352, 353, 355, 366–369]. Proliferating synovium, joint deformities, synovial cysts, and rheumatoid nodules are predisposing factors. There are also numerous reports of posterior interosseous nerve entrapments, generally attributed to synovitis or synovial cysts at the elbow [370]. Tibial, femoral, common peroneal, digital, proximal median, and distal ulnar nerve entrapments are more rarely encountered [7, 371–373].

Other Phenotypes

There are rare reports of CIDP [352]; GBS [357]; trigeminal sensory and other cranial mononeuropathies [374]; lumbar radiculopathies caused by intraspinal extradural rheumatoid nodules [375], lumbar pachymeningitis [376], facet joint pannus [377], or rheumatoid diskitis [378]; and amyloid neuropathies [352]. Secondary or reactive amyloid A (AA) amyloidosis occurs in many chronic inflammatory diseases, including RA, due to increased synthesis of serum amyloid A (SAA), an acute-phase reactant [379, 380], but neuropathies are rare [381, 382].

Treatment/Prognosis

No RCT of treatment in RA-associated neuropathies has been reported. Patients with indolent neuropathies are usually managed supportively. Patients with entrapments can be splinted or treated with local CS injections. Surgical release is reserved for those with progressive deficits or severe symptoms. Many patients require treatment for neuropathic pain. Biopsy-proven vasculitic neuropathies should be treated with CS monotherapy or CS combined with a cytotoxic agent (see above). Although no prospective studies have addressed the prognosis of rheumatoid neuropathy, one retrospective analysis of patients with vasculitic rheumatoid neuropathy demonstrated a 5-year survival of 57 % [51]. Cutaneous vasculitis, neuropathy affecting three or four limbs, and reduced C4 level were independent predictors of mortality in this study. Sustained remission occurred in 55 % of patients and 25 % relapsed.

Sjögren's Syndrome

Definition/Epidemiology

Sjögren's syndrome is an autoimmune disease characterized by lymphocytic infiltration of exocrine glands, especially the lacrimal and salivary glands, producing the primary clinical manifestations of dry mouth (xerostomia) and dry eyes (keratoconjunctivitis sicca) [383–385]. The disorder has an estimated prevalence of 0.5–1 % in adults [386, 387]. It can develop at any age, but onset in the fourth and fifth decades is typical; 90 % of cases occur in women. The term *primary* Sjögren's syndrome (pSS) is applied when the disorder occurs in isolation; *secondary* Sjögren's (sSS) refers to cases developing in conjunction with another autoimmune CTD, most commonly RA. The primary and secondary forms of SS occur with approximately equal prevalence [388].

Etiology/Pathogenesis

The etiology of pSS is unknown, but environmental factors may trigger chronic inflammation in genetically susceptible individuals [383, 385, 389, 390]. One theory holds that immunologically activated and apoptotic glandular epithelial cells expose autoantigens in genetically predisposed patients, thereby driving an injurious immune response [390–392]. For example, the disease may result from an aberrant immune response to a virus latently infecting the epithelial cells of salivary and other exocrine glands [383, 389, 390]. The genetic aspects of pSS have not been as well investigated as those of RA [393, 394]. The strongest associations are those between the HLA-DQA1*0101, *0301, *0201, and *0501 alleles and subsets of autoantibodies, not the disease itself [390]. The glandular cellular infiltrate consists primarily of activated T cells, with less frequent B cells, plasma cells, macrophages, and NK cells [385, 388]. CD4+ Th2 cells predominate in early stages of the disease, while Th1 and Th17 cells take precedence in later stages [388, 390, 395]. Germinal center-like structures are found in 17–28 % of minor salivary gland biopsies [390, 391, 396]. They are presumed to be sites of helper T cell-dependent B cell proliferation and maturation. B cell activation is evidenced by circulating immune complexes, multiple autoantibodies, cryoglobulinemia, RFs, hypergammaglobulinemia, oligoclonal B cell expansions, and increased risk of B cell lymphoma [397]. Autoantibodies are directed against such antigens as Ro/SSa, La/SSB, α-fodrin (constituent of the epithelial cell cytoskeleton), M3R muscarinic receptors, carbonic anhydrase II, and proteasomal subunits [398]. pSS is most closely linked to antibodies against Ro/SSA and La/SSB. Microarray analyses of minor salivary gland tissue and peripheral blood mononuclear cells from patients with pSS show enhanced levels of type I IFN-inducible gene expression, i.e., a type I IFN *signature* [389, 399]. Type I IFN consists of five classes of molecules: IFN-α, IFN-β, IFN-ε, IFN-κ, and IFN-ω. Most cells make small amounts of type I INF, but the principal producer is the plasmacytoid dendritic cell. Type I IFN has many immunomodulatory effects, all of which have the potential to perpetuate an autoimmune disease.

Clinical Presentation

pSS presents in an indolent fashion over years to decades, manifesting with slowly evolving symptoms of dry eyes and dry mouth [383–385, 388, 400–405]. Unilateral or bilateral, chronic or recurrent salivary gland enlargement occurs in 25–50 % of patients, usually involving the parotid gland (Fig. 36.5). Dental caries, accelerated periodontal disease, and oral candidiasis are common. Other exocrine glands may also be affected, resulting in dryness of the skin and mucosal surfaces of the upper respiratory tract, GI tract, and vagina. Dysphagia develops in 75 % of patients, caused by mucosal dryness, reflux, and esophageal dysmotility. Chronic cough secondary to tracheitis occurs in 40–50 % of patients.

Some 50 % of patients with pSS develop a multisystem disorder heralded by fatigue, fever, myalgias, and arthralgias [383–385, 388, 400–405]. Symptoms result from lymphocytic invasion of organ epithelia (e.g., interstitial nephritis, autoimmune hepatitis, and interstitial pneumonitis) or immune complex disease (e.g., vasculitis, arthritis, and glomerulonephritis). Manifestations include nonerosive arthritis (~50 % of patients), skin involvement (~50 %), Raynaud's phenomenon (15–50 %), autoimmune thyroid disease (~35 %) [406], lymphadenopathy (10–30 %), neuropathy (~20 %), CNS disease (6 %, except cognitive impairment in 20–50 %) [407, 408], interstitial lung disease (10 %), distal renal tubular acidosis (5–10 %), glomerulonephritis (1–2 %), autoimmune hepatitis (2–4 %), primary biliary cirrhosis (5–10 %), and polymyositis (1–2 %). Some patients develop extra-nodal, mantle zone, B cell, mucosa-associated lymphoid tissue-type lymphoma or Waldenström's macroglobulinemia [409].

Fig. 36.5 Patient with Sjögren's syndrome showing typical enlargement of the right parotid gland (Photograph courtesy of Dr. Carl M. Allen)

Table 36.10 Revised international classification criteria for Sjögren's syndrome [419]

Criterion	Definition
I. Ocular symptoms	Dry eyes every day for more than 3 months, recurrent sensation of sand or gravel in the eyes, or use of tear substitutes more than three times a day
II. Oral symptoms	Daily feeling of dry mouth for more than 3 months, recurrent or persistently swollen salivary glands as an adult, or use of liquids to aid in swallowing dry food
III. Ocular signs	Abnormal Schirmer's I test (≤5 mm in 5 min) or rose bengal score (≥4 according to van Bijsterveld's scoring system)
IV. Histopathology	Focus score ≥1 in a minor salivary gland biopsy
V. Salivary gland involvement	Positive result in one of the following tests: salivary scintigraphy, parotid sialography, salivary flow (≤1.5 ml in 15 min)
VI. Autoantibodies	Antibodies to Ro (SS-A) or La (SS-B) antigens
Primary Sjögren's syndrome:	(a) Any 4 of 6 items present (including IV or VI); or (b) 3 of 4 objective items present (III, IV, V, VI)
Secondary Sjögren's syndrome:	(a) Another well-defined connective tissue disease (b) Item I or II present plus 2 items from among III, IV, and V
Exclusion criteria:	Past head or neck radiation treatment Hepatitis C infection Human immunodeficiency virus infection Preexisting lymphoma Sarcoidosis Graft-versus-host disease Use of anticholinergic drugs

Vasculitis

Vasculitis develops in 10 % of patients with pSS [400, 403, 404, 410–412]. Nearly all patients with vasculitis have skin manifestations, notably recurrent purpura. Neuropathies occur in 35 % of patients [403, 410, 413, 414]. Other involved organs include the joints, kidneys, GI tract, lungs, and CNS. Vasculitis is associated with ANA, RF, anti-Ro antibodies, hypocomplementemia, and cryoglobulinemia [414, 415].

Evaluation and Diagnostic Criteria

The diagnosis of pSS can be challenging for several reasons. First, the clinical manifestations may be subtle and attributed to normal aging. Second, in patients with more pronounced symptoms, it may be difficult to document objective exocrine gland dysfunction. Finally, other disorders can present with chronic sicca symptoms, including sarcoidosis, IgG4-related disease, chronic graft-versus-host disease, amyloidosis, lymphoma, primary biliary cirrhosis, Vogt-Koyanagi-Harada syndrome, and HCV, HIV, and HTLV-1 infections [383, 385, 416, 417]. An American-European Consensus Group revised the 1993 European classification criteria for pSS in 2002 (Table 36.10) [418, 419]. In addition to sicca symptoms, these criteria require objective evidence of keratoconjunctivitis sicca or xerostomia plus positive histopathology (minor salivary gland biopsy) or serology (SSA or SSB antibodies).

Objective evidence of keratoconjunctivitis sicca can be obtained by the Schirmer's I test or rose bengal dye staining [420–422] (Fig. 36.6), but the new standard for assessing keratoconjunctivitis sicca in SS combines fluorescein staining to grade the cornea with lissamine green staining to grade the conjunctiva [423]. Objective evidence of salivary gland involvement requires abnormal parotid gland sialography, salivary scintigraphy, sialometry (unstimulated salivary flow), or labial salivary gland biopsy [383, 385, 418, 419, 424]. Sialography is not usually performed because of its invasiveness and potential to induce flares of glandular pain and swelling [385, 424]. Unstimulated salivary flow <1.5 ml

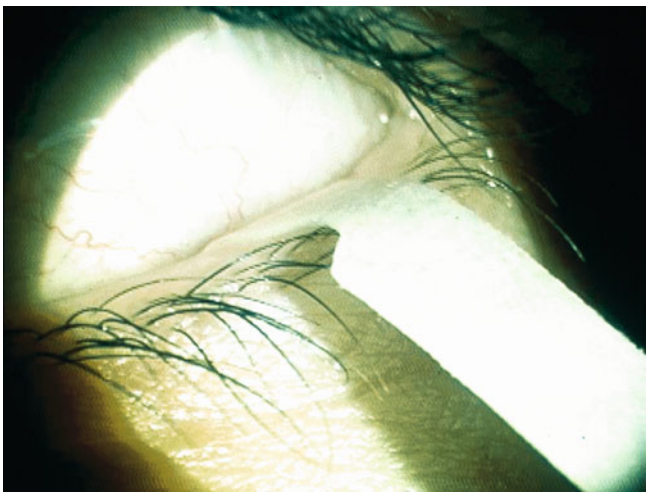

Fig. 36.6 Patient with Sjögren's syndrome undergoing Schirmer's testing. A strip of filter paper has been placed in the lower conjunctival sac. After 5 min, only 3 mm of paper has been moistened by spontaneous tear production (*grayish* paper), compared with a normal value of >5 mm (Photograph courtesy of Dr. Tom Mauger)

in 15 min is abnormal. Salivary gland scintigraphy shows delayed uptake, reduced concentration, and/or reduced excretion of the tracer, but neither the test protocol nor its interpretation is standardized [425]. In a labial salivary gland biopsy, abnormal histopathology is defined by a focus score of ≥1, where the focus score is the number of lymphocytic collections adjacent to normal mucous acini with >50 cells per 4 mm^2 of tissue (Fig. 36.7) [426]. There are several limitations to the assessment, including poor inter-examiner reliability among pathologists [427] and lack of specificity for pSS. Some 10–20 % of specimens from unaffected postmortem subjects and healthy living controls have focus scores ≥1 [428–430], and many patients with CTDs and myasthenia gravis have focal lymphocytic infiltrates [431]. Thus, labial salivary gland biopsies need to be interpreted in light of the patient's clinical picture and pathologist's experience.

The sensitivity of anti-Ro/SSA and anti-La/SSB antibodies is about 60 and 40 %, respectively [400–405]. These antibodies should thus not be used as screening tests. Moreover, they are not specific for pSS and occur in ~35 and 15 % of patients with SLE. Other laboratory abnormalities include elevated ESR in 80–90 % of patients, RFs in 40–60 %, ANAs in 85 %, hypergammaglobulinemia in 50 %, hypocomplementemia in 10–25 %, cytopenias in 15–20 %, cryoglobulinemia in 15–20 % [383–385, 388, 400–405], pANCAs in 6–26 % [432–435], and CCP antibodies in 4–10 % [402, 411, 436]. IgG and IgA antibodies against α-fodrin also occur in patients with pSS [398, 437]. A meta-analysis showed IgG α-fodrin antibodies to have low sensitivity (40 %) but relatively high specificity (82 %) [438]. They might be considered in patients with an appropriate clinical phenotype who are negative for Ro/La antibodies.

Treatment/Prognosis

pSS without extra-glandular manifestations is a relatively benign entity. Treatment is supportive and includes the use of artificial tears, lubricating ointments, cyclosporine ophthalmic emulsion, pilocarpine tablets, cevimeline capsules, punctual plugs, or lacrimal duct cauterization for dry eyes, and meticulous dental care, frequent oral fluids, sugar-free gums and lozenges, artificial saliva, lubricating gels and mouthwashes, maltose lozenges, mucin-containing oral products, pilocarpine, cevimeline, or sorbitol-/xylitol-containing lozenges for dry mouth [383–385, 388]. The secretagogues pilocarpine and cevimeline (an M3 receptor agonist) have both been shown to be effective for dry mouth and eyes in RCTs [439, 440]. Topical cyclosporine has also been evaluated in RCTs with demonstrated efficacy in the treatment of keratoconjunctivitis sicca [441, 442]. Musculoskeletal symptoms are often treated with CS and hydroxychloroquine, but a RCT of hydroxychloroquine showed no significant benefit for myalgias, arthralgias, or fatigue [443]. CS and hydroxychloroquine have no effect on exocrine gland symptoms. RCTs of infliximab and etanercept demonstrated no benefit [444, 445]. A small RCT of rituximab revealed significant improvements in the primary and secondary endpoints, but larger confirmatory studies are ongoing [446]. Patients who develop systemic vasculitis are treated in the same fashion as patients with primary small- and medium-vessel vasculitides.

The long-term prognosis of pSS is good, except for increased risk of lymphoma. Longitudinal studies have revealed salivary and lacrimal function to remain relatively stable [447]. Most patients show no progression or systemic spread after 10 years of follow-up [400]. Mortality rate is not significantly increased compared to that of the general population [448]. Purpura, decreased C4, cryoglobulinemia, persistent parotid gland swelling, splenomegaly, vasculitis, and CD4+ lymphocytopenia are adverse prognostic factors, increasing the risk for multisystem disease and B cell lymphoma [448].

Neuropathies

Neuropathies are more common in pSS than other CTDs due, in part, to the fact that the disorder targets not only exocrine glands but also dorsal root and autonomic ganglia. The reported prevalence of neuropathy in pSS is highly variable, but in prospective studies, mean neuropathy prevalence is ~20 % [407, 449–454]. In ~70 % of patients, neuropathy precedes the diagnosis of pSS by a median of 24 months [246, 455–459]. Almost any pattern of neuropathy can occur in pSS, including a length-dependent sensory or sensory-motor polyneuropathy, ataxic sensory neuronopathy, painful small-fiber-predominant neuropathy, multifocal neuropathy, polyradiculoneuropathy, or cranial neuropathy. Approximately 60 % of neuropathies are predominantly or

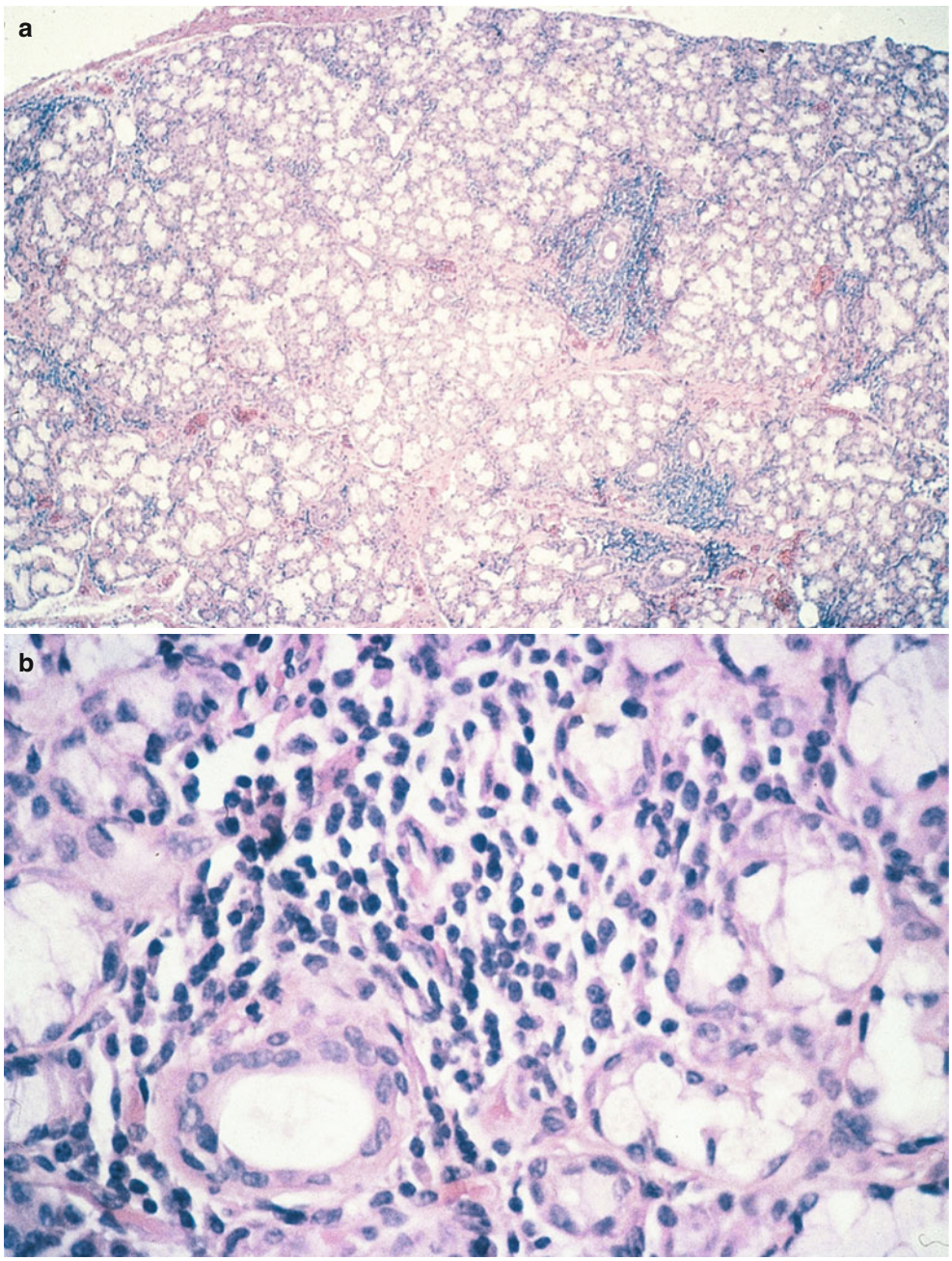

Fig. 36.7 Minor salivary gland biopsy from patient with Sjögren's syndrome. Low power view (**a**) shows intense collections of blue-staining inflammatory cells amid the normal glandular architecture. A higher power view (**b**) shows that the cells surround and distort the salivary gland lobules (hematoxylin and eosin) (Photographs courtesy of Dr. Carl M. Allen)

purely sensory, and 40 % are asymmetric [451, 455, 456, 458, 460–464]. In patients with a pSS-related neuropathy, the prevalence of anti-Ro/SSA and anti-La/SSB antibodies is 50–55 and 20 %, respectively [412, 455, 459].

Vasculitic Neuropathy

Most patients with a pSS-related multiple mononeuropathy have PNS vasculitis. Multifocal neuropathies occur in 4 % of patients and constitute 15 % of pSS-associated neuropathies [451, 452, 456, 458–460, 462, 464, 465]. From a different perspective, since systemic vasculitis develops in 10 % of pSS patients, and 1/3 have a neuropathy, it can be inferred that vasculitic neuropathy will occur in 3–4 % of Sjögren's patients. The clinical presentation, electrodiagnostic features, and biopsy findings of vasculitic neuropathy are similar to those in any other vasculitis [459]. Clinical predictors of vasculitic neuropathy are acute-onset (1 month), multifocal pattern, sensory-motor involvement, constitutional symptoms, elevated CRP, RF, decreased complement, and elevated β2-microglobulin [246].

Ataxic Sensory Neuronopathy

Ataxic sensory neuronopathy is a distinctive but uncommon pSS-related neuropathy, occurring in 2–3 % of patients and

accounting for up to 15 % of all neuropathies in the disease [412, 449–451, 456, 458, 462, 463, 466]. The mean age of onset is 56 years [11, 459, 466–469]. The neuronopathy develops before sicca symptoms in 50 % of patients. Patients usually present with chronically progressive numbness and paresthesias in the limbs, trunk, and face in an asymmetric/non-length-dependent pattern, associated with unsteady gait and loss of proprioception in the extremities, resulting in ataxic limb movements. The onset is acute or subacute in 15 % of patients. Only 50 % of patients have pain. Face and truncal regions are affected in 40–45 % each. Examination reveals prominent large-fiber sensory loss, sensory ataxia, pseudoathetosis, diffuse hypo-/areflexia, and milder impairment of small-fiber modalities. Strength is preserved. Autonomic dysfunction occurs in 40–50 % of patients, resulting in tonic pupils, anhidrosis, orthostatic hypotension, facial flushing, and constipation/diarrhea.

Electrodiagnostic studies reveal absent or low-amplitude SNAPs in affected limbs with normal or mildly reduced conduction velocities [11, 459, 466–468, 470]. SNAP abnormalities have non-length-dependent features, such as interside asymmetries, greater upper limb than lower limb involvement, and lower amplitude proximal than distal SNAPs. H reflexes are typically absent. In patients with trigeminal involvement, blink reflexes and masseter cutaneous silent period are usually absent or abnormal, while the masseter reflex is spared, indicative of trigeminal ganglion dysfunction [471, 472]. Motor studies and F waves are preserved. EMG examination is usually normal, but minimal denervation can be seen.

Laboratory findings include positive ANA in 85 %, Ro/SSA antibodies in 55 %, La/SSB antibodies in 15 %, RFs in 40 %, and decreased complement in 20 %. CSF is normal except for mildly to moderately elevated protein in 20 %. Cervical spine MRI shows high signal abnormalities in the dorsal columns in 75 % of patients, reflecting degeneration of the central afferent projections of the dorsal root ganglion neurons [459]. Distal cutaneous nerve biopsies reveal preferential loss of large myelinated nerve fibers, Wallerian-like degeneration, and scant regenerating axonal clusters, consistent with the presumptive cell body source of pathology. While epineurial perivascular inflammation is not uncommon (35 % of biopsies), vasculitis was noted in only one large series, occurring in 20 % of patients [11, 459, 468, 469]. Despite the widely held conviction that this syndrome is caused by dorsal root ganglionitis, the pathologic evidence behind this conclusion is limited [11], and one autopsy study showed the pathologic process to be more diffuse, targeting not only the sensory/sympathetic ganglia but also peripheral nerves, with some vasculitic involvement [459].

Non-ataxic Sensory Neuropathy

The other pSS-associated polyneuropathies are more common but less well characterized. As previously noted, about 60 % of pSS-related neuropathies affect only sensory nerves. Since 15 % of these sensory neuropathies are ataxic sensory neuronopathies, the other 45 % should be non-ataxic small-fiber-predominant sensory disorders, consistent with pooled data from five series [412, 456, 463, 473, 474]. This would thus appear to be the most common pSS-related polyneuropathy.

Patients usually present with distally accentuated pain, numbness, and tingling [459, 463, 473, 475, 476], but many patients also manifest non-length-dependent features [459, 463]. The onset is typically insidious, but acute presentations with total-body pain have been described [459]. Neurologic examination is normal except for impaired pain/thermal sensation, allodynia, and hyperpathia, but in some patients, milder large-fiber sensory loss is demonstrated. Muscle stretch reflexes are preserved. The majority have autonomic signs and symptoms, especially anhidrosis and orthostasis [360].

In patients with small-fiber neuropathies, standard electrodiagnostic testing is normal. A minority of patients have low-amplitude or non-reproducible distal SNAPs, but SNAP abnormalities are not as severe or pervasive as those in the ataxic sensory neuronopathy syndrome. ANAs are often positive, but less than half have anti-Ro/La antibodies [459, 476]. Cervical spine MRIs sometimes reveal increased T2 signal in the dorsal columns [459]. Sural nerve biopsies show predominant small myelinated and unmyelinated fiber loss, Wallerian-like degeneration, essentially no axonal sprouting, no vasculitis, and rare perivascular inflammation [459, 475]. Skin biopsies reveal decreased epidermal nerve fiber density [463, 476]. The pathology of this small-fiber syndrome is unknown, but it probably represents a sensory ganglionopathy predilected for smaller ganglion cells.

Distal Sensory-Motor Polyneuropathy

Distal sensory-motor polyneuropathies constitute about 25 % of pSS-related neuropathies. Patients present with slowly progressive numbness, tingling, and pain in the feet [455, 458, 461, 465, 470, 474]. Sensory deficits typically involve all modalities. Weakness is usually mild, distal, and often restricted to the toes. Ankle jerks are depressed or absent. Autonomic symptoms are uncommon. Electrodiagnostic studies are characteristic of a length-dependent axonal process, with decreased sensory nerve and compound muscle action potential amplitudes in the distal lower limbs, normal or mildly reduced sensory-motor conduction velocities, and distal-predominant active and chronic partial denervation in the needle EMG examination. The mechanisms underlying distal sensory-motor polyneuropathies in pSS are enigmatic, but in patients with subacute or acute progression and asymmetries, PNS vasculitis should be suspected. For patients with symmetric signs and symptoms, some biopsy studies have revealed definite or probable vasculitis [413, 455, 461], while others have not [407, 451, 458, 470].

Other Phenotypes

Polyradiculoneuropathies or polyradiculopathies occur rarely in pSS and are more commonly axonal than demyelinating [452, 456, 458, 459, 474, 477]. There are also rare reports of GBS and acute inflammatory polyradiculopathy [478, 479]. The axonal polyradiculoneuropathies generally produce subacutely or chronically progressive, distally accentuated, large- to small-fiber sensory loss, often accompanied by proximal and distal weakness. Reflexes are depressed or absent, and CSF protein is elevated. MRIs of the lumbar spine can show enhancement of the cauda equina and dorsal roots [459]. Sural nerve biopsies reveal variably decreased myelinated nerve fiber density, mildly increased demyelination/remyelination, no vasculitis, and perivascular inflammation. Pure motor neuronopathies or axonopathies are also rarely described. In patients not responding to immunosuppressive therapy, the development is likely by chance [480–482], but rare patients with ALS, brachial amyotrophic diplegia, or primary lateral sclerosis have improved or stabilized when treated, suggesting that immunopathogenic mechanisms might be operative in some cases [407, 482, 483].

Entrapments

Entrapment neuropathies are uncommon in pSS. Carpal tunnel syndrome occurred in 8 % of patients in 14 studies; ulnar nerve entrapment at the elbow was diagnosed in 5 % in two series [484, 485].

Cranial Neuropathies

Cranial neuropathies occur in approximately 5 % of patients with pSS, with the trigeminal nerve most commonly affected [407, 412, 449, 450, 452, 456, 461, 462, 464, 465, 485, 486]. Patients with trigeminal sensory neuropathies present with subacutely or chronically progressive numbness in the second and third divisions of this nerve; occasionally, all three divisions are affected [461]. Symptoms commence unilaterally but become bilateral in 40 % of patients [459, 461, 487]. Facial pain is uncommon. These neuropathies sometimes develop as part of a more generalized sensory neuronopathy. The pathogenesis is probably lymphocytic infiltration of the trigeminal sensory ganglion. All other cranial nerves are less commonly affected, with predominant seventh or eight nerve involvement. A potentially self-limited, occasionally recurrent, acute or chronic cranial polyneuropathy is rarely encountered [456, 459, 488].

Treatment/Prognosis

Only class IV data is available to inform treatment decisions in patients with pSS-related neuropathies. Patients with mild neuropathy are generally managed with supportive care. Those with proven or suspected vasculitic neuropathy are treated with an immunosuppressive regimen as discussed above. Of all the Sjögren's-related neuropathies, a multifocal vasculitic neuropathy is the only condition that routinely responds to immunosuppression [246, 459]. Uncontrolled data suggests that 80 % of these neuropathies improve with CS monotherapy, CS combined with various immunosuppressive agents, pulse IV CYC, or rituximab [246, 457–459, 461, 489]. The cranial polyneuropathy is also reported to be CS responsive [459, 488, 490], but this syndrome is often self-limited without treatment [491, 492]. No treatment has been shown to be consistently effective in patients with the pSS-related sensory neuropathies, but for the ataxic sensory neuronopathy, favorable responses to CS monotherapy or IVIg have been reported in 15–25 % of patients [459, 493]. Infrequent ataxic patients improve with plasma exchange or immunosuppressive agents such as AZA or CYC. Isolated patients have responded to D-penicillamine [494], interferon-α [495], infliximab [496], and rituximab [497]. Patients with a pSS-related, painful, small-fiber neuropathy do not generally improve with CS [246, 457–459, 476] but may respond to IVIg [493, 498, 499]. There is little data on treatment of the trigeminal sensory neuropathy [459, 461, 493]. Based on limited data, the chronic axonal and demyelinating polyradiculoneuropathies associated with pSS may respond better to IVIg than CS [459].

There is little information on the long-term prognosis of the various pSS-related neuropathies. Most patients with the ataxic sensory neuronopathy and trigeminal sensory neuropathy continue to progress indefinitely, but spontaneous stabilization and improvement occur in a minority of patients [11, 466]. In the non-ataxic painful neuropathy, symptoms persist and slowly spread over time, with evolution of sensory ataxia in less than 20 % of patients [459].

Systemic Lupus Erythematosus

Definition/Epidemiology

SLE is a multisystem disorder characterized clinically by exacerbations and remissions and immunologically by production of multiple autoantibodies, activation of complement, immune complex generation, and altered cellular immunity [500–502]. It is the third most common CTD, with a prevalence of 20–70 cases per 100,000 [503]. The incidence of SLE peaks between 15 and 40 years, but it can develop at any age. Women are preferentially affected. The female/male ratio decreases from 12:1 during childbearing years to 2:1 in children and those older than 45 [504].

Etiology/Pathogenesis

SLE is a disorder in which multiple genetic, environmental, and hormonal influences produce abnormalities of the innate

and adaptive immune systems, resulting in breakdown of B and T cell tolerance to self-antigens normally sequestered in the cell nucleus [502, 505, 506]. Key aberrations include reduced clearance of apoptotic cells by macrophages; persistent exposure of self-antigens (nucleosomal DNA/protein, RNA/protein, and others) in surface blebs of apoptotic cells; activation of myeloid dendritic cells by viral RNA or self-DNA/RNA complexed to adjuvant proteins; activation of autoreactive T helper cells by mature dendritic cells; selection of germinal center B cells with self-reactivity against nuclear antigens exposed in the apoptotic blebs; T cell-dependent affinity maturation and isotype switching of these activated B cells with subsequent production of autoantibodies to epitopes on the nuclear antigens; binding of these anti-DNA antibodies to DNA to form immune complexes that, in turn, activate plasmacytoid dendritic cells to produce INF-α; and deposition of circulating DNA-anti-DNA immune complexes in various tissues with ensuing injury [502, 505–509]. Similar to pSS, the type I IFN system is fundamental in perpetuating autoimmunity in SLE [510]. Another key cytokine is IL-17 [511].

Genome-wide association studies have revealed more than 30 confirmed or candidate genes associated with SLE [512, 513]. The implicated genes have functional roles in antigen presentation, B and T cell signaling, T helper cell regulation, type I INF signaling, TLR-7/9 signaling, immune complex clearance/processing, apoptosis, and DNA methylation. Two environmental risk factors for SLE are well established: exposure to UV light and gender [502, 506]. Viral infections (e.g., EBV) are believed to be another important precipitating environmental factor. The majority of autoantigens in SLE can be grouped into one of three categories: DNA/protein complexes derived from the nucleosome, small nuclear RNPs (snRNPs) derived from the spliceosome, and hYRNA-Ro/La (see pSS) [514, 515]. Double-stranded (ds) DNA antibodies are the pathogenic hallmark of SLE. The primary RNA-associated autoantigens involve the U1 snRNP complex, which contains 8 Smith (Sm) proteins and the U1 snRNP-specific proteins U1-70, U1-A, and U1-C. Anti-Sm antibodies occur infrequently, but they are highly specific for SLE. Other autoantigens include cardiolipins, cell surface molecules (e.g., on erythrocytes, lymphocytes, and platelets), and complement components.

The clinical disease phase of SLE is characterized by autoantibody-mediated tissue injury [505, 506, 514]. Lupus vasculitis is probably mediated by deposition of circulating immune complexes, possibly augmented by AECAs.

Clinical Presentation

The clinical spectrum of SLE is diverse (Table 36.11) [500, 501, 516, 517], and essentially any organ can be affected. The hallmark of the disease is its protean clinical manifestations and fluctuating clinical course. Most patients experience

Table 36.11 Clinical manifestations of systemic lupus erythematosus

Constitutional symptoms (95 %)
Fatigue, weight loss, fever, anorexia
Musculoskeletal symptoms
Arthralgias/myalgias (95 %)
Arthritis (80 %)
Fibromyalgia (20–30 %)
Myositis (5 %)
Osteonecrosis (5–15 %)
Hematologic disorders
Anemia of chronic disease (40–60 %)
Autoimmune hemolytic anemia (5–20 %)
Leukopenia (40–50 %)
Thrombocytopenia (20 %)
Thrombotic thrombocytopenic purpura (rare)
Antiphospholipid antibodies (10–30 %)
Lymphadenopathy (25 %)
Skin lesions (80 %)
Malar butterfly rash (50–55 %)
Subacute cutaneous lupus (10 %)
Alopecia (40 %)
Discoid lupus (20–25 %)
Photosensitivity (70 %)
Oral and nasal ulcers (35–40 %)
Raynaud's phenomenon (30–40 %)
Nervous system complications
Seizures (10–20 %)
Psychosis (5–10 %)
Acute confusional state (rare)
Cognitive impairment (up to 80 %)
Strokes (5–20 %)
Chorea (1–5 %)
Aseptic meningitis (1–5 %)
Myelopathy (<1 %)
Optic neuritis/multiple sclerosis-like (rare)
Neuropathy (15–20 %)
Kidney involvement (50 %)
Mesangial proliferative lupus nephritis (class II)
Focal or diffuse proliferative lupus nephritis (classes III, IV)
Membranous glomerulonephritis (class V)
Sclerotic nephritis (class VI)
Ocular lesions (15–20 %)
Sicca syndrome (10–15 %)
Cotton wool spots
Conjunctivitis, episcleritis
Retinal vasculitis
Pulmonary involvement
Pleuritis (30 %)
Acute lupus pneumonitis (1–5 %)
Interstitial lung disease (5–10 %)
Diffuse alveolar hemorrhage (1–5 %)
Pulmonary artery hypertension (11–43 %)

(continued)

Table 36.11 (continued)

Cardiac disorders
Pericarditis (20 % symptomatic; 60 % at autopsy)
Libman-Sacks endocarditis (40–45 % by TEE; 15–60 % at autopsy)
Myocarditis (1–5 %)
Gastrointestinal disorders
Abnormal LFTs (40 %)
Autoimmune hepatitis (2–5 %)
Pancreatitis (3 %)
Vasculitis (10 %)

TEE transesophageal echocardiogram

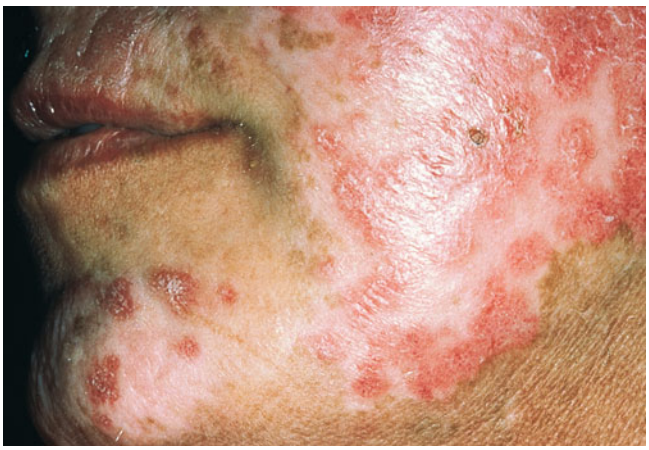

Fig. 36.8 This patient with acute cutaneous systemic lupus erythematosus has a severe morbilliform malar rash with adherent scaling plaques (Photograph courtesy of Dr. Carl M. Allen)

periods of disease quiescence interrupted by "flares" [518]. Fatigue, fevers, weight loss, anorexia, and nausea are prevalent at onset and during exacerbations. The most common sites of initial involvement are the joints and skin. Almost all patients experience musculoskeletal pain, while 60–80 % develop nonerosive arthritis. Skin manifestations are next most frequent (Fig. 36.8). Other commonly affected organs are the kidneys, blood, CNS, lungs, and heart. Nephritis is one of the most serious manifestations of SLE and a leading cause of death [519]. The most common cardiac lesion is pericarditis, but patients also have a seven- to tenfold increased risk of vascular events because of accelerated atherosclerosis [501]. The leading pulmonary manifestation is pleurisy. Anemia and lymphopenia are common but do not require treatment.

Many CNS and PNS syndromes are associated with SLE. To standardize reporting, an ACR Ad Hoc Committee published case definitions and diagnostic criteria for 19 neuropsychiatric manifestations [520]. Excluding headaches, which occur at a rate similar to the general population [521], the most common CNS manifestations are cognitive dysfunction (75–80 % of patients), psychiatric disturbances, seizures, strokes, chorea, and aseptic meningitis [522, 523].

Vasculitis

Biopsy studies have indicated that vasculitis occurs in approximately 20 % of SLE patients [517, 524–527]. The most commonly affected organ is the skin (80–85 % of patients), followed by the PNS (10–15 %), which suggests that 2–3 % of patients with SLE will develop a vasculitic neuropathy at some time in their life [42, 524, 525]. GI involvement (especially mesenteric vasculitis) is the most prevalent visceral manifestation (5–10 % of patients) [524, 525, 528, 529]. Renal, retinal, and pulmonary vessels are less frequently involved. As compared to SLE without vasculitis, cutaneous vasculitis does not increase mortality, but survival is decreased in visceral SLE vasculitis [524].

Evaluation and Diagnostic Criteria

The differential diagnosis of SLE is broad, especially early in the course of the disease when only a few organs are affected. The ACR classification criteria for SLE are widely applied as a guide to diagnosis (Table 36.12) [530]. These criteria reflect the major clinical and laboratory features of the disease. In patients presenting with isolated nervous system involvement, the diagnosis can be challenging. Positive ANA is detected in greater than 95 % of patients and is thus an ideal screening test, but it is not specific to SLE and can be seen in other autoimmune diseases, drug reactions, infections, and healthy individuals (including 10–35 % of individuals older than 65) [500]. More specific to SLE are antibodies against dsDNA and the Sm antigen. Up to 70 % of patients have dsDNA antibodies, while anti-Sm antibodies occur in 15–20 % [500, 527]. dsDNA antibodies increase and circulating levels of C3 and C4 decrease in patients with active disease, especially glomerulonephritis [501, 531]. Antiphospholipid antibodies are found in about one-third of patients; of these patients, 20–50 % develop thromboembolic events [532]. A clue to the presence of SLE is lymphopenia, which occurs in 50 % of patients [501]. Another characteristic feature is an elevated ESR with a concomitantly normal CRP [533].

Treatment/Prognosis

For SLE, the goals of therapy are to control acute symptoms, prevent exacerbations, and limit systemic spread with resulting end-organ dysfunction. Patients with mild disease are managed with NSAIDs, topical CS for rashes, hydroxychloroquine, and/or low-dose oral CS [500, 501, 534]. Clinically significant cytopenias are treated with CS [535]. Nonrenal manifestations can also be managed with MMF, AZA, or MTX [501]. Glomerulonephritis is typically treated with high-dose CS combined with IV pulses of CYC or oral MMF [501, 536, 537]. Calcineurin inhibitors are an option for patients with resistant lupus nephritis [538]. There are no large RCTs analyzing treatment responses for life-/organ-threatening manifestations other than lupus nephritis, but class IV evidence supports the efficacy of IV CYC/CS for

Table 36.12 Revised criteria for the classification of systemic lupus erythematosus [530]

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	(a) Pleuritis – convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion; *or* (b) Pericarditis – documented by ECG or rub or evidence of pericardial effusion
7. Renal disorder	(a) Persistent proteinuria greater than 0.5 g/day or greater than 3+ if quantification not performed; *or* (b) Cellular casts – may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	(a) Seizures – in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance; *or* (b) Psychosis – in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic disorder	(a) Hemolytic anemia – with reticulocytosis; *or* (b) Leukopenia – less than 4,000/mm^3 total on two or more occasions; *or* (c) Lymphopenia – less than 1,500/mm^3 on two or more occasions; *or* (d) Thrombocytopenia – less than 100,000/mm^3 in the absence of offending drugs
10. Immunologic disorder[a]	(a) Anti-DNA: antibody to native DNA in abnormal titer; *or* (b) Anti-Sm: presence of antibody to Sm nuclear antigen; *or* (c) Positive finding of antiphospholipid antibodies based on (1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, (2) a positive test result for lupus anticoagulant using a standard method, or (3) a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

Criteria of *American College of Rheumatology*: four or more criteria mandatory for diagnosis
[a]Modified from Hochberg [682]

alveolar hemorrhage, vasculitis, neurologic disease, severe thrombocytopenia, and severe dermatological manifestations [500]. Rituximab has been used off label in SLE patients for several years but is of questionable efficacy based on two RCTs [539, 540]. Belimumab, a human monoclonal antibody that blocks binding of B cell-activating factor (BAFF) to its B cell receptor, significantly improved the SLE Responder Index at 52 weeks in two RCTs [541–543].

Patients with SLE still have a two- to fivefold increased risk of death compared to the general population, to include significantly increased rates of death from cardiovascular disease, infection, cancers, and kidney disease [544]. Survival rates are about 95 % at 5 years, 91–93 % at 10 years, and 80 % at 15 years [503, 544]. Patients with SLE are at increased risk of developing hematologic (especially non-Hodgkin lymphoma), lung, and hepatobiliary malignancies [545]. Remissions lasting more than 1 year occur at an annualized rate of 28 % and often persist for multiple years [546].

Neuropathies

The reported frequency of neuropathy in SLE is highly variable, but in prospective studies devoted to neuropathy, they occurred in 15–20 % of patients by clinical criteria [28, 408, 522, 523, 547–551] and 30 % when nerve conduction criteria were employed [28, 547–549, 552–557]. Unlike pSS, most SLE-related neuropathies evolve in the setting of established disease. In one study, the mean age of onset of the neuropathy was 45 years, corresponding to a mean SLE disease duration of 8 years [10]. Neuropathies in SLE are associated with SLE disease activity but not SLE-related serologic and clinical manifestations. The most common phenotypes are a distal symmetric or asymmetric sensory-motor polyneuropathy, multifocal/presumably vasculitic neuropathy, and inflammatory demyelinating neuropathy. Electrodiagnostic studies usually reveal evidence of a predominantly axonal, sensory-motor, distal-predominant process, but 20 % of neuropathies were demyelinating in one series [10, 549, 556, 557]. Skin biopsy may reveal significantly decreased intraepidermal nerve fiber density in the leg [548, 549]. Most of these patients had no symptoms or nerve conduction abnormalities.

Vasculitic Neuropathy

Approximately 15 % of SLE-related PNS disorders are discrete or overlapping multifocal neuropathies, characteristic of vasculitis [10, 408, 522, 547, 550, 551, 557]. Given the 15–20 % incidence of SLE-related neuropathies, some 2–3 % of patients are predicted to develop a vasculitic neuropathy. In SLE patients with pathologically proven or suspected vasculitic neuropathy, 75–80 % have an asymmetric or multifocal neuropathy [42, 47, 210, 524, 558–560]; 10–15 % a symmetric sensory-motor polyneuropathy [560–562]; 5–10 % an acute, GBS-like disorder [563]; and 2 % a lumbosacral polyradiculopathy [564]. Electrodiagnostic studies reveal asymmetric, predominantly axonal, sensory-motor changes. Nerve biopsy reveals changes typical of necrotizing vasculitis.

Distal Sensory-Motor Polyneuropathy

A more common phenotype is that of a distally accentuated, axonal, sensory-motor polyneuropathy, a pattern that accounts for 75–80 % of SLE-related neuropathies. The initial symptoms are usually distal tingling, numbness, and pain that spread proximally over weeks to months [552, 560, 565, 566]. In 1/3 of patients, mild to severe distal weakness also emerges [10]. About 40 % are asymmetric [10]. The signs and symptoms usually progress slowly over years [567]. Electrodiagnostic studies demonstrate predominantly axonal features, with reduced or absent SNAPs and normal or mildly reduced motor conduction velocities and amplitudes [28, 552, 556, 560]. Needle EMG examination reveals chronic partial denervation in distal muscles with only rare fibrillation potentials [552]. Nerve biopsy should be considered when vasculitis is suspected because of an asymmetric onset, stepwise clinical course, acute/subacute progression, or greater-than-expected motor involvement. Only a few nerve biopsies have been reported in patients with SLE and a distal symmetric polyneuropathy. These biopsies revealed mild vasculitis or changes suspicious for a vasculitic neuropathy, but this data is insufficient to generalize to others with this phenotype [560, 566].

Inflammatory Demyelinating Polyradiculoneuropathies

Inflammatory demyelinating neuropathies are another PNS manifestation of SLE. Many case reports have documented the occurrence of chronic progressive or relapsing demyelinating neuropathies reminiscent of CIDP [568–573]. If the number of published reports is an indication, CIDP occurs more commonly in SLE than any other CTD, with approximately half of the cases developing concurrently with SLE [569, 570, 572, 573]. The clinical and electrodiagnostic picture is indistinguishable from idiopathic CIDP. Although GBS is now one of the reportable SLE-related neuropsychiatric syndromes, reported GBS frequencies range from 0 % (multiple studies) to 5 %, suggesting that an acute demyelinating polyradiculoneuropathy is *not* a pathogenically related SLE syndrome. Since lupus patients exhibit multiple autoantibodies, it is appealing to postulate that "anti-nerve" autoantibodies might initiate the neuropathy in some patients, but no study has established a clear relationship between any autoantibody and inflammatory demyelinating neuropathies in SLE.

Entrapments

There is sparse information on the prevalence of entrapment neuropathies in SLE due, in part, to the fact that "mononeuropathy or mononeuropathy multiplex" is an ACR neuropsychiatric syndrome but not carpal tunnel syndrome or any other nerve entrapment. Several prospective clinical and electrodiagnostic investigations have revealed signs, symptoms, and/or nerve conduction evidence of carpal tunnel syndrome in 10 % of SLE patients [523, 547, 552, 554].

Cranial Neuropathies

Cranial neuropathy develops in ~3 % of SLE patients (data from 19 series). The most commonly affected nerves are the optic and cochlear. Optic neuropathies occur in about 1 % of patients and are often bilateral [574–576]. In case–control studies, sensorineural hearing loss has been identified with increased frequency in patients with SLE (16–21 %) compared to healthy controls [577, 578]. There are many reports of isolated cochlear, abducens, or vagal neuropathies (especially recurrent laryngeal nerve palsies) and less frequent cases of trigeminal sensory, oculomotor, and facial neuropathies [579–584]. The presumed mechanism is vasculitis-related ischemia, but optic neuritis can also ensue from CNS demyelination.

Other Phenotypes

There are rare reports of SLE-associated acute or chronic sensory ataxic neuronopathy [585, 586], neuromyotonia [587], bilateral phrenic nerve palsies [588], and motor neuron disease [589].

Treatment/Prognosis

Treatment of PNS involvement in lupus is tailored to the pathogenesis, severity, and tempo of the neuropathy. No controlled trials have been performed. Vasculitic neuropathies are usually managed with combination therapy [558, 561, 590]. Whereas prednisone monotherapy has been ineffective in the majority of reported cases of SLE-related vasculitic neuropathy [559, 560, 563, 564], CYC or CYC/CS produced complete or partial remission in almost all reported patients. Inflammatory demyelinating neuropathies are managed identically to the idiopathic cases. Acute cranial mononeuropathies are generally treated with CS. Symptoms usually improve or resolve, but recovery is more unpredictable for optic neuropathies, recurrent laryngeal nerve palsies, and sudden hearing loss [584]. Some patients with acute deafness have responded to plasma exchange [584]. For SLE-related optic neuropathies, treatment with IV methylprednisolone followed by high-dose prednisone is recommended [576].

Treatment decisions are most difficult for patients with the common distal symmetric polyneuropathy. Patients with this pattern of neuropathy who exhibit acute or subacute progression and nerve biopsy evidence of definite or probable vasculitis should be treated akin to the primary small- and medium-vessel systemic vasculitides. For patients who undergo nerve biopsy with a finding of nonspecific perivascular inflammation, a trial of high-dose CS alone is an acceptable but unproven option. Most patients with SLE who develop an indolent or nonprogressive distal polyneuropathy are treated symptomatically without undergoing nerve biopsy.

Systemic Sclerosis

Definition/Epidemiology

SSc (or scleroderma) is a complex disorder of unknown etiology characterized by alterations of the microvasculature, disturbances of the humoral and cellular immune system, and massive proliferation of collagen and extracellular matrix proteins, resulting in fibrosis of the skin, visceral organs, or both [591–593]. Scleroderma is classified as *localized* if restricted to the skin and *systemic* if other organs are affected [594]. The localized forms are rarely associated with neuropathy and will not be further discussed. SSc is, in turn, subdivided into *limited* and *diffuse cutaneous* forms [595]. Limited cutaneous SSc is defined by skin involvement that does not extend proximal to the knees or elbows. If both proximal and distal limbs and the trunk are affected, the disorder is termed diffuse cutaneous SSc. Facial involvement occurs in both types. Many patients with limited cutaneous SSc fulfill diagnostic criteria for CREST syndrome (*c*alcinosis, *R*aynaud's phenomenon, *e*sophageal dysmotility, *s*clerodactyly, and *t*elangiectasia) [596], but these findings may also occur in diffuse cutaneous SSc. The prevalence of SSc generally ranges from 50 to 300 cases per 1,000,000 and its annual incidence from 2 to 23 cases/million, excepting geographical/ethnic clusters [597, 598]. It affects all ages but is uncommon in children. The peak age of onset is the fifth decade. Women are three times more commonly affected than men [597].

Etiology/Pathogenesis

The etiology of SSc is unknown [592]. Environmental risk factors include CMV and parvovirus B19 infections and exposure to silica, polyvinyl chloride, epoxy resins, toluene, and trichloroethylene [591, 598]. As in the other CTDs, multiple weakly contributing genetic susceptibility loci are involved 603]. Most of the associated genes play a role in innate or adaptive immunity. Genetic factors may underlie not only disease susceptibility but also the predisposition to develop specific clinical phenotypes and specific SSc-associated autoantibodies. For example, the associated HLA genes primarily influence anti-centromere or anti-topoisomerase I antibody production, not the disease itself [591, 599].

The three cardinal pathogenic features are microangiopathy, cellular and humoral autoimmunity, and progressive visceral and vascular fibrosis [591, 600, 601]. The earliest pathologic change is damage to small arteries and microvessels in the skin and viscera. Endothelial injury results in dysregulated production of vasodilatory and vasoconstrictive factors, increased expression of adhesion molecules, enhanced permeability, activation of prothrombotic and fibrinolytic pathways, and proliferation/fibrosis of all layers of the vessel wall, resulting in widespread capillary loss and obliterative vasculopathy. Despite the diffuse microvascular loss, compensatory vasculogenesis is dysregulated and does not occur [602]. Skin biopsies in early stages of the illness show infiltration of CD4+ T cells and macrophages, suggesting that SSc may result from a primary immune microvasculopathy [591, 600, 601]. The activated CD4+ cells secrete Th2 and other pro-fibrotic cytokines [603]. B cells are also activated in lesional tissues, signified by the presence of multiple autoantibodies, polyclonal hypergammaglobulinemia, cryoglobulinemia, and increased RFs [591, 600, 604]. Autoantibodies directed against cell surface antigens and secreted proteins may play a pathogenic role in the disease, e.g., antibodies against fibroblasts (stimulatory), endothelial cells, PDGF receptor (stimulate fibroblasts), fibrillin-1 (activate fibroblasts), MMP-1,3 (inhibitory), and Nag-2 (induce endothelial cell apoptosis and activate fibroblasts) [603, 604].

Other antibodies are directed against ubiquitous autoantigens with no established pathogenic role [515, 592, 605]. Several mutually exclusive autoantibodies are specific markers of SSc and have strong associations with disease phenotype and HLA haplotypes. Examples include antibodies against Scl-70 or topoisomerase I (associated with diffuse cutaneous SSc, interstitial lung disease, severe cardiac involvement, increased mortality), centromere proteins CENP-A through F (limited cutaneous SSc, digital ischemia, isolated pulmonary arterial hypertension, calcinosis, decreased risk of death and pulmonary fibrosis), RNA polymerases I and III (diffuse cutaneous SSc, extensive skin involvement, renal crisis, increased mortality), U3 RNP/fibrillarin (diffuse cutaneous SSC, pulmonary arterial hypertension, interstitial lung disease, renal crisis, severe heart disease, myositis), and Th/T0 (limited cutaneous SSc, pulmonary fibrosis, pulmonary arterial hypertension, renal crisis) [515, 592, 605].

Fibrosis is triggered by and eventually replaces the inflammatory vascular phase [601, 603, 606, 607]. The primary mediator of fibrosis is deregulated TGF-β. It stimulates fibroblast proliferation, migration, differentiation, and production of collagen and matrix proteins. It also enhances PDGF and connective tissue growth factor (CTGF) production from fibroblasts, vascular smooth muscle cells, and endothelial cells. Activated by TGF-β, CTGF, PDGF, Th2 cytokines, IL-1/IL-6, stimulating autoantibodies, chemokines, tissue hypoxia, endothelin-1, and reactive oxygen species, fibroblasts then proliferate and secrete increased collagen, fibronectin, and other extracellular matrix proteins. The net result is an obliterative vasculopathy with dense fibrosis replacing the normal tissue architecture [606].

Clinical Presentation

Patients with SSc present with a sensation of tightness in the fingers associated with soft tissue swelling, pruritus, and hyperpigmentation [591–593, 608–611]. Joint pains, reduced range of motion, and a nonerosive inflammatory arthritis

(15 % of patients) are common accompaniments [612]. Onset is usually indolent in limited cutaneous SSc and more rapidly progressive in diffuse cutaneous SSc. In the ensuing weeks to years, the inflammatory edematous stage is superceded by a fibrotic phase, characterized by bilaterally symmetric skin thickening, hair loss, xerosis, hypohidrosis, and finger flexion contractures (Fig. 36.9). In diffuse cutaneous cases, similar skin changes and joint contractures emerge in the proximal limb. The affected skin eventually becomes atrophic and may ulcerate, especially on the dorsal PIP joints, fingertips, elbows, and malleoli. In the limited cutaneous form of the disorder, small areas of fingertip necrosis are common and autoamputation or acro-osteolysis may ensue. Telangiectasias and calcinosis also occur in the limited cutaneous form of the disease. In one-third of cases, the face is involved, resulting in a tight, shiny, featureless, masklike appearance (Fig. 36.10). Raynaud's phenomenon occurs in virtually every patient (>95 %). Patients with limited cutaneous SSc generally have severe Raynaud's for many years before the other clinical manifestations appear. In the diffuse cutaneous variant, Raynaud's usually appears coincident with the skin disease.

Virtually every organ is affected in SSc. Diffuse cutaneous SSc is associated with earlier and more prominent internal organ involvement than limited cutaneous SSc. The GI tract is affected in 80–90 % of patients, causing esophageal dysfunction (dysphagia, GERD), gastroparesis, gastric antral vascular ectasia with recurrent GI bleeding, lower GI bleeding from telangiectasia, fecal incontinence, and intestinal hypomotility with secondary bacterial overgrowth, malabsorption, vitamin B12 and D deficiency, pseudo-obstruction, constipation, diarrhea, and diverticular perforation [613]. Oral mucosal involvement produces xerostomia, dental caries, and periodontal disease. Myositis develops in 10–20 % of patients, but pathologic confirmation is often lacking. Up to 25 % develop hypothyroidism [593].

Serious pulmonary, renal, and cardiac manifestations may also occur. Pulmonary disease is the leading cause of death [614]. The two main types of pulmonary involvement are fibrosis-related interstitial lung disease and pulmonary arterial hypertension. Fibrosis is more common in diffuse cutaneous SSc. Interstitial lung disease occurs in 80–90 % of patients, but only 40 % develop symptoms. Pulmonary arterial hypertension emerges in about 10 %. Renal involvement develops in ~20 % of patients and predisposes to hypertension and proteinuria [615]. Scleroderma renal crisis, resulting from obliterative microvasculopathy of the kidneys, occurs in 10–15 % of patients with diffuse cutaneous SSc, manifesting with malignant hypertension and acute renal failure. Risk factors include extensive skin involvement, exposure to CS, and RNA polymerase I/III antibodies. Clinically important cardiac disease develops in 10 % of patients, with atrial and ventricular tachycardia, heart block, other cardiac conduction defects, pericarditis, myocarditis, valvular incompetence, and congestive failure [616].

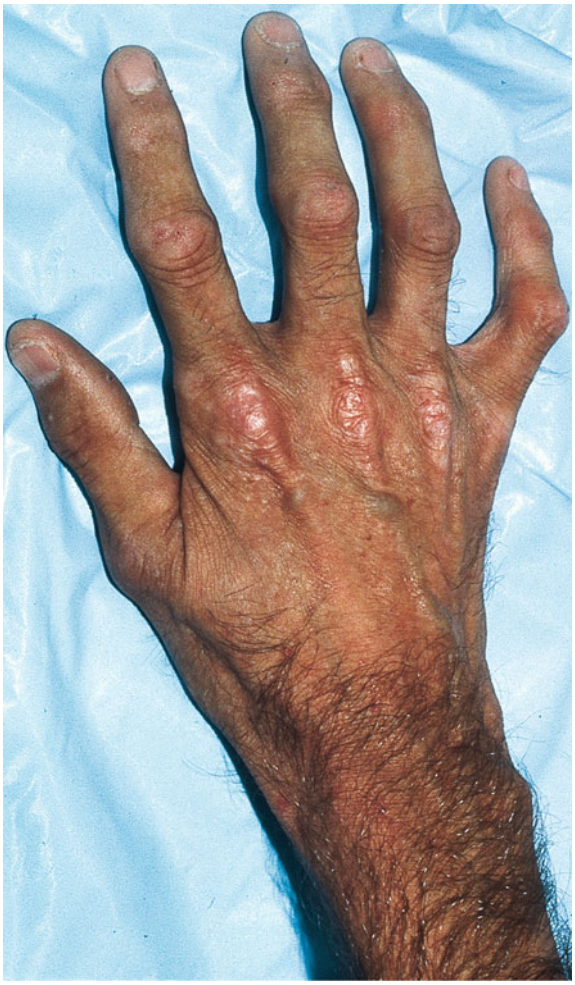

Fig. 36.9 This is a 32-year-old man with systemic sclerosis whose hands exhibit the characteristic skin changes of the disease, including hyperpigmentation, sclerodactyly, atrophy, and calcinosis, with secondary finger flexion contractures

Vasculitis

Vasculitis occurs uncommonly in SSc (1–7 % of patients in clinical reports and 9 % in one autopsy series) [608, 617–619]. MPO/PR3-ANCAs appear to be markers of systemic vasculitis in this disorder [620–622]. MPO or PR3-ANCAs occur in about 5 % of patients with SSc [623, 624]. Mean age of onset is 57 years. Patients with diffuse cutaneous SSc are more commonly affected than those with limited cutaneous SSc. Scl-70 antibodies occur in 70–75 % of patients. Most of the ANCAs target MPO. The most common clinical feature is rapidly progressive glomerulonephritis in 85 % of patients. Other manifestations include GI involvement (55–60 %), fever (40 %), alveolar hemorrhage (25 %), limb ischemia (10–15 %), skin vasculitis (10–15 %), and neuropathy (5 %) [625–628]. The most important differential diagnosis is

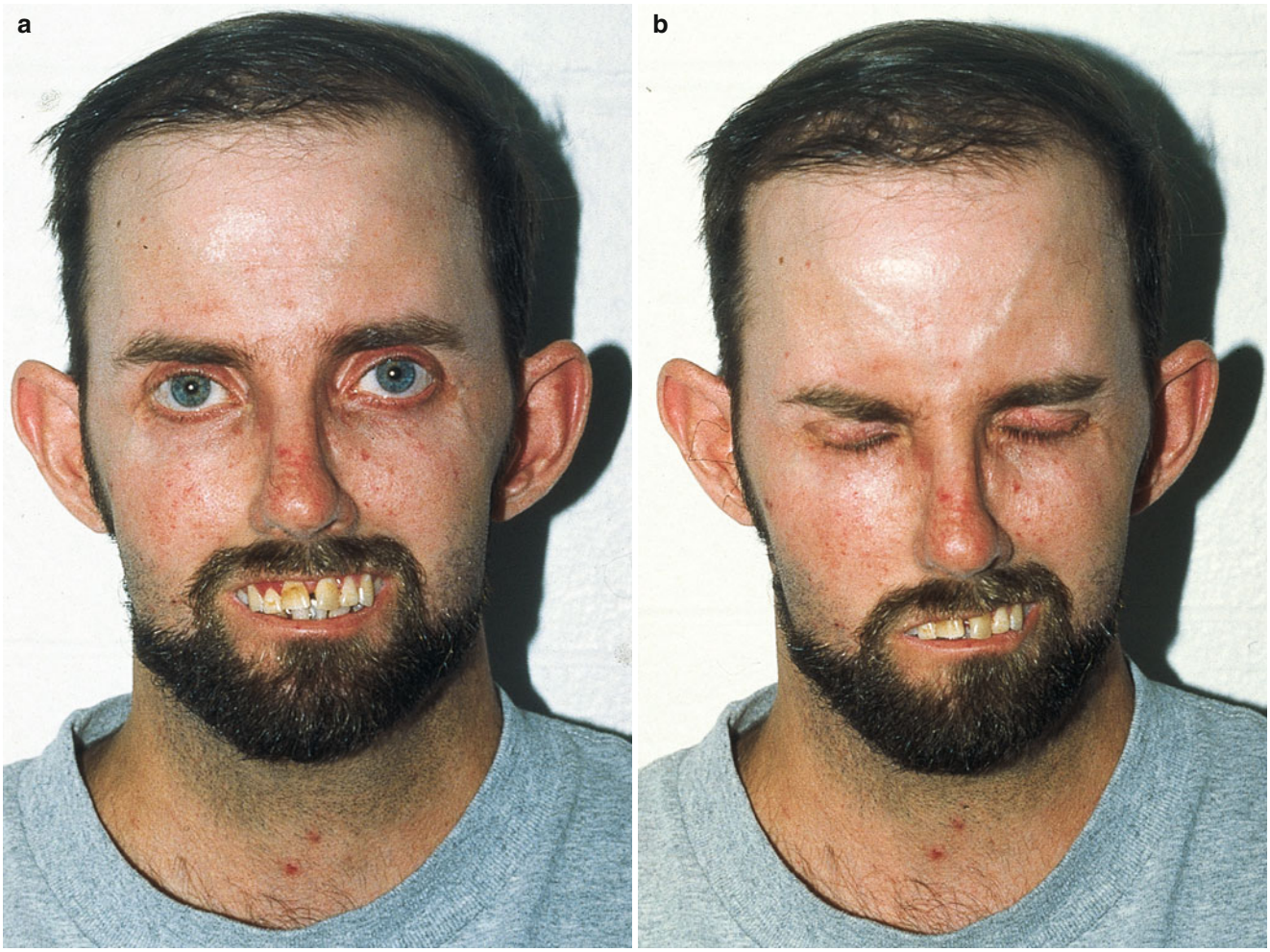

Fig. 36.10 These facial views of the same patient shown in Fig. 36.11 demonstrate the tight, drawn, masklike appearance typical of severe systemic sclerosis (**a**). This patient developed a right facial nerve palsy (**b**), which had partially resolved when this picture was taken

scleroderma renal crisis. In SSc patients with rapidly progressive renal failure, factors suggesting vasculitis are normotension, fever, elevated ESR, active urinary sediment, normocytic nonhemolytic anemia, alveolar hemorrhage, MPO-pANCAs, Scl-70 antibodies, and renal biopsy evidence of necrotizing, crescentic glomerulonephritis with small-vessel vasculitis.

Evaluation and Diagnostic Criteria

The clinical picture of SSc is sufficiently distinctive that the diagnosis is usually straightforward. In patients with mild disease, the differential diagnosis includes other CTDs that can be associated with Raynaud's phenomenon, environmental exposures that can cause scleroderma-like illnesses, and other scleroderma-like skin diseases such as scleredema, diabetic scleredema, scleromyxedema, stiff skin syndrome, chronic graft-versus-host disease, eosinophilic fasciitis, eosinophilia-myalgia syndrome, POEMS syndrome, nephrogenic systemic fibrosis, paraneoplastic sclerodermiform syndrome, amyloidosis, sarcoidosis, myxedema, and acromegaly [591, 593]. The ACR diagnostic criteria require either the one major criterion – proximal scleroderma (skin tightness, thickening, and non-pitting induration proximal to the MCP or MTP joints in the extremities or involving the face, neck, or trunk) – or two or more of the three minor criteria: (1) sclerodactyly, (2) digital pitting scars of fingertips or loss of substance of distal finger pad, or (3) bibasilar pulmonary fibrosis [629].

ANAs occur in 90–95 % patients [591, 593, 608, 611, 612]. Two mutually exclusive autoantibodies – anti-centromere and anti-topoisomerase I (Scl-70) – are highly specific (99 %) for SSc. Anti-topoisomerase I antibodies are found in 30–40 % of all patients with the disorder, 40–55 % of those with diffuse cutaneous SSc, and 15–25 % of those with limited cutaneous disease [605, 608, 611, 612, 630]. Anti-centromere antibodies are found in 30 % of all patients with SSc, 45–50 % of those with limited cutaneous disease, and only 5 % of those with the diffuse cutaneous subtype. Antinuclear antibodies directed against RNA polymerase III (5–20 % incidence) and Th/T0 (2–5 % incidence) are also highly specific for SSc [591, 605, 631]. In contrast to most

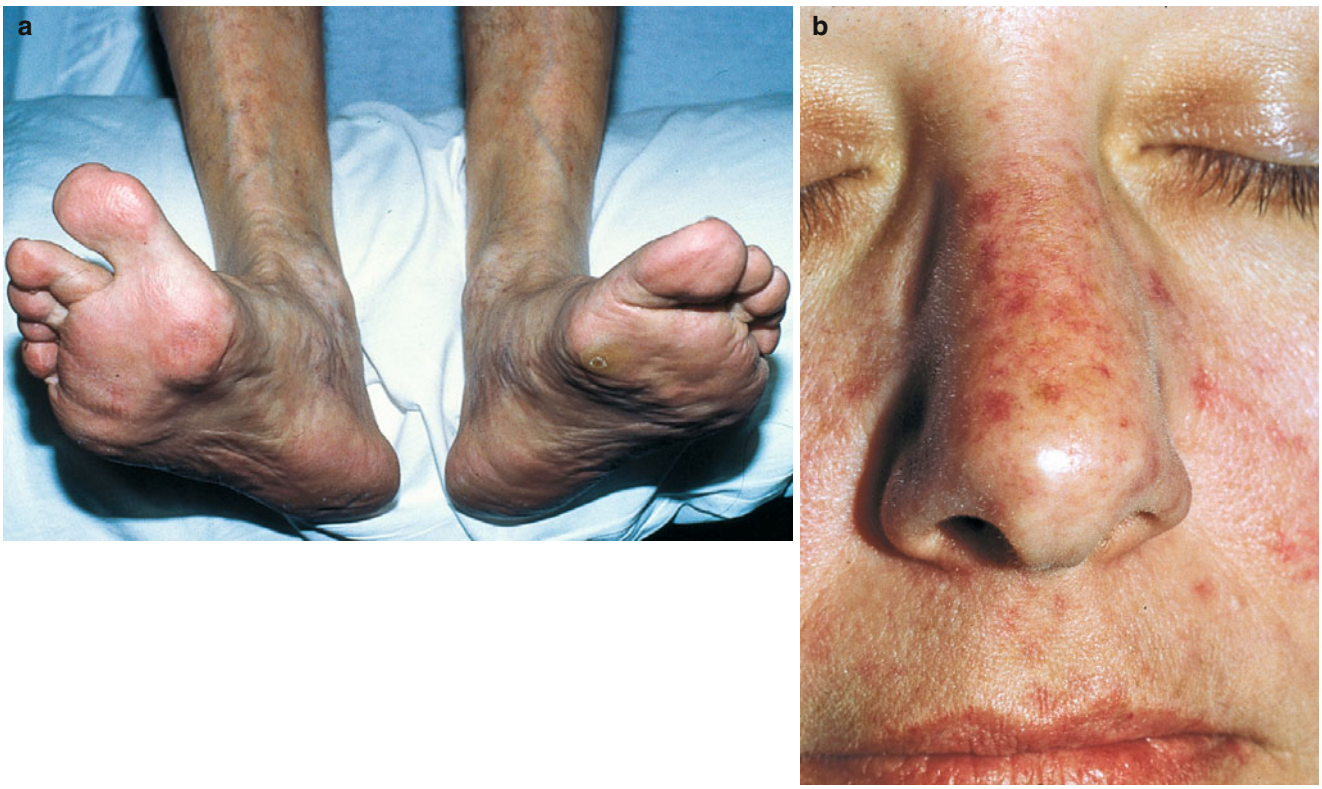

Fig. 36.11 This patient with known CREST syndrome (limited cutaneous systemic sclerosis) presented with distal sensory loss and slight weakness of left ankle dorsiflexion (**a**). She had characteristic small telangiectasias over her face (**b**)

CTDs, ESR is usually normal (mildly elevated in 25 % of patients) [592, 608]. Low-titer RFs occur in 25 % of patients [593, 608]. A mild anemia due to chronic inflammation is uncommonly present [593]. Chronic GI bleeding may result in iron-deficiency anemia, while macrocytic anemia can emerge with B12 or folate deficiency. Microangiopathic hemolytic anemia is a signature of renal crisis. Other cytopenias are uncommon.

Treatment/Prognosis

Treatment is generally symptomatic [591, 592, 632, 633]. Although no intervention has been proven to modify the natural history of the disease, autologous hematopoietic stem cell transplantation has emerged as a possible treatment for severe SSc [634]. In a 1-year RCT of oral CYC versus placebo for SSc-related interstitial lung disease, CYC was associated with modest but significant improvements in lung function, dyspnea, skin scores, and quality of life [635], but apart from a sustained impact on dyspnea, all of these effects were no longer apparent at 24 months [636, 637]. CS can be used for inflammatory joint symptoms, early edematous skin disease, serositis, myositis, and tenosynovitis, but they do not influence the progression of the disease [591]. Because high-dose CS increase the risk of renal crisis, CS should only be used in low doses for short periods of time. Other immunomodulatory agents have not been adequately studied, but MTX is sometimes used for skin involvement [633, 638]. Arthralgias can be treated with NSAIDs. There is no established anti-fibrotic treatment. Patients with Raynaud's phenomenon respond to calcium channel blockers, 5-phosphodiestease inhibitors, angiotensin II receptor antagonists, alpha$_1$-receptor blockers, serotonin reuptake inhibitors, topical nitroglycerin, and botulinum toxin A [639]. For digital ischemic ulcers, the endothelin-1 receptor antagonist bosentan reduces new ulcer development [640]. Short-acting ACE inhibitors are the drugs of choice for renal crisis. Proton pump inhibitors are used for reflux. Promotility agents can be tried for gastroparesis. Bacterial overgrowth responds to short courses of rotating antibiotics. Options for pulmonary artery hypertension include bosentan, sildenafil, and the prostacyclin analogues epoprostenol or treprostinil [641].

In patients with established disease, prognosis depends on the severity and extent of the cutaneous and visceral involvement [592, 593]. Patients with limited cutaneous disease and anti-centromere antibodies have a more favorable prognosis, characterized by indolent progression, less common visceral involvement, and 10-year survival of 75 % [609]. On the other hand, their skin manifestations do not usually regress, and progressive pulmonary artery hypertension can emerge late in the clinical course (10–15 %). In contrast, patients with diffuse cutaneous SSc and anti-Scl-70 antibodies exhibit

more rapid progression, increased internal organ involvement, and 10-year survival of only 55 % [609]. In patients with this form of the disease, cutaneous fibrosis usually plateaus after 2–4 years. Paradoxically, skin thickening then slowly regresses, to the extent that patients with late-stage disease often have soft and atrophic skin. Internal organ involvement almost always evolves in the first 4 years of the illness. Age- and gender-adjusted standardized mortality rates (SMRs) are two to five times higher than the general population [642]. Survival has improved in recent decades, but the SMR has not significantly changed [642, 643]. Death usually results from pulmonary causes. Patients with SSc are also at mildly increased of developing a malignancy, most commonly a lung or breast cancer [644].

Neuropathies

Traditionally, PNS involvement has been considered rare in SSc [608–610, 645]. However, in neurologically focused studies, clinical or electrodiagnostic examination evidence of a polyneuropathy has been demonstrated in 15–20 % of patients [646–648]. Skin biopsy studies suggest a much higher incidence of subclinical neuropathy, especially in the later stages of the illness [649, 650].

Vasculitic Neuropathy

Vasculitic neuropathy occurs in ~5 % of cases of ANCA-associated vasculitis/SSc overlap. The incidence of vasculitic neuropathy in all SSc patients is under 1 % [618, 651, 652]. Of reported patients with SSc and vasculitic neuropathy, 80 % had CREST syndrome or limited cutaneous SSc (Fig. 36.11) [618, 625–628, 651–656]. An asymmetric/multifocal, distally accentuated, sensory-motor neuropathy is almost always observed.

Distal Sensory-Motor or Sensory Polyneuropathy

Sensory-motor and sensory polyneuropathies in SSc often begin asymmetrically, but more than 50 % evolve into a distal, symmetric pattern [646–648, 651, 652, 657–661]. These neuropathies can be either motor or sensory predominant [660, 661]. Electrodiagnostic studies typically demonstrate axonal features. Although the asymmetric onset in many patients suggests vasculitis, there are few nerve biopsy-proven cases of vasculitis [618, 626, 652–654, 656]. In non-vasculitic cases, nerve biopsies have revealed myelinated nerve fiber loss and axonal atrophy; endoneurial, perineurial, and epineurial fibrosis; and endoneurial microangiopathy [659, 660, 662]. In these patients, the neuropathy may have resulted from a chronic noninflammatory vasculopathy or endoneurial connective tissue proliferation.

Other Phenotypes

Isolated reports have described SSc patients with a slowly progressive ataxic sensory neuronopathy [663]; progressive, painful, asymmetric/non-length-dependent, sensory axonal neuropathy or neuronopathy with mixed or small-predominant involvement [661, 664]; acute or chronic progressive brachial plexopathy [648, 665, 666]; or distal acquired demyelinating symmetric (DADS) neuropathy with anti-myelin-associated glycoprotein antibodies [667].

Entrapments

Somewhat surprisingly, symptomatic carpal tunnel syndrome has been reported in only 5 % of patients with SSc [647, 658, 668, 669], but prospective nerve conduction studies have revealed asymptomatic carpal tunnel syndrome in 10 % [646, 650, 670, 671]. Pressure palsies of other nerves are more rarely reported, to include ulnar mononeuropathies at the wrist and elbow, meralgia paresthetica, and median nerve entrapment in the forearm caused by thickened fascia [670–674].

Cranial Neuropathies

Trigeminal sensory mononeuropathy is the most common cranial neuropathy in SSc, affecting 3 % of patients [646–648, 656, 657, 669, 675–677]. Its features are identical to the trigeminal sensory neuropathy associated with pSS and SLE. It occurs bilaterally but asymmetrically in 60 % of cases. In a minority of patients, trigeminal sensory mononeuropathy is but one manifestation of a more widespread, multifocal sensory neuropathy or neuronopathy [661, 676]. It can be accompanied by facial nerve involvement [676]. This disorder is assumed but not proven to result from an inflammatory ganglionitis of the trigeminal sensory ganglia. There are also rare reports of optic, trochlear, and recurrent laryngeal mononeuropathies [678–680]. Audiovestibular involvement is reported more commonly [681].

Treatment/Prognosis

No treatment has been shown to consistently improve the sensory-motor polyneuropathy or trigeminal sensory neuropathy in these patients. Entrapment neuropathies can be managed with NSAIDs, splinting, or surgical release. Patients with vasculitic neuropathy can be treated with the combination regimen discussed above. Patients with asymmetric sensory neuropathies or neuronopathies and brachial plexopathies sometimes respond to IVIg, CS and CYC, or CS alone [663–666].

Conclusion

Neuropathy in the setting of a CTD usually occurs in patients with a previously diagnosed condition. In these patients, the neurologist's primary goal is to determine whether the neuropathy is due to immunologic injury or some other process, such as entrapment or medication effect. Less commonly, neuropathy is the predominant or presenting feature in a patient with no known CTD. In these cases, the clinician must integrate the neurologic findings with other clinical and laboratory data to

formulate a diagnosis that explains all the patient's manifestations and can be confirmed through further testing or biopsy. A fundamental goal must always be to determine if vasculitis is the cause of the neuropathy; as such, a diagnosis has a profound effect on therapy.

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Nonvasculitic Ischemic Neuropathies

37

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Compartment Syndromes

Introduction

Although various subgroups of what are now designated compartment syndromes (CSs) were first well described during the latter half of the nineteenth century, apparently the term was not used until 1963. Moreover, it was only in the 1960s and 1970s that modern concepts regarding these disorders evolved, when it became apparent that a considerable number of what had appeared to be diverse clinical entities actually were merely different manifestations of a common underlying pathophysiology [1–4].

A CS can be "… defined as a condition in which the circulation and function of tissues within a closed space are compromised by increased pressure within that space" [5]. Characteristically, the structures at risk are muscles, usually accompanied by major peripheral nerves, which are injured when their blood supply (i.e., their capillary perfusion) is reduced below a level required for tissue viability [6–9].

Established CSs generally have four components: (1) a closed space formed by a limiting envelope, which may consist of fascia alone, fascia and bone, epimysium, skin, or various external boundaries (e.g., circumferential bandages); (2) pressure elevation within that space due to an increase either in its volume or contents, usually resulting from fluid accumulation (e.g., interstitial or intracellular fluid) or a restriction of its size; (3) reduced perfusion of the muscles and nerves within the compartment because their microcirculation is compromised by the elevated pressure; and (4) progressive ischemic damage of the intracompartmental structures if the pressure is not reduced rather promptly. Noteworthy is that normal compartment pressures typically range from 0 to 8 mm Hg. Consequently, most injurious elevated pressures usually are much less than mean arterial pressure at approximately 100 mm Hg [4, 6, 10–12].

Approximately 50 different compartments have been described in humans, and all can be sites of CSs (Table 37.1). However, only a relatively few of these are of significance to physicians in other than a few surgical specialties, because only they compromise major muscles or neural structures or occur with any appreciable frequency [4].

Relatively few of the compartments contain solely nerve fibers (i.e., no muscles) [4, 8, 9, 13]. The CSs involving these have been designated "neurovascular injuries" or "hemorrhagic compressive neuropathies." "Acute carpal tunnel syndrome" often refers to abrupt median nerve compression within the carpal tunnel [14–16]. However, this term is highly inaccurate and misleading, since neither the clinical nor the electrodiagnostic (EDX) features seen with it are similar to the classic presentation of carpal tunnel syndrome (CTS) (i.e., chronic compression of the median nerve beneath the transverse carpal ligament) [17].

The CSs are divided into two general types: (1) acute and (2) chronic, the former has by far the most serious potential medical consequences [18–20].

Acute CSs (ACSs) result from a number of traumatic and nontraumatic conditions. Their pathophysiology is rather well established, and typically, they require prompt treatment to prevent irreparable damage, principally to muscles, nerves, and sometimes even limbs. They are one of the few "surgical emergencies" in the field of neuromuscular disorders; hence, they fall primarily in the realm of emergency,

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Table 37.1 Elements of seven of the major compartments

Compartment	Boundaries	Structures Compromised
Forearm volar	Antebrachial fascia, ulna, radius, interosseous membrane	*Muscles*: flexor carpi ulnaris, palmaris longus, flexor carpi radialis, pronator teres (superficial group), flexor digitorum superficialis, flexor digitorum profundus, flexor pollicis longus, pronator quadratus (deep group) *Nerves*: median, ulnar, anterior interosseous
Medial brachial fascial	Medial brachial fascia	*Muscles*: none *Nerve*: components of infraclavicular brachial plexus, especially median
Anterior of leg	Crural fascia, anterior intermuscular septum, fibula, tibia, interosseous membrane	*Muscles*: tibialis anterior, extensor digitorum longus, extensor hallucis longus, peroneus tertius *Nerve*: deep fibular (peroneal)
Deep posterior of leg	Transverse intermuscular septum, fibula, tibia, interosseous membrane	*Muscles*: tibialis posterior, flexor digitorum longus, flexor hallucis longus *Nerve*: posterior tibial
Psoas	Psoas major epimysium, psoas fascia	*Muscle*: psoas major *Nerve*: lumbar plexus
Iliacus	Psoas major, psoas minor, iliacus fascia	*Muscle*: iliacus *Nerve*: femoral[a]
Gluteal (3 separate compartments)	Fascia lata	*Muscles*: gluteus maximus, gluteus medius and minimus, tensor fascia lata *Nerves*: sciatic,[a] inferior gluteal, superior gluteal

[a]Not actually within the involved compartment but may be compromised by swelling of nearby muscle

orthopedic, and vascular physicians. Although ACSs may affect any compartment, the majority involve those in the leg (especially the anterior compartment) and those in the forearm (especially the volar compartment). In contrast to ACSs, *chronic CSs* (CCSs) are due almost entirely to exercise and overuse, many aspects of their pathophysiology are debated, they do not require urgent operative treatment (unless they convert to ACSs, a relatively rare occurrence), they generally resolve spontaneously with rest, and the majority are managed by sports medicine physicians [6, 18]. The majority of CSSs affect solely the compartments of the leg, especially the anterior and the posterior compartments.

Some terms require definition. Those ACSs that are evolving or developing are referred to as "incipient," whereas those that are full blown are labeled "established." Frequently, CCSs are referred to as "exertional," "exercise induced," "recurrent," or "intermittent" [6, 7, 18–21]. Two severe complications of ACSs, both of which result from irreversible damage to the muscles within the affected compartment(s), merit specific names: Volkmann's ischemic contracture and crush syndrome. *Volkmann's ischemic contracture (Volkmann's contracture, Volkmann's ischemia)*, which is an old term, is the end-stage clinical manifestation of an ACS in which marked tissue (muscles, nerves, etc.) necrosis has evolved into muscle fibrosis and resultant contractures; it is most commonly used to describe the limb deformities resulting from a volar forearm ACS. *Crush syndrome (Bywaters syndrome)* concerns the systemic manifestations that follow ACS-induced massive rhabdomyolysis: myoglobinuria, acidosis, hyperkalemia, and third-space fluid loss, which can produce renal failure, shock, and cardiac arrhythmia. Typically, this entity results from multiple ACSs or involvement of a large muscle mass within a single compartment (e.g., gluteal ACS) [1, 2, 22, 23].

Etiology and Pathogenesis

A considerable number of specific causes for ACSs have been described. Most result from an increase in compartment contents (volume), including: (1) post-ischemic edema (e.g., following arterial injuries, thrombosis, or embolism; vascular surgery; tourniquet application; and prolonged immobilization with limb compression), (2) blood accumulation (e.g., anticoagulation, bleeding disorders, and infiltrating transfusions), and (3) combinations of edema and blood accumulation (e.g., following fractures and soft tissue injuries). The less common mechanism of ACS production is boundary restriction, which reduces compartment size and thereby decreases the amount of swelling necessary to cause elevated intracompartmental pressure. It results from casts, splints, circumferential dressings, eschars from burns, and closure of fascial defects.

An underrecognized and potentially treatable form of ACS is the medial brachial fascial compartment (MBFC) syndrome that follows injury to the axillary or brachial artery (e.g., after axillary angiography, axillary regional block during which the axillary artery is punctured, or local trauma) [24, 25]. The

MBFC is formed by tough brachial fascia that extends from the axilla to the elbow and contains the axillary sheath, which in turn envelopes the axillary vessels and infraclavicular brachial plexus, including the terminal nerves. Puncturing the axillary vessels can lead to hematoma or pseudoaneurysm formation within the MBFC – and not just within the axillary sheath, which is friable and ruptures at relatively low pressure – and sufficiently elevated intracompartmental pressure leads to injury of the median, ulnar, radial, musculocutaneous, axillary, and suprascapular nerves (in descending order of frequency) [24, 25]. Various combinations of terminal nerve injury also occur, and most commonly involve the median and ulnar nerves, followed by the median, ulnar, and radial nerves [24, 25]. The MBFC syndrome is thus a form of "neurovascular injury" that differs from other forms of ACS in that the MBFC solely contains blood vessels and nerves and, thus, does not involve muscle necrosis.

Overall, the most common causes for ACSs are fractures, soft tissue injuries, arterial injuries, prolonged limb compression, and burns; muscle exertion, in contrast, seldom produces ACSs [6, 11, 26, 27]. Regardless of etiology, ultimately one mechanism is responsible for all ACSs: elevated intracompartmental pressure, which decreases the arterial-venous (A-V) pressure gradient across the capillary circulation, thereby lessening tissue perfusion. If untreated, ischemia results and may produce irreversible changes, depending upon the degree and duration of the elevated pressure (i.e., pressure and time thresholds) [5, 6, 10].

Concerning CCSs, there is essentially only one etiology: exertion/overuse. Nonetheless, the exact cause (e.g., increased contents vs. decreased space) in a particular patient often is unclear, and the pathogenesis is less well understood. Various theories have been proposed to explain why repeated contraction of the muscles within the compartment causes the intracompartmental pressure to rise to a point that symptoms are produced [6, 7, 18–21].

Clinical Presentation

The first symptom of ACS, which may appear many hours after the inciting event, is pain, localized to the involved compartment. Typically, it is deep, out of proportion to what would be expected based on the clinical situation, persistent, and increasingly severe over time. When the compartment is more superficially located (e.g., anterior compartment of leg), it may appear swollen, as well as tense and tender to palpation. As the process evolves, paresthesias, hypesthesias, and then anesthesia appear in the distribution of nerves that traverse the affected compartment. Ultimately, the muscles within the compartment and those innervated by nerves that traverse the compartment become paretic and, if the process is unrecognized or untreated, paralyzed [4, 6, 11, 27].

In contrast to most forms of ACS, symptom onset in the context of the MBFC syndrome can occur within minutes or hours but on occasion may be delayed for days or even a few weeks. This time lapse is due to slow accumulation of blood within the compartment or, alternatively, to the time it takes for pseudoaneurysm formation of the axillary or brachial vessel to occur. In either event, the lag in symptom onset may contribute to a delay in recognition of the disorder [24, 25]. As with other forms of "neurovascular injury," the MBFC syndrome is not accompanied by signs of arterial occlusion (i.e., pallor or pulselessness); furthermore, the degree of ecchymosis overlying the site of puncture or trauma and the presence or absence of a palpable hematoma do not correlate with the amount of compression that occurs within the MBFC [24, 25].

With CCS, typically the only symptom is pain localized to the involved compartment (or, occasionally, more general in distribution) and that is provoked by exercise, relieved by rest, and, often, that progressively worsens with exercise over time. Muscle tenderness or tenseness may be present, and rather infrequently, there may be paresthesias in the distribution of nerves that traverse the compartment or weakness of muscles within the compartment. All these symptoms regress with cessation of exercise, but, at times, a CCS converts to an ACS [6, 18–21].

Differential Diagnosis

The clinical presentations of both ACS and CCS are similar in various respects to many other disorders. For ACS, these include primary arterial injury, deep venous thrombosis, cellulitis, and primary nerve injury (particularly when a limb fracture coexists) [10, 11, 27]. For CCS, these include vascular claudication, various strains and sprains, stress fractures, tendonitis, and periostitis. Moreover, lower limb CCS may be confused with shin splints and tenosynovitis of the anterior tibial or peroneal muscles, whereas the symptoms of upper limb CCS may mimic the referred pain caused by cardiac abnormalities [10, 18–21].

Evaluation and Diagnosis

The early recognition of an ACS is crucial because irreversible damage may be prevented with prompt treatment. Generally, the diagnosis is based on the clinical presentation; formal pressure measurements may or may not be necessary. The clinician must possess a high index of suspicion whenever conditions favorable for the development of an ACS are encountered. Pain, more severe than anticipated from the primary problem, usually is the first and most important symptom of a developing ACS. When it is absent, nearly always

there are coexisting central or peripheral nervous system disorders that mask it. The first objective finding, which may be difficult to confirm in many patients and not detectable at all in others, is a palpably tense, swollen compartment accompanied by tenderness along the extent of the compartment, rather than being localized to the site of injury. Often, there is pain with passive stretch of the muscles within the compartment. Sensory deficits are the first signs of concomitant nerve ischemia. Typically, decreased sensation to pain and light touch is demonstrated in the distal sensory distribution of the nerve or nerves that traverse the involved compartment. Weakness of muscles within the compartment, or of muscles innervated by nerves that traverse the compartment, is a late finding with ACS; it indicates that, unless intracompartmental pressure is promptly reduced, irreversible damage to muscles and nerves is imminent. A critical point worth reiterating is that ACSs characteristically are not associated with substantial impairment of the distal limb circulation (except in the presence of a major arterial injury). Consequently, absent pulses, poor capillary filling, and skin pallor generally are not seen. This is because the elevated intracompartmental pressure, although substantial enough to collapse capillaries and thereby cause ischemia of the contents within the compartment, typically is well below the mean arterial pressure and, therefore, does not restrict blood flow in major arteries that pass through the affected compartment [10–12, 27].

Actual measurements of the intracompartmental pressure can be performed at the bedside. Various techniques for doing so have been described by different investigators. Currently, the two most commonly used are the slit catheter and the miniature transducer-tipped catheter [6, 11]. Unfortunately, there is no general agreement on what pressure value is critical to trigger decompression, in part because the pressure threshold depends on the patient's blood pressure. The most widely quoted pressures, in this regard, are those above 30–45 mm Hg (in absolute terms) and those within 4–10 mm Hg of diastolic blood pressure [6, 10, 11, 28]. Noteworthy is that in a recent article, two of the leading investigators in the field recommended that "… when possible, physicians should weigh clinical signs more heavily than (intra-compartmental pressures) when diagnosing compartment syndromes" [6]. This admonition stems mainly from the fact that substantial pressure gradients may be present within an affected compartment, presumably due to local hematomas. As a result, pressure measurements obtained at one site may be quite misleading [6]. If the differential diagnosis includes arterial injury, then arteriograms and Doppler blood flow studies may be required. Similarly, in the appropriate clinical situations (e.g., severe or multiple ACSs), plasma creatine kinase (CK) levels and urinalysis for myoglobinuria are also helpful. When abnormal, these changes typically reflect the presence of an established, rather than an incipient, ACS [11, 28].

It is imperative that the MBFC syndrome be immediately recognized on clinical grounds alone since the likely period for reversible peripheral nerve injury appears to be less than 4 h [24, 25]. The role of ancillary diagnostic tests (e.g., CT, MRI, Doppler blood flow studies, and compartment pressure measurements) is less well defined, and their routine use is not recommended unless they can be performed within the 4-h "golden period" from the time of symptom onset.

Identifying ACSs based on clinical findings, however, is particularly difficult in those patients who are uncooperative (e.g., children), are obtunded, or have known peripheral nerve deficits from other causes in the affected limbs. In these situations, compartment pressure measurements often are critical for diagnosis as long as they do not substantially delay treatment [11, 24, 29].

The majority of CCSs can be diagnosed solely by the history. In marked contrast to ACSs, there typically are no clinical findings, although swelling over the involved compartment, particularly immediately after exercise, has been reported. The diagnosis must be confirmed (and the specific compartment involved identified) by direct measurement of intracompartmental pressures. Although techniques are available for continuous pressure monitoring before, after, and, particularly, during exercise, there is no consensus regarding what results are crucial for diagnosis. Various investigators have championed: (1) comparing pre-exercise and intraexercise pressure measurements, (2) intraexercise absolute pressure measurements, (3) the value of pressure drops during the intraexercise relaxation phase, and (4) postexercise pressure measurements [4]. This marked divergence of opinion most likely results from the lack of understanding of the underlying pathophysiology of CCS [18–21]. Some elaborate laboratory procedures may ultimately prove to be more helpful for diagnosis; thus, thallous chloride scintigraphy with single-photon emission computed tomography (SPECT) scanning, near-infrared spectroscopy, and methoxyisobutyl isonitrile (MIBI) perfusion imaging has impressed some investigators [20, 30]. In contrast, magnetic resonance imaging (MRI) has not proven itself to be particularly helpful, although, along with venograms, triple-phase bone scans, and bone X-rays, it may assist in excluding some of the disorders included in the differential diagnosis [18–21].

Treatment and Management

Developing and early established ACSs generally are surgical emergencies requiring decompression of the affected compartment by operative means, usually fasciotomies. In the case of the MBFC syndrome, immediate puncture site exploration is indicated to identify and remove the compressive hematoma or repair the pseudoaneurysm within the compartment. Occasionally, however, depending upon the

cause, elevated compartmental pressure can be reduced nonoperatively. Examples of the latter include preventing limb elevation, which reduces the mean arterial pressure, thereby causing decreased blood flow to the compartment and removing constricting structures (e.g., casts, dressings) that are serving as external inelastic envelopes [10, 11, 27]. Decompression of a compartment will only result in symptom reversal if it is performed within a certain time period. Unfortunately, this is dependent upon many unknown factors (e.g., exactly when in the course the pressure became elevated and the exact degree of elevation throughout the time period) [6]. Consequently, only general guidelines are applicable. Nonetheless, the sooner the compartmental pressure is lowered, the more likely recovery is to follow. Operations performed within eight, and especially four, hours after neurological symptoms have appeared frequently are successful. Conversely, operations performed after 12 or more hours seldom have any beneficial effect [4, 10, 11, 13, 24, 25].

The only two major ACSs for which the most appropriate treatment is debated are those that compromise the lumbar plexus and the femoral nerve (psoas and iliacus ACSs, respectively). Some investigators believe that these can be managed conservatively [4, 15].

There are a variety of treatments for CCS. In many instances, because the condition is self-limited, patients elect to merely stop or reduce the activity that causes symptoms (e.g., long-distance running), rather than seek active therapy. Correction of factors thought to contribute to the development of CCSs (e.g., inappropriate footwear, running on hard surfaces, excessive foot pronation, and increased activity) is advocated, although none of these have been shown scientifically to be detrimental. Conservative treatments include rest, ice, heat, physiotherapy, steroid injections, analgesics, and antiinflammatory medications. While these may reduce the symptoms to varying degrees, they do not actually cure the underlying condition. Even complete rest for prolonged periods is ineffective in this regard. In general, the only means of successfully treating a CCS is elective fasciotomy, although the more recent development of minimally invasive techniques (e.g., endoscopic compartmental release) appears to offer an alternative and at least equally effective therapy compared to conventional open fasciotomy [18–21, 31].

Prognosis

With ACS, the ultimate outcome depends on whether the elevated intracompartmental pressure is reduced before the muscles and nerves within the compartment sustain irreversible damage. With successful decompression, all symptoms usually promptly resolve. Conversely, with no or unsuccessful treatment, the results usually are grave, often permanent, and sometimes life-threatening. These include muscle fibrosis with resulting contractures, permanent nerve deficits, limb deformities (including abnormalities of limb growth in children), and, when muscle necrosis is extensive, renal failure, sepsis, shock, and hyperkalemia [7, 10, 11, 23].

Generally, the prognosis following fasciotomy for CCS is very good, although it may vary somewhat, depending upon the specific compartment affected. Thus, in one study, anterior leg compartment decompression had much more satisfactory results, overall, than did deep posterior leg compartment decompression. Whether elective surgery in these instances is successful may also depend on the management in the immediate postoperative period. The effects of fasciotomies are maximized if limb mobilization occurs at the earliest possible moment, to prevent the healing fascia from reverting back to its original size [18–21].

Ischemic Monomelic Neuropathy

Introduction

Ischemic monomelic neuropathy (IMN) is a relatively rare ischemic neuropathy in which nerve damage occurs in the more distal portion of a limb because of compromised blood flow in a major artery of the limb located more proximally, either by noncompressive occlusion or diversion. Often, the ischemic event is relatively short-lived (e.g., few hours at most) [32]. Both upper and lower limb IMN occur (UL-IMN and LL-IMN, respectively), which differ somewhat in several respects. UL-IMN is less common, invariably unilateral, and nearly always iatrogenic in nature. In contrast, LL-IMN is more common, occasionally bilateral, and iatrogenic or noniatrogenic in nature. A feature characteristic of every IMN, regardless of etiology or limb affected, is that the clinical and EDX changes are most severe in the most distal portion of the limb and shade proximally (i.e., they demonstrate a marked distal-to-proximal gradient). Moreover, at any given limb level, nerve fibers composing different peripheral nerves are affected in a uniform manner. This is more obvious with UL-IMN, wherein the amount of involvement of median and ulnar nerve fibers in the hand invariably is very similar, if not identical, as judged both by severity of motor and sensory nerve conduction study (NCS) amplitude reduction and by the amount of fibrillation potentials and motor unit action potential (MUAP) loss on needle electromyography (EMG) [32, 33].

Etiology and Pathogenesis

Nearly all the reported cases of UL-IMN have occurred following placement of A-V shunts in the antecubital fossa or proximal arm for dialysis purposes in patients with end-stage

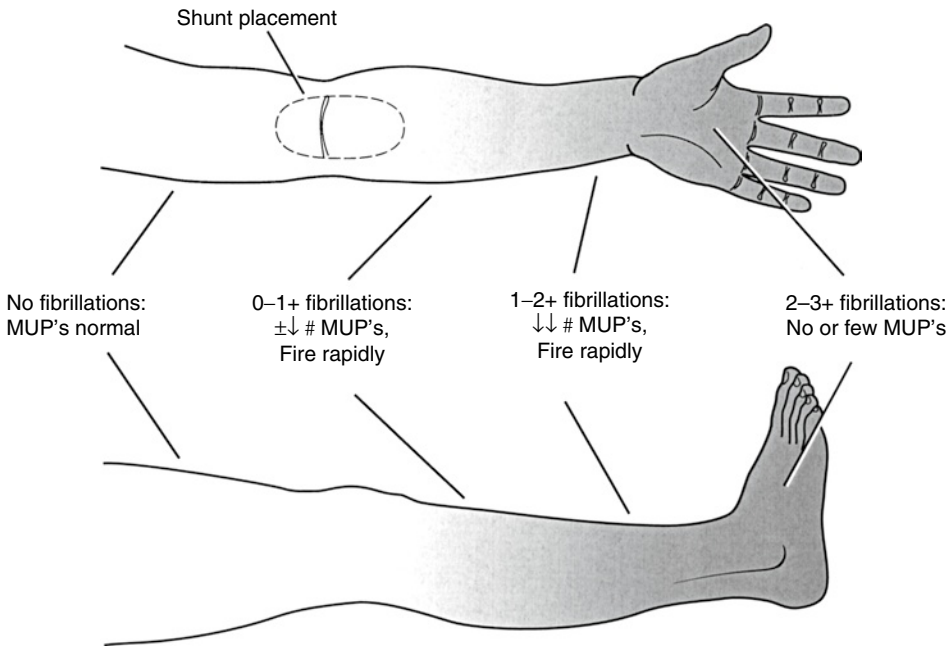

Fig. 37.1 The distal-to-proximal gradient of needle EMG examination changes characteristically seen with ischemic monomelic neuropathy (Modified with permission from Wilbourn and Levin [4])

diabetic nephropathy [34–37]. Conversely, LL-IMN has had several reported causes initiated by compromise of the following arteries: the proximal popliteal (embolus), the superficial femoral (intra-aortic balloon pump placement, cardiopulmonary bypass cannulation, and thrombosis), the iliofemoral (thrombosis), and the aortoiliac (embolus) [32, 33]. At least two patients reportedly have developed LL-IMN (one unilateral, one bilateral) following the use of either ergotamine tartrate or a semisynthetic ergot alkaloid, methysergide [38, 39]. However, in both patients, some features – clinical, EDX, or both – were inconsistent with IMN, particularly in regard to the requisite distal-to-proximal gradient of abnormalities (see below).

The etiologic factor common to all cases of IMN is a sudden decrease in arterial blood flow to the more distal portion of the limb. This produces limb ischemia which, although severe enough to damage distal nerve fibers and their associated symptoms and signs, is too brief or otherwise insufficient to cause muscle or skin damage. The underlying pathology with IMN is axon loss. Its striking distal-to-proximal distribution and its marked uniformity at any given limb level are demonstrated most convincingly during the needle electromyography (EMG) portion of the EDX assessment (Fig. 37.1) [32]. One group of investigators has suggested that, very early in its course, UL-IMN may present as multifocal ischemic conduction block in the forearm, principally or solely along the median nerve. Using motor NCS, they demonstrated such lesions in three patients (all diabetic, two immediately following A-V shunt placement, and one with sudden occlusion of the brachial artery in the upper arm). All showed rather rapid resolution of these conduction blocks following treatment [40]. One major problem with this concept is that similar conduction blocks, to the same degree and at the same limb level, were not demonstrated along the motor fibers of the ulnar nerves in the affected limbs. Yet, by definition, with UL-IMN, the distal median and ulnar nerves (as well as the distal radial nerve) consistently are damaged to the same degree.

Clinical Presentation

The cardinal symptom of IMN is pain – usually deep and burning in character, constant, and persistent – in the hand or foot, sometimes with coexisting paresthesias. Certain patients, particularly those with UL-IMN, also complain of distal sensory deficits. Weakness of intrinsic hand and foot muscles invariably is present, usually accompanied by wasting with lesions of more than several weeks duration; this is much more clinically obvious with UL-IMN. The symptoms usually appear promptly after the inciting event, but they often do not reach maximal intensity for several days [32, 33].

On neurological examination, there is impairment of all sensory modalities in a prominent distal-to-proximal gradient. Generally, no sensory changes are detectable proximal to the midforearm or midcalf. Weakness, and sometimes atrophy, is evident in the more distal limb muscles and is always most severe in, if not limited to, the intrinsic hand and foot muscles. Signs of ongoing vascular insufficiency (coolness, pallor, atrophic skin or hair changes, absent pulses) or muscle infarction (induration, tenderness, contractures) are not usually present.

Differential Diagnosis

Delays in diagnosis and treatment are common with IMN. Frequently, it is confused with other disorders, such as psychogenic limb pain and peripheral nerve injuries caused by malpositioning on the operating table. In addition, LL-IMN has been mistaken for lumbosacral radiculopathy, sciatic nerve infarction, and intermittent claudication, whereas UL-IMN symptoms have been attributed to plexopathies resulting from axillary blocks, to CTS, and, particularly, to "steal syndrome" ("venous sink") [32–35, 37, 41]. Concerning the latter, a "steal phenomenon" exists to some degree distal to most A-V fistulas. In the arterial segment distal to the fistula, a major drop in pressure occurs, which can be alleviated to some degree by collateral arterial circulation. However, if the decrease is severe enough, blood flow through the artery distal to the fistula may actually reverse, producing distal ischemia. Hye and coworkers view A-V fistula formation as producing two distinct clinical syndromes: (1) the typical "steal syndrome," in which distal limb ischemic changes (nonhealing wounds, impending tissue loss) overshadow mild distal neurological changes (rest pain, sensory loss), and (2) IMN, in which severe neurological dysfunction in the distal limb occurs with little to no evidence of concurrent ischemic tissue damage. These two syndromes are readily distinguished from one another by clinical examination, EDX studies, and digital arterial pressure indices [37].

Evaluation and Diagnosis

The laboratory test of most value in the diagnosis of IMN is the EDX examination. Unfortunately, these are usually conducted well after the optimal time period for symptom reversal (e.g., surgical correction) has lapsed. On NCSs, the sensory and motor responses, recording distally, typically are low in amplitude or unelicitable, with the sensory NCSs the most severely affected. Latencies and conduction velocities, when obtainable, characteristically are within normal limits unless a generalized polyneuropathy, customarily diabetic, coexists. If NCSs are performed using more proximal recording sites, the recorded amplitudes are either less effected or normal. On needle EMG, fibrillation potentials and MUAP dropout are prominent in the intrinsic hand or foot muscles while less severe, in a graded manner, in progressively more proximal muscles. Also, there is no evidence of coexisting ischemic muscle damage (i.e., the MUAPs that can be activated do not show suggestive "myopathic" configurational changes). In summary, the EDX changes with IMN are identical to those seen with a dying back axon loss polyneuropathy, except that they usually involve only a single limb. Advanced age, a concurrent axon loss polyneuropathy, and coexisting mononeuropathies (particularly CTS with UL-IMN) can render the EDX results less definite [32, 33]. In certain instances, arteriograms, digital artery pressure measurements, and other vascular tests are of value, primarily for excluding other disorders [37, 41, 42].

Treatment and Management

Any ongoing ischemia should be promptly rectified, if possible. This typically is the case with UL-IMN, in which shunt ligation is indicated [32, 34, 36, 37, 41]. With the majority of LL-IMN, however, the arterial compromise already has been corrected by the time the patient is assessed. The pain of IMN may be helped by a variety of neuropathic pain medications; sympathectomies have yielded variable results [32, 33]. Concerning UL-IMN, Hye and coworkers have recommended preventive measures, such as awareness of the disorder developing following A-V shunt placement, avoiding the dominant limb, and performing careful postoperative assessments [37]. Valji and coworkers have noted that, with IMN-induced hand pain, arteriograms are of no value and should not be performed [42]. Of importance is that a correct diagnosis not only results in appropriate therapy but also, given the many iatrogenic cases, often prevents inappropriate litigation.

Prognosis

A variable outcome is seen among patients with IMN. In some, the symptoms are only partially relieved by treatment and, thus, persist indefinitely, whereas in others, the pain ceases spontaneously after several months, even when there is no clinical or EDX evidence of axon regeneration [32, 33, 35]. Regarding UL-IMN, there are several reports of substantial improvement, both clinically and electrically, occurring within several months of graft ligation [36, 37, 41].

Acute Ischemic Mononeuropathy/Plexopathy

Introduction

Most mononeuropathies and plexopathies resulting from acute ischemia are due to small vessel disease (e.g., vasculitis), acute compression, or ACS. Occasional cases of abrupt onset ischemic mononeuropathy result from large vessel atherosclerotic disease, either directly or indirectly (i.e., their surgical repair), as well as from several miscellaneous causes [43, 44]. Thus, these entities are both iatrogenic and noniatrogenic in nature. Typically, either the lumbosacral plexus or various lower extremity nerves (e.g., femoral, sciatic, common peroneal) are affected. In many reports, however, the exact location of the lesion is unclear (e.g., lumbosacral

plexus vs. cauda equina, femoral nerve vs. lumbar plexus, sciatic nerve vs. sacral plexus) [45–47].

Etiology and Pathogenesis

Among those cases resulting from atherosclerotic disease or its surgical treatment, the blood vessels characteristically involved are the distal aorta, the common iliac artery, the internal and external iliac arteries (particularly the former), and the branches of the internal iliac artery. Noteworthy is that the cauda equina and at least the sacral plexus, if not the lumbar plexus as well, receive their principal blood supply from branches of the internal iliac artery [46, 48]. The neural structures most often reported to have sustained ischemic damage are the lumbosacral plexus and the femoral nerve [44–55]. Immediate causes for the ischemia have varied in these instances, but probably the single most common is abdominal aortoiliac surgery, usually for ruptured aneurysms and less often for infected grafts and graft failures [44–60]. Nonsurgical etiologies include atherosclerotic stenosis or occlusion of the iliac arteries or branches arising from them (e.g., the superficial femoral artery), radiation therapy to the pelvic region, the use of intra-aortic balloon pumps, and intra-arterial injections of various medications into the iliac or gluteal arteries [45, 48, 55].

The immediate cause for the nerve fiber ischemia – specifically, why it occurs in a few of the many patients who have the same vascular problems and undergo the same surgical procedures – often is unclear but is thought to be multifactorial, including significant periods of hypotension, emboli, failure to heparinize, and, particularly, cross clamping of the major vessels [47, 53]. Attempts to correlate the level of vascular compromise with the particular neural structure damaged by ischemia have met with limited success; for example, isolated ischemic femoral neuropathies have resulted not only from common iliac artery occlusion but also from cross clamping of the aorta [52, 53]. Wohlgemuth et al. described a series of patients who experienced intermittent ischemia of the lumbosacral plexus due to stenosis of the common iliac and internal iliac arteries related to muscular effort [48]. Sciatic neuropathies and common peroneal neuropathies resulting from ischemia have also been reported. The former, in one series, all resulted from lesions of the common iliac artery [45, 56].

Diabetic lumbosacral radiculoplexus neuropathy (*DLRPN*), known by many other names, including the Bruns-Garland syndrome, diabetic lumbosacral radiculopathy, and diabetic amyotrophy, is one form of noniatrogenic lower limb ischemic neuropathy [57]. The pathophysiology of DLRPN is postulated to be an immune attack resulting in microvasculitic-induced ischemic nerve injury. This condition is clinically and pathologically indistinguishable from nondiabetic lumbosacral radiculoplexus neuropathy (LRPN) [57].

Clinical Presentation

With atherosclerotic disease, sensory loss and weakness typically appear abruptly in the distribution of the affected neural structures, or, when they result from various vascular reconstructive procedures, the features first become apparent in the postoperative period. The changes present prior to such surgery often have been overshadowed by symptoms of acute vascular insufficiency (cold, painful, pulseless limb with persistent resting pain) or by progressive limb claudication [52, 53]. The rare patient who has exercise-induced ischemia of the lumbosacral plexus presents with pain in the buttocks and leg, sometimes accompanied by hypesthesias and less often weakness, following muscular exertion (e.g., walking) [48]. With DLRPN, the typical presentation is sudden or subacute onset pain and weakness in an asymmetric distribution. The weakness often has an initial predilection for proximal nerve fiber segments (e.g., roots) and quickly spreads to adjacent segments and the contralateral side (i.e., territorial extension) so that by the time of evaluation the disorder often is bilateral and widespread and may appear symmetric [57, 58]. All patients with DLRPN should be specifically queried about preceding weight loss as approximately two-thirds will have an associated weight loss of greater than 10 lbs. There appears to be a correlation of DLRPN with the earlier stages of type 2 diabetes (compared to the more indolent and less painful form of polyneuropathy associated with long-term disease). In summary, DLRPN tends to affect diabetics with better glycemic control, lower body mass index, and less long-term complications of diabetes (e.g., retinopathy or nephropathy) [57, 58].

Differential Diagnosis

Lumbosacral plexopathy must be distinguished from conus medullaris and cauda equina lesions. Ischemic femoral neuropathies can be confused with psoas and iliacus ACSs, which also compromise femoral nerve fibers. Sciatic neuropathies must be differentiated from incomplete cauda equina lesions and sacral plexopathies, as well as from IMN [32, 43, 45, 53].

Evaluation and Diagnosis

Determining the level of the lesion – that is, the exact neural structure affected – often is difficult. A detailed neurological examination, typically supplemented with EDX and neuroimaging studies, is required. Lumbosacral plexopathies usually can be distinguished from distal spinal cord and cauda equina lesions because frequently (but not always) they are unilateral, and they do not cause urinary incontinence. They are distinguished from proximal peripheral nerve lesions because

their motor and sensory deficits and reflex abnormalities are outside the distribution of an individual peripheral nerve. With lumbosacral plexopathies, neuroimaging techniques may show abnormalities in the plexus but not in the spinal cord or lumbosacral roots. The classic EDX presentation of a lumbosacral plexus lesion is low amplitude or unelicitable sensory responses and low or normal motor responses on NCS in the affected limb. On needle EMG, there are fibrillation potentials and MUAP loss in limb muscles innervated by multiple roots or peripheral nerves but sparing the ipsilateral lumbosacral paraspinal muscles. The NCS profile in DLRPN and nondiabetic LRPN likewise reflects low amplitude or unelicitable sensory and motor amplitudes, but, in contrast to pure lumbosacral plexus lesions, fibrillation potentials are frequently identified in the paraspinal muscles, and the overall EDX abnormalities tend to be much more widespread than the clinical deficits [58]. Unfortunately, in some patients, definite EDX localization remains elusive. For example, when the sensory NCS responses are unelicitable bilaterally, the patient has an underlying polyneuropathy, is of advanced age, or has some other potential explanation for the absent sensory responses. In addition, although the presence of paraspinal muscle fibrillation potentials excludes an isolated plexopathy, their absence does not exclude an intraspinal canal lesion [43, 46]. Quantitative sensory and autonomic testing in patients with DLRPN and nondiabetic LRPN shows unequivocal sensory abnormalities in the foot, leg, and thigh, as well as moderate to severe autonomic dysfunction [58].

Exercise-induced ischemia of the lumbosacral plexus has characteristic clinical features. Typically, patients are asymptomatic and have normal neurological examinations when inactive but developing pain and progressive sensory and motor deficits in the distribution of the plexus during exertion. Buttock pain is a common manifestation and may be the first symptom to appear with exercise [48]. Ischemic femoral neuropathies are diagnosed clinically by the presence of weakness, sensory loss, and reflex changes limited to the femoral nerve distribution. Pertinent negative findings include the absence of a groin mass, groin tenderness, and pain on hip flexion (all of which characteristically are seen with iliacus ACS). On EDX studies, the femoral NCS response typically is very low in amplitude or unelicitable, and, on rare occasions, a saphenous NCS response may be unelicitable on the affected side while present in the contralateral, uninvolved limb. On needle EMG, there are fibrillation potentials and MUAP loss in the quadriceps muscles but not the thigh adductors or ipsilateral lumbar paraspinal muscles [43, 45].

Although both components of the lumbosacral plexus (i.e., lumbar and sacral) may be damaged simultaneously by ischemia, each component can be injured in isolation. Whenever this occurs, lumbar plexopathies must be distinguished from femoral neuropathies, and sacral plexopathies must be differentiated from high sciatic neuropathies.

Most ischemic sciatic neuropathies present with motor and sensory deficits in the distribution of the common fibular (peroneal) and tibial nerves (i.e., all abnormalities are distal to the knee). Thus, they apparently affect the sciatic nerve distal to the motor branches supplying the hamstring muscles. Consequently, the latter, as well as more proximally situated muscles innervated by the same roots (e.g., glutei and lumbosacral paraspinal muscles), appear normal [43]. When assessed within a few months after onset, either by clinical or EDX examination, ischemic sciatic neuropathies are readily separated from lower extremity IMN because, unlike the latter, they manifest a definite line of demarcation, separating abnormal from normal. However, as time passes, and the more proximally located muscles are reinnervated via collateral sprouting, these sciatic neuropathies exhibit a distal-to-proximal gradient of abnormalities that appear very similar to those seen at the onset of IMN [32].

Treatment and Management

Only supportive therapy is available for established iatrogenic ischemic plexopathies and most ischemic peripheral neuropathies. This includes analgesics, physical therapy, and orthotics (if necessary). Similarly, there is no proven treatment for DLRPN or nondiabetic LRPN; the best evidence to date suggests that pain, but not sensorimotor function, may improve with intravenous methylprednisolone. Results from an ongoing randomized, double-blind, placebo-controlled study comparing high- and low-dose intravenous immunoglobulin against placebo in patients with DLRPN are not yet available [59]. Unfortunately, preventive measures for these disorders are essentially unknown [43]. Intermittently appearing lumbosacral plexopathies resulting from exercise can be treated with interventional radiological therapy (e.g., stent placement in the common or internal iliac arteries) [48].

Prognosis

Unlike ischemic lower spinal cord and cauda equina lesions, established ischemic lumbosacral plexopathies and patients with DLRPN and nondiabetic LRPN may recover, although many show delayed and only partial recovery [43, 46, 49, 59]. In contrast to the uncertain prognosis of ischemic plexopathies, femoral nerves damaged by ischemia typically improve considerably with the passage of time. For example, one patient who presented with virtual paralysis of the quadriceps muscles had an "excellent return of function" 1 year after onset [52, 53]. Although definitive information is sparse, ischemic sciatic neuropathies probably would also improve substantially.

Chronic Limb Ischemia

Chronic limb ischemia, characteristically involving one or both lower extremities, is almost invariably caused by atherosclerotic occlusion of the arterial vascular system, also known as peripheral arterial disease (PAD). For more than a century, investigators have attempted to demonstrate – first using clinical and pathological studies and later supplementing them with EDX studies – an association between the chronic ischemia in these limbs and damage to peripheral nerve fibers. Unfortunately, despite the great number of reports on the subject that have appeared over the years, no consensus has been achieved. Instead, far too often, the published results have been contradictory. Controversies include (1) whether the ischemia itself results in definite clinical abnormalities and, if so, what these consist of; (2) whether nerve damage caused by ischemia can be demonstrated pathologically; and (3) whether EDX changes unequivocally attributable to nerve ischemia can be found and, if so, how they present [4, 43, 44, 60]. The term "ischemic neuritis" aptly illustrates the problem. Although it has been used for decades to describe the lower extremity pain (burning, often diffuse, and particularly severe at night) and hyperpathia reported by patients with peripheral vascular disease, "In fact, there is no direct evidence to relate these symptoms in patients with arteriosclerotic occlusive disease to nerve fiber damage" [60].

There are cogent reasons for the controversies surrounding PAD and the peripheral nerve fiber injury that may or may not result from it. First, chronic limb ischemia is not stereotyped in its presentation. Rather, it varies greatly in degree from one limb to another. Thus, the clinical, pathological, and EDX manifestations of PAD are on a continuum. At one extreme is asymptomatic PAD, demonstrable only with various diagnostic vascular studies. At the opposite extreme is the severely compromised limb manifesting persistent rest pain and impending distal gangrene. Between these two extremes is the limb that is normal at rest, which exhibits intermittent claudication with exercise [44]. Second, "… in comparison to the extensive physiologic and pathologic investigations of impaired circulation of the brain, such studies of peripheral nerve have been meager and monotonously incomplete" [60]. Many of the reported EDX studies on the subject, for example, consisted of only one or two NCSs, often with only conduction velocities reported (no response amplitudes), or needle EMG of only one or two muscles [4]. Third, many of the reports have lacked adequate controls. Fourth, patients with diabetes mellitus were included in the study population in some investigations [4, 44, 60]. Finally, several of the reported studies focused on strictly unilateral PAD, with the contralateral, uninvolved limb serving as a control. Unfortunately, in many of these patients, the limb temperatures differ, with the affected limb being cooler; these temperature differences alone often could explain the relatively slight NCS differences reported between them [4].

Even though the evidence is conflicting, it appears likely that at least some patients with PAD develop nerve damage in the affected limb(s) because of the chronic ischemia present. This view is supported by two relatively recent reports on the topic. England and coworkers, after having previously observed histologic evidence of denervation in gastrocnemius biopsies from the symptomatic limb in patients with unilateral PAD, detected both histologic and EDX evidence of such changes in another series of patients [61]. All six of the patients in the latter group were considered to have unilateral "mild-to-moderate" PAD, presenting as stable intermittent claudication with no neurological changes in the symptomatic limbs. On EDX studies, they found significant abnormalities only on the needle EMG, specifically suggestive chronic neurogenic MUAP changes in several muscles assessed distal to the knee. These were confirmed by quantitative EMG studies performed on the gastrocnemius muscles in the symptomatic and asymptomatic limbs. The authors concluded that either the "distal motor axons or motor nerve twigs in or near the denervated muscles" had been compromised by ischemia that occurred during the bouts of intermittent claudication that their patients had experienced. This nerve damage, in turn, leads to chronic denervation and reinnervation in the affected muscles [61]. Papapetropoulou and coworkers performed clinical and EDX studies on 40 patients with more severe unilateral PAD. Nearly half (45 %) of their patients had neurological abnormalities on clinical assessment, consisting of depressed Achilles tendon reflexes, distal sensory abnormalities, or, less often, slight muscle weakness. On routine needle EMG, the authors found no evidence of chronic partial denervation. However, on bilateral quantitative EMG analysis of the tibialis anterior and medial gastrocnemius muscles, they detected MUAP changes (increased mean duration and mean amplitude) in the symptomatic, but not the contralateral and asymptomatic, limbs. Moreover, they noted that even though several of the NCS results in the symptomatic limbs were still within normal limits in absolute terms, they were significantly different from those in the control limbs. They concluded that routine EDX studies simply are not sensitive enough for detecting neuromuscular changes caused by PAD, although mild abnormalities are present [62].

The treatment of the ischemic nerve damage in these instances essentially is similar to the symptomatic therapy provided for any painful polyneuropathy [43]. Noteworthy is that these nerve alterations may not be alleviated by restoration of the blood supply of the affected limb. Thus, Hunter and coworkers performed EDX studies on ischemic lower extremities both before and after operative revascularization [63]. They found that the postoperative results were either unchanged or worse than the preoperative ones. Their data suggest that ischemic polyneuropathies resulting from PAD have a poor prognosis. Unfortunately, this conclusion can neither be confirmed nor refuted by clinical

studies, because none has been reported that documents prognosis over a long time period [43].

Frostbite

The human body can sustain both local and systemic cold-induced injuries (referred to as frostbite and hypothermia, respectively) [64]. Frostbite is defined as localized tissue injury resulting from exposure to temperatures below the freezing point of intact skin [6, 65, 66]. All actual frostbite entails some – at least minimal – tissue destruction; the term "frostnip" is applied to the transient numbness and blue-white discoloration that affects the face or fingertips after cold exposure, that promptly resolves with rewarming, and that leaves no evident tissue damage [67, 68]. Historically, most reports of frostbite concerned military personnel. More recently, however, frostbite occurring in rural and urban civilian populations has been described [65, 66]. Pertinent risk factors include homelessness, increased participation in outdoor winter recreational activities, alcohol consumption, illicit drug use, psychiatric illness, and vehicular trauma or failure (leaving occupants with inadequate protection from the elements). Psychiatric illnesses were so prominent in certain urban frostbite studies that some medical centers now advocate psychiatric screening in all such patients [65, 66, 69]. At present, adult males between 30 and 49 years of age constitute the highest risk group (men outnumber women by a ratio of 10 to 1 or more) [66]. The distal extremities, particularly the feet, account for more than 90 % of reported frostbite injuries. Less often, the ears, nose, cheeks, and penis are frostbitten [66, 70].

The pathogenesis of frostbite is quite complex. It can be divided into direct and indirect injury with three phases. Surprisingly, the direct injury at which most therapy is aimed at limiting or preventing is probably of relatively limited clinical significance compared to the indirect injury [65–67]. Direct injury occurs during the prefreeze phase and a portion of the freeze-thaw phase. During the prefreeze phase, superficial tissue cooling results in microvascular vasoconstriction and endothelial leakage. This occurs when the skin temperature is below 10 °C (but not yet at or below freezing, 0 °C) [65, 67]. During the freezing phase, large ice crystals form in the extracellular fluid, causing increased extracellular osmotic pressure. This, in turn, produces fluid shifts from the intracellular space to the extracellular space that results in intracellular dehydration and in membrane lipoprotein complex denaturation. When approximately one-third of the cellular volume is lost, the cells collapse and die [65, 67, 70]. The amount of permanent damage resulting from direct injury is linked to the total duration of freezing, and, unfortunately, there is no effective therapy for this component of frostbite except rewarming [65, 70]. The indirect injury portion of frostbite occurs during the thaw portion of the freeze-thaw phase and during the vascular stasis and progressive ischemia phase that manifests during rewarming [65, 67]. The majority of tissue destruction takes place during, or immediately after, the thaw phase and is "possibly preventable and potentially reversible" [65]. The vascular stasis and progressive ischemia stage, which occurs during the first few hours after tissues are thawed, is characterized by progressive microvascular collapse, affecting first venules and then arterioles. These result from a number of adverse events occurring near simultaneously, including (1) intense cold-induced local microvascular constriction, (2) intravascular thrombosis resulting both from vascular endothelial damage with platelet clots forming at the damaged regions and from increased blood viscosity that causes red blood cells to form clumps and occlude small blood vessels, and (3) arteriovenous shunting. Due to these processes, failure of capillary wall integrity occurs, and plasma protein leaks into the extracellular space, with resultant edema formation and more cell destruction, which produces histamine release and more edema. Because of the endothelial damage, the hypoxia, and the local thrombosis, inflammatory mediators are released, particularly prostaglandin F_2 and thromboxane A_2. These, in turn, trigger vasoconstriction, platelet aggregation, and blood vessel thrombosis, leading to further ischemia. Their release peaks during rewarming [65, 67, 70].

The clinical features of frostbite are rather stereotyped [70]. In the *prefreeze stage*, the first symptoms are sensory nerve dysfunction, consisting of cutaneous sensory loss (numbness). Clinical examination at this point reveals abnormalities in light touch, pain, and temperature. These are due to vasoconstrictive ischemia and neurapraxia involving the nerve fibers, which are very susceptible to cold, similar to muscles and much more than connective tissue [64, 65, 67, 70]. These changes usually are accompanied by edema. At this stage, patients often complain of the hands or feet being "clumsy." During the *freezing stage*, the direct injury of frostbite occurs and is divided into two groups: superficial and deep. *Superficial frostbite* causes minimal, if any, tissue loss. On examination, before rewarming, the damaged areas appear painful but supple (i.e., the skin indents to pressure), and sensation is intact on formal testing. After thawing, either no blisters appear or large ones develop that contain only clear fluid. With *deep frostbite*, there is usually significant tissue loss. On examination, the area is anesthetic, has a blue-gray skin discoloration, and does not indent (i.e., feels "wooden"). After thawing, small hemorrhagic blisters appear, the skin continues to feel wooden, and a black dry eschar may develop [65–67, 70]. If partial tissue destruction occurs, intermittent pain may appear during ongoing cold exposure.

The optimal treatment of frostbite injury is quite complicated, and its details are beyond the scope of this chapter. It can be divided into three phases. In the "pre-thaw field phase," the

most important factor is to prevent uncontrolled or partial rewarming during transport, which can be disastrous in regard to tissue loss. It is much preferable, in general, to maintain the tissue in the frozen state until proper thawing can occur. The "rewarming phase," for anything but relatively minor frostbite, should occur in a hospitalized setting, preferably in a specialized center, such as one devoted to burns. During this phase, rigid protocols are followed, with rewarming achieved by the limb(s) being placed in a water bath containing a mild antibacterial agent (povidone-iodine or chlorhexidine). More recent recommendations are for a lower water bath temperature at 37–39 °C for 15–30 min (water temperatures outside this narrow range can increase tissue damage) [71]. Significant pain usually occurs during rewarming as tissue perfusion is reestablished. Commonly, an initial dull, continuous ache is present that evolves into severe throbbing pain 48–72 h after rewarming; this can persist for weeks (until demarcation occurs) [67, 68, 70]. During the "post-thaw phase," one of the most difficult tasks is to determine the extent of tissue loss that will ultimately occur. Consequently, most authorities recommend avoiding amputation until demarcation of nonviable tissue is evident. It has been noted that "the amount of tissue eventually salvaged often exceeds even optimistic initial estimates" [67]. Consequently, the adage usually followed in this regard is "frostbite in January, amputate in July" [65, 66]. Early surgical intervention, in the form of fasciotomies, in the immediate "post-thaw" scenario, is required for ACS [71]. The role of adjunctive therapies, including hyperbaric oxygen, vasodilators, tPA, and sympathectomy, is reviewed elsewhere [71]. Even when tissue loss is not prominent, long-term residuals are common. In one series, 65 % of patients manifested such problems. Most of them are due to direct nerve fiber damage or to one of its complications: residual abnormalities in sympathetic tone [67]. These consist of residual pain ("ischemic neuritis"), sensory loss, vasomotor dysfunction, cold intolerance, hyperhidrosis, pigment changes, and skin atrophy [65, 67, 70].

Hand-Arm Vibration Syndrome

That vibration can be one of the occupational causes of secondary Raynaud's phenomenon was first reported in 1911, although the most influential article on the subject appeared in 1918. Initially caused by the use of pneumatic drills and referred to as "vibration white finger," the disorder was renamed "hand-arm vibration syndrome (HAVS)" in 1985 by international consensus [70–74].

HAVS is reported to have three components: (1) a circulatory disturbance (i.e., vasospasm with finger blanching [secondary Raynaud's phenomenon] which is invariably present), (2) sensorineural changes (principally limited to the fingers), and (3) various hand and forearm abnormalities (mainly skeletal) [72, 73].

The majority of attention initially was focused on the vascular disturbances, because they were the most obvious clinical manifestations. Thus, workers using a handheld vibrating tool experience attacks of finger blanching on exposure to cold, usually accompanied by numbness and decreased sensitivity of the affected finger(s). Initially, only the tip of one or more fingers is affected, particularly the most exposed finger (e.g., the index finger that holds the "trigger" of the vibration tool). Eventually, however, as this disorder progresses, all fingers may be affected throughout their length. Generally, the palms are not involved. Each attack lasts anywhere from 1 to 60 min, and they are especially common in the morning, particularly during the winter months. With continued exposure to vibration, the attacks become more frequent and prolonged. They cease when the hands are warmed but then are replaced by hyperemia and pain [72]. In addition to the vascular problems, sensory disturbances occur with HAVS. Initially, these consist of paresthesias, numbness, and sometimes pain of the fingertips that are experienced during, and immediately after, each use of vibration tools and also during blanching attacks. Soon, decreased sensitivity and a loss of temperature perception are noted in the affected fingers. With continued vibration exposure, these intermittent sensory complaints become constant. Ultimately, they are joined by motor changes, resulting in decreased strength and manual dexterity of the intrinsic hand muscles [72]. With prolonged use of pneumatic percussive tools that vibrate at a low frequency (less than 40 Hz), wrist and elbow osteoarthrosis can develop [72].

Vibration tools known to cause HAVS include pneumatic drills and hammers, electric grinders and polishers, and petrol-driven chain saws. These tools are used in mining, foundries, road construction, tree cutting, and in many manufacturing plants [73]. Typically, there is a latent period between the initial exposure to vibration and the onset of symptoms. This latent period is variable and depends upon the tool vibration frequency, the total time of exposure, handgrip strength, climatic conditions, and individual susceptibility [72]. In general, HAVS does not occur until patients have had more than 1,000 h of exposure to vibration tools [72]. Once present, the symptoms increase with the intensity of the vibration exposure and the exposure time [73]. In England, it was recently estimated that approximately one out of 25 (4 %) workers exposed to vibration has moderate to severe HAVS [72].

Finger biopsies of patients with HAVS have shown (1) substantial thickening of the muscular layers of the arterial walls; (2) demyelination of peripheral nerve fibers; and (3) an increase in the amount of connective tissue, resulting in both perivascular and perineural fibrosis [72].

In regard to the neural component, several types of mechanoreceptors in the skin respond to vibration and may suffer vibration damage. These consist of fast-adapting receptors

(FA-1, Meissner's corpuscles; FA-2, Pacini's and Golgi-Mazzoni corpuscles), which react solely to skin deformation, and slowly adapting receptors (SA-1, Merkel's cell neurite complexes; SA-2, spindle-shaped Ruffini's nerve endings), which respond both to constant skin deformation and to moving stimuli [75]. Initially, only the FA-2 receptors are injured, but with more severe sensory loss, deterioration of both FA-1 and SA-1 receptors also occurs. In addition, much of the vascular phenomenon presumably is due to autonomic nervous system dysfunction. This is thought to be on a central level, due to sympathetic hyperactivity and parasympathetic depression [72].

The diagnosis of HAVS depends on a history of exposure to vibration, coupled with suggestive symptoms in the absence of other possible causes. A number of laboratory procedures, most of which assess the status of the vascular system, can be performed in an attempt to confirm the clinical diagnosis. These include motor and sensory NCS, measures of distal sensory appreciation (vibration, thermal, two-point perception), cold provocation testing, vibrotactile thresholds, thermal thresholds, grip strength, aesthesiometry, and both two-point and depth perception [72, 73, 76]. However, these are not standardized, and many are reported to be of "questionable reliability" [76].

The differential diagnosis of HAVS includes, for the vascular symptoms, primary and secondary Raynaud's phenomenon and, for the neurological symptoms, CTS. The exact relationship between HAVS and CTS is quite controversial. The basic source of the dispute revolves around the question of whether the finger pain and paresthesias experienced by patients with HAVS simply are due to coexisting CTS – some investigators consider HAVS to be a specific predisposing factor for CTS – or result from a separate abnormality of peripheral nerve fibers (e.g., injuries to the receptors or digital nerves in the fingertips and injury to nerve fibers within the carpal canal but caused by vibration, not compression) [74, 75, 77, 78]. The debate is of more than academic importance since, according to many investigators, CTS caused by HAVS responds poorly to conservative therapy and only temporarily to surgical release [74, 75].

The paramount aspect of treatment for HAVS is stopping all exposure to vibration. If this occurs in the early stages, there is improvement in both the subjective and objective findings. If it does not occur until the process is more advanced, some changes may persist. In regard to specific disturbances, the vasospastic problems, which often progress with continued exposure, tend to stop or regress when exposure to vibration ceases. Conversely, the neural symptoms may not regress, even when exposure ceases [79]. Suggestive preventive measures include avoiding medications that cause peripheral vasoconstriction, maintaining body temperature while working, and fitting tools with antivibratory mechanisms [72].

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Infectious and Granulomatous Peripheral Neuropathies

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Introduction

The infectious and granulomatous neuropathies constitute a variety of inflammatory conditions, often termed "neuritis." In some, the infectious agent or its neurotoxic products are known such as botulism, syphilis, leprosy, Lyme disease, diphtheria, and herpes. In others, the pathogenesis is uncertain or indirect, as in tuberculosis, HIV infection, sarcoidosis, and brucellosis (insert Table 38.1). Peripheral nerve involvement in these disorders may manifest clinically as mononeuropathy, mononeuropathy multiplex, polyneuropathy, and polyradiculopathy. As a group, these disorders are the world's most common causes of neuropathy and, in general, are treatable or preventable. Nerve pathology may result from the inflammatory reaction induced by the infection and from the host's immunological reaction. An infectious organism is considered an etiologic agent when (1) the inflammatory reaction occurs during serologically proven infection, (2) other causes are excluded, and (3) nerve histology demonstrates the infectious organism [1].

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HIV-Associated Neuropathies

Introduction

The earliest descriptions of neurological complications of acquired immune deficiency syndrome (AIDS) include multiple peripheral nervous system (PNS) disorders [2–5]. More than one-third of AIDS patients are estimated to have a peripheral neuropathy [5, 6]. Human immunodeficiency virus (HIV) neuropathy may affect proximal and distal components of the motor, sensory, and autonomic PNS, from the neuronal cell body to terminal nerve fibers. Since other AIDS-related neurological conditions, such as myelopathy, myopathy, and dementia, may coexist, the diagnosis of neuropathy may be particularly complicated and challenging.

A wide range of potential etiologies underlies peripheral neuropathy in HIV-infected patients (insert Table 38.2). Inflammatory demyelinating polyneuropathy (IDP) also occurs, particularly in early HIV infection [7, 8]. Distal symmetrical polyneuropathy (DSP) generally occurs in patients with advanced immunosuppression and is also a neurotoxic effect of certain antiretroviral medications [9–13]. Opportunistic infections, such as cytomegalovirus (CMV), can affect nerve roots [14], as does cancer in lymphomatous meningitis [15]. Autoimmune disorders occur in HIV-infected patients and may manifest as IDP or mononeuropathy multiplex (MM) [16]. In addition, noninfectious causes of polyneuropathy such as diabetes mellitus, uremia, alcoholism, and vitamin B12 deficiency must be considered.

Highly active antiretroviral therapy (HAART) has changed the natural history of AIDS. As patients live longer, the incidence and prevalence of neurological complications are likely to increase. The prevalence of HIV-associated sensory neuropathy is reported to be 57.2% in the era of combination antiretroviral therapy [17]. Prompt recognition and treatment of neuropathy may significantly benefit a patient's quality of life. Traditional, symptomatic therapy for neuropathy coupled with new pathogenesis-based treatments may offer pain relief and improve motor function for patients with HIV neuropathy.

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Table 38.1 Non-HIV-associated infectious and granulomatous neuropathies

Diagnosis	Etiology	Presenting symptoms	Neurological signs	Diagnostic studies	Treatment
Leprosy	*Mycobacterium leprae* bacillus	Rash, numbness Decreased sweating	Anesthesia w/in areas of rash Cranial neuropathy Autonomic neuropathy	Lepromin skin test – + >5mm Skin biopsy NCV – segmental demyelination EMG – denervation	Dapsone 100mg/day Rifampin 600mg/day Clofazimine 300mg/day
Lyme disease	*Borrelia burgdorferi* spirochete	Drooling, xerophthalmia; LE weakness, incontinence, confusion, HA	Facial palsy, cranial neuropathy Paraparesis, meningismus, ataxia	Elisa/Western blot serology, PCR CSF – pleocytosis, ↑ prot. EMG – axonal neuropathy, radiculopathy	Cetriaxone 2g/day IV Cefotaxime 6g/day IV Doxycycline 200mg/day
Zoster neuropathy	*Varicella zoster* virus	Painful rash, weakness (incl facial) Radicular pain (w/o rash)	Meningismus, vesicular eruption, cranial neuropathy, dermatomal sensory loss	Exam – vesicular rash CSF PCR for VZV EMG – denervation (if weakness)	Acyclovir 300mg/5× day Valaciclovir, famciclovir TCA's, opioids, topical lidocaine High-concentration capsaicin dermal patch
Diphtheria	*Corynebacterium diphtheriae*	Sore throat, weakness (all extremities) Hoarseness, SOB	Cranial neuropathy, quadraparesis, ↓ pulmonary function tests	Pharyngeal culture for C. diphtheriae EMG/ NCV – demyelination	Penicillin Erythromycin
Botulism	*Clostridium botulinum* toxin	Blurred vision, diplopia, dysphagia, weakness, SOB	Loss of convergence, ophthalmoplegia, flaccid paralysis, ↓ PFTs	Clinical exam and history, diagnosis of exclusion	Gastric lavage, botulinum antitoxin
Syphilis	*Treponema pallidum* spirochete	Lancinating pains, incontinence, paresthesias	Ataxia Loss of DTRs in lower extremities	CSF: VDRL +, pleocytosis	Penicillin, doxycycline
Brucellosis	*Brucella suis*, *B. melitensis*, *B. abortus* bacteria	Weakness, incontinence, diplopia	Cranial neuropathy, paraparesis	Serum and CSF serology and culture Clinical exam	Rifampin, doxycycline, streptomycin, sulfa
Tuberculosis	*Mycobacterium tuberculosis*	Diplopia, HA, confusion.	Cranial neuropathy, paraparesis	PPD + >5–10mm CSF – lymphocytic pleocytosis AFB culture	Isoniazid, ethambutol, rifampin, etc.
Tick paralysis	Tick bite – Dermacentor species	Weakness after tick bite	Ascending paralysis, ↓ DTRs in legs	Normal CSF Exam for ticks on skin	Removal of tick, supportive care
Sarcoidosis	Unknown	HA; weakness, numbness in any distribution, confusion	Meningismus, hydrocephalus, motor/ sensory neuropathy	↑ ACE level in serum/ CSF, nerve or muscle biopsy (granulomas)	Corticosteroids, cyclosporine

Etiology and Pathogenesis

The etiologies of HIV-associated neuropathy are diverse, and a broad range of mechanisms may cause PNS dysfunction (Table 38.3) and include cytotoxic effects due to direct HIV infection, cytokine dysregulation, opportunistic infections, neoplastic processes, autoimmune disorders, metabolic abnormalities, and toxic effects of medications.

Direct and Indirect Effects of HIV

Although the direct pathogenesis of HIV-associated degeneration of peripheral nerve fibers is unknown, investigators have suggested that peripheral neuropathy in AIDS is due to direct HIV infection [18]. Ho et al. was able to culture HIV from sural nerve homogenates of two AIDS patients who did not have symptomatic peripheral neuropathy [16, 19]. De la Monte et al. also proposed that direct infection of the peripheral nerve caused AIDS neuropathy [20]; this was based on the observation of perineural mononuclear infiltration, suggesting a cell-mediated response against the virus. Another report provided electron microscopic evidence of HIV infection of the sural nerve [21]. However, initial attempts to demonstrate HIV in dorsal root ganglion cells, nerve roots, or peripheral nerves were unsuccessful [20, 22–24]. While in vitro studies demonstrated neurotropism of certain HIV

Table 38.2 Differential diagnosis in HIV neuropathy

Diagnoses
Distal symmetrical polyneuropathy
HIV-related
Neurotoxic drugs
Vitamin B12 deficiency
Diffuse infiltrative lymphocytosis syndrome (DILS)
Ethanol use
Uremia
Diabetes mellitus
Inflammatory demyelinating polyneuropathy (acute or chronic)
Autoimmune
CMV
Progressive polyradiculopathy
CMV
Lymphoma
Syphilis
Monoradiculopathy due to degenerative disc disease
TB
Cryptococcus
Mononeuropathy multiplex
Autoimmune
Vasculitis
CMV
Entrapment neuropathy (e.g., carpal tunnel syndrome)
Cranial neuropathy
Cryptococcus
Lymphoma
TB
AIDP
CMV
Syphilis
Symptoms
Weakness
IDP
MM
DILS
PP
Myelopathy, myopathy, cachexia
Pain
DSP (paresthesias)
PP (low-back pain, paresthesias)
MM (asymmetric, focal)

IDP Inflammatory demyelinating polyneuropathy, *CMV* Cytomegalovirus, *MM* Mononeuropathy multiplex, *PP* Progressive polyradiculopathy, *DSP* Distal symmetrical polyneuropathy, *TB* Tuberculosis, *DILS* Diffuse infiltrative lymphocytosis syndrome

isolates [25–27] through a CD4-independent mechanism (apparently mediated by the gp120 glycoprotein) [28–31], autopsy and biopsy material revealed HIV only in macrophage-derived cells and endothelium of the central and peripheral nervous systems [32–36]. Using improved molecular techniques, HIV-1 nucleic acid may be identified in a small percentage of astrocytes and neurons of advanced AIDS patients [37, 38]. Up to a quarter of neurons from the dorsal root ganglion of some AIDS patients have HIV-1 nucleic acid detected by in situ hybridization [39]. Acharjee et al. reported that transcripts and proteins from an HIV accessory protein, viral protein R (Vpr), were detected in dorsal root ganglion and peripheral nerves of HIV-infected patients. Furthermore, retraction of neurites was seen in HIV-infected human dorsal root ganglion cultures. Dorsal root ganglion neuronal damage is theorized to occur via Vpr-related cytosolic calcium activation and changes in the cytokine system [40]. Ultimately, HIV infection of glia and neurons may not be pathogenic but may prove to be a viral reservoir [41].

Widespread functional and pathological damage to the PNS and the absence of significant in vivo infection of neurons suggest indirect mechanisms, such as cytokine dysregulation and immunologic dysfunction, as etiologic factors. Elevations of several proinflammatory cytokines in chronic HIV infection are associated with clinical manifestations including wasting syndrome, aphthous ulcers, chronic diarrhea, and dementia [42]. Similarly, elevation of tumor necrosis factor alpha (TNF-α), interleukin-1, and interleukin-6 occurs in peripheral nerve and dorsal root ganglia of AIDS patients [43–45]. Low level HIV-1 replication through cytotoxic T lymphocytes may induce cytokine expression and consequent degeneration of sensory neurons of the dorsal root ganglion [45]. This process may be mediated by the HIV glycoprotein gp120, which activates T lymphocytes [42] and binds to sensory ganglion neurons [28]. Proposed mechanisms of neuronal injury include oligodendrocyte injury by TNF-α, quinolinic acid-induced neurotoxicity via the N-methyl-D-aspartate receptor [46], and complement-dependent or calcium-mediated injury triggered by gp120 binding [28, 46]. Apoptotic macrophages and neurons are observed in the sensory ganglia of AIDS patients, [47] and DNA breaks, suggestive of apoptosis, are found in dorsal root ganglion cells [48]. Therefore, AIDS-associated peripheral neuropathy may be a final common pathway of apoptosis mediated by global dysfunction of the immune and cytokine systems.

Paraproteinemic neuropathy may be another indirect mechanism that causes DSP in AIDS patients. In one study, IgM and IgG reactivity against myelin proteins was detected in 25 sera of 35 HIV-infected patients, but none of the 48 controls [49]. However, the seropositive patients in this cohort did not have clinical neuropathy, and a causal relationship is presumptive.

Drug Toxicity

Some therapies for HIV infection are neurotoxic, and the neuropathy that develops is usually clinically and electrophysiologically indistinguishable from DSP. Certain adjunctive therapies for AIDS-related conditions and at least

Table 38.3 Diagnosis of HIV-related peripheral neuropathies

Diagnosis	CD4+ (cells/mm^3)	Presenting symptoms	Neurological signs	Diagnostic studies
DSP	<200	Distal numbness, paresthesias, pain	Stocking-glove sensory loss, ↓ ankle reflexes	EMG: distal axonopathy
IDP	>500, <50	Progressive weakness, paresthesias	Weakness, areflexia, mild sensory loss	CSF: ↑WBC, ↑↑ protein EMG: demyelination
MM	>500, <50	Facial weakness, foot drop, wrist drop	Multifocal cranial and peripheral neuropathies	EMG: multifocal axonal Neuropathy CSF: CMV cultures, PCR Nerve bx: inflammation, vasculitis, CMV inclusions
PP	<50	Lower extremity weakness, paresthesias, urinary dysfunction	Flaccid paraparesis, saddle anesthesia, ↓ reflexes, urinary retention	CSF: ↑↑ PMNs, CMV culture, PCR, EMG: polyradiculopathy

Modified from Simpson and Tagliati [99]. With permission
CSF Cerebrospinal fluid, *MM* Mononeuropathy multiplex, *WBC* White blood cells, *EMG* Electromyography, *CMV* Cytomegalovirus, *PMNs* Polymorphonuclear leukocytes, *IDP* Inflammatory demyelinating polyradiculopathy, *PP*: Progressive polyradiculopathy, *DSP* Distal symmetrical polyneuropathy

Table 38.4 Commonly used neurotoxic medications in patients with HIV infection

Drug	Indication	Neuropathy type
Didanosine (ddI)	Antiretroviral	Sensory, axonal
Zalcitabine (ddC)	Antiretroviral	Sensory, axonal
Stavudine (d4T)	Antiretroviral	Sensory, axonal
Thalidomide	Aphthous ulcers	Sensory, axonal
Dapsone	Pneumocystis carinii pneumonia (PCP) prophylaxis	Motor>sensory, axonal
Isoniazid	Tuberculosis	Sensorimotor, axonal
Pyridoxine (vitamin B6)	Supplementation with isoniazid	Sensory neuronopathy; worse in slow acetylators
Metronidazole	Antimicrobial (anaerobic infections)	Sensory, axonal
Vincristine	Lymphoma	Sensory, axonal
Etoposide	Kaposi's sarcoma	Sensory, neuronopathy
Chloramphenicol	Antimicrobial (salmonella infections)	Sensory, demyelinating; related to B12 metabolism
Ethambutol	Mycobacterial infections	Sensorimotor, axonal; may precede optic neuritis

three antiretroviral agents are neurotoxic (see below and Table 38.4). Isoniazid for tuberculosis, particularly when not supplemented with pyridoxine [50, 51], and vincristine and etoposide chemotherapy for lymphoma and Kaposi's sarcoma produce DSP [52, 53]. Thalidomide, a long-known cause of sensory axonal neuropathy, [54–56] is used to treat HIV-associated aphthous ulcers and may cause DSP; [57] however, controlled trials suggest a low incidence [58]. Neuropathy is caused by high-dose pyridoxine [59, 60] and the widely used antimicrobials, metronidazole, dapsone, and chloramphenicol [61–66]. Finally, the commonly abused neurotoxin, ethanol, may be the cause of neuropathy in some AIDS patients.

The dideoxynucleoside analogues didanosine (ddI), zalcitabine (ddC), and stavudine (d4T) possess dose-dependent neurotoxicity [11, 67]. Peripheral neuropathy may occur in 20% of patients taking ddI for at least 10 months, but neuropathic symptoms may resolve after discontinuation of ddI and most patients tolerate rechallenge with half the initial dose [68]. The incidence of neuropathy in Phase I and II studies of ddI and ddC ranges from 25% to 66% [69–71]. Neuropathic manifestations were more common in patients taking higher daily ddC doses (27.2mg/kg vs. 13.9mg/kg). Patients generally improve after withdrawal of the neurotoxic agent, although some worsen for several weeks before improvement, a phenomenon known as "coasting." Some patients may not improve after drug discontinuation and may have coexistent DSP related to primary HIV infection.

Stavudine (d4T) and ddI have similar neuropathic effects, although the incidence of neuropathy appears lower as compared with ddC. In a phase I trial of d4T at a maximum tolerated daily dose of 2.0mg/kg, neuropathy occurred in 55% of patients [72]. Larger studies using lower daily doses of 0.5mg/kg and 1.0mg/kg documented neuropathy in 6–21% of patients [11]. Similarly, ddI is linked with neuropathy in 12–34% of patients in phase I studies [73]. Severe immunosuppression of advanced HIV disease, low hemoglobin, and history of neuropathy are associated with nucleoside analogue-associated DSP [11, 74, 75]. Longer survival with combination antiretroviral therapy, higher CD4+ counts, and better overall health may prolong use of these agents with lower cumulative side effects. A controlled study evaluating ddI and ddC in patients with CD4+ counts between 200 and 500 cells/mm^3 confirms this prediction, with neuropathy rates between 3 and 6% [76]. While neurotoxic d-drug ARV use is now infrequently used in the USA, Europe, and other industrialized countries, its use in the developing world remains common, as is the frequency of neurotoxic neuropathy.

The mechanism of nucleoside analogue neurotoxicity is unknown. A few studies suggest that ddC may be cytotoxic by causing defective mitochondrial DNA replication, possibly by reversible inhibition of DNA gamma-polymerase [76–79].

Autoimmune Mechanisms

Patients infected with HIV may develop acute inflammatory demyelinating polyneuropathy (AIDP), although it is not clear that the incidence is greater than that in the general population. AIDP most often occurs early in HIV infection. Seropositive and negative patients with AIDP have similar clinical and electrophysiological features. The autoimmune pathogenesis of AIDP is likely similar to patients without HIV infection [6, 7]. The HIV genome is not detectable in Schwann cells or perineural cells by in situ hybridization, indicating that direct HIV infection of peripheral nerve is not responsible for the syndrome [6]. Immune dysregulation is supported by detection of anti-myelin antibodies with titers that decrease with convalescence [80] and increased cerebrospinal fluid (CSF) levels of soluble CD8 and neopterin [81, 82]. The treatment of IDP in HIV infection is similar to that in HIV-uninfected patients, including IVIg and plasmapheresis, although there are no controlled trials.

Mononeuropathy multiplex (MM) has clinical and electrophysiological similarities to AIDP, but its pathology is restricted to single or multiple nerves. When MM occurs early in HIV infection, autoimmune mechanisms are likely responsible, and improvement occurs with corticosteroids or intravenous immunoglobulin. Early MM may also remit spontaneously and has a relatively good prognosis [83, 84].

Metabolic Abnormalities

As HIV infection progresses to AIDS, some patients become malnourished from several causes. Dementia can decrease appetite and compromise swallowing, candida esophagitis produces odynophagia, and wasting syndrome leads to cachexia. Some investigators compare AIDS-related DSP to that of other chronic illnesses. [85] In a series of 251 patients, worsening nerve conduction values correlated with low serum albumin, low hemoglobin, and weight loss [10].

Although vitamin B12 deficiency is not a common cause of DSP in AIDS patients, it is treatable and therefore, prudent to screen for B12 deficiency in all patients with neurologic complaints. One small study showed that 29% of HIV-seropositive patients with abnormal vitamin B12 metabolism (serum level or Schilling test) had DSP [86], but others could not confirm this observation [2, 10, 20, 87]. No difference in vitamin B12 levels was found in 153 HIV-seropositive patients compared to 57 HIV-seronegative controls, but the cohort included only 15 patients with AIDS [87].

Although malnutrition, weight loss [2, 5, 85, 87], and wasting syndrome [5, 10] are common among patients with AIDS and DSP [88], they are also common in advanced AIDS patients *without* neuropathy. Therefore, a causal relationship may not be present between DSP and malnutrition except when associated with discrete vitamin deficiency or other systemic illnesses known to cause neuropathy.

Opportunistic Infections

Most opportunistic infections involve the central nervous system (CNS), and not the PNS, with the major exception of CMV infection. Some patients with progressive polyradiculopathy (PP) have overt or subclinical evidence of widespread CMV infection (e.g., retinitis, gastroenteritis). Almost all autopsy cases show signs of CMV in peripheral nerve [16]. A causal relationship between PP and CMV is supported by necrosis and inflammation of nerve roots with polymorphonuclear and mononuclear infiltrates and positive immunocytochemistry for cytomegalic inclusions [89–92]. CMV DNA may be detected by polymerase chain reaction (PCR) in CSF of patients with MM and advanced AIDS [93].

Clinical Presentation

AIDS patients present with a variety of PNS syndromes. These include inflammatory demyelinating neuropathy (acute and chronic), mononeuropathy multiplex (MM), progressive polyradiculopathy (PP), autonomic neuropathy, and a rare sensory ataxic neuropathy due to ganglioneuronitis [93]. Weakness or paresthesias may be acute, subacute, or chronic. With the exception of cranial neuropathies and some cases of MM, lower extremity complaints predominate.

Distal Symmetrical Polyneuropathy (DSP)

A painful, peripheral neuropathy occurs in 30% of AIDS patients. In the original description, 7 of 50 patients had neuropathy characterized by painful dysesthesias, a moderate, symmetrical, distal sensory loss involving large and small fibers in a stocking-and-glove distribution, and absent or depressed ankle reflexes [2]. Since this original description, the clinical features of DSP has been well characterized [3, 5, 20, 21, 24, 88, 94–97].

The cardinal feature of DSP is pain. Patients complain of numbness, burning, and paresthesias of the feet with pain usually beginning in the toes and soles of the feet. Symptoms may become severe that patients develop an antalgic gait and are unable to tolerate light contact with clothing or bedsheets. Often, the degree of pain appears disproportionate to objective findings on neurological examination. The most common, and often only, signs of DSP are depressed or absent ankle reflexes [5, 9, 10, 88, 95]. Relatively normal ankle reflexes together with hyperactive knee reflexes, in particular in the presence of Babinski sign, suggest coexistent myelopathy. Sensory examination typically reveals increased

vibratory thresholds and reduced pinprick and temperature in a stocking-and-glove distribution. However, joint position sense is usually relatively normal [5, 16]. The arms may become involved later in the disease. Weakness is not a prominent feature of DSP but if present is usually restricted to distal muscles [5].

Inflammatory Demyelinating Polyneuropathy (IDP)

HIV-infected patients with IDP present similarly to patients with IDP without HIV infection. AIDP produces rapidly progressive weakness of two or more limbs, often starting in distal muscles. Areflexia or hyporeflexia is an essential, diagnostic feature. Patients may have only minor sensory complaints and occasionally have facial diparesis. AIDP is usually monophasic that progresses rapidly over 4 weeks [98]. The most serious complications are autonomic instability and respiratory failure from diaphragmatic weakness [7, 99, 100]. CIDP may be associated with more prominent sensory complaints and is characterized by a relapsing-remitting course and a spectrum of disability from weakness [7, 101–106].

Mononeuropathy Multiplex (MM)

MM is an inflammatory neuropathy that affects single or multiple nerves causing asymmetric motor and sensory complaints. Patients typically complain of weakness or dysesthesias in the distribution of cutaneous nerves, mixed nerves, and nerve roots [83]. Characteristically, tendon reflexes are depressed in the distribution of affected nerves. Cranial neuropathies are frequently present [16, 95, 100]. MM is often self-limited when presenting early in HIV infection. In one study, eight of ten HIV patients with MM improved after 1 year without treatment [84]. In more advanced HIV disease, particularly when CD4+ counts are below 50/mm^3, confluence of neurologic deficits in peripheral nerves may simulate IDP or progressive polyradiculopathy [84, 95, 100]. Severe immunosuppression predisposes to systemic CMV infection, which may be an etiology of MM [107].

Progressive Polyradiculopathy (PP)

PP presenting as a rapidly, progressive cauda equina syndrome was described by Eidelberg and associates in 1986 [91]. Leg weakness and difficulty walking are the usual presentation [14]. Other symptoms include bladder and bowel dysfunction, low-back pain, and leg paresthesias. Flaccid paraparesis is accompanied by depressed or absent deep tendon reflexes. Pan-sensory loss is usually present [14, 89, 91, 93]. A characteristic distribution of numbness in the S4 and S5 dermatomes occurs in about 10% of patients [14], and urinary retention is present in over two-thirds [92]. Arm involvement may occur late in PP, and cranial nerves may be involved in severely immunosuppressed patients [89]. PP may simulate confluent, progressive MM [108], although sphincter dysfunction is a differentiating feature. CMV is detected in peripheral nerves of almost all autopsy cases [16]. Rare HIV patients may have syphilitic or lymphomatous PP.

Cranial, Autonomic, and Ganglio Neuropathies

Cranial neuropathies in HIV disease may herald serious illness and must be evaluated promptly. In a study of 2,370 HIV-infected patients, cranial neuropathies occurred in 98 (4.1%) [109]. These neuropathies may be relatively benign, as in facial neuropathy in relatively immunocompetent patients, or may be manifestations of lymphomatous meningitis or severe opportunistic infections, such as CMV encephalitis or cryptococcal meningitis. Occasionally, cranial neuropathies are caused by primary CNS lymphoma, non-Hodgkin's lymphoma, or brain stem glioma [110].

Orthostatic hypotension and lightheadedness with abnormal autonomic testing may occur in AIDS patients [111, 112]. Early reports involved small numbers of end-stage AIDS patients with other causes of hypotension, such as diarrhea and dehydration. However, larger series documented up to a 50% incidence of abnormal sympathetic and parasympathetic system functions [113–115]. Identification of autonomic denervation in the jejunal mucosa of HIV-infected patients further supports autonomic pathology [116].

Rarely, a sensory ataxic neuropathy occurs. One patient was reported with neuronal loss in the sensory ganglia [94]. The clinical picture of sensory ataxia is similar to tropical ataxic neuropathy, associated with HTLV-1 infection [117].

Differential Diagnosis

The differential diagnosis of HIV neuropathy is large and challenging including many treatable conditions (Table 38.2). While more than 30% of AIDS patients can be diagnosed with DSP, many confounding neurological disorders can lead to an incorrect diagnosis. Among patients with DSP, other common causes of distal polyneuropathy such as vitamin B12 deficiency, ethanol abuse, neurotoxic medications, uremia, and diabetes must be considered. A rare cause of painful peripheral neuropathy known as diffuse infiltrative lymphocytosis syndrome (DILS) can occur in some patients with CD8+ hyperlymphocytosis resulting in a Sjögren-like syndrome. The painful symptoms can be similar to those found in DSP, but the symptom onset is often more acute, motor involvement is frequent, and findings may be asymmetric or only restricted to the arms [118–120]. Although the cause of DILS is unclear, HIV-mediated immune dysregulation, rather than monoclonal T-lymphocyte expansion, is likely [121, 122].

Progressive polyradiculopathy is among the most serious PNS manifestations of HIV infection. Empiric therapy with ganciclovir is indicated in most severely immunosuppressed

patients [90, 92, 123–125]. If improvement does not occur, other causes, such as lymphomatous meningitis, syphilis, or degenerative disc disease, must be considered [15, 126, 127]. Similarly, CMV infection should be considered with rapidly progressive MM, especially in patients who do not respond to immunomodulatory therapy.

Evaluation and Diagnosis

The first and most important step in the evaluation of an AIDS patient with neuropathy is a thorough history and physical examination. Symptom duration, pain location, distribution of weakness, medication use, and concurrent illness should guide diagnosis. Ancillary tests, such as nerve conduction studies (NCS), needle electromyography (EMG), autonomic testing, and blood, CSF, and neuroradiological studies, are often confirmatory (Table 38.4).

NCS characterize the physiology of nerve involvement and identify subclinical nerve pathology. The most common NCS abnormality in DSP is reduced or absent sural sensory nerve action potentials (SNAPs) [2, 10, 88, 128]. Although sensory complaints predominate, motor fibers are often affected . In a small study, all patients had abnormal peroneal and tibial motor conduction studies [88]. Generally, motor nerve conduction velocities are mildly reduced compared to amplitude reduction [2, 88, 128], consistent with axonopathy. Median and ulnar sensory and motor amplitudes may be reduced [2, 10, 88]. Rarely, NCS may be normal [2, 88, 96, 97]. F-wave and H-reflex latencies may be prolonged [10, 21, 96]. The electrophysiologic abnormalities in drug-induced and HIV-related DSP are indistinguishable [70].

The NCS findings in inflammatory demyelinating polyneuropathies are similar to those of patients without HIV infection [129, 130]. They are characterized by reduced motor conduction velocities in two or more nerves, occasional conduction block between proximal and distal nerve stimulation sites, and prolonged distal latencies. If axonal degeneration is present or distal conduction block occurs, reduced compound muscle action potential (CMAP) amplitudes may be observed. Differentiation of CIDP from AIDP by electrophysiologic parameters is often difficult. AIDP is usually an acute, monophasic illness, whereas CIDP is subacute and marked by progression or fluctuating symptoms. Electrophysiological abnormalities are more pronounced in CIDP than in AIDP [7, 101].

Typically, MM produces reduced CMAPs, SNAPs, and mild slowing of motor or sensory conduction velocities. NCS abnormalities are multifocal and asymmetric [96]. Rapidly progressive and confluent MM may have findings similar to IDP and PP. However, since PP is restricted to lumbosacral nerve roots producing a proximal axonopathy, preserved SNAPs, reduced CMAP amplitudes, and diffuse denervation of multiple proximal and distal muscles in the legs and lumbar paraspinal muscles can help differentiate PP from other neuropathies [7]. F-wave latencies may be prolonged, whereas distal conduction velocities are usually only mildly affected [92].

Needle EMG is most valuable in the diagnosis of HIV myopathy but may assist in neuropathy evaluation. Denervation on EMG may discriminate among PP, DSP, and MM. Active or chronic partial denervation with reinnervation in distal leg muscles can be demonstrated in some DSP patients [21, 88, 96, 97]. Needle EMG evaluation of lumbosacral paraspinal muscles in PP patients will often demonstrate denervation. AIDP and CIDP patients have reduced motor unit recruitment patterns, which is usually caused by conduction block rather than axonal degeneration [7, 101].

Autonomic function testing has limited clinical applications. Lightheadedness and syncope are not unusual in the severely ill AIDS patient. Dehydration, anemia, and cardiomyopathy must be excluded before ascribing symptoms to dysautonomia. Autonomic nervous function tests include orthostatic blood pressure measurements, provocative tests such as Valsalva maneuver and tilt table, the cold pressor test, and the quantitative sudomotor axon reflex test (QSART). Plasma catecholamine levels may be inappropriately low, but this is not a consistent finding [111–113, 115, 131–133].

Certain clinical situations warrant lumbar puncture. Examples include any neuropathy associated with encephalopathy or myelopathy, constitutional symptoms (e.g., fever, weight loss), rapid symptom progression, or a history of lymphoma or CMV disease. However, interpretation of CSF values in HIV-infected, asymptomatic individuals must be done with caution. CSF abnormalities are found in 60%–90% of infected persons without neurological abnormalities or opportunistic infections [134, 135]. A predominantly lymphocytic CSF pleocytosis is present in 18%–65% of asymptomatic HIV-infected patients [136–139].

The character of the pleocytosis can help in diagnosis of peripheral neuropathies in AIDS patients. In contrast to HIV-seronegative patients with AIDP, HIV patients usually have a lymphocytic pleocytosis of up to 50 cells/mm^3. [7] CSF protein is elevated, as in seronegative patients. A nonspecific, mild, mononuclear pleocytosis is not unusual in DSP and MM patients [83, 138, 140–142]. A pronounced polymorphonuclear pleocytosis with elevated protein and hypoglycorrhachia is a discriminating feature of PP caused by CMV. CSF pleocytosis to 2,000/mm^3, protein concentrations as high as 1,000 mg/dl, and glucose often below 40 mg/dl occur [90, 123]. A mononuclear pleocytosis raises the concern for lymphomatous meningitis, especially if CSF leukocyte counts are less than 200/mm^3 [126].

CSF glucose concentration is often normal in HIV patients [3, 143, 144], and a very low concentration suggests an opportunistic infection or neoplasm. Elevated CSF protein is common [137, 139, 145] and generally not useful in diagnosis

unless well above normal. PCR detection of CMV DNA in the CSF may provide a more specific diagnosis in suspected PP or MM [93, 146], since CSF cultures for CMV are positive in only half of HIV-infected patients with PP [90, 92, 123].

Exhaustive laboratory investigations for reversible causes of neuropathy in AIDS patients are usually uninformative. Serum vitamin B12 levels, folate, erythrocyte sedimentation rate, antinuclear antibodies, fasting blood glucose, liver enzymes, creatinine, thyroid function tests, and serum protein electrophoresis are usually normal [2, 5, 21]. In most patients, neuroimaging does not add to evaluation of HIV-related neuropathy. Patients with cranial neuropathy should have magnetic resonance imaging (MRI) or computed tomography (CT) of the brain to exclude CNS pathology, such as toxoplasmosis encephalitis, cryptococcal meningitis, or lymphoma. Lumbosacral spine imaging may exclude abscess or neoplasm in suspected cases of PP. In PP caused by CMV, lumbosacral spine MRI often demonstrates enhancement of the thecal sac, leptomeninges, and cauda equina [122, 147, 148].

Nerve biopsy is rarely necessary in AIDS patients with neuropathy. Diagnosis is usually made by clinical and laboratory examinations. The most common nerve biopsy finding in DSP is axonal degeneration of myelinated and unmyelinated fibers [20, 21, 24], which is indistinguishable from other toxic axonopathies. Nonspecific, mild epineural and endoneurial mononuclear inflammation may be observed [24, 29, 83]. While demyelination occurs with DSP [20, 21], this appears not to be segmental [21, 24]. The diagnosis and etiology of MM may be facilitated by nerve biopsy. CMV virions are detected in mononuclear, endoneurial, and endothelial cells [149]. Cytomegalic inclusion bodies were identified in eight peroneal nerve biopsies of MM patients, who improved with ganciclovir [93]. Necrotizing arteritis occurs in some patients with progressive sensorimotor neuropathy, and in these patients, muscle biopsy may be a more sensitive diagnostic test compared to nerve biopsy [150].

Recently, skin biopsy has been utilized to evaluate patients with symptoms of small fiber neuropathy (SFN). Symptoms of SFN include numbness, burning, paresthesias, and painful dysesthesias. Skin biopsy is a minimally invasive procedure that can be used to assess the epidermal nerve fiber density (ENFD), which is reduced in small fiber neuropathies. The sensitivity and specificity of the test has been reported to be 88.4% and 96%, respectively [151–155]. A longitudinal study conducted by Herrmann et al. reported serial measurements of ENFD in HIV patients and found a 14-fold greater risk of developing symptomatic HIV-associated DSP in 6–12 months with ENFD <10 fibers/mm versus HIV patients with >10 fibers/mm who did not develop symptomatic DSP [151]. Skin biopsy can be a useful test to demonstrate peripheral nerve pathology when symptoms occur in the setting of normal electrodiagnostic studies.

Treatment

The treatment of HIV-related peripheral neuropathy depends on etiology. The rationale for therapy is based on four objectives: antiviral treatment, immunomodulation, treatment of underlying causes, and symptom reduction.

Antiviral Therapy

Anecdotal cases report treatment responses with zidovudine for DSP [156] and HIV-related vasculitis [157], but nucleoside analogue antiretroviral therapy does not play a major role in the treatment of neuropathy. Emerging reports suggest that combination therapy may decrease DSP incidence, but it remains to be determined if HAART with combination regimens including protease inhibitors will have an impact on the natural history of DSP [158].

Ganciclovir is a nucleoside analogue that is effective for treating CMV retinitis and can benefit PP, and some MM patients. Severely immunosuppressed patients with MM, unresponsive to plasmapheresis and corticosteroids, may benefit from empiric ganciclovir treatment. Ganciclovir may be effective for MM in AIDS patients with CMV DNA in the CSF [93, 108, 159]. Ganciclovir should be initiated in AIDS patients with PP, particularly those with a CSF polymorphonuclear pleocytosis [14, 123]. Improvement often occurs within 2–4 weeks, but a therapeutic effect may take several months, and lifelong maintenance therapy is recommended [92, 123, 160]. Patients with severe paraparesis who are not treated for more than 3 weeks are unlikely to improve [90]. For patients who deteriorate despite early treatment initiation, drug resistance should be considered [161], and an alternative antiviral agent, such as foscarnet or cidofivir, may be warranted [90, 125, 160, 162, 163]. A study of antiviral therapy for HIV-associated CMV disease was halted because of a markedly reduced CMV incidence in the current era of HAART.

Immunotherapy

Corticosteroids are useful in the treatment of inflammatory neuropathy associated with HIV infection. While controlled studies are not available, case series indicate that prednisone is often effective in treating CIDP, although relapse is common when therapy is stopped [7, 107, 164]. Prolonged corticosteroid treatment leads to further immunosuppression and increased risk of opportunistic infection, which further complicates treatment of AIDS patients. In some patients with early MM and delayed or incomplete recovery, corticosteroids may be beneficial [101]. Plasmapheresis and intravenous immunoglobulin are effective in CIDP [7, 97, 101, 164] and MM [101]. However, improvement is often transient, and frequent, regular treatments may be required. Immunotherapy is not effective in the treatment of DSP [83, 101]. Immunomodulating therapies await placebo-controlled trials in HIV patients with peripheral neuropathy [107, 165].

Other Treatments

DSP is among the most painful and debilitating neurologic complications of AIDS. Current therapy is largely symptomatic. Other possible causes of DSP should first be treated, for example, vitamin B12 replacement, diabetic management, withdrawal of offending drugs, and alcohol abuse treatment.

Mild symptoms of DSP may improve with nonsteroidal anti-inflammatory agents or acetaminophen [11, 164]. Tricyclic antidepressants, such as amitriptyline or desipramine, at doses up to 150mg/day, and anticonvulsants, such as carbamazepine and phenytoin, often moderate neuropathic pain [11, 99, 166]. New anticonvulsants may also be of benefit. Lamotrigine reduced pain compared to placebo in 42 patients; [167] this positive effect was also seen in a large placebo-controlled study of 92 patients [168]. To avoid rash, lamotrigine must be titrated slowly. Gabapentin, which has a favorable pharmakokinetic profile and sparse drug-drug interactions, has been used successfully in other neuropathic conditions [169, 170], but reports of its effectiveness in HIV-associated DSP are anecdotal [171]. A placebo-controlled study demonstrated that pregabalin was not superior to placebo in the treatment of painful HIV neuropathy [172].

For refractory pain, adjunctive treatment with topical lidocaine 5% and capsaicin 0.075% may be beneficial [11, 166]. A double-blind controlled multicenter study showed significant improvement in 307 HIV patients with DSP using a high-concentration capsaicin dermal patch. However, a second similar study could not replicate these results [173]. The treatment was shown to be safe and symptomatic relief lasted for up to 12 weeks [174]. However, some patients with DSP may have severe and debilitating pain that requires narcotic analgesia [11, 164]. Antiarrhythmic medications that block sodium channels, such as mexiletine, have been used without success [175]. A controlled trial of mexiletine and amitriptyline did not demonstrate a difference compared to placebo [176]. Efficacy of alternative therapies have not held up to rigorous scientific scrutiny. A controlled trial of acupuncture was not superior to sham acupuncture for HIV neuropathy [177].

Laboratory data and studies of animal models suggest that recombinant human nerve growth factor (rhNGF) as a potential treatment of peripheral neuropathy, in particular diabetic and HIV-related neuropathies [178]. In a placebo-controlled trial of 270 patients with painful HIV neuropathy, subcutaneously administered rhNGF produced significant pain reduction [179]. However, most secondary measures of nerve regeneration, including quantitative sensory tests and epidermal skin biopsies, did not show improvement and the future of rhNGF therapy is uncertain.

Prognosis

Currently, there is no cure for AIDS or most HIV-related PNS disorders. Many opportunistic infections can be treated, but the response is often transient or incomplete. In a study of sixteen PP patients treated with ganciclovir, six improved, three stabilized, and the remainder died shortly after treatment initiation [160]. In the current era of HAART, a dramatic increase in survival has occurred. The Multicenter AIDS Cohort Study (MACS) demonstrates that the incidence of sensory neuropathy between 1985 and 1992 has increased, perhaps as a result of longer survival [9]. However, as therapies evolve and more AIDS patients benefit from viral suppression, combination antiretroviral therapy may improve the prognosis of AIDS-related neuropathies [158].

Leprous Neuropathy

Introduction

In 1873, Dr. Gerhard Henrik Armauer Hansen identified that the acid-fast bacillus, *Mycobacterium leprae* caused a chronic infectious disease that affects skin and peripheral nerve [180]. Since then leprosy is also known as Hansen's disease. The prevalence of leprosy has fallen greatly in developed countries and is seen only rarely in immigrants from endemic areas [181]. The vast majority of patients are found in the tropic and subtropic regions [182] due to *M. leprae*'s maximal reproduction at 26–30 °C [183]. This characteristic also accounts for its predilection for cooler areas of the body such as the nose, skin, testes, anterior portions of the eye, and superficial nerves. HLA-linked genes, through immune regulation [184] and by T lymphocytes [185], play an important role in leprous clinical manifestations. The host's cellular immunity dictates the peripheral nerve sequelae of leprosy.

Etiology and Pathogenesis

M. leprae is an acid-fast, gram-positive bacillus and an obligate intracellular parasite with a generation time among the longest of all bacteria [186]. The *M. leprae* genome contains 72 loci [187], and identification of coding sequences for heat shock and superoxide dismutase genes make possible PCR detection of bacteria in skin and nerve biopsy specimens [188]. The pathogenesis and transmission of leprosy are not understood well. The viability of *M. leprae* outside the body varies from 7 to 46 days [189] and the incubation period ranges from 2 to 7 years [190]. The main mode of transmission is via the upper respiratory tract. *M. leprae* exist in the nasal mucosa in up to 50% of untreated patients [180, 191], and the bacilli are found in breast milk of infected mothers [192].

The clinical manifestations of leprosy depends on the host's immune response to *M. leprae*. Indeterminate leprosy refers to early stadium of disease with one or several cutaneous lesion and irregular and asymmetrical nerve involvement.

At this stage, spontaneously healing is possible, or progression into one of the manifestations along the clinical spectrum of leprosy. The Ridley-Jopling classification is most commonly used to classify the clinical manifestations of leprosy along a continuum between two poles (*lepromatous and tuberculoid*) with several subdivisions that fall in-between those two extremes (borderline lepromatous, borderline, borderline tuberculoid) [182]. Lepromatous type, or the malignant form, is a stable form that is negative to the Mitsuda skin reaction test (described below). Tuberculoid type, or the benign form, is positive to skin testing. The most common type and group are lepromatous and borderline. The age-related incidence is bimodal, with peaks during preadolescence and adulthood (30–60 years) [193].

In the lepromatous type, the bacilli multiply unchecked and, with an abnormal cell-mediated immune response, can disseminate hematogenously [194]. In the tuberculoid type, preserved cell-mediated immunity prevents disease dissemination [195]. With skin lesion development, peripheral nerves in the cooler areas of the body are damaged in a diffuse, bilateral and generally symmetrical fashion. In these forms, the host is unresponsive to circulating mycobacterial antigens found within polymorphonuclear leukocytes, circulating histiocytes, and monocytes [193, 194]. The balance between CD4+ and CD8+ lymphocytes and cytokine production [196] determines the pathological lesions of the different forms of leprosy. Elevations of cytokines including interleukin (IL)-2 and gamma interferon (gamma-IFN) [197] are found in tuberculoid lesions and high levels of cytokines IL-4 and IL-10 in lepromatous lesions [198].

The lepromatous type is characterized in the early stages of infection of Schwann cells of myelinated fibers by the *M. leprae* and a sparse inflammatory response with few foamy macrophages. In general, nerve architecture is well preserved; however, in more advanced stages, an extensive inflammatory reaction in the epineurium and perineurium produces nerve enlargement. Some nerve fascicles have an "onion skin" hypertrophic appearance from multiple episodes of demyelination and remyelination. Segmental demyelination and axonal degeneration in clustered nerve fibers are also seen in advanced stages [199]. Scarring from intense fibroblast infiltration and increased collagen synthesis may hamper growth of regenerating fibers [200]. In the tuberculoid type and borderline group, leprosy is characterized by total disruption of nerve architecture and an intense inflammatory granulomatous reaction [201].

Clinical Presentation

Sensory loss due to intracutaneous nerve damage is the hallmark of leprous neuropathy. Early involvement of unmyelinated and small myelinated nerve fibers is responsible for the pain, temperature, and sweat loss observed in skin lesions [202]. Histopathologic type and group dictate the clinical presentation, as follows:

Lepromatous type: Early stages may be asymptomatic due to the absence of significant neuronal inflammation [195]. The initial skin lesions may be small individual macules, papules, or nodules or a symmetric rash of the face, forearms, buttocks, and knees. Loss of pain and temperature sensation first appears on the dorsum of the hands and feet, ears, lateral leg, and forearms. At pressure points, perforating skin ulcers may appear. Progressive autonomic and cranial nerve damage produce destruction of nasal bones, lateral eyelid loss, atrophy or hypertrophy of forehead skin, iritis, and alopecia responsible for the "leonine face." [203] In advanced stages, hoarseness, orthostatic hypotension, Raynaud's phenomenon, respiratory stridor, testicular atrophy, systemic amyloidosis, concurrent infection, and renal failure may occur.

Tuberculoid type: The clinical features are isolated to anesthetic skin plaques with central hypopigmentation and erythematous borders on the extensor surfaces of the face, buttocks, and extremities [195]. Generally, only one or two lesions are present over the entire body.

Indeterminate group: This disease form is seen during early immunological reaction. Single or few hypopigmented skin lesions (macules) without sensory loss are present. The lesions usually resolve spontaneously, although some may progress to more extensive disease [204].

Borderline group: This group represents the intermediate cases between the lepromatous and tuberculoid types. The borderline lepromatous group is marked by poorly defined skin lesions of variable shape and size with a tendency to progress to a confluent rash. Patients in the borderline tuberculoid group generally have smaller and less numerous lesions [204].

Novel manifestations, known as "leprosy reactions," may arise secondary to host immune responses during therapy. The type I reaction, also known as the reversal or upgrading reaction, is usually seen in the borderline group caused by heightened cell-mediated immunity. Fever, malaise, swelling, and exacerbation of preexisting skin and nerve lesions characterize the reaction appearing during the first year of dapsone monotherapy in up to 50% of patients [205]. The type II reaction, or erythema nodosum leprosum (ENL), is almost exclusively seen in the lepromatous type caused by antigen-antibody complex deposition (Arthus phenomenon) at multiple sites throughout the body because of massive death of *M. leprae* secondary to therapy. This reaction affects about half of patients during the first year of therapy [206] and is characterized by fever, arthritis, acute peripheral nerve damage, myalgias, and iridocyclitis. Tumor necrosis factor alpha (TNF-alpha) and IL-1 are important in the reaction's incidence and severity [207].

Clinical Presentation

To assess a patient's immune response to *M. leprae* antigen and classify the leprosy subtype, the lepromin skin test is used in endemic areas. The lepromin antigen consists of killed *M. leprae* from infected armadillos (lepromin A) given intradermally as a 0.1ml solution (equivalent to 35 million *M. leprae* bacilli/ml) [208]. The skin response, or Mitsuda reaction [209], is observed at the injection site after 3–4 weeks. In lepromatous type, there is minimal or no reaction, but in the tuberculoid type and borderline tuberculoid group, a positive reaction of greater than 5 mm of induration at the injection site occurs. False-positive reactions are observed with previous subclinical infection, Bacille Calmette-Guérin (BCG) vaccination, or as a response to a nonspecific stimulus.

The diagnosis is supported by a skin biopsy that demonstrates granulomas in skin lesions even if no *M. leprae* bacilli are present. Using Fite stain, skin and nasal smears may have detected the acid-fast *M. leprae* [195]. Nerve biopsy is generally reserved for differential diagnosis of other infectious neuropathies and evaluation of treatment [210].

Electrodiagnostic studies demonstrate axonal degeneration and segmental demyelination in affected nerves. Slow motor nerve conduction velocities can be seen in clinically affected and asymptomatic nerves. SNAP amplitudes usually are reduced, and needle EMG demonstrates denervation with positive sharp waves, fibrillation potentials, and large polyphasic motor unit action potentials in affected muscles [211].

Treatment and Prognosis

The goal of treatment for leprous neuropathy is eradication of *M. leprae*. Therapy for the tuberculoid type and borderline tuberculoid group is dapsone 100mg/day and rifampin 600mg/day for 6 months. The patient should be monitored for 2 years after treatment cessation. In lepromatous type, dapsone 100mg/day with clofazimine 300mg/day for a minimum of 2 years is given and continued until skin smears are negative. Upon completion of therapy, observation for at least 5 years is necessary. New, effective agents include clarithromycin, ofloxacin, pefloxacin, sparfloxacin, and minocycline [212].

Treatment of immune-mediated "reaction states" is focused primarily on early recognition and prevention of disability. In mild reactions with only skin manifestations, oral nonsteroidal anti-inflammatory agents and analgesics are recommended. In more severe cases, high-dose corticosteroids (prednisone 40–120 mg/day) are indicated. Symptoms usually improve in 72 h, but high doses should be continued until the reaction subsides [213]. In severe cases, other agents including clofazimine, thalidomide, plasmapheresis, intravenous immunoglobulin, and cyclosporine have been added to prednisone [214].

The management of leprous neuropathy includes prevention of injury to anesthetic areas, attention to foot hygiene, and reconstructive plastic surgery. The prognosis for neuropathy depends on the type of leprosy, the time of diagnosis, chemotherapeutic response, and reactive states.

Lyme Neuropathy

Introduction

Lyme disease was first recognized in the United States in 1975 in Old Lyme, Connecticut, with outbreak of a disease characterized by recurrent attacks of large joint arthritis in patients with an antecedent tick bite and typical annular skin lesions [215]. In 1982, Burgdorfer et al. isolated a treponema-like spirochete from the *Ixodes dammini* tick that bound serum immunoglobulins from Lyme disease patients [216]. The spirochete was classified in 1984 as a species of the genus *Borrelia* and was named *Borrelia burgdorferi* to honor Willy Burgdorfer [217]. A similar syndrome was observed in Europe in 1922 and recognized as Bannwarth's syndrome since 1944 [218].

Etiology and Pathogenesis

Lyme disease is the most common tick-borne disease in the United States [219]. It is transmitted by tick vectors which include *Ixodes dammini*, *Ixodes scapularis,* and *Ixodes pacificus* in North America and *Ixodes ricinus* in Europe [220]. *B. burgdorferi* is a the gram-negative spirochete that causes Lyme disease. The pathogenesis of Lyme disease is not clear. Different pathogenic mechanisms have been proposed, including direct tissue infection (from the skin via hematogenous spread), indirect effects due to autoimmune responses (autoantibodies to axonal proteins, gangliosides, and myelin), and continuous inflammation (histopathologic changes, vasculopathy) [221]. Peripheral nerve damage may be mediated by B-cell-induced cytokines, such as IL-1, IL-6, and TNF-alpha [222]. Monoclonal antibodies against *B. burgdorferi* epitopes cross-react with PNS axons, Schwann cells, myelin, and other autoantigens [223].

Clinical Presentation

The incubation period ranges from 3 to 30 days, after which the illness follows three clinical stages. Stage I (early localized disease) is characterized by rash (*erythema chronicum*

migrans) at the tick bite site and 3–4 weeks of constitutional symptoms [224]. Neurological complications may appear at stage II (early disseminated disease) and stage III (late disseminated disease) .

Lymphocytic meningitis is the most common finding and lymphocytic meningoradiculitis (LMR) is characteristic in early neuroborreliosis. Patients with LMR usually have variable motor and sensory involvement of multiple nerves, and symptoms may wax and wane over several months [222]. Focal and multifocal peripheral and cranial nerve involvement is observed in half of patients [222]. Facial nerve paralysis is the most common sign with facial diplegia seen in half of patients [225]. Vestibulocochlear, optic, oculomotor, and trigeminal nerves may be affected. In Europe, neuroborreliosis usually presents as a meningoradiculoneuritis, characterized by severe radicular pain with or without paresis [226, 227].

Late neuroborreliosis is marked by peripheral neuropathy and encephalomyelitis [221, 228]. Polyneuritis is seen in a symmetrical, distal pattern [229], and in general, the PNS abnormalities of this stage last for weeks to months. A predominantly sensory neuropathy may be seen in up to two-thirds of untreated patients. Physical signs are uncommon. Weakness is rare, tendon reflexes are preserved, and most patients do not have sensory loss [221].

Stage III is characterized by an asymmetric oligoarthritis, cardiac involvement, and a variety of CNS syndromes including subacute encephalitis, demyelinating disease, cognitive impairment, ataxia, spastic paraparesis with bladder dysfunction, cerebral vasculitis, and dementia [225]. Myositis is reported in some patients [229]. Acrodermatitis chronica atrophicans (Herxheimer) is a late skin manifestation seen in European borreliosis that is associated with a sensory neuropathy [230].

Evaluation and Diagnosis

Serological screening for *B. burgdorferi* is of limited diagnostic value because of seroprevalence of 3% to 10% in the general population [231]. A low pretest probability is likely to lead to a false-positive result. A two-test protocol for the diagnosis of Lyme disease is recommended by the US Centers for Disease Control and Prevention: the whole cell extract enzyme-linked immunoabsorbant assay (ELISA) and the Western blot, which can be performed on serum and CSF [232]. In patients with suspected early or late neuroborreliosis, the demonstration of intrathecal spirochetal antibody production by Western blot, immunoglobulin G and M index, and the spirochetal CSF titer index all support the diagnosis of Lyme disease [221]. The diagnosis of neuroborelliosis is supported by CSF lymphocytic pleocytosis, protein elevation, and elevated immunoglobulin [233]. In inconclusive situations, serology can be repeated in 3–4 weeks or CSF PCR using a variety of borrelial specific primers may be employed. The specificity of PCR approaches 100%, although its sensitivity may not be as high [221]. Electrodiagnostic studies show an axonal neuropathy [234].

Treatment and Prognosis

PNS complications of Lyme disease are treated by Borrelia eradication. Oral doxycycline (200mg/day) and intravenous cefotaxime (6g/day), ceftriaxone (2g/day), or penicillin G (20 million units/day) are recommended [222]. Corticosteroids for pain management is controversial, although prednisolone 50mg/day for 3 days may treat severe pain [235]. Neurological manifestations carry a good prognosis after antimicrobial therapy. Cranial neuropathy recovers within weeks to months, and symptoms of radiculopathy usually abate in 2–16 weeks. Antibiotic therapy also aids in rapid pain resolution and improvement of peripheral neuropathy [222], although neuropathy associated with acrodermatitis chronica atrophicans may be less responsive to treatement [236].

Herpes Zoster Neuropathy

Introduction

Approximately 95% of the United States population is infected with varicella zoster virus (VZV), the causative agent of chicken pox. Latent, lifelong infection persists in sensory nerve ganglia and can reactivate to cause zoster neuropathy, or "shingles." [237]

Etiology and Pathogenesis

Herpes zoster neuropathy results from reactivation of latent virus or from a primary infection. Transmission is by inhalation of infectious particles or direct contact with active lesions. The typical vesicular exanthem of chickenpox develops 10–21 days after infection. VZV is distinguished from herpes simplex by deep dermal invasion producing infarctive necrosis and scar formation. VZV infection is more commonly recurrent and chronic in AIDS and cancer patients receiving chemotherapy and radiotherapy [237]. VZV migrates from sensory nerve fibers into the skin and subcutaneous tissues, producing local tissue damage and inflammation with secondary nociceptor sensitization leading to spontaneous local pain and hyperalgesia. Failure of sensitized nociceptors to normalize after tissue damage and inflammation, collateral local reinnervation, and changes in

central pathways of pain perception play important roles in development of postherpetic neuralgia (PHN) [238].

Clinical Presentation

The most common PNS manifestations of VZV infection include PHN, radiculopathy, zoster sine herpete (zoster without rash), and cranial nerve palsies [239]. Three distinct pain syndromes occur in PHN in the involved dermatomal distributions: (1) an electric shock-like, knifelike, lancinating pain; (2) a monotonous, continuous burning and aching sensation; or (3) pain produced by normally innocuous stimulation (allodynia) [240]. In patients with radicular involvement, motor impairment occurs with sensory abnormalities and local pain in the dermatome of the vesicular rash and follows the corresponding myotome [241]. Patients with motor involvement have an increased incidence of malignancy [242]. Some patients may experience radicular pain, often prolonged, without zosterform rash, known as zoster sine herpete. This entity must be considered in the differential diagnosis of long-standing radicular pain, which also includes diabetic radiculopathy, and carcinomatous or lymphomatous nerve root infiltration [242]. One third of patients with herpes zoster ophthalmicus develop cranial nerve abnormalities [242]. Other HSV cranial neuropathies are most commonly partial or complete oculomotor palsies, optic neuritis, facial palsy, and vestibulocochlear dysfunction (Ramsay-Hunt syndrome) [243].

Evaluation and Diagnosis

The diagnosis of VZV neuropathy largely depends on neurological manifestations and characteristic skin eruptions, which may be biopsied to confirm diagnosis. CSF pleocytosis and elevated protein occurs in up to 50% of patients [239]. PCR for VZV DNA in the CSF may provide confirmation [242]. Segmental denervation is evident by EMG in patients with weakness.

Treatment and Prognosis

Vaccines are available for the prevention of chicken pox in children and for risk reduction of zoster and PHN in adults [244]. Antiviral treatment with acyclovir, valaciclovir, and famciclovir may reduce the duration of an acute attack, provide prophylaxis against recurrent episodes, and decrease the incidence of HSV. Antidepressants, such as amitriptyline, desipramine, and nortriptyline, may relieve pain associated with PHN, but side effects limit their use [245]. Anticonvulsants are of limited value in the management of neuritic pain. Opioids are the most effective therapeutic agents for severe neuritic pain [246]. Recent trials of topical lidocaine 5% in gel and patch form show some effectiveness and may provide a useful adjunctive therapy [247]. Nerve blocks, skin infiltration, transcutaneous electrical nerve stimulation, and intravenous lidocaine may also provide relief of severe pain in some PHN patients [246]. In 2010, the FDA approved a high-dose (8%) capsaicin dermal patch, trade name Qutenza, for the treatment of postherpetic neuralgia. This patch was studied in a randomized, double-blind, multicenter controlled study comparing the high-concentration patch (8%) versus a low-dose capsaicin patch (0.04%). Patients received a single 60-min application and found significant reduction in pain symptoms that was maintained over a 12-week period [248]. The prognosis for recovery in PHN is generally good, although when PHN symptoms become chronic a multidimensional approach to pain therapy will help patients manage their symptoms.

Other Infectious Neuropathies

There are several other causes of infectious neuropathy (Table 38.4). Diphtheria is a rare disease in the United States, generally encountered in developing countries. Diphtheritic neuropathy may be confused with Guillain-Barré syndrome unless a history of pharyngitis is elicited. Oropharyngeal and diaphragmatic weakness occur 5–7 weeks after infection. A demyelinating sensorimotor polyneuropathy involving the trunk and extremities develops 2–3 months after infection [249]. Because the toxin produced by *Corynebacterium diphtheriae* (the causative agent of diphtheria) does not easily cross the blood–brain barrier, myelin damage of cranial and peripheral nerves is limited [250].

Brucella neuropathy is the result of infection by *Brucella suis*, *B. melitensis*, or *B. abortus*. This blood-borne infection involves nerve roots and cranial nerves by a granulomatous meningeal reaction. Diagnosis is based on clinical manifestations, positive serum and CSF serology, and culture of the organism. Treatment requires combination therapy with rifampin, doxycycline, streptomycin, and trimethoprim-sulfamethoxazole [251].

The granulomatous basal meningitis of tuberculosis may involve cranial nerves and nerve roots. Cranial nerves II, III, VI, and VIII are the most commonly affected. Certain therapies for tuberculosis, such as isoniazid, may also precipitate peripheral nerve injury. In HIV-infected patients, *M. tuberculosis* rarely causes acute lumbosacral polyradiculopathy [252].

Finally, tick paralysis is an easily overlooked form of ascending paralysis that presents similarly to AIDP. In North America, *Dermacentor andersoni* (the Rocky Mountain wood tick) and *variabilis* (the common dog tick)

cause most cases. Patients present with weakness and absent lower extremity deep tendon reflexes. Bulbar or respiratory paralysis may occur and prove fatal. Diagnosis and treatment involve finding and removing the offending tick. EMG may show repetitive compound muscle action potentials with a single stimulus. The specific pathophysiology is unknown [253].

Sarcoid Neuropathy

Introduction

Sarcoidosis is a multisystem granulomatous disorder that affects young adults and is manifested clinically with bilateral hilar adenopathy, pulmonary infiltration, and reticuloendothelial system, ocular, and cutaneous involvement. The Johns Hopkins Hospital Sarcoidosis Clinic reported in 1985 that approximately 5% of patients with sarcoidosis develop nervous system complications, and of these, the PNS is affected in approximately 85% of patients [254]. Subsequent studies suggested that the prevalence of neurosarcoidosis is may be as high as 10%. [255]

Etiology and Pathogenesis

The etiology of sarcoidosis and the pathophysiology of nerve fiber damage is unknown. A mixture of vascular compromise and localized granulomatous infiltration probably plays important roles in the pathogenesis of neuropathy. Noncaseating granulomas occur within the endoneurium of peripheral nerves, spinal nerve roots, and cranial nerves. In the absence of angiopathy, some investigators consider that neuropathy is the result of compression of fibers by granulomatous infiltration [256, 257]. Others report granulomas only in the epineurium and perineurium without evidence of direct compression of nerve fascicles but coexisting with varying degrees of angiopathy [258, 259]. Signs of demyelination and remyelination along with small and large fiber loss are usually seen [257, 259].

Clinical Presentation

Sarcoid neuropathy can affect large nerve fibers or small nerve fibers. Large fiber neuropathy presents as cranial neuropathy, mononeuropathy multiplex, radiculopathy, or symmetric polyneuropathy. Any nerve, motor or sensory, may be involved. Cranial neuropathy is most common and often involves the facial nerve, which may be bilateral [254, 260, 261]. Other nerves occasionally involved include the vestibulocochlear nerve and the optic nerve. Patients with eighth-nerve involvement may present with either sensorineural hearing loss or vestibular dysfunction. Papilledema or scotomata in a patient with known sarcoidosis may indicate optic nerve involvement [4, 254]. Patients may complain of diplopia due to meningeal or intraorbital involvement of ocular motor nerves. Horner's syndrome is also reported [254].

Intradural and extradural granulomatous masses may cause radiculopathy. Cauda equina syndrome and arachnoiditis occur [254]. Peripheral neuropathy is seen in up to 14% of patients in some series [256, 257]. Neuropathy may be predominantly sensory with paresthesias and posterior column dysfunction [256] or a more generalized sensorimotor neuropathy or mononeuropathy multiplex [254, 256, 258]. Patients with mononeuropathy multiplex often demonstrate a fluctuating pattern of sensory and motor deficits which may include large areas of anesthesia on the trunk, a distribution referred to as "intercostal neuritis." [260]

Small fiber neuropathy may present with restless leg syndrome or periodic leg movement disorder [261]. Other symptoms include sensory disturbances, such as pain (which can be disabling), numbness, burning, dysesthesias, sheet intolerance, electric-shock-like sensations, as well as autonomic disturbances, such as changes in sweating pattern, sicca syndrome, facial flushing, sexual dysfunction, and bowel/bladder dysfunction [262–264]. On neurologic examination, patients may demonstrate loss of pinprick and temperature sensation as well as allodynia.

The diagnosis of sarcoid neuropathy is straightforward, if the patient is known to have sarcoid. In patients presenting with the clinical syndromes described above and no other potential etiologies, a high degree of suspicion should be maintained and an evaluation for systemic sarcoid initiated when indicated. Tuberculosis and certain forms of leprosy may also be characterized by granulomatous nerve damage, but their clinical features can usually differentiate these forms of neuropathy.

Evaluation and Diagnosis

The diagnosis of sarcoid neuropathy is straightforward when accompanied by recognized systemic involvement. The presence of a recurrent or bilateral facial nerve paralysis suggests the diagnosis of neurosarcoidosis in a patient with established disease [254]. Electrodiagnostic studies help to clarify the type of peripheral nerve involvement in large fiber neuropathy. Motor nerve amplitudes are often markedly reduced, and sensory responses may be absent or of reduced amplitude. Conduction velocities are slowed but conduction block is unusual. Needle EMG may show evidence of denervation [256, 257, 259]. CSF analysis shows a nonspecific mild lymphocytosis and elevation of protein [254].

In patients with mononeuropathy multiplex, muscle biopsy is more likely to demonstrate noncaseating granulomas than sural nerve biopsy.

In small fiber neuropathy, skin biopsy shows reduced intraepidermal nerve fiber density [262, 263, 265]. Autonomic testing such as quantitative sudomotor axon reflex test (QSART), has a sensitivity of approximately 72% [263] and is often used in conjunction with skin biopsy.

Treatment and Prognosis

In spite of their potential side effects, corticosteroids remain the mainstay of therapy. Abdogu et al [260]. reported good response with cyclosporine in 75% of patients with neurosarcoidosis, although most of the patients relapsed after discontinuation of therapy. In certain refractory cases, radiation therapy has some benefit [259, 260, 266]. Lower et al. reported that methotrexate is well tolerated, has minimal side effects, and controlled disease in 61% of 28 patients studied [267]. Case reports suggest that intermittent, intravenous cyclophosphamide may produce symptomatic improvement in some patients [260, 268]. Sarcoid facial nerve paralysis is a short-term complication of the disease, and the prognosis is generally good in patients whose only manifestation of disease is cranial neuropathy. However, less than half of patients with eighth-nerve involvement have good recovery of hearing [254]. Treatment with intravenous immunoglobulins and infliximab appears to be effective in small fiber neuropathy [269, 270].

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Peripheral Nerve Injury

39

Amparo Gutierrez and John D. England

Introduction

Injuries to peripheral nerves constitute a large and increasing medical and public health problem and are a frequent accompaniment to other bodily trauma. Although many of these injuries result from accidents involving motor vehicles, motorcycles, etc., an unfortunately increasing number are due to acts of violence, especially gunshot wounds. Among all patients admitted to level I trauma centers, peripheral nerve injury is estimated to occur in 2–3% of patients. If plexus and root injuries are also included, the incidence is close to 5% [1]. Peripheral nerve injuries occur most commonly in young adults between the age of 18 and 35 years.

Early recognition of patients with peripheral nerve injury is crucial to optimize evaluation and management. These patients are best evaluated and treated in specialized centers which have the expertise to provide all levels of care, including prompt intervention if warranted or careful sequential monitoring to ensure the best possible outcome. The indications and timing of surgical therapy for peripheral nerve injuries are complex and best made by experienced peripheral nerve experts. Even in the best of hands, recovery from peripheral nerve injuries can be disappointing. Understanding the molecular factors involved in nerve regeneration is undoubtedly the key to improving functional recovery after peripheral nerve injury. Current research is focused upon promising new agents which have the potential to stimulate and guide axonal regeneration. Within the next few years, some of these agents may become part of the standard treatment for peripheral nerve injuries.

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Classification and Prognosis in Peripheral Nerve Injury

Although there are several classifications of peripheral nerve injury, the most useful classification of nerve injury is that of Sunderland [2], which categorizes nerve injury into five degrees (Fig. 39.1). *First-degree injury* represents disruption of the myelin sheath, the axons are intact with a completely intact stroma. *Second-degree injury* involves the transection of axons with the stroma remaining intact. *Third-degree injury* represents a transection of the axon as well as the endoneurial tubes. In this injury the surrounding perineurium remains intact. *Fourth-degree injury* involves loss of continuity of axons, endoneurial tubes, and perineurium. Individual nerve fascicles are transected, and the continuity of the nerve trunk is maintained only by the surrounding epineurium. Traction injuries commonly produce these types of lesions. *Fifth-degree injury* is a transection of the entire nerve trunk.

Seddon classified nerve injury into three categories [3]: (1) *neurapraxia* in which axons are intact but fail to conduct action potentials because of focal demyelination, (2) *axonotmesis* where axons themselves have been transected but the nerve trunk is still in continuity, and (3) *neurotmesis* where the nerve trunk has been divided. There is some overlap between these two classification systems (Table 39.1).

The determining factors for prognosis in peripheral nerve injury are the degree of injury, the extent of internal disorganization in the nerve, the site of injury, and the distance of the injury from the target organ. In the first-degree injury (neurapraxia), the prognosis for recovery is excellent since only remyelination of the injured axons is required. By contrast, in the fifth-degree injury (neurotmesis), the hope for recovery is not possible unless surgical repair of the lesion is performed. In the second- to fourth-degree injuries (axonotmesis), the prognosis ranges from intermediate to poor and depends not only on the degree of nerve injury but also on the number of transected axons and the site of nerve injury. Injuries grade 2 or higher result in wallerian degeneration of

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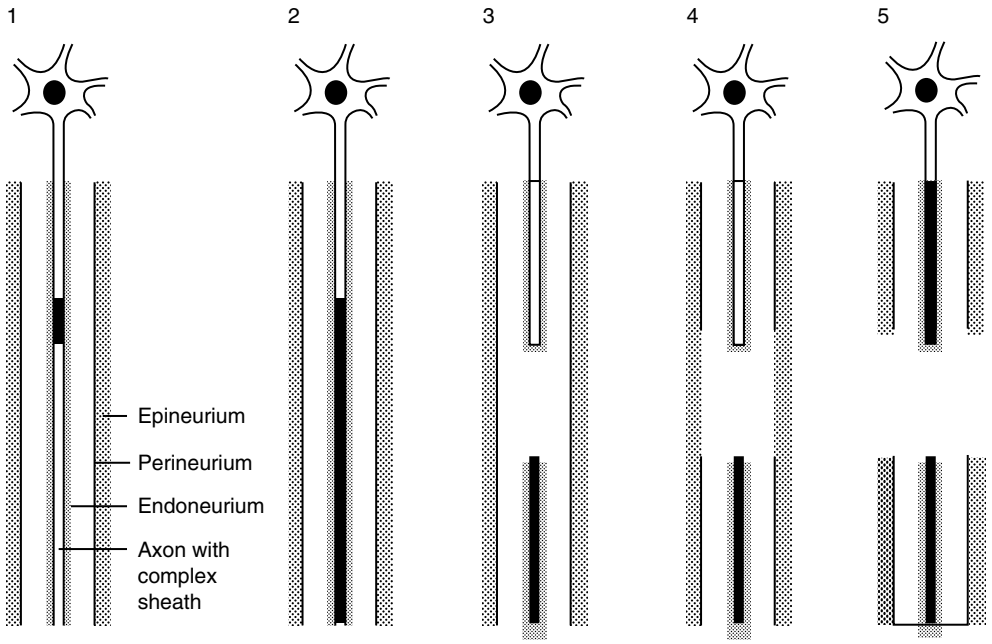

Fig. 39.1 The five degrees of nerve injury: demyelination of the axon with preservation of axonal continuity (1); transection of the axon with preservation of the endoneurium (2); transection of the axon with disruption of the endoneurium but preservation of the perineurium (3); transection of the axon with disruption of the endoneurium and perineurium but preservation of the epineurium (4); and transection of the entire nerve trunk including the epineurium (5) (Modified from Sunderland [1]. Reprinted with permission from John England, Current Opinion in Orthopedics, 1995/6;VI)

Table 39.1 Comparison of classifications in peripheral nerve injury

Sunderland	Seddo	Injury
First degree	Neurapraxia	Disruption of myelin; intact axons and stroma
Second degree		Transection of axons with stroma intact
Third degree	Axonotmesis	Transection of axons and endoneurial tubes
Fourth degree		Transection of axons, endoneurium, and perineurium
Fifth degree	Neurotmesis	Transection of the entire nerve

the distal stump, making recovery less favorable. Also, when a nerve is injured far from its muscle, recovery is poor. This principle is maximally evident with nerve root avulsions, where no functionally useful axon regeneration occurs.

Reactions of Peripheral Nerve to Injury

Cellular

Peripheral nerve has a limited range of pathological responses to injury. The most common response to trauma is wallerian degeneration of axons. Segmental demyelination may contribute to the clinical deficit although it is rarely the predominant pathology in peripheral nerve injury. Wallerian degeneration is a sequence of cellular events that mainly involves the distal nerve stump. Soon after an axonal lesion has occurred, there are changes in both the proximal and distal axonal stump as well as the nerve cell body [4]. Myelin begins to retract from the axons at the nodes of Ranvier as early as 6–16 h after neural insult. In the distal nerve stump, a number of changes occur in the first 2 days. These include leakage of axoplasm from the severed nerve, retraction of the severed ends, swelling of the distal nerve segment, and subsequently the disappearance of neurofibrils in the distal segment. By day 3, there is a fragmentation of both axon and myelin with the start of digestion of myelin components. By day 8, the axon is digested, and Schwann cells are attempting to bridge the gap between the two nerve segments. Proximal nerve fibers also degenerate for a variable distance depending on the severity of the lesion. This retrograde degeneration may extend for several centimeters. If the lesion is sufficiently proximal, there are a number of changes that occur at the nerve cell body. Initially, within the first 48 h, the Nissl bodies (the cell's rough endoplasmic reticulum) break apart into fine particles. By 2–3 weeks after injury, the cell's nucleus becomes displaced eccentrically and the nucleolus is also eccentrically placed within the nucleus.

Molecular

Although the histological alterations that occur in wallerian degeneration have long been known, recent observations have provided insight into the molecular responses that occur after axotomy. The key to promoting successful axonal regeneration may lie in understanding these molecular changes. Breakdown of the axon initiates retrograde signaling to the nerve cell body that leads to a switch in gene expression and cell physiology from the normal operating state to the growth mode. Molecular changes in the distal stump include the enhanced expression of neurotrophins, cytokines, and other growth factors, as well as cell adhesion

molecules, lipid carriers, myelin proteins, extracellular matrix proteins, and integrins, thus, creating a microenvironment in the distal stump that supports regeneration of nerve fibers [5]. Schwann cells play a dominant role in creating the regeneration-supportive molecular microenvironment in the distal nerve stump. This switch from the normal "operating" mode of the myelin-forming differentiated Schwann cells into the "proliferation" mode is initiated by removal of axon-neuronal contact [6]. Schwann cells in acutely denervated nerve sections rapidly upregulate the expression of several factors including leukemia inhibitory factor [7], interleukin-6 [8], neuropeptides [9] and neuregulins [10]. These factors all appear to be involved in changing the microenvironment, upregulating the extracellular matrix constituents, and modifying the basal lamina of the distal stump for effective growth-promoting activity. In chronic nerve lesions, there are further and different changes in the Schwann cell expression of these and other chemicals, which may partly explain the markedly reduced long-term potential for axon regeneration [11]. Recent studies suggest that axon guidance depends on chemoattractant molecules, which entice axons, but also upon chemorepellents, which repel axons. Two families of proteins, the semaphorins and the netrins, have potent repellent effects [12]. Most studies have shown that these molecules selectively repel some types of axons but have no effect on others, providing selective steering of regenerating axonal tips.

The role of macrophages in peripheral nerve damage and repair is a central question in current neural regeneration investigations. The mechanism of recruitment of hematogenous macrophages into injured nerve is still unclear. Vougioukas et al. showed that intercellular adhesion molecule (ICAM-1) deficient mice have significantly reduced macrophage recruitment during wallerian degeneration, significantly delaying the process [13]. Similarly wallerian degeneration is retarded by the immunosuppressing drug, cyclosporin A [14]. Such observations suggest that immunosuppression may play an important role in promoting axonal regeneration.

Neuronal

Nerve trauma is tied inextricably to neuromas which histopathologically appear as tangled masses of regenerating axons embedded within the connective tissue of an injured nerve. Neuroma formation requires that the regenerating axons escape their confining endoneurial sheath. Thus, they occur when nerve injury is third degree or greater. The axons within a neuroma not only fail to reinnervate their original targets, but they may also develop abnormal electrical hyperexcitability [15]. The tips of injured sensory fibers often become generators of painful impulses and may also develop exquisite mechanosensitivity, which is demonstrable clinically by the Tinel sign. Recent studies suggest that there is an excessive accumulation of sodium channels within the axons of neuromas [16]. These sodium channels are usually restricted to the demyelinated segments of axons and occur at regenerating neurite tips devoid of myelin [17]. Such focal abnormal accumulations of axonal sodium channels may account, at least in part, for the ectopic axonal hyperexcitability of painful neuromas. The electrical hyperexcitability of neuromas may also be influenced by abnormal distributions of potassium channels [18]. More needs to be learned regarding neuromas. Major areas of inquiry include understanding further the basis of neuroma hyperexcitability and pain and understanding the reasons that neuroma axons fail to reach their target organs.

Electrophysiological Evaluation of Nerve Injury and Regeneration

The evaluation of peripheral nerve injuries is very complicated and should be performed in specialized centers. Referrals should be done in a timely fashion to ensure optimal recovery of function. The most important thing most physicians can do for peripheral nerve injury patients is to refer them quickly to centers with expertise in this area.

The electromyographer is frequently asked to participate in the clinical evaluation and therapeutic decision-making of patients with peripheral nerve injury. The electrodiagnostic (EDX) examination should try to address several key issues: (1) the injury site, (2) the pathophysiology of the injury, (3) the severity of the dysfunction, (4) the prognosis of the lesion, and (5) the progress of reinnervation. These issues can be addressed by assessing the compound motor action potential (CMAP) and the sensory nerve action potential (SNAP) and by performing a detailed needle electromyographic (EMG) examination of muscles.

The timing of the EDX evaluation is very important, as there is an orderly sequence of electrophysiological changes that follow nerve injury when wallerian degeneration occurs. Knowledge of these changes is necessary for proper interpretation of results. In humans, the distal CMAP can be recorded for 1–2 days after all voluntary muscle contraction is lost. The distal CMAP amplitude begins to decline by the third to fifth day after injury, and excitability is lost by the seventh to ninth day [19]. For sensory nerves, the loss of SNAP amplitude lags behind the motor nerves by 2–3 days, with the beginning of loss of amplitude occurring on the fifth to seventh day, and disappearance of the response by the ninth to eleventh day (see Fig. 7.68, in Chap. 7). The difference between the CMAP and SNAP responses is due to earlier physiological changes which occur at the neuromuscular junction [20]. In motor nerve fibers, the earlier deterioration

of neuromuscular transmission results in the earlier (≈2 days) failure of motor nerve conductions compared with sensory nerve conductions. The distal nerve segment continues to have an elicitable evoked response until the above changes have taken place.

Along a distal nerve segment undergoing wallerian degeneration, conduction velocity is unchanged as long as an electrical response can be elicited. This indicates that degenerating axons conduct normally until complete failure and that the largest, fastest conducting axons continue to conduct for the longest time [21]. Thus, before wallerian degeneration of axons is complete, EDX abnormalities resemble demyelinative conduction block: that is, whereas a distal electrical response is elicited, no response (or one of reduced amplitude with partial lesions) can be evoked proximally. It is important to recognize this axonal "noncontinuity conduction block" because it has a poor prognosis for recovery, while "demyelinative conduction block" usually recovers. In axonal-type injuries, the distal CMAP will decrease to approach the CMAP obtained proximally as wallerian degeneration takes place in the distal stump. *For these reasons, an electrophysiological evaluation performed within the first week post injury may result in underestimation of the severity of the injury. Sequential studies at least 2–3 weeks after the injury are necessary to quantify the severity of axonal degeneration.*

Changes in the electrical activity of muscles parallel the changes seen in motor nerves. Immediately following complete nerve transection, voluntary recruitment of motor unit action potentials (MUAPs) is abolished, and no abnormal spontaneous activity is seen yet on needle EMG. With partial resection, recruitment is reduced and is proportional to the loss of motor axons. Early on, the surviving MUAPs have a normal configuration. As wallerian degeneration proceeds, the trophic influence of nerve on muscle is lost, leading to denervational changes. Initially, there is an increase in insertional activity, followed by the appearance of abnormal spontaneous activity, i.e., fibrillation potentials and positive sharp waves, indicating active denervation. This spontaneous activity appears 2–5 days after the CMAP is lost and soon after the loss of the SNAP. It becomes profuse about 2–3 weeks after injury. The time to the appearance of spontaneous activity depends on the length of the distal stump, appearing sooner in more proximally denervated muscles than distal muscles [22].

When a complete nerve injury is clinically suspected, the EDX examination is oriented first toward confirming that there is a total nonfunction distal to the lesion and second to establishing that the pathophysiology is exclusively axonal in nature. Complete absence of volitional MUAP activity, lack of response to motor nerve stimulation distal to the site of injury, and active denervation in muscle suggest axonal injury to all motor nerve fibers. The amount of spontaneous activity observed is an unreliable indicator of axonal loss. *The best estimate of lesion severity is the diminution in size of the CMAP in response to distal stimulation* [23]. In partial lesions, the estimation of lesion severity is more complex. Localization of nerve injuries requires in-depth knowledge of the normal anatomy of myotomes, dermatomes, and peripheral nerve distributions as well as the numerous possible anatomical variations.

Partial peripheral nerve injuries that leave the nerve in continuity represent 60 to 70% of all peripheral nerve injuries [24]. They present a complex EDX challenge. A single EDX l assessment at 2–3 weeks after injury does not adequately discriminate between second-, third-, and fourth-degree injuries. All three of these grades of injury can show profound loss of motor axons. Serial EMGs should be performed over the course of 2–4 months to allow for grade 2 injuries to be distinguished from the more severe insults. Recovery of function occurs more frequently in grade 2 lesions. This recovery occurs both by distal collateral sprouting of remaining intact axons and regeneration of transected axons. During reinnervation by collateral sprouting, more muscle fibers are incorporated into the territory of each surviving motor unit. Electromyographically, this collateral sprouting is mirrored by an increase in duration, amplitude, and polyphasia of MUAPs. By contrast, the earliest definite evidence of muscle reinnervation by axonal regeneration following severe axonal loss is the appearance of one or a few small, complex, unstable MUAPs, sometimes referred to as "nascent" MUAPs. Immature sprouts conduct very slowly and their neuromuscular transmission is insecure. Like fibrillation potentials, these nascent or regenerating MUAPs develop in a centrifugal manner. Needle EMG may detect these MUAPs several weeks to months before there is any evidence of clinical improvement. The more severe nerve injuries, such as Sunderland grades 3 or 4, declare themselves by a lack of documentable recovery both clinically and electrophysiologically. *For most nerve lesions in continuity, surgical exploration is generally recommended, if there is no evidence of axonal regeneration by 3–6 months post injury.*

Therapeutic Interventions

Surgical

During the last quarter of a century, several significant development in the surgical tools available to treat nerve injuries have occurred: (1) the magnification by either an operating microscope or eye loupes, (2) the utilization of the bipolar coagulator, (3) the use of some microinstruments, and (4) the use of relatively fine suture [25]. Timing of the surgical repair depends on the type of injury as well as the degree

Table 39.2 Therapy of peripheral nerve injuries

Nerve lesion	EMG	Operative NAP	Therapy
Nerve transection	Not done acutely	Not done acutely	Early operation (72)h Sharp laceration = repair by end-to-end suture Blunt laceration = repair 2–4 weeks later Nerve intact = conservative
Nerve in continuity (focal lesion)	Serial EMG : 2–4 months Axonal integrity/regeneration = conservative Rx No axonal integrity = surgery with operative CNAP	Surgery: CNAP present→ CNAP absent→	 Simple neurolysis Resection and repair (graft)
Nerve in continuity (long lesion)	Serial EMG : 4–6 months Axonal integrity or regeneration = conservative Rx No axonal integrity = surgery with operative CNAP	Surgery: CNAP present→ CNAP absent→	 Simple neurolysis Resection and repair (graft)

EMG electromyography, *CNAP* compound nerve action potential

of injury. What follows is a brief summary of the current strategy for the surgical therapy of peripheral nerve injuries (Table 39.2).

Nerve Transection

Immediate repair is warranted in a nerve injury that has resulted in a relatively sharp transection, such as may be found with injuries due to glass, knives, or sharp metal edges. In this setting, the amount of tissue to be trimmed from each stump is minimal, the anatomy is not greatly distorted, and nerve repair can occur at the same time as other soft tissue repair. In contrast, the damage sustained by each stump in blunt transections is difficult to delineate acutely. These injuries are usually the result of propeller blades, power saws, or compound fractures. In blunt transection, immediate end-to-end repair of potentially damaged stumps leads to a poor result. Therefore, a formal repair is best accomplished after a delay of several weeks, when the amount of neuroma and scar tissue to be trimmed is very evident.

Lesions in Continuity

The majority of peripheral nerve injuries are of this variety. Most lesions in continuity are due to blunt trauma, stretch, and contusion, resulting in a mixture of grades 2, 3, and 4 nerve injuries. Gunshot wounds, which unfortunately account for a significant proportion of nerve injuries, also usually result in nerve lesions in continuity. Patients with total palsy of the brachial plexus following an accident have almost no chance for spontaneous recovery; this is different for partial injury which may have some spontaneous recovery. Patients with complete injury may benefit from earlier surgery. In a review of 335 adult patients with total palsies, operated between the third and sixth month after injury, they had good results with the return of elbow flexion. In partial injuries, some good results were observed even 10 months after the accident [26]. The type of surgical intervention performed on injured nerve depends on whether any axons extend across the lesion. Visual inspection of a surgically exposed nerve is necessary but is notoriously inadequate in determining the severity of the nerve injury. The best method for determining this is to use *intraoperative nerve action potential recordings*. Operative exploration not only allows for direct visualization of the injured site but provides the opportunity for direct recordings of evoked nerve activity of a lesion in continuity. The surgeon then has a solid physiological basis for deciding which sections of the nerve need to be resected or repaired. Intraoperative recordings are performed by placing stimulating and recording electrodes directly on the exposed nerve and attempting to elicit a nerve action potential. Muscle activity distal to the point of stimulation in the distribution of the nerve being stimulated is also monitored. The presence of a compound nerve action potential (CNAP) across and distal to the injury site is a direct evidence of viable axons. The amplitude of the action potential is indicative of the number of functioning axons within the nerve, as long as the stimulus used is sufficient to activate all axons. *The presence or absence of the CNAP is the single most important determinant of the type of surgical intervention to be used.* For a lesion in continuity, an absent CNAP usually indicates the need for resection and repair of the nerve, while the presence of a response usually indicates that a better result can be achieved with neurolysis or repair of only the damaged fascicles. Each component of the nerve can thus be tested and treated individually, as some fascicles or groups of fascicles may conduct while others may not.

Surgical techniques used in nerve repair are end-to-end suture, neurolysis, split repair, and graft repair. *End-to-end suturing* is still the procedure of choice for cleanly transected nerve or severe focal lesions in continuity where opposition of stumps can be done without excessive tension. With respect to *neurolysis*, there are two types, external and internal. External neurolysis consists of the dissection of nerve, freeing it from the surrounding tissues. Exposure of the entire circumference of the nerve is performed, allowing for intraoperative stimulation and recording studies. If a CNAP cannot be elicited across the nerve injury site, the nerve is resected beginning at the segment proximal to the lesion where a CNAP is first recordable. Internal neurolysis is then

done, and the nerve is repaired by end-to-end suture if mobilization of the stumps provides enough length for repair with minimal tension.

Occasionally a lesion conducting a CNAP will look and feel worse over a portion of its circumference than in other areas. Proximal and distal nerve is then split into its fascicular structure and traced as best as possible through and beyond the lesion. Recording at a fascicular level is then performed to identify those fascicles that are most severely involved. *Split repair* and internal neurolysis is then restricted to the most severely injured fascicles.

Many injuries produce lengthy lesions that if resected will lead to a gap not readily repaired by end-to-end suturing. Several techniques for repair are utilized, nerve grafts, nerve transfers, and tendon and muscle transfers. The gold standard in nerve gap management remains *autogenous nerve grafting* [27]. The most popular graft technique is an interfascicular grouped fascicular approach [28]. Groups of fascicles are isolated both proximally and distally, and a number of small caliber nerves are used to span the gap. Common donor nerves include the sural and antebrachial cutaneous nerves. Patients with injuries that are able to be reconstructed with both root grafting and nerve transfers have been shown to have better results [29]. More recently, nerve conduits, allografts, and nerve expansion have been investigated. Nerve conduits have been constructed of bone, silicone conduits, vein, artery [30], amnion [31], polyglactin 910 [32], and collagen [33]. Silicone conduits are rarely used since they have been implicated with serious problems, including chronic compression of the regenerating axons necessitating surgical removal. Clinical application of peripheral nerve allografting remains under experimental investigation and requires immunosuppression in the host. Typically, the nerves are harvested from a donor undergoing harvest of other organs. Tissue expansion has been fraught with difficulties, including compromised nerve perfusion and progressive demyelination. Muscle grafts have been used for peripheral nerve repair with good results over short distances [34].

Stimulation of Axonal growth

In all cases of nerve injury except neurapraxia, regeneration is slow and incomplete. In humans, nerves regenerate at an average rate of 1–2 mm/day [35]. Enhancing the rate and completeness of regeneration may significantly improve nerve repair results. There are two major determinants of successful nerve regeneration, intrinsic growth ability and an extrinsic permissive environment [36]. Axonal regeneration depends on Schwann cells and a substrate along which the axon can grow and presumably also on diffusible factors produced within the nerve and the peripheral target (neurotrophic and neurophilic factors). A major change in thinking regarding nerve regeneration is taking place. Recent research indicates that reinnervation of target organs depends not only upon the potency of axonal regeneration but also upon physical and chemical factors external to the axon. Schwann cells are now known to be very important in stimulating and guiding successful axonal regeneration. Along neural tubes and at the level of the neuromuscular junction, the Schwann cells elaborate processes that help guide the regenerating fibers to the muscle [37].

Several neurotrophic factors applied locally or systemically enhance nerve regeneration. The immunosuppressant drug FK506, a ligand of the immunophilin FK506 binding protein-12, increases the rate of axonal regeneration in lesioned rat peripheral nerve [38]. Nonimmunosuppressive analogues of FK506, rapamycin and cyclosporin, are potent drugs in promoting nerve fiber growth in vitro and in vivo [39]. The potential effectiveness of these compounds in promoting axonal regeneration is great, and they are being studied by many investigators.

Significant enhancement of nerve regeneration has also been reported by implanting prosaporin (a protein precursor of saporins), between proximal and distal stumps of transected peripheral nerve [40]. Studies with insulin-like growth factor (IGF) have identified that it has a neurotrophic effect upon motor axons [41]. Nerve growth factor (NGF) has yielded conflicting results [42], and epidermal growth factor (EGF) has been shown not to influence regeneration [43]. Gangliosides are abundant in axonal membranes, and topical GM1 ganglioside has resulted in a small improvement in regenerating axon diameter following nerve crush injury [44]. There have also been reports that use of direct current electric fields [45] and hyperbaric oxygen [46] may enhance axonal regeneration.

Another strategy that may promote axonal recovery is attenuation of neuronal cell death following axotomy. Recent attempts to rescue injured neurons with exogenous neurotrophins [47] (nerve growth factor {NGF}, brain-derived neurotrophic factor {BDNF}, neurotrophin-3 {NT-3}, and neurotrophin −4/5 {NT-4/5}) and neurokines (ciliary neurotrophic factor {CNTF}) have been very promising in some experimental studies.

A recent growth of knowledge has occurred in axonal guidance research. Certain proteins, netrins [47] and semaphorins [48], which are secreted by neuronal target cells into the surrounding tissue can act as either chemorepellents or as chemoattractants for axons. The presence of such proteins at critical locations along with a nerve helps to steer growing axons along the most appropriate pathways to their target organs. Ultimately, the signals are integrated into specific regulators of the nuclear transcription factors that induce the expression of large ensembles of distinct genes sequentially and under tight control. These include c-Jun, sox-11, CREB, Smad1, ATF3, AKRD1, NFILS, p53, STAT3, C/EBPβ, and several KLF family members. Although there is a theoretic

appeal of enhancing regeneration with the above-mentioned agents, the role that these agents may play in promoting axonal regeneration in humans must await further research.

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Compressive and Entrapment Neuropathies of the Upper Extremity

40

David C. Preston

Median Neuropathy at the Wrist

Median neuropathy is the most common entrapment neuropathy affecting the upper extremity, with the usual site of compression occurring at the wrist. Entrapment of the median nerve at the wrist usually presents with *carpal tunnel syndrome* (*CTS*), a characteristic syndrome of wrist pain and digital paresthesias, often provoked during sleep or other activities that increase carpal tunnel pressure.

Anatomy (Fig. 40.1)

The median nerve is formed by a contribution of the lateral and medial cords of the brachial plexus [1]. The lateral cord fibers comprised of C6–C7 fibers and supply sensory fibers to the thenar eminence and thumb (C6), index (C6–C7), and middle (C7) fingers as well as motor fibers to the proximal median forearm muscles. The medial cord contribution comprised of C8–T1 fibers and supplies motor fibers to the distal median muscles of the forearm and hand, as well as sensory fibers to the lateral half of the ring finger.

In the upper arm, the median nerve descends giving off no branches. In the antecubital fossa, the nerve lies adjacent to the brachial artery. Passing into the forearm, the nerve runs between the two heads of the pronator teres before giving off muscular branches to the pronator teres, flexor carpi radialis, flexor digitorum sublimis, and, in some individuals, the palmaris longus muscles. The anterior interosseous nerve is given off next in the proximal forearm, innervating the flexor pollicis longus, medial head of the flexor digitorum profundus to index and middle fingers, and the pronator quadratus muscles.

Just proximal to the wrist and carpal tunnel, the palmar cutaneous sensory branch arises, running subcutaneously to supply sensation over the thenar eminence. The median nerve then enters the wrist through the carpal tunnel. Carpal bones make up the floor and sides of the carpal tunnel, with the transverse carpal ligament forming the roof. In the palm, the median nerve divides into motor and sensory divisions. The motor division travels distally into the palm supplying the first and second lumbricals. In addition, the recurrent thenar motor branch supplies muscular branches to most of the thenar eminence including the opponens pollicis, abductor pollicis brevis, and superficial head of the flexor pollicis brevis. The sensory fibers of the median nerve that course though the carpal tunnel supply the medial thumb, index and middle finger, and lateral half of the ring finger in most individuals.

Etiology and Pathogenesis

There are numerous etiologies of median neuropathy at the wrist, although most are idiopathic [1, 2]. Idiopathic cases were long considered to be tenosynovitis of the transverse carpal ligament. However, pathology typically shows little evidence of inflammation with the major findings being edema, vascular sclerosis, and fibrosis, most consistent with repeated stress to connective tissue. Median neuropathy at the wrist is more common in patients who have a narrow carpal canal [3, 4]. Imaging studies have demonstrated that the narrowest part of the canal is 2 to 2.5 cm distal from the entrance. Detailed nerve conduction studies with inching show the area of maximal slowing to be slightly distal to the wrist crease in the palm [1]. Demyelination follows compression and ischemia of the median nerve, and if severe enough, axonal loss ensues. Occupations or activities which

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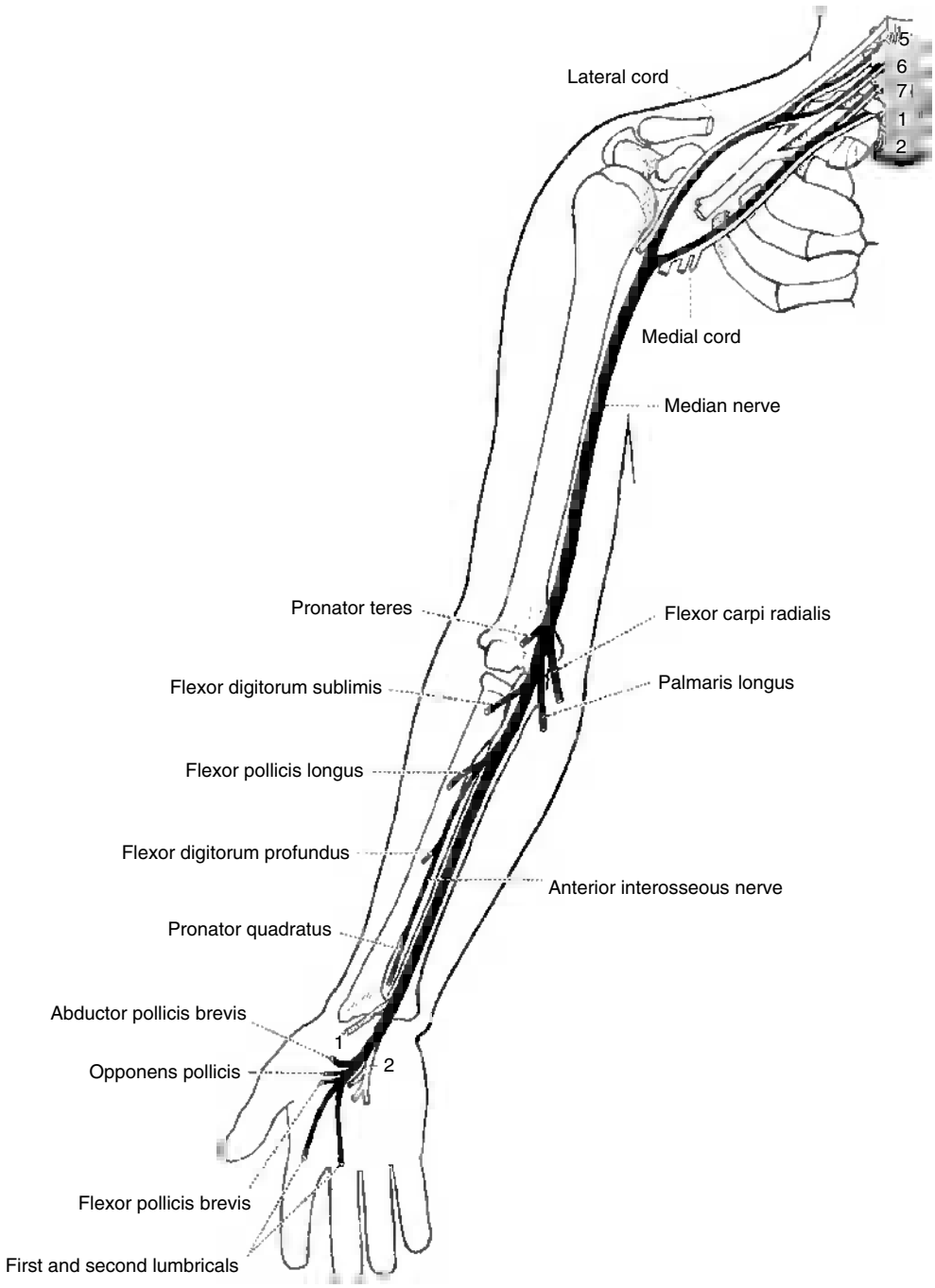

Fig. 40.1 Anatomy of the median nerve. The median nerve is derived from a combination of the lateral and medial cords of the brachial plexus. Motor innervation is supplied to forearm muscles and to muscles of the thenar eminence. Sensation is supplied to the thenar eminence by the palmar cutaneous sensory branch (*1*) and to the first three and one-half digits by several digital sensory branches (*2*) (Adapted from Haymaker and Woodhal [102]. With permission)

involve repetitive hand use increase the risk of CTS. Other predisposing etiologies include certain systemic disorders, most notably endocrine (e.g., hypothyroidism) or connective tissue diseases (e.g., rheumatoid arthritis); unusual mass or infiltrating lesions of the carpal tunnel; some congenital conditions; various infectious and inflammatory diseases such as Lyme disease and sarcoidosis; trauma, especially Colles fracture; and several other conditions including amyloidosis, hemodialysis, and pregnancy.

Clinical Presentation

CTS may present with a variety of symptoms and signs [1, 5, 6]. Women are more often affected than men. Although usually bilateral, the dominant hand is usually more severely affected, especially in idiopathic cases. Patients complain of wrist and arm pain associated with paresthesias in the hand. The pain may be localized to the wrist or may radiate to the forearm, arm, or rarely the shoulder. Some patients may describe a

Table 40.1 Clinical symptoms and signs

Highly suggestive of CTS	Possible CTS	Inconsistent with CTS
Nocturnal paresthesias awakening patient from sleep Shaking or ringing the hands	Hand, wrist, forearm, arm, and/or shoulder pain	Neck pain
Pain/paresthesias with driving and holding a phone, book, or newspaper	Perception of paresthesias involving all five digits	Radiating paresthesias from the neck down the arm
Sensory disturbance of the thumb and index, middle, and ring fingers; splitting the ring finger	No fixed sensory disturbance, or sensory disturbance of the thumb and index, middle, and ring fingers	Unequivocal numbness over the thenar eminence
Weakness/wasting of thenar eminence	Decreased hand dexterity	Weakness/wasting of hypothenar muscles, thumb flexion (IP joint), arm pronation, and/or elbow flexion/extension
Phalen's maneuver reproduces symptoms	Tinel's sign over the median nerve at the wrist	Reduced biceps or triceps reflexes

Source: Adapted from Preston and Shapiro [103]

diffuse, poorly localized ache involving the entire arm. Paresthesias are frequently present in a median nerve distribution (i.e., medial thumb, index, middle, and lateral ring fingers). While many patients report that the entire hand falls asleep, if asked directly about little finger involvement, most will subsequently note that the little finger is spared.

Symptoms are often provoked when either a flexed or extended wrist posture is assumed. Most commonly, this occurs during ordinary activities, such as driving or holding a phone, book, or newspaper. Nocturnal paresthesias are particularly common. During sleep, persistent wrist flexion or extension leads to increased carpal tunnel pressure, nerve ischemia, and subsequent paresthesias. Patients are frequently awakened from sleep and shake or ring out their hands or hold them under warm running water.

Sensory fibers are involved early in the majority of patients. Hence, pain and paresthesias are usually the presenting symptoms. Motor fibers may become involved in more advanced cases. Weakness of thumb abduction and opposition may develop, followed by atrophy of the thenar eminence. Some patients describe difficulty buttoning shirts, opening a jar, or turning a doorknob. However, it is unusual to develop significant functional impairment from loss of median motor function in the hand.

The sensory examination may disclose hypesthesia in the median distribution. Two-point discrimination is generally affected before pain and temperature. Sensation over the thenar area in spared, as this area is innervated by the palmar cutaneous sensory branch, arising proximal to the carpal tunnel. Often, paresthesias may be elicited by tapping over the median nerve (*Tinel's sign*) or by having the patient hold their wrists in a flexed position (*Phalen's maneuver*) [6, 7]. The Tinel's sign is present in over half of CTS cases; however, false-positive Tinel's signs are common in the general population. A Phalen's maneuver, which usually produces paresthesias within 1–2 min in CTS, is more sensitive than the Tinel's sign and has fewer false positives. Most commonly, the Phalen's maneuver will produce paresthesias in the middle or index fingers. The motor examination involves inspection of the hand looking for wasting of the thenar eminence in more severe cases and testing the strength of thumb abduction and opposition.

Differential Diagnosis

There are several peripheral as well as central nervous system lesions that may result in symptoms similar to CTS (Table 40.1). The peripheral lesions that may mimic CTS include median neuropathy in the region of the elbow, brachial plexopathy, and cervical radiculopathy. Cervical radiculopathy is the most common disorder confused with CTS, especially lesions of the C6 or C7 roots, which may cause both pain in the arm and paresthesias similar to CTS. The important clinical points that suggest radiculopathy rather than CTS are neck pain radiating to the shoulder and arm and exacerbation of symptoms by neck motion. Key points in the physical examination that suggest radiculopathy are abnormalities of the C6–C7 reflexes (biceps, brachioradialis, triceps), diminished power in proximal muscles (especially elbow flexion, elbow extension, arm pronation), and sensory abnormalities in the palm and/or forearm, which are beyond the distribution of sensory loss in CTS.

Median neuropathy in the elbow and brachial plexopathy are uncommon, especially when compared to the incidence of CTS. If present, however, they may easily lead to clinical confusion. Important points on physical examination that suggest a more proximal lesion of the median nerve are sensory disturbance over the thenar eminence and weakness of median muscles proximal to the carpal tunnel, especially distal thumb flexion, arm pronation, and wrist flexion. In brachial plexus lesions, the neurologic examination may reveal abnormalities similar to those noted in cervical radiculopathy, although the distribution of reflex abnormalities, weakness, and sensory loss may be more widespread, beyond the distribution of one spinal segment.

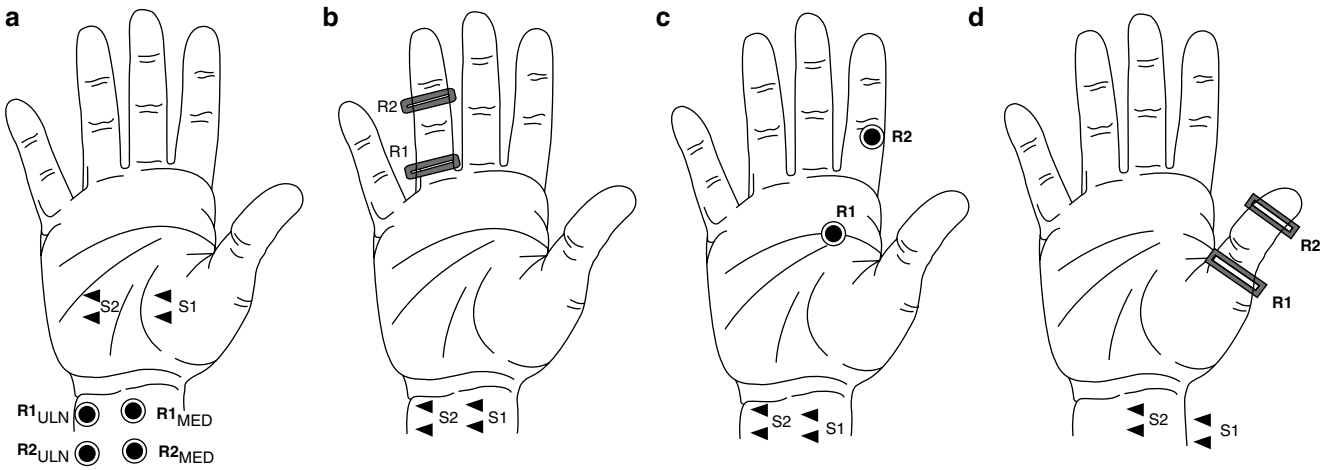

Fig. 40.2 Internal comparison studies. (**a**) Palmar-mixed studies, (**b**) ring finger sensory studies, (**c**) lumbrical-interosseous studies, and (**d**) thumb sensory studies. *S1*: median stimulation point, *S2*: ulnar/radial stimulation point, *R1*: active recording electrode, and *R2*: reference recording electrode. In each study, identical distances between stimulation and recording sites are used for the median and ulnar/radial nerves (Adapted from Preston and Shapiro [103])

As for central nervous system disorders, transient paresthesias in the hand may be seen in patients with seizures, migraine, and transient ischemic attacks and are occasionally misinterpreted as symptoms of CTS. Rarely, patients referred for CTS are found to have a small lacunar infarct involving the lateral thalamus and internal capsule, causing hand clumsiness and sensory disturbance predominantly affecting the median-innervated digits.

Evaluation and Diagnosis

The median nerve is easily studied in the EMG laboratory. A large number of nerve conduction studies are available to assess the median nerve across the carpal tunnel [1, 8]. Similar to the clinical examination, the goals of electrodiagnostic testing (EDX) are to demonstrate a distal lesion of the median nerve and exclude other peripheral conditions which can result in similar symptoms, especially high median neuropathy, C6–C7 radiculopathy, or lesions of the brachial plexus.

In most cases of compressive median neuropathy at the wrist, demyelination is present at the site of lesion with more severe cases demonstrating axonal loss. In moderate or severe cases, routine median motor and sensory nerve conduction studies easily demonstrate slowing of distal latency across the wrist. In cases with either conduction block at the wrist or secondary axonal loss, median motor and sensory amplitudes are reduced. Median motor conduction in the forearm may be slightly slowed if some of the largest and fastest median fibers are blocked or have undergone Wallerian degeneration [9]. Median minimum F wave latencies may be prolonged, especially in comparison to the ulnar nerve, reflecting the F wave response must also transverse the carpal tunnel [10]. It is essential that the electromyographer studies at least one additional motor and sensory nerve to ensure that the abnormalities seen in the median nerve do not simply represent a brachial plexopathy or more widespread polyneuropathy. Indeed, patients with an underlying polyneuropathy often are at risk for developing superimposed entrapment neuropathies, including distal median neuropathy.

Although patients with distal median neuropathy typically display prolonged median motor and sensory latencies, a substantial number of patients (approximately 10–25 %) will have normal routine studies. The diagnosis will be missed in these patients unless further testing is performed. Most often, a study to an adjacent nerve of similar length and size in the same hand is used (internal comparison study). These studies are most useful in patients with mild abnormalities or in those patients with an underlying polyneuropathy. The internal comparison studies most often employ the ulnar nerve and occasionally the radial nerve (Fig. 40.2). The common comparison studies include (1) the median vs. ulnar palm-to-wrist mixed nerve latencies [11], (2) the median vs. ulnar wrist-to-ring finger sensory latencies [12], (3) the median (second lumbrical) vs. ulnar (interossei) distal motor latencies [13, 14], and (4) the median vs. radial wrist-to-thumb sensory latencies [15–17].

In each comparison study, identical distances are employed between the stimulator and recording electrodes for the median and other adjacent nerve [18]. These techniques create an ideal internal control in which several variables that are known to affect conduction time are held constant, including distance, temperature, age, and nerve and/or muscle size. Thus, any mild slowing of the distal median nerve is much easier to appreciate. However, it is important to appreciate that these sensitive comparison studies rely on very small

differences in latencies as measures of distal median nerve dysfunction [1]. Therefore, meticulous attention must be paid to all technical factors, especially distance measurement, stimulus artifact, supramaximal stimulation, and electrode placement, in order to obtain reliable and reproducible data. In addition, avoiding overstimulation, which may cause unintentional stimulus spread to an adjacent nerve, is essential to avoid.

Each of the internal comparison studies has certain advantages. The median vs. ulnar palm-to-wrist mixed nerve studies take advantage of measuring the mixed nerve potential which contains both motor and sensory fibers, including the largest sensory fibers, the Ia afferents from the muscles spindles. Because these fibers are the largest and contain the most myelin, they are susceptible to demyelination, the primary pathology in distal median neuropathy. The mixed nerve study also has the advantage of conducting over a very short distance (typical distance 8 cm). By using such short distances, most of the conduction time is computed over the area of pathology, with the length of normal nerve that could potentially dilute the slowing being minimized. The median vs. ulnar wrist-to-ring finger sensory latency study makes use of the sensory innervation to the ring finger which is split by the median and ulnar nerves in most individuals. Using identical distances, the median sensory latency to the ring finger can be directly compared to the ulnar sensory latency to the ring finger. The studies can be performed either antidromically or orthodromically. The median vs. ulnar distal motor latencies, recording the second lumbrical and interossei, respectively, is an internal comparison technique using motor studies. This technique has the advantage that motor fibers are more easily recorded than sensory fibers and that in the case of polyneuropathy, the study can still be easily performed even if all the sensory responses are absent. Also, in severe CTS with absent routine median CMAPs and SNAPs, this study is able to localize the lesion to the wrist in over 90 % of cases. Identical distances are used and the distal latencies compared. Lastly, the median vs. radial sensory distal latencies recording the thumb are the only internal comparison study which utilizes the radial nerve. In most individuals, sensory innervation to the thumb is split between the median and radial sensory nerves. Thus, similar to the median ulnar to ring finger sensory studies, the median sensory latency can be directly compared to the radial sensory latency to the thumb, provided identical distances are used.

Using the above sensitive internal comparison studies, focal slowing of the distal median nerve can usually be demonstrated. However, none of the internal comparison studies or routine median motor and sensory studies are informative about the presence of conduction block. Indeed, low median motor or sensory amplitudes stimulating at the wrist may signify secondary axonal loss, conduction block, or a combination. The differentiation is important in regard to prognosis and possibly treatment. Secondary axonal loss signifies greater injury to the distal median nerve and a much longer or incomplete recovery even after appropriate therapy. Conduction block, which signifies demyelination, is readily reversible, provided that initial inciting event is no longer present. Conduction block across the distal median nerve can be recognized and quantitated in the EMG laboratory by comparing motor and sensory amplitudes with stimulation at the wrist and in the palm (Fig. 40.3) [19]. Although useful, technical factors sometimes limit these studies. Because of close distances between the stimulator and recording electrodes, stimulus artifact may obscure the baseline. In addition, one must be aware that there is always some drop in amplitude proximal to the wrist compared to distal due to normal temporal dispersion and phase cancelation with proximal stimulation. The effects of temporal dispersion and phase cancelation are greater for sensory fibers than motor fibers. In normal median nerves, the ratio of the distal/proximal motor amplitude does not exceed 1.2, whereas the distal/proximal sensory amplitude ratio does not exceed 1.6 [19]. Ratios larger than these suggest some element of conduction block. It is important that both stimulations are supramaximal, that there is no co-stimulation of adjacent nerves, and

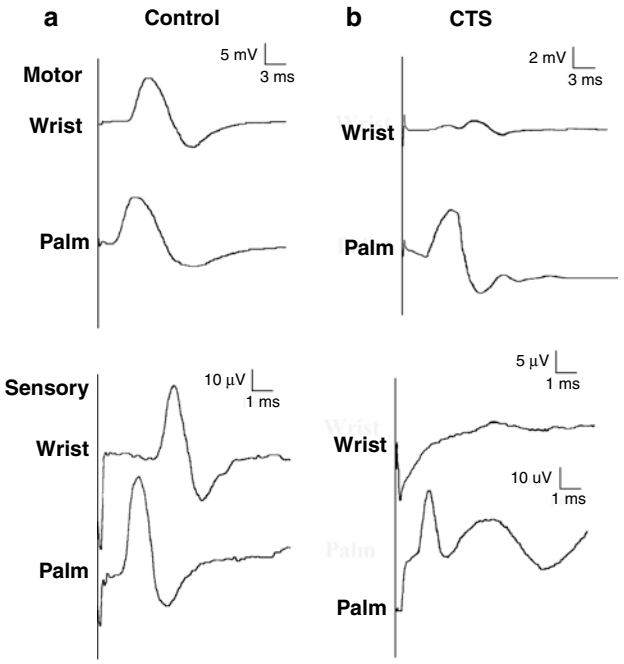

Fig. 40.3 Change in CMAP and SNAP amplitude across the carpal tunnel. To assess possible conduction block across the carpal tunnel, either the median CMAP or SNAP can be recorded, stimulating the wrist and palm. (**a**) Note in controls, there is only a slight increase in amplitude between palm and wrist stimulation sites. (**b**) A large difference between palm and wrist sites in CTS patients signifies conduction block. For motor studies, a normal palm/wrist amplitude ratio is 1.2; for sensory studies 1.6 (From Lesser et al. [19]. Reprinted by permission of John Wiley & Sons, Inc.)

that the baseline is not obscured by shock artifact or noise which precludes an accurate amplitude measurement.

Nerve conduction studies are often the principal test to confirm median neuropathy at the wrist. However, needle EMG should be employed in all cases to help assess the severity of the median neuropathy and help exclude other superimposed conditions, especially high median neuropathy, brachial plexopathy, or C6–C7 radiculopathy. The presence of fibrillation potentials or large reinnervated motor unit action potentials (MUAPs) in the abductor pollicis brevis or opponens pollicis signifies active or chronic denervation, respectively. These signs of axonal loss imply a more severe or advanced case and may have direct ramifications for recommendations for further therapy. It is important to note that in mild or early cases of distal median neuropathy, the thenar muscles are usually normal on needle EMG.

Other muscles which are useful to sample in selected cases are the proximal median muscles (e.g., flexor pollicis longus, flexor carpi radialis, pronator teres) and C6–C7-innervated muscles (e.g., pronator teres, triceps). If any abnormality is found, a more extensive needle EMG examination needs to be performed to localize the lesion. Of course, it is not uncommon that two peripheral nervous system conditions are present in the same patient (e.g., distal median neuropathy and polyneuropathy, distal median neuropathy and C6–C7 radiculopathy). In those cases, it is especially valuable for the electromyographer to assess the severity of each in relation to each other to help guide decisions regarding therapy.

EDX Studies After Carpal Tunnel Release

It is not uncommon to have a patient referred for EDX studies who has previously undergone carpal tunnel release surgery. Typically, the patient will have undergone surgery with no clinical improvement or will have developed recurrent symptoms months or years later after successful carpal tunnel decompression. In many cases, the patient will not have had a preoperative EDX study to confirm the diagnosis of CTS. Thus, one needs to be aware of what happens to nerve conduction study abnormalities after successful carpal tunnel release surgery [20]. In general, the distal median motor and sensory latencies and amplitudes improve. However, this may take many weeks to months, and in some studies, improvement continues up to a year after surgery. However, some slowing may persist indefinitely. In the authors' experience:

1. Median distal motor latencies improve and usually return to the "normal" range. Never do distal latencies remain in the demyelinating range (i.e., >130 % the upper limit of normal) after successful carpal tunnel release.
2. Median sensory latencies improve and usually return to the "normal" range. Never do conduction velocities remain in the demyelinating range (i.e., <75 % the lower limit of normal) after successful carpal tunnel release.
3. Median motor amplitudes improve and return to the normal range.
4. Median sensory amplitudes may or may not improve. Many remain in a slightly reduced or borderline normal range.
5. The sensitive internal comparison studies (i.e., palmar mixed studies, ring finger study, thumb study, lumbrical-interosseous study, and segmental sensory study) remain abnormal indefinitely, showing some slowing of median conduction across the carpal tunnel.

Although these findings are seen most often after carpal tunnel release surgery, similar findings are seen in other entrapment neuropathies. These persistent "abnormalities" occur as the result of remyelination. In entrapment neuropathies, such carpal tunnel syndrome, demyelination occurs at the site of compression, resulting in interruption of the internodes at the site of compression. When the compression is successfully released, remyelination can then occur. However, the new internodes are short. Therefore, more nodes are required to remyelinate the original site of compression. When remyelination is completed, nerve impulses can once again travel successfully up and down the nerve. However, the time of conduction (and hence conduction velocity) is completely dependent on the depolarization time at the nodes of Ranvier. The greater the number of nodes of Ranvier, the more depolarizations, and hence the longer total time of depolarization. Thus, conduction velocity across the remyelinated area of compression will be slower than normal, because of the increase in number of nodes. In any situation where there has been demyelination and then remyelination, sensitive techniques will always demonstrate a slightly slower conduction time across the remyelinated segment. Accordingly, one must always be cautious when interpreting any mild "slowing" on nerve conduction studies in patients who have undergone carpal tunnel release.

As noted above, median neuropathy at the wrist is more often idiopathic, the result of strain or repetitive use on the transverse carpal ligament. However, there are a large number of underlying medical conditions associated with entrapment of the distal median nerve. Some conditions (e.g., hypothyroidism, rheumatoid arthritis) are highly associated with distal median neuropathy. The decision to pursue an underlying diagnosis and additional testing must be made individually, based on each patient's medical background and other symptoms at the time. The routine use of screening tests (e.g., thyroid function test, rheumatoid factor, Lyme antibody) has a very low yield and is usually not indicated without the presence of other symptoms or other risk factors from the patient.

Rarely, imaging studies with CT or MRI are indicated in suspected distal median neuropathy. Nerve tumors (e.g., schwannoma, neurofibromas) and ganglion cysts can affect peripheral nerves including the distal median nerve. A fullness in the wrist or palm is an indication for imaging.

Likewise, the history of a slowing progressive deficit without intermittent fluctuations often calls for imaging studies to exclude a structural lesion.

Management and Prognosis

The practical management of distal median neuropathy is straightforward. In idiopathic cases, therapy involves (1) withdrawal of provoking factors, (2) neutral wrist splint, (3) local corticosteroid injections, and (4) surgical decompression [5].

In some patients, there are clear provoking factors, such as writing, typing, or playing a musical instrument. For instance, CTS can sometimes develop in college students who spend long hours on the computer or typing papers. If it is possible to curtail the activity, it is advisable to do so. At times, a change in posture or workstation may improve many of the symptoms. For example, a wrist pad on a computer keyboard can be used to keep the wrists in a neutral position while typing.

Other than curtailing provocative factors, the first course of treatment is usually the prescription of a neutral wrist splint worn on the symptomatic hand(s) during sleep. A neutral wrist splint at night prevents wrist flexion and extension which increases the pressure within the carpal tunnel. In addition to wrist splints, a 2–3-week course of a nonsteroidal anti-inflammatory drug is often useful to decrease pain and swelling in the carpal tunnel, provided there is no medical contraindication (e.g., gastritis, peptic ulcer disease).

If simple maneuvers are not helpful, local corticosteroids can often be helpful. Corticosteroids are injected adjacent to the carpal tunnel (typically 40–80 mg of Depo-Medrol) [5]. Care must be taken not to inject within the carpal tunnel itself due to the concern of increasing the intra-carpal pressure and inducing acute median nerve compression. Steroid injections begin to work within a few days and often last for several weeks or months. Their main disadvantage is that they are usually a temporary measure, and repeated use of more than two or three injections is not advised due to the possibility of local tendon damage. They are most useful as a temporizing measure before surgery, in mild cases, or in cases where the syndrome may be time limited, such as in pregnancy.

Definite treatment of distal median neuropathy usually involves surgical decompression. The transverse carpal ligament is sectioned, decompressing the underlying median nerve. The proper surgical technique involves a longitudinal incision which extends from the wrist into the palm. Endoscopic release has been used in some cases of median nerve compression, offering a much shorter recovery time. The main disadvantage of this technique over the commonly performed open technique is the incomplete direct visualization of the transverse carpal ligament and the possibility of either incomplete section or damage to the median nerve or other nearby structures.

Surgical decompression is indicated in patients who are symptomatic and have failed conservative measures and in those patients whose distal median neuropathy is severe and associated with axonal loss. Clinically, patients with thenar atrophy and persistent hypesthesia on physical examination require surgical compression. Likewise, patients with low median motor and sensory amplitudes from axonal loss on nerve conduction studies or evidence of ongoing axonal loss in distal median-innervated muscles on needle EMG typically require surgical decompression. Surgery is also indicated in the presence of a mass lesion (e.g., nerve tumor, ganglion) or urgently in cases of acute carpal tunnel syndrome, which may follow local trauma [5]. In these cases, the wrist and hand is swollen and numb shortly after trauma.

The prognosis of distal median neuropathy is usually very good. Pain and paresthesias bring most patients to medical attention before any significant axonal loss has occurred. In addition, the large number of sensitive EDX tests available to study the distal median nerve allows early recognition and diagnosis. Patients with intermittent pain and paresthesias without any fixed motor or sensory deficits whose course is short often respond well to conservative therapy. Surgery is usually highly effective (response rate of 85–90 %) [21, 22]. Pain, other than at the surgical incision, disappears or is greatly reduced within the first hours or days. Recovery of motor or sensory deficit depends on whether the underlying pathology is demyelination, axonal loss, or a combination. Remyelination is usually complete within several weeks. Axonal loss recovers slowly over several months. In severe cases with near complete thenar atrophy, recovery of motor and sensory function may occur incompletely or not at all, although often pain is significantly improved.

Proximal Median Neuropathy

Proximal median neuropathy is distinctly uncommon compared to median entrapment at the carpal tunnel [23]. Differentiating between median neuropathy at the wrist and more proximal entrapments can be difficult on clinical grounds alone, especially in mild cases. EDX plays a key role in localizing the lesion in these unusual cases, especially in traumatic or compressive lesions.

Anatomy

As the median nerve descends in the upper arm, it runs medial to the humerus and anterior to the medial epicondyle [1]. In a small minority of individuals, a bony spur originates from the shaft of the medial humerus just cephalad to the

medial epicondyle. A tendinous band may occur at this point (ligament of Struthers), stretching between the spur and the medial humeral epicondyle. In the antecubital fossa, the median nerve travels adjacent to the brachial artery. As it enters the forearm, it runs first beneath the lacertus fibrosus, a thick fibrous band that runs from the medial aspect of the biceps tendon to the proximal forearm flexor musculature. The median nerve then runs between the two heads of the pronator teres muscle to provide innervation to that muscle. In some individuals, there are fibrous bands within the two heads of the pronator teres muscle. The anterior interosseous nerve is given off posteriorly after the median nerve passes between the two heads of the pronator teres. As the median nerve runs distally, it passes deep to the flexor digitorum sublimis muscle and its proximal aponeurotic tendinous edge, known as the sublimis bridge.

Etiology and Pathogenesis

Proximal median neuropathy is described as a consequence of external compression from casting, trauma, venipuncture, and as the result of compressive mass lesions including tumor or hematoma. Rare cases of brachial artery puncture and subsequent hematoma formation have led to compartment syndromes and subsequent injury of the proximal median nerve. The proximal median nerve, especially the anterior interosseous nerve, may be involved in cases of neuralgic amyotrophy (see Chap. 46).

In addition, several sites of proximal median entrapment have been reported. All are uncommon and remain controversial [23–26]. These potential sites of entrapment include the ligament of Struthers, a hypertrophied lacertus fibrosus, the pronator teres muscle, and the sublimis bridge (see below).

Clinical Presentation

The clinical syndromes of proximal median neuropathy depend on the underlying etiology.

Traumatic Lesions

In traumatic lesions, there is usually an obvious, acute disturbance of median motor and sensory function. Importantly, sensory disturbance in proximal median neuropathy is noted in the entire median territory, including the thenar eminence, as well as the thumb, index, middle fingers, and lateral ring finger. This is distinctly different from CTS, where sensation over the thenar eminence is spared because the palmar cutaneous sensory branch, which innervates the thenar eminence, leaves the median nerve proximal to the carpal tunnel. Depending on the site of the lesion, weakness may include some or all of the proximal median forearm muscles, including the pronator teres, flexor carpi radialis, flexor digitorum sublimis, flexor digitorum profundus to index and middle fingers, flexor pollicis longus, and pronator quadratus, as well as the distal median-innervated muscles, including the abductor pollicis brevis, opponens pollicis, and first and second lumbricals. There is often local tenderness or pain at the site of compression or trauma.

Entrapment Syndromes

The symptoms and signs in the proximal median entrapment syndromes are much less specific. Typically, there is pain or discomfort in the region of the entrapment. Unlike CTS, there is no nocturnal exacerbation of symptoms. The two major syndromes include (1) proximal entrapment of the median nerve by the ligament of Struthers [26] and (2) median nerve entrapment more distally, either beneath the lacertus fibrosus, in the substance of the pronator teres, or beneath the sublimis bridge. These latter entrapments are usually referred to as "pronator syndrome" [24–27]. Although strictly speaking, the term is often reserved for nerve entrapment within the substance of the pronator teres muscle proper, entrapment at any of these last three locations usually produces a similar clinical syndrome. Lastly, the anterior interosseous neuropathy may occur as a separate entity.

Ligament of Struthers Entrapment

This is a very rare syndrome characterized by pain in the volar forearm and paresthesias in the median digits exacerbated by supination of the forearm and extension of the elbow. The radial pulse may also be attenuated with these maneuvers. A bony spur may be palpable at the distal humerus (Fig. 40.4). Weakness of the pronator teres and other median-innervated muscles may occur, and subtle sensory loss may be noted in the median distribution including the thenar eminence.

Pronator Syndrome

Though rare, this syndrome occurs more often than entrapment at the ligament of Struthers. The pronator teres muscle may be enlarged or firm, with a Tinel's sign over the site of entrapment. Maneuvers that may produce symptoms of pain in the forearm and paresthesias in the median digits depend on the site of entrapment: forced supination and elbow flexion (for the lacertus fibrosis), forced pronation and elbow extension (for the pronator teres), and flexion of the proximal interphalangeal joint of the middle finger (for the sublimis bridge). The sole finding of increased pain with these maneuvers is an unreliable sign, unless accompanied by paresthesias in the median nerve distribution. Significant weakness or wasting of median-innervated muscles is rare, but mild weakness of the flexor pollicis longus and abductor pollicis brevis is not uncommon, with occasional involvement of the

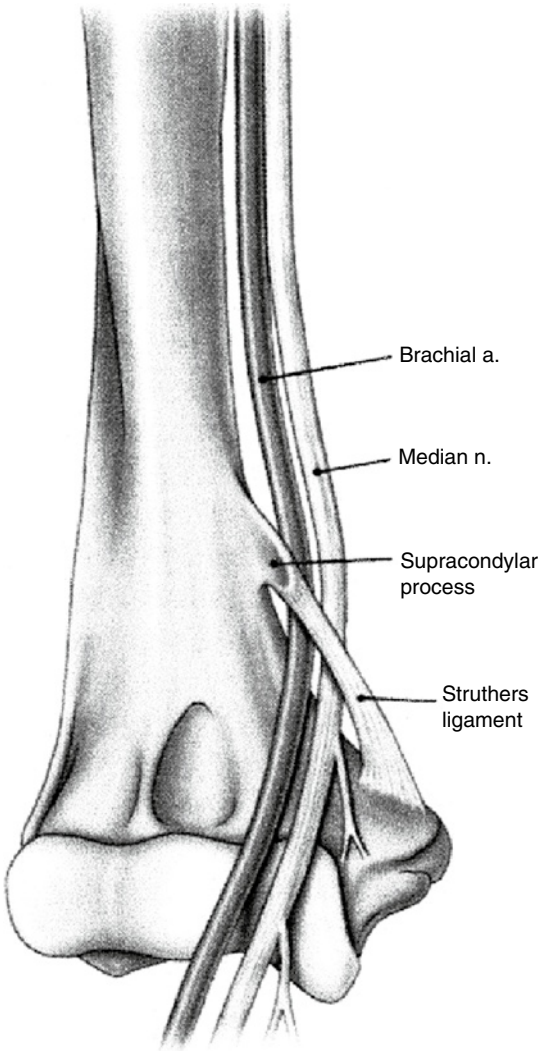

Fig. 40.4 Ligament of Struthers and high median neuropathy. The ligament of Struthers runs between the medial epicondyle and a supracondylar process of the distal humerus, creating a potential entrapment site of the high median nerve (From Gross and Tolomeo [104]. With permission from WMC. © 1998 Labey Clinic)

flexor digitorum profundus. There may be occasional paresthesias radiating into the median-innervated digits, with subtle impairment of sensation in the median nerve distribution including the thenar eminence.

Anterior Interosseous Nerve Syndrome

Clinically, patients present with inability to flex the distal phalanx of the thumb and index finger with weakness of pronation. Weakness of the pronator quadratus is best tested with the elbow flexed, to avoid the contribution from the pronator teres. There is no sensory loss. However, prominent pain may be present from involvement of deep sensory fibers to the wrist and interosseous membrane. A characteristic compensatory posture occurs when the patient attempts to make the "OK" sign and is unable to flex the distal thumb and index fingers: hyperextension of the distal interphalangeal joint of the index finger and interphalangeal joint of the thumb [1].

Differential Diagnosis

In cases of acute trauma or injury, the differential diagnosis is usually quite limited and straightforward. However, with the entrapment syndromes in the region of the elbow, the symptoms are often vague, and the differential diagnosis is extensive. For example, local orthopedic problems may present in a similar fashion. Median neuropathy at the carpal tunnel may also give rise to diagnostic confusion. Patients with CTS can present with vague pain or heaviness in the forearm associated with median paresthesias, similar to symptoms in the proximal median entrapment syndromes. Cervical radiculopathy may present with radiating pain and paresthesias into the hand. In cervical radiculopathy, however, there is usually a history of neck pain which radiates into the arm. Examination in cervical radiculopathy may reveal weakness and sensory disturbance outside the median territory, as well as depressed biceps, brachioradialis, or triceps reflexes.

The proximal median nerve and especially the anterior interosseous nerves can be involved in cases of neuralgic amyotrophy (aka, brachial neuritis) [29]. Indeed, in some cases, the syndrome is limited to the anterior interosseous nerve alone. It is important to question the patient about possible immunologic triggers (e.g., infection, vaccination) which can be identified in many but not all cases. Most cases of neuralgic amyotrophy have prominent pain which lasts a few days to weeks followed by weakness and wasting which slowly improves over months.

Evaluation and Diagnosis

EDX testing should be employed in all suspected cases of high median neuropathy, ideally to demonstrate median nerve abnormalities proximal to the wrist and exclude a more proximal lesion in the brachial plexus or cervical nerve roots [1]. Nerve conduction studies should include routine median motor studies stimulating the median nerve at the wrist and elbow, in addition to stimulation at the axilla. In all suspected median neuropathies, it is imperative to perform one of the median vs. ulnar internal comparison studies across the wrist to exclude the common median neuropathy at the wrist.

A lesion of the median nerve that results in Wallerian degeneration, regardless of the lesion site, results in decreased compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) amplitudes. Often distal latencies are slightly prolonged and conduction velocity mildly slowed due to drop out of the fastest conducting axons.

However, while such findings are abnormal and indicate a median nerve lesion, they do not localize the lesion site. If there is focal demyelination at the ligament of Struthers, one might expect to see either focal slowing or a drop in CMAP amplitude (i.e., conduction block or temporal dispersion) between the elbow and the axilla sites. If there is a focal lesion in the region of the elbow, there may be focal slowing or conduction block between the wrist and elbow sites. However, while such findings are expected, in fact, they only rarely occur. In true cases of proximal median entrapment, EDX is often normal or nonspecific, despite what might be expected on theoretical grounds.

In addition, a plain X-ray of the distal arm and elbow may be helpful in suspected median neuropathy secondary to a ligament of Struthers in order to demonstrate a supracondylar bone spur on the median humerus.

Management and Prognosis

As high median neuropathies are rare, management is not as straightforward as in common median neuropathy across the wrist. In cases secondary to external compression (e.g., casts), observation is recommended. In patients with pronator syndrome secondary to repetitive pronation/supination, rest and splinting are indicated first. Otherwise, the treatment of high median neuropathy is usually surgical with exploration and decompression of the high median nerve. Obviously, in cases with vague symptoms and indeterminate EDX findings, such decisions should not be considered lightly. Surgery is best reserved for patients with continued or progressive symptoms who have not benefited from conservative therapy. Caution should always be given to any patient considering surgery for an anterior interosseous neuropathy. Many of these cases are likely inflammatory in nature (i.e., neuralgic amyotrophy) and will improve without surgery, although recovery may be delayed months or longer [28].

Ulnar Neuropathy at the Elbow

Ulnar neuropathy is second only to median nerve entrapment at the wrist as the most common entrapment neuropathy affecting the upper extremity, with the usual site of compression at the elbow. In contrast to CTS, however, exact localization of EDX is often much more demanding and treatment options more limited.

Anatomy (Fig. 40.5)

The ulnar nerve is derived from the C8 and T1 roots [1]. A small minority of patients receive a minor component

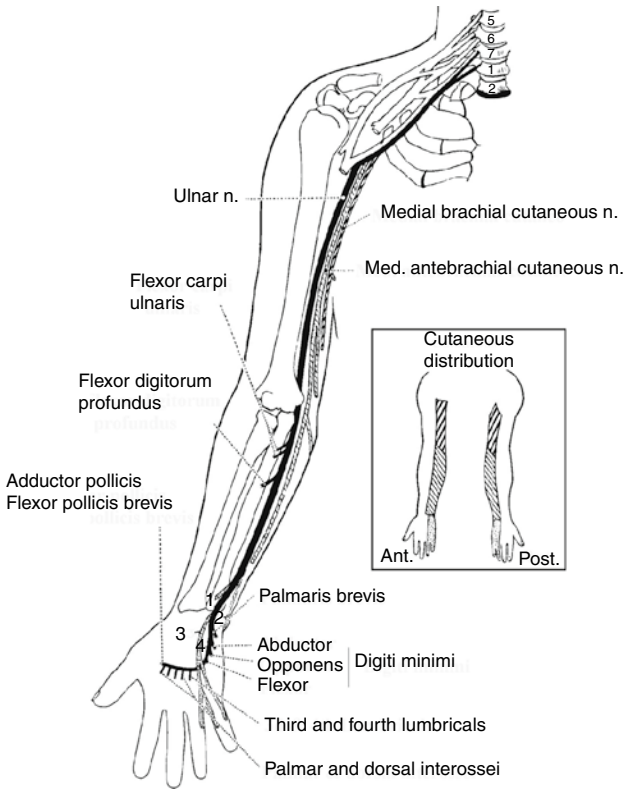

Fig. 40.5 Ulnar nerve anatomy. The ulnar nerve, along with the medial brachial and medial antebrachial cutaneous nerves, is derived from the medial cord of the brachial plexus. Insert: Cutaneous distributions of the ulnar, medial brachial cutaneous, and medial antebrachial nerves (Reprinted from Haymaker and Woodhal [102]. With permission)

from C7. Accordingly, nearly all ulnar fibers travel through the lower trunk and medial cord of the brachial plexus. The terminal extension of the medial cord becomes the ulnar nerve. The medial brachial and antebrachial cutaneous sensory nerves and a large part of the median nerve are derived from the medial cord as well. As the ulnar nerve descends through the medial arm, it gives off no muscular branches.

At the elbow, the nerve becomes superficial and enters the ulnar groove formed between the medial epicondyle and the olecranon process (Fig. 40.6). Normally, the ulnar nerve remains in the groove, although in some individuals, flexing the elbow results in subluxing of the nerve out of the groove and medially over the medial epicondyle. In a small number of individuals, a dense fibro-tendinous band and/or an accessory epitrochleoanconeus muscle may be present between the medial epicondyle and the olecranon process. Slightly distal to the groove in the proximal forearm, the ulnar nerve travels under the tendinous arch of the two heads of the flexor carpi ulnaris muscle, known as the humeral-ulnar aponeurosis (HUA) or "cubital tunnel" [29]. Muscular branches are then given off to the flexor carpi ulnaris and the medial division (fourth and fifth digits) of the flexor digitorum profundus. In the cubital tunnel, the ulnar nerve then continues under the flexor carpi ulnaris to exit 3–7 cm distal, between

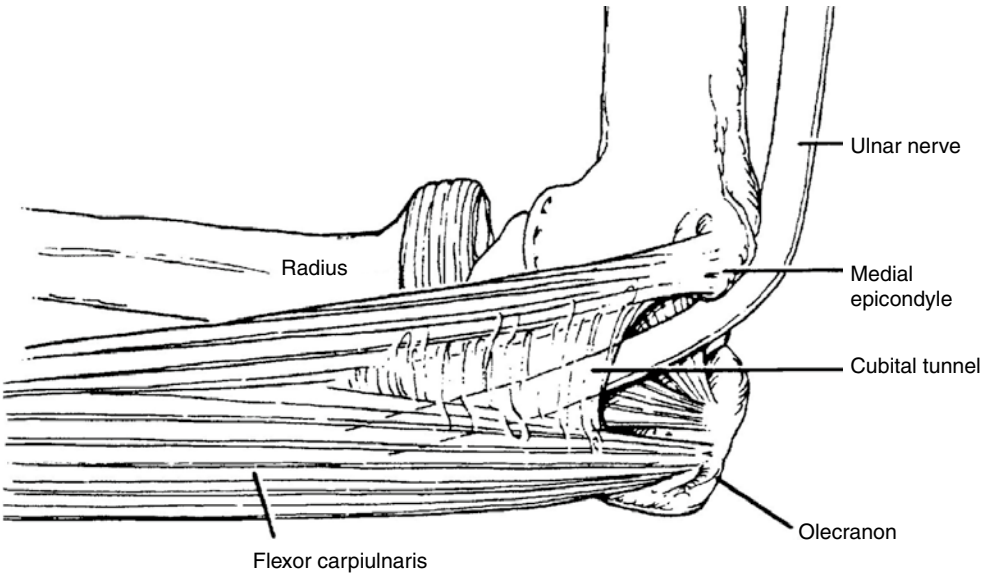

Fig. 40.6 Ulnar nerve anatomy at the elbow. Entrapment of the ulnar nerve can occur either at the ulnar groove between the medial epicondyle and the olecranon, or distally at the cubital tunnel (Adapted from Kincaid [35]. Reprinted by permission of John Wiley & Sons, Inc.)

the deep fascia separating the flexor carpi ulnaris and flexor digitorum profundus.

Next the ulnar nerve descends through the medial forearm, giving off no further muscular branches until after the wrist. Five to eight centimeters proximal to the wrist, the dorsal ulnar cutaneous sensory branch exits to supply sensation to the dorsal medial hand and the dorsal fifth and medial fourth digits. The palmar cutaneous sensory branch originates at the level of the ulnar styloid to supply sensation to the proximal medial palm. The ulnar nerve then enters the medial wrist through Guyon's canal to supply sensation to the volar fifth and medial fourth digits. It also supplies muscular innervation to the hypothenar muscles, the palmar and dorsal interossei, the third and fourth lumbricals, and two muscles in the thenar eminence, the adductor pollicis and the deep head of the flexor pollicis brevis.

Etiology and Pathogenesis

Ulnar neuropathy usually occurs as a result of chronic mechanical compression or stretch of the ulnar nerve [30]. In the elbow region, ulnar neuropathy can occur either at the groove or at the cubital tunnel. Although rare cases of ulnar neuropathy at the groove are caused by ganglia, tumors, fibrous bands, or accessory muscles, most are caused by external compression and repeated trauma. Trauma and subsequent arthritic changes at the elbow joint, often years before clinical presentation, may result in so called *tardy ulnar palsy*. Chronic minor trauma and compression, including leaning on the elbow, can either exacerbate or cause ulnar neuropathy at the groove. Ulnar neuropathy at the groove is also common in patients who have been immobilized because of surgery or who sustain compression during anesthesia or coma. Whether repeated subluxation of the ulnar nerve out of the groove also leads to ulnar neuropathy is controversial.

The other major site of compression of the ulnar nerve in the region of the elbow is distal to the groove in the cubital tunnel. Although some use the term *cubital tunnel syndrome* to mean all lesions of the ulnar nerve around the elbow, it is more properly used to denote compression of the ulnar nerve under the humeral-ulnar aponeurosis. Some individuals have congenitally tight cubital tunnels that predispose them to compression. Repeated and persistent flexion stretches the ulnar nerve, which along with increasing the pressure in the cubital tunnel, leads to subsequent ulnar neuropathy.

Clinical Presentation

Ulnar neuropathy at the groove or the cubital tunnel presents in a similar manner [1]. In contrast to CTS in which sensory symptoms predominate, motor symptoms are common in ulnar neuropathy, especially in chronic cases. In some patients, motor loss may develop insidiously without any sensory symptoms, particularly in those with slowly worsening mechanical compression. Since most of the intrinsic hand muscles are ulnar innervated, weakness of these muscles leads to loss of dexterity, with decreased grip and pinch strength. However, thumb abduction is spared in ulnar neuropathy, innervated via the median and radial nerves. Weakness of ulnar-innervated flexor digitorum profundus may result in inability to flex the distal interphalangeal joints of the ring and little fingers. There may be atrophy of both the hypothenar and thenar eminences.

Examination may reveal one of the classic hand postures that occurs with ulnar muscle weakness. The most widely recognized is the *benediction posture* (ulnar clawing). In this posture, the ring and little fingers are clawed with the

Table 40.2 Clinical differentiating factors in ulnar neuropathy

	UNW⁻	UNE	Medial cord	Lower trunk	C8–T1
Weakness – interossei	X	X	X	X	X
Weakness – hypothenar muscles	X	X	X	X	X
Weakness – third/fourth lumbricals	X	X	X	X	X
Weakness – distal finger flexion of little and ring fingers		X	X	X	X
Weakness – thumb abduction			X	X	X
Weakness – thumb flexion			X	X	X
Weakness – index finger extension				X	X
Sensory loss – volar medial hand and little finger, medial half of ring finger	X	X	X	X	X
Sensory loss – dorsal medial hand and dorsal little finger, half of ring finger		X	X	X	X
Sensory loss – medial forearm			X	X	X
Tinel's sign – elbow		X			
Neck pain					X

Source: Adapted from Preston and Shapiro [103]
X, may be abnormal; UNW, ulnar neuropathy at the wrist; UNE, ulnar neuropathy across the elbow; –, assumes both motor and sensory branches are involved; some cases of UNW may spare the hypothenar muscles and/or the sensory branch (see text for details)

metacarpophalangeal joints hyperextended and the proximal and distal interphalangeal joints flexed, due to weakness of the third and fourth lumbricals. The fingers and thumb are held slightly abducted due to weakness of the interossei and adductor pollicis. The *Wartenberg's* sign is recognized as abduction of the little finger due to weakness of the third palmar interosseous muscle. Patients may report that their little finger gets caught when trying to put their hand in their pocket. The *Froment's* sign is seen when attempting to pinch an object or piece of paper. In order to compensate for intrinsic ulnar hand weakness, the long flexors to the thumb and index finger (median innervated) are used to pinch, creating a flexed thumb and index finger posture.

Sensory disturbance may involve the medial hand and the volar and dorsal fifth and medial fourth digits. Sensory disturbance does not extend much beyond the wrist crease. Sensory involvement extending into the medial forearm or arm implies a more proximal lesion in the plexus or cervical nerve roots. The medial brachial and antebrachial cutaneous sensory nerves which supplies sensation to the medial forearm and arm, respectively, arise from the medial cord of the brachial plexus. Pain, when present, may localize to the elbow or radiate down to the medial forearm and wrist. Paresthesias may be reproduced by placing the elbow in a flexed position or applying pressure to the groove behind the medial epicondyle. The ulnar nerve may be palpably enlarged and tender in the groove. Especially in patients with ulnar neuropathy at the cubital tunnel, the nerve may be palpably taut with decreased mobility.

Differential Diagnosis

The differential diagnosis in a patient suspected of having ulnar neuropathy at the elbow includes C8–T1 radiculopathy, lower trunk or medial cord brachial plexopathy, or rare cases of ulnar nerve entrapment distally in the arm or forearm (Table 40.2). Ulnar nerve entrapment at the wrist, discussed later in this chapter, presents in a somewhat different fashion.

A cervical radiculopathy at the C8–T1 level from cervical disk disease or spondylosis, although less common than C6 or C7 radiculopathy, may be difficult to differentiate clinically from ulnar neuropathy. The major differentiating features that point toward cervical radiculopathy include neck pain and radiation into the arm, sensory disturbance extending into the forearm, and weakness involving ulnar-, median-, and radial-innervated C8–T1 muscles. Of course, weakness is often minimal and sensory loss often vague in radiculopathy, making the differentiation between a mild C8–T1 radiculopathy and ulnar neuropathy at the elbow demanding, if based on clinical exam alone.

Lower trunk/medial cord brachial plexopathies are uncommon. Entrapment of the lower trunk by a fibrous band or hypertrophied muscle may rarely result in neurogenic thoracic outlet syndrome (see Chap. 46). Lower trunk plexopathies may also result from infiltration by neoplasm, prior radiation, or self-limited inflammatory processes. As in C8–T1 radiculopathy, lower trunk plexopathies present with weakness that usually includes ulnar as well as non-ulnar C8–T1 muscles and sensory disturbance that extends into the medial forearm.

Entrapment of the ulnar nerve in the arm or forearm is uncommon. Rarely, the ulnar nerve may become entrapped at the exit of the cubital tunnel by the deep fascia between the flexor carpi ulnaris and flexor digitorum profundus [31]. Unusual cases of ulnar neuropathy in the distal forearm have also been reported due to a fibrovascular band supplying blood to a hypertrophied flexor carpi ulnaris muscle [32]. Differentiating these unusual cases clinically from typical ulnar neuropathy at the elbow is quite difficult. They are

usually discovered either by careful EDX testing, or at the time of surgery, or occasionally when a failed ulnar surgery at the elbow requires a second surgical exploration.

Evaluation and Diagnosis

EDX testing plays the principle role in assessing suspected ulnar nerve disorders [30–34]. The EDX evaluation of ulnar neuropathy at the elbow, however, is more demanding than many other entrapment neuropathies. Many cases show a nonlocalizing axonal loss pattern. Localizing ulnar neuropathy at the elbow relies upon the demonstration of focal demyelination across the elbow. Motor conduction studies should be performed recording the hypothenar muscles and stimulating at the wrist, below and above the elbow. A flexed elbow is the preferable position when performing ulnar motor studies, as the surface measured nerve length is more accurate than when performing the study in the straight elbow position [35–39]. A drop in amplitude of greater than 20 % across the elbow, or focal slowing greater than 11 m/s across elbow compared to forearm conduction velocity, is consistent with focal demyelination. In addition to recording the abductor digiti minimi (ADM), recording the first dorsal interosseous (FDI) muscle increases the yield of finding focal slowing or conduction block [33].

The other issue that must be considered when performing EDX studies for suspected UNE is the proper interpretation of a Martin-Gruber anastomosis (MGA). MGA is a normal anatomic variant resulting in a crossover of median to ulnar fibers in the forearm. It is typically recognized as a drop in amplitude between wrist and below-elbow stimulations on routine ulnar motor studies and mimics a "conduction block" in the forearm. The site of the MGA is typically between 3 and 10 cm distal to the medial epicondyle, a location that is not thought to interfere with electrodiagnostic evaluation of UNE. However, there are rare reports of very proximal MGAs wherein the drop in amplitude and area occurs between the below-elbow and above-elbow stimulation sites – that is, across the elbow. Thus, in all cases of ulnar conduction block across the elbow, it is prudent to also check for a MGA (by stimulating the median nerve at the wrist and antecubital fossa, and recording the ulnar muscle). When a MGA is present, a potential (or higher potential) will be seen when stimulating the median nerve at the antecubital fossa as compared to the median nerve at the wrist, while recording an ulnar-innervated muscle [40].

To exactly localize the site of demyelination, short segment incremental studies ("inching") can also be performed, stimulating the ulnar nerve in successive one centimeter increments across the elbow, looking for either an abrupt drop in amplitude or increase in latency (>0.5 ms) [1, 39, 40]. This technique is potentially useful in planning subsequent surgery. Ulnar neuropathy at the cubital tunnel (typically 1–2 cm distal to the medial epicondyle) may be treated by simple decompression, whereas ulnar neuropathy at the retrocondylar groove requires ulnar transposition surgery [41].

Ulnar sensory nerve conduction studies are helpful in identifying an ulnar neuropathy and differentiating it from a cervical radiculopathy. Ulnar sensory studies recording the little finger are more sensitive than motor studies in detecting ulnar neuropathy, but cannot localize the lesion other than to the peripheral nerve. Performing the dorsal ulnar cutaneous sensory study can be useful; abnormalities of this nerve imply the lesion is higher than the wrist [42, 43].

The strategy in the needle EMG exam of suspected ulnar neuropathy at the elbow is to identify denervation and/or reinnervation limited to the ulnar-innervated hand and forearm muscles [1]. Median- and radial-innervated C8–T1 muscles are screened to rule out evidence of a C8 radiculopathy or lower trunk/medial cord brachial plexopathy. Interestingly, the flexor carpi ulnaris is often normal or only minimally affected in many surgically proven cases of ulnar neuropathy at the elbow [44]. Overall, involvement of the flexor carpi ulnaris correlates with the severity of the ulnar neuropathy, both clinically and electrically.

It is important to emphasize if nerve conduction studies do not identify focal slowing or conduction block around the elbow, needle EMG can only be used to identify the lesion at or above to the most proximal abnormal muscle. Although most ulnar neuropathies are due to a lesion at the elbow, if there is no focal slowing or conduction block, EDX testing cannot exclude an unusual ulnar neuropathy in the proximal arm or a lower trunk/medial cord brachial plexopathy which selectively involves ulnar fibers. If a lower trunk or medial cord brachial plexus lesion is a diagnostic consideration in this situation, then examination of the medial antebrachial cutaneous sensory nerve, which comes directly off the medial cord of the plexus, may help clarify the situation.

Management and Prognosis

Management of ulnar neuropathy at the elbow is predominantly surgical [5]. Conservative therapy is often first employed with advice to avoid leaning on the elbows and curtail any activity which results in repetitive or sustained elbow flexion [45]. Often, using a simple elbow pad is helpful. In some cases, a physical therapist can fashion an elbow splint to prevent elbow flexion.

In patients who do not improve with conservative therapy, and especially those who have progressive weakness and wasting, surgery in indicated. A variety of surgical procedures are available including simple decompression of the cubital tunnel, medial epicondlectomy, and sub-

muscular transposition of the ulnar nerve. There is no clear consensus of which procedure is optimal. In general, submuscular transposition has a higher success rate but is a more complex surgery with greater morbidity, including the risk of nerve devascularization. Some have advocated that surgery be tailed to the underlying etiology. In cases where the lesion is at the cubital tunnel, simple decompression may be optimal [41]. In cases where the lesion is at the ulnar groove, transposition would be indicated. Most surgical series demonstrated a high rate of success with operative management. Advanced age and symptoms present for over a year correlate with a poorer prognosis [46].

Ulnar Neuropathy at the Wrist

Ulnar neuropathy at the wrist is a rare condition, sometimes confused with ulnar neuropathy at the elbow or more often with cervical radiculopathy or early motor neuron disease. Because of local complex anatomy, several possible clinical and electrophysiologic patterns are caused by a lesion here.

Anatomy (Fig. 40.7)

At the wrist, the ulnar nerve enters Guyon's canal at the level of the distal wrist crease [1]. The canal is formed proximally by the pisiform bone and distally by the hook of the hamate. The floor is formed by a combination of the thick transverse carpal ligament and adjacent hamate and triquetrum bones. The roof is loosely formed. However, there is a thick band at the outlet that runs from the hook of the hamate to the pisiform bone, known as the pisohamate hiatus. Before exiting through the pisohamate hiatus, motor fibers are given off to the hypothenar muscles (abductor digiti minimi, flexor digiti minimi, opponens digiti minimi, palmaris brevis). In the canal, the nerve divides into the superficial branch and the deep palmar branch. After the hiatus, the superficial branch supplies sensation to the volar little and medial ring fingers, while the deep palmar branch innervates the third and fourth lumbricals, the four dorsal and three palmar interossei, the adductor pollicis, and the deep head of the flexor pollicis brevis muscles.

Etiology and Pathogenesis

Entrapment of the ulnar nerve at the wrist is uncommon. It may occur in association with trauma and wrist fracture or as a result of mass lesions, often a ganglion, within Guyon's canal (Fig. 40.8) [47–50]. In addition, certain occupations or activities that involve repetitive movement or pressure against the ulnar wrist predispose to lesions here. This is especially

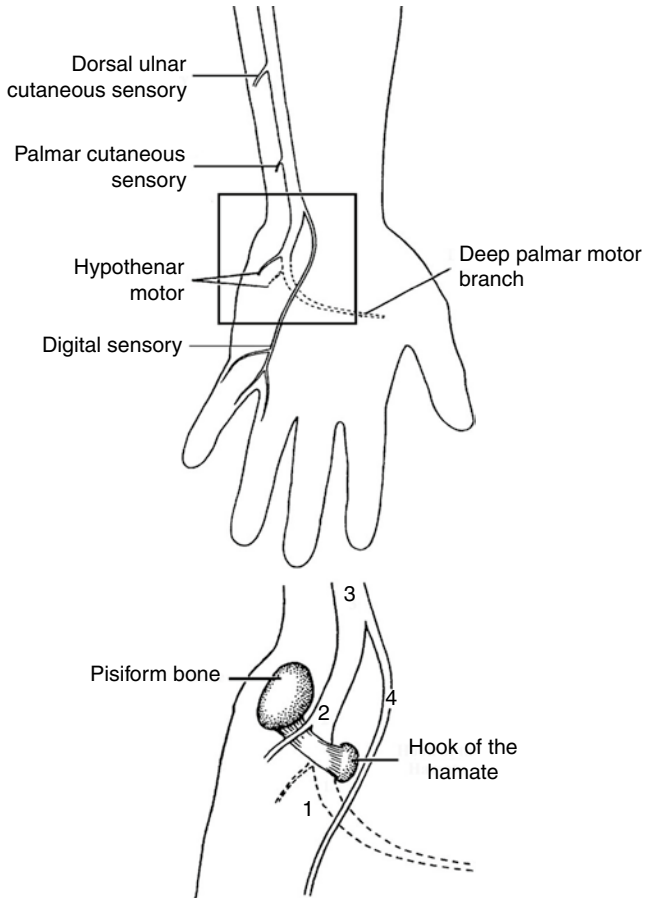

Fig. 40.7 Detailed anatomy of the ulnar nerve at the wrist. Entrapment of the ulnar nerve at the wrist can take on several patterns: (*1*) pure motor lesion affecting only the deep palmar motor branch, (*2*) pure motor lesion affecting the deep palmar and hypothenar motor branches, (*3*) motor and sensory lesion (proximal canal lesion) affecting the hypothenar and deep palmar motor and digital sensory branches, and rarely (*4*) pure sensory involving only the digital sensory fibers to the volar 4th and medial 5th fingers (Adapted from Olney and Hanson [49]. Reprinted by permission of John Wiley & Sons, Inc.)

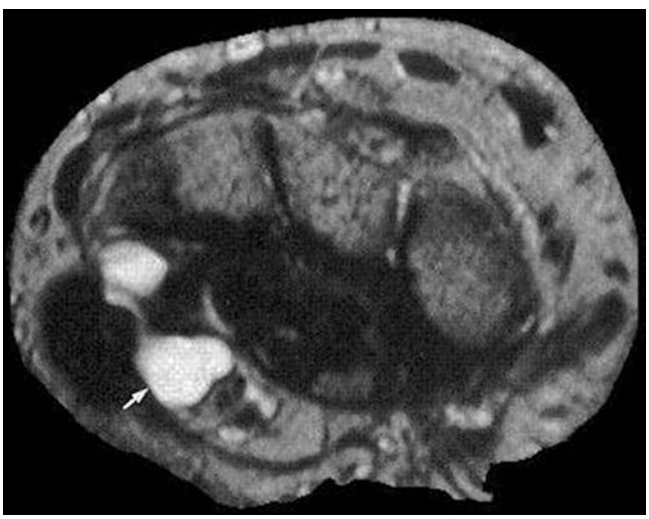

Fig. 40.8 Ulnar neuropathy at the wrist from a ganglion cyst. Axial T1-weighted MRI of wrist. Note the dumbbell-shaped high T1 signal abnormality displacing the ulnar nerve in Guyon's canal (*arrow*) (From Kothari et al. [57]. Reprinted by permission of John Wiley & Sons, Inc.)

Table 40.3 Various types of distal ulnar mononeuropathies

Lesion site	Nerve affected	Clinical presentation
Proximal Guyon's canal	Main trunk of ulnar nerve or ulnar cutaneous branch	Sensory loss of the medial palm, little finger, and medial half of ring finger, along with weakness of all ulnar intrinsic hand muscles or sensory loss of the medial palm, little finger, and the medial half of ring finger only
Distal Guyon's canal	Deep palmar branch (proximal to the branches to the hypothenar muscles)	Weakness of all ulnar intrinsic hand muscles (interossei, ulnar lumbricals, and hypothenar muscles) without sensory loss
Pisohamate hiatus	Deep palmar branch (distal to the branches to the hypothenar muscles)	Weakness of all ulnar intrinsic hand muscles with sparing of the hypothenar muscles and without sensory loss
Mid-palm (rare)	Deep palmar branch (distal in the palm)	Weakness of adductor pollicis; first, 2nd, and possibly the third interossei only, sparing fourth interossei and without sensory loss

Source: Adapted from Katirji [109]. With permission

true for bicyclists, or laborers who use the same hand tools repetitively causing pressure on the hypothenar eminence [51–53]. In such patients, the hypothenar area may be calloused at the compression site.

Clinical Presentation

There are several subtypes of ulnar neuropathy at the wrist, depending on the localization of the lesion in the wrist and which fibers are affected (Table 40.3) [48]. Lesions of the deep palmar branch result in weakness and wasting of the interossei and ulnar-innervated thenar muscles, with sparing of the hypothenar muscles and sensory branch. Lesions proximal to the hypothenar branches result in a similar motor syndrome but also affect the hypothenar muscles. Proximal lesions of the canal affect hypothenar and deep palmar motor fibers as well as involving volar sensory fibers to the medial hand and ring and little fingers. Lastly, rare lesion affects only the sensory fibers at the wrist resulting in sensory loss of the medial hand and ring and little fingers with sparing of all motor fibers.

The first two patterns are the most common and are easily confused with early motor neuron disease. Patients present with painless weakness and atrophy of ulnar intrinsic hand muscles, sparing sensation. As the ulnar-innervated adductor pollicis and deep head of the flexor pollicis brevis are in the thenar eminence, both the hypothenar and thenar eminences may be wasted in these lesions. Motor neuron disease is often suspected because of the complete absence of sensory loss or symptoms.

In more proximal lesions, the sensory branch is also affected, leading to sensory disturbance of the volar little and medial ring fingers. In contrast, the dorsal aspect of the medial hand and fingers are spared, being innervated by the dorsal ulnar cutaneous sensory branch which arises several centimeters proximal to the wrist. In addition, the proximal volar medial hand is also spared as the palmar cutaneous branch arises just proximal to the wrist as well.

Differential Diagnosis

In cases of ulnar neuropathy at the wrist which involve both motor and sensory fibers, the differential diagnosis includes more proximal entrapment of the ulnar nerve at the elbow, lower trunk/medial cord brachial plexopathies, and C8–T1 radiculopathies. In the more common presentation involving the deep palmar branch alone, early motor neuron disease is the main concern as the patient usually has no pain or sensory symptoms. Preservation of strength and bulk of the abductor pollicis brevis muscle (median innervated) is the key finding on physical exam in helping to exclude early motor neuron disease clinically.

Evaluation and Diagnosis

EDX testing is essential to differentiate ulnar neuropathy at the wrist from the more common ulnar neuropathy at the elbow and from early motor neuron disease. EDX findings depend on which branches are affected – sensory branch, hypothenar muscle branches, deep palmar motor branch, or all three [1]. If there is a distal lesion affecting only the deep palmar motor branch, then ulnar sensory and motor conductions recording the little finger and ADM, respectively, are normal. In all cases of suspected ulnar neuropathy at the wrist, it is imperative to perform motor studies recording the FDI. In lesions of the deep palmar motor branch, the latency to the FDI may be prolonged with a decreased CMAP amplitude, while the ADM latency and amplitude remain normal [1, 48]. Comparison with the contralateral asymptomatic side is often helpful. If the lesion is more proximal, affecting the hypothenar branches, the distal motor latency to the ADM may also be prolonged. However, even in such proximal lesions, the deep palmar motor branch is often affected out of proportion to the hypothenar branch, and the amplitude and latency to the FDI are still relatively worse than to the ADM.

If the lesion involves the distal sensory branch, the routine ulnar SNAP recording the little finger is abnormal.

In contrast, the dorsal ulnar cutaneous SNAP is normal in lesions at the wrist. This combination of an abnormal ulnar SNAP and a normal dorsal ulnar cutaneous SNAP is highly suggestive of a lesion at the wrist. However, this finding alone is not sufficient to diagnose ulnar neuropathy at the wrist, due to fascicular sparing of the dorsal ulnar cutaneous SNAP in some proximal ulnar nerve lesions including those at the elbow [54, 55].

There are two other potentially very helpful EDX tests in suspected ulnar neuropathy at the wrist: the distal latency comparison of the median and ulnar nerves recording the lumbrical and interossei muscles, respectively, and inching across the wrist. The lumbrical-interosseous distal latency comparison test is usually done for suspected CTS to identify relative slowing of the median nerve across the wrist. Since the ulnar interossei are innervated by the deep palmar motor branch, this test can be very useful in identifying differential ulnar slowing at the wrist as well in lesions that involve the deep palmar motor branch [56]. A distal motor latency difference > 0.5 ms comparing the ulnar interossei to second lumbrical suggests focal slowing across the wrist [57]. Similar to inching across the elbow, inching can also be performed across the ulnar nerve at the wrist while recording the FDI (Fig. 40.9). This technique can be very useful in demonstrating a conduction block or focal latency shift signifying focal demyelination. Care must be taken to avoid high stimulation currents distal to the wrist which might inadvertently co-stimulate the median nerve.

The needle EMG examination of suspected ulnar neuropathy at the wrist is straightforward. The FDI and ADM must be sampled looking for involvement of the deep palmar motor and hypothenar branches, respectively. Needle EMG of the 4th or 3rd dorsal interosseous is also helpful in lesions of the deep palmar branch at the pisohamate hiatus. An abrupt change from a normal ADM to denervated 4th and 3rd interosseous may occur [58]. The flexor digitorum profundus (ulnar slip) and flexor carpi ulnaris must be sampled to exclude an ulnar neuropathy proximal to the wrist. Finally, median and radial C8–T1 muscles (i.e., abductor pollicis brevis, flexor pollicis longus, extensor indicis proprius) and the lower cervical paraspinal muscles must be sampled to exclude a cervical root or motor neuron lesion.

Lastly, MRI of the wrist is frequently helpful in identifying structural lesions with Guyon's canal, including ganglion cysts and nerve sheath tumors [58]. Imaging should be considered in patients with ulnar neuropathy at the wrist who have a history of progressive worsening and in especially those who do not have clearly identified occupational wrist factors.

Management and Prognosis

Similar to the management of other entrapment neuropathies, ulnar neuropathy at the wrist can be managed both conservatively and surgically. Surgery is indicated for any mass lesion in the canal and in cases in progressive symptoms. In patients who have obvious occupational risks (e.g., bicyclists), many can be managed with simply curtailing the offending activity and observing.

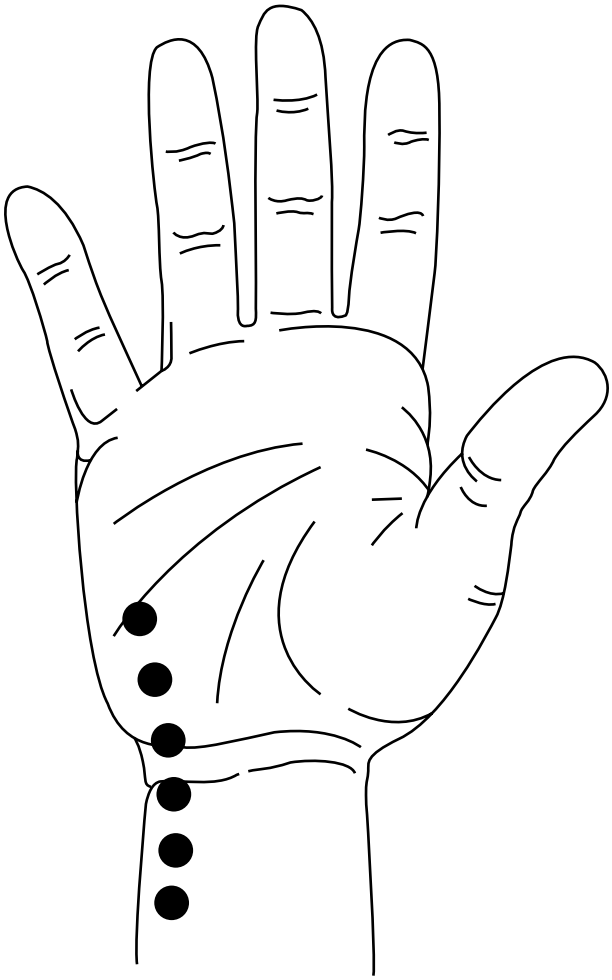

Fig. 40.9 Ulnar inching across the wrist. Recording the first dorsal interosseous, the ulnar nerve can be stimulated in successive 1 cm increments across the wrist

Radial Neuropathy

Entrapment of the radial nerve occurs less frequently than the more common lesions of the median and ulnar nerves. However, because of its long circuitous course, the radial nerve can be potentially entrapped in several sites along its course, most often in the upper arm and axilla. In addition, isolated lesions of its terminal divisions in the forearm, the posterior interosseous and superficial radial sensory nerves, also occur.

Anatomy (Fig. 40.10)

The radial nerve receives innervation from the C5–T1 nerve roots and, correspondingly, a contribution from all three

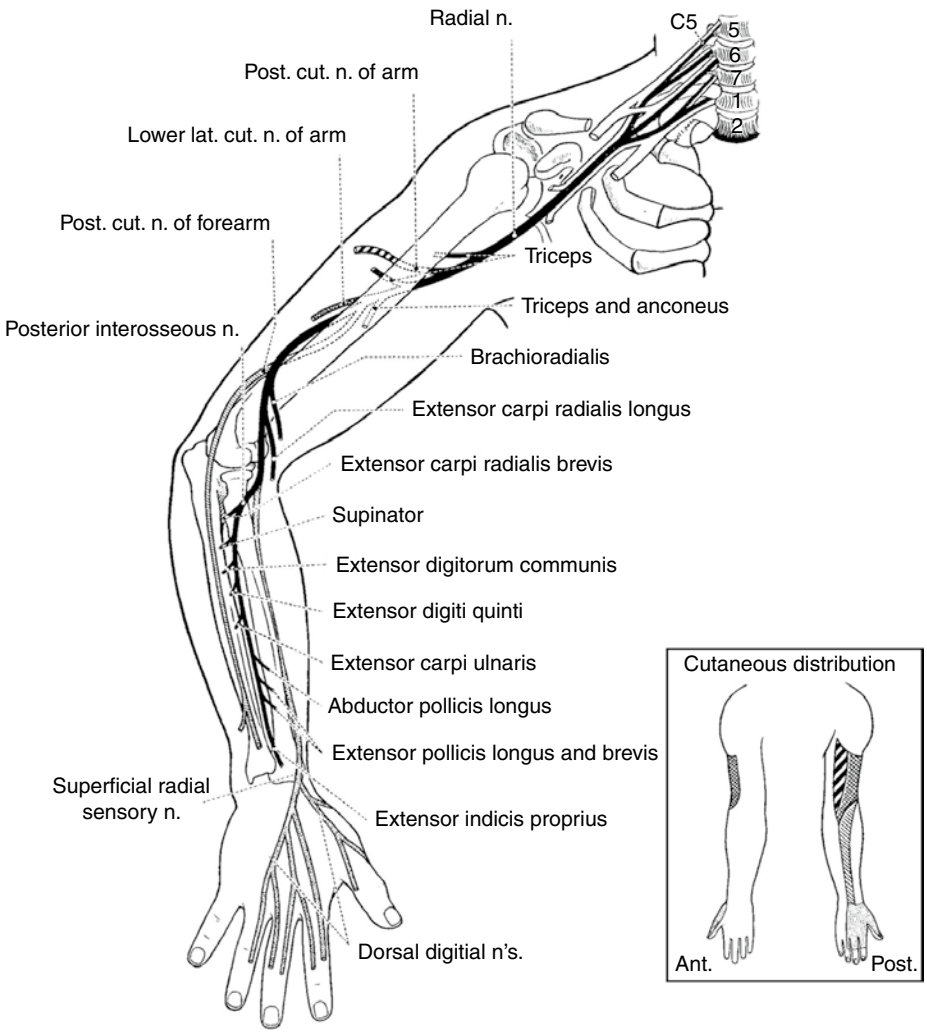

Fig. 40.10 Anatomy of the radial nerve. The radial nerve is derived from the posterior cord of the brachial plexus. In the proximal arm, the radial nerve first gives off the posterior cutaneous nerve of the arm, lower lateral cutaneous nerve of the arm, and the posterior cutaneous nerve of the forearm, followed by muscular branches to the triceps brachii and anconeus. The nerve then wraps around the humerus, descending into the region of the elbow, where muscular branches are given off to the brachioradialis, extensor carpi radialis-long head, and supinator. More distally, the nerve bifurcates into the superficial radial sensory and posterior interosseous nerves. The posterior interosseous nerve supplies the remainder of the wrist and finger extensors, as well as the supinator and abductor pollicis longus. Insert: Sensory territories supplied by the radial nerve (Adapted from Haymaker and Woodhal [102]. With permission)

trunks of the brachial plexus [1]. After each trunk divides into an anterior and posterior division, the posterior divisions from all three trunks unite to form the posterior cord. From the posterior cord, the axillary, thoracodorsal, and subscapular nerves are given off before it becomes the radial nerve. In the proximal arm, the radial nerve first gives off the posterior cutaneous nerve of the arm, lower lateral cutaneous nerve of the arm, and the posterior cutaneous nerve of the forearm, followed by muscular branches to the three heads of the triceps brachii (medial, long, and lateral) and the anconeus. The anconeus is a small muscle in the proximal forearm that is effectively an extension of the medial head of the triceps brachii. After giving off these muscular branches, the radial nerve wraps around the humerus in the spiral groove. As the nerve descends into the region of the elbow, muscular branches are given off to the brachioradialis, extensor carpi radialis-long head, and supinator. Three to four centimeters distal to the lateral epicondyle, the radial nerve bifurcates into two separate nerves, one superficial and one deep.

The superficial branch continues as the superficial radial sensory nerve and descends distally into the forearm over the radius to supply sensation to the lateral dorsum of the hand as well as part of the thumb and dorsal proximal phalanges of the index, middle, and ring fingers. Distally, the nerve is quite superficial, running over the extensor tendons to the thumb, where it is easily palpated. The deep motor branch usually supplies the extensor carpi radialis brevis and the supinator before it enters the supinator muscle under the arcade of Frohse at the elbow (Fig. 40.11). At that point, the deep motor nerve is known as the posterior interosseous nerve which supplies the remaining extensors of the wrist, thumb, and fingers (extensor digitorum communis, extensor carpi ulnaris, abductor pollicis longus, extensor indicis proprius, extensor pollicis longus, and extensor pollicis brevis). Although the posterior interosseous nerve is usually considered a pure motor nerve (supplying no cutaneous sensation), it does in fact carry sensory fibers to supply deep sensation to the interosseous membrane and the joints between the bones of the radius and ulnar.

Etiology and Pathogenesis

Radial neuropathy most often occurs following external compression [1, 5, 59, 60]. The main radial nerve can be affected in both the axilla and mid-arm. It is most vulnerable in the

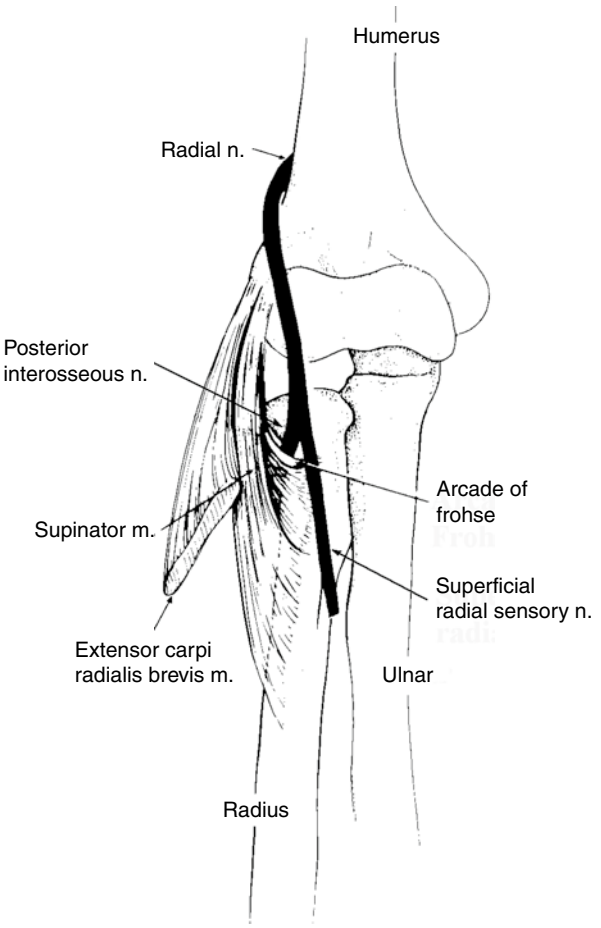

Fig. 40.11 Anatomy of the radial nerve at the elbow. Distal to the elbow, the radial nerve bifurcates into the superficial radial (sensory) and deep radial (motor) nerves. When the deep radial motor nerve enters the *arcade of Frohse*, it is known as the posterior interosseous nerve. The posterior interosseous nerve supplies most of the extensors of the wrist, and the thumb and finger extensors. (The main radial nerve only supplies on extensor: the extensor carpi radialis-long head) (From Wilbourn [105]. Adapted with permission from American Association of Electrodiagnostic Medicine)

mid-arm as it wraps along the spiral groove of the humerus where it lies adjacent to bone. The superficial radial sensory branch also lies adjacent to bone, in this case the radius, where it too can be affected from external compression in the distal forearm. Rarely is the radial nerve or its branches compressed by internal structures. The posterior interosseous nerve may potentially become entrapped at the arcade of Frohse [61]. Exceptional cases of radial neuropathy are reported secondary to muscular contraction of the triceps muscle around the radial nerve [62]. Similar to other upper extremity nerves, radial neuropathy may occur secondary to trauma and fracture, hematoma formation, nerve sheath tumors, or as a part of the presentation of neuralgic amyotrophy.

Clinical Presentation

Radial neuropathies can be divided into those caused by lesions at the spiral groove, in the axilla, and isolated lesions of the posterior interosseous and superficial radial sensory nerves. They can usually be differentiated by findings on the clinical examination (Table 40.4) [1].

Radial Neuropathy at the Spiral Groove

The most common radial neuropathy occurs at the spiral groove, also known as *Saturday night palsy* or *honeymoon palsy.* At the spiral groove, the nerve lies juxtaposed to the humerus, making it quite susceptible to compression, especially following prolonged immobilization. This characteristically occurs when a person has fallen asleep with their arm draped over a chair or bench, especially during a deep sleep or following intoxication. The resultant prolonged immobilization leads to compression and demyelination of the radial nerve. Other lesions at this location may occur following fracture of the humerus, infarction

Table 40.4 Clinical differentiating factors in radial neuropathy

	PIN	Radial-spiral groove	Radial-axilla	Posterior cord	C7
Wrist/finger drop	X	X	X	X	X
Radial deviation on wrist extension	X				
Weakness of supination (mild)		X	X	X	
Weakness of elbow flexion (mild)		X	X	X	
Decreased brachioradialis tendon reflex		X	X	X	
Weakness of elbow extension			X	X	X
Decreased triceps tendon reflex			X	X	X
Weakness of shoulder abduction				X	
Sensory loss – lateral dorsal hand		X	X	X	X
Sensory loss – posterior arm/forearm			X	X	X
Weakness of wrist flexion					X

Source: From Preston and Shapiro [103]
X, may be abnormal

from vasculitis, or after strenuous muscular effort. Clinically, patients present with a marked wrist and finger drop, along with mild weakness of supination (due to weakness of the supinator muscle) and elbow flexion (due to weakness of the brachioradialis). Notably, elbow extension (triceps brachii) is spared. Sensation is disturbed over the lateral dorsal hand and dorsal aspects of the thumb and index, middle, and ring fingers, in the distribution of the superficial radial sensory nerve.

In isolated radial neuropathy at the spiral groove, median- and ulnar-innervated muscles are normal. However, if tested in a dropped posture, finger abduction may appear weak and give the mistaken impression of ulnar nerve dysfunction [63]. To avoid this error, finger abduction (ulnar-innervated function) should be tested with the fingers and wrist held passively extended to a neutral wrist position. This can often be accomplished by placing the hand on a flat surface.

Although demyelinating lesions of the radial nerve most often result from external compression, they also occur rarely in acquired demyelinating polyneuropathies, especially multifocal motor neuropathy with conduction block (MMNCB) (see Chap. 29). MMNCB is a rare condition that results in conduction block along motor nerves, with a predilection for certain sites, especially the radial nerve. Patients often come to neurologic attention with a wrist drop. However, in contrast to most radial neuropathies which present acutely from a compressive lesion, this condition evolves slowly, and a careful neurologic exam usually reveals more widespread weakness involving distal more than proximal muscles. In patients with a wrist drop from MMNCB, nerve conduction studies may reveal conduction blocks anywhere along the course of the radial nerve.

Radial Neuropathy in the Axilla

Radial neuropathy from prolonged compression may also occur in the axilla. This can occur in patients on crutches, who use them incorrectly, applying prolonged pressure to the axilla. The clinical deficit is similar to that seen in radial neuropathy at the spiral groove, with the key exception of weakness of arm extension (triceps brachii) and sensory disturbance extending from the lateral dorsal hand into the posterior forearm and arm (lateral cutaneous nerve of the arm, posterior cutaneous nerves of the forearm and arm). Radial neuropathy in the axilla is differentiated from a more proximal lesion in the posterior cord of the brachial plexus by findings of normal strength in the deltoid (axillary nerve) and latissimus dorsi (thoracodorsal nerve).

Posterior Interosseous Neuropathy

Posterior interosseous neuropathy (PIN) may superficially resemble entrapment of the radial nerve at the spiral groove. In both, patients present with wrist and finger drop, with sparing of elbow extension. However, several important features easily separate the two. In PIN, there is sparing of radial-innervated muscles above the takeoff to the posterior interosseous nerve (i.e., brachioradialis, extensor carpi radialis-long head, triceps). When patients with PIN attempt to extend their wrist, they may do so weakly, with a radial deviation. The wrist deviates radially in extension due to the relative preservation of the extensor carpi radialis, in comparison to the weak extensor carpi ulnaris, which comes off distally to the lesion. The second major difference involves the sensory findings. In PIN, there is no cutaneous sensory loss. There may be pain in the forearm from dysfunction of the deep sensory fibers supplying the interosseous membrane and joint capsules. In contrast, radial neuropathy at the spiral groove results in cutaneous sensory loss in the dorsal hand.

Rarely, mass lesions (e.g., ganglion cysts, tumors) result in PIN. PIN usually results from entrapment under the tendinous arcade of Frohse of the supinator muscle (aka radial tunnel). True neurogenic radial tunnel syndrome is identifiable by motor weakness in the distribution of the posterior interosseous nerve [64]. Others have used the term radial tunnel syndrome in patients with forearm pain and tenderness in the region of the supinator muscle who do not have any weakness. This latter syndrome remains controversial [64]. As opposed to patients with a true posterior interosseous neuropathy (see above), these patients typically have no objective neurologic signs on examination and accordingly have normal EDX studies. They are said to have increased pain with maneuvers that contract the extensor carpi radialis or the supinator (e.g., resisted extension of the middle finger or resisted supination, respectively). However, there is has been no compelling evidence that this chronic pain syndrome is caused by any nerve entrapment. Whether entrapment of the posterior interosseous nerve results in such a syndrome, and likewise if surgical decompression is indicated, continues to be debated.

Superficial Radial Sensory Neuropathy

The superficial radial sensory nerve is derived from the main radial nerve in the region of the elbow. It runs subcutaneously next to the radius in the distal third of the forearm. This superficial location next to the bone makes it extremely susceptible to compression [65, 66]. Tight fitting bands, such as watches or bracelets, may result in compression. Handcuffs, especially when excessively tight, characteristically result in a superficial radial sensory neuropathy [66]. Injury during intravenous cannulation by a needle or following hematoma may occur. As the superficial radial sensory nerve is purely sensory, there is no associated weakness. A characteristic patch of altered sensation develops over

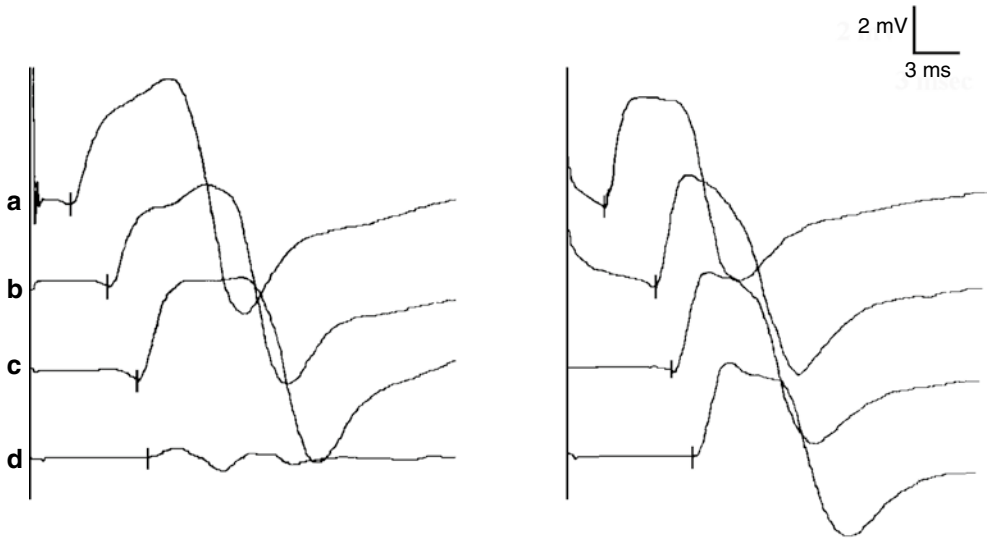

Fig. 40.12 Radial motor studies: radial neuropathy at the spiral groove. Left traces, symptomatic arm; right traces, contralateral asymptomatic arm. Recording extensor indicis proprius; stimulating (top to bottom traces): forearm, elbow, below spiral groove, above spiral groove. Note marked drop in amplitude and area across spiral groove on the left (conduction block) and symmetric distal CMAP amplitudes. Both imply a predominantly demyelinating lesion at the spiral groove (From Preston and Shapiro [103])

the lateral dorsum of the hand, part of the dorsal thumb, and the dorsal proximal phalanges of the index, middle, and ring fingers.

Differential Diagnosis

Radial neuropathies, including lesions of the PIN, most often present with a wrist drop. A similar clinical presentation also includes unusual C7–C8 radiculopathies, brachial plexus lesions, and central causes [1]. Since most muscles that extend the wrist and fingers are innervated by the C7 nerve root, radiculopathy may rarely present solely with a wrist and finger drop, with relative sparing of nonradial C7–innervated muscles. Radial neuropathy at the spiral groove or axilla should result in weakness of the brachioradialis, a C5–C6 muscle, which is not affected by a lesion of the C7 nerve root. In contrast, radial neuropathy at the spiral groove spares the triceps, which would be weak in a C7 radiculopathy. If a C7 radiculopathy is severe enough to cause muscle weakness, other nonradially innervated C7 muscles should also be weak (e.g., pronator teres, flexor carpi radialis), leading to weakness of arm pronation and wrist flexion. However, in rare situations, nonradial C7 muscles may be relatively spared, and the clinical differentiation is quite difficult to make.

While lesions of the posterior cord of the brachial plexus result in weakness of radial-innervated muscles, the deltoid (axillary nerve) and latissimus dorsi (thoracodorsal nerve) should also be weak. Central lesions may also result in a wrist and finger drop. The typical upper motor neuron posture results in flexion of the wrist and fingers, which in the acute phase, or when the lesion is mild, may superficially resemble a radial neuropathy. Central lesions are identified by increased muscle tone and deep tendon reflexes (unless acute), slowness of movement, associated findings in the lower face and leg, and the absence of altered sensation in the superficial radial distribution.

Evaluation and Diagnosis

Similar to other entrapment neuropathies, EDX plays a critical role in the evaluation and management of radial neuropathy in helping localize the site of the lesion [1, 59]. The most important nerve conduction study to perform is the radial motor study. The radial nerve can be stimulated in the forearm, at the elbow, and below and above the spiral groove while recording a distal radial muscle (e.g., extensor indicis proprius or extensor digitorum communis). Often, comparison to the contralateral asymptomatic side may be useful. The value of performing radial motor studies usually lies in looking for a focal conduction block between the proximal and distal sites and in determining the relative CMAP amplitude to assess axonal loss (Fig. 40.12).

In radial neuropathy at the spiral groove, CMAPs recorded with stimulation at the forearm, elbow, and below the spiral groove may be completely normal, if the lesion is purely demyelinative. However, stimulation proximal to the spiral groove will result in either marked temporal dispersion and/or conduction block.

Rarely, there may be conduction block between the forearm and elbow sites in PIN. However, most cases of PIN are pure axonal lesions and no conduction block is demonstrable. In these cases, the distal and proximal radial CMAP amplitudes are equally low in proportion to the amount of axonal loss.

In contrast to radial motor studies, the superficial radial sensory nerve is easy to record. If there has been secondary

axonal loss, the response is diminished in amplitude or absent. If the pathology is one of pure or predominant demyelination, the radial SNAP is normal. Similar to motor studies, it is often useful to compare the response with the contralateral asymptomatic side. A normal superficial radial SNAP is also seen in PIN, as expected, as the nerve carries no cutaneous sensory fibers.

In patients with suspected radial neuropathy, an extensive needle EMG study is usually indicated. The role of needle EMG is to differentiate between PIN, radial neuropathy at the spiral groove, radial neuropathy in the axilla, a lesion of the posterior cord of the brachial plexus, a C7 radiculopathy, and a central lesion. In PIN, denervating potentials, decreased MUAP recruitment, and large MUAPs are limited to those muscles innervated by the posterior interosseous nerve. As one moves more proximally to radial neuropathy at the spiral groove, the brachioradialis, extensor carpi radialis-long head, and supinator will also be affected, but the triceps is spared. If the lesion is even more proximal at the axilla, the triceps and anconeus will be involved. Moving more proximally to a lesion of the posterior cord of the plexus, additional abnormalities are seen in the deltoid and latissimus dorsi. A C7 radiculopathy will include abnormalities in the cervical paraspinal muscles and nonradial-innervated C7 muscles (e.g., pronator teres, flexor carpi radialis). Lastly, in central lesions, MUAPs are normal in weak muscles, though one expects to see decreased activation of MUAP firing.

Management and Prognosis

Management of radial neuropathies from external compression is conservative in nearly all cases. Simple avoidance of the offending compression is first recommended (e.g., proper use of crutches, not wearing constrictive wrist bands). Most cases of radial neuropathy at the spiral groove occur from prolonged compression from one specific incident. Splinting the wrist and fingers is indicated in patients with any significant finger or wrist drop. Whether the compression resulted in demyelination or axonal loss has direct consequences on length of recovery. This determination is usually easily made on EDX studies. Most patients with demyelinative lesions recover well after several weeks; axonal loss cases may require many months to over a year to effect recovery.

Decisions regarding surgical treatment, especially entrapment of the PIN, are more controversial [67]. In patients with progressive symptoms and in those who have not responded to conservative treatment (i.e., rest, splinting, anti-inflammatory agents), surgical exploration and release may be advisable and to exclude a structural lesion (e.g., nerve sheath tumor, lipoma, fibrous band).

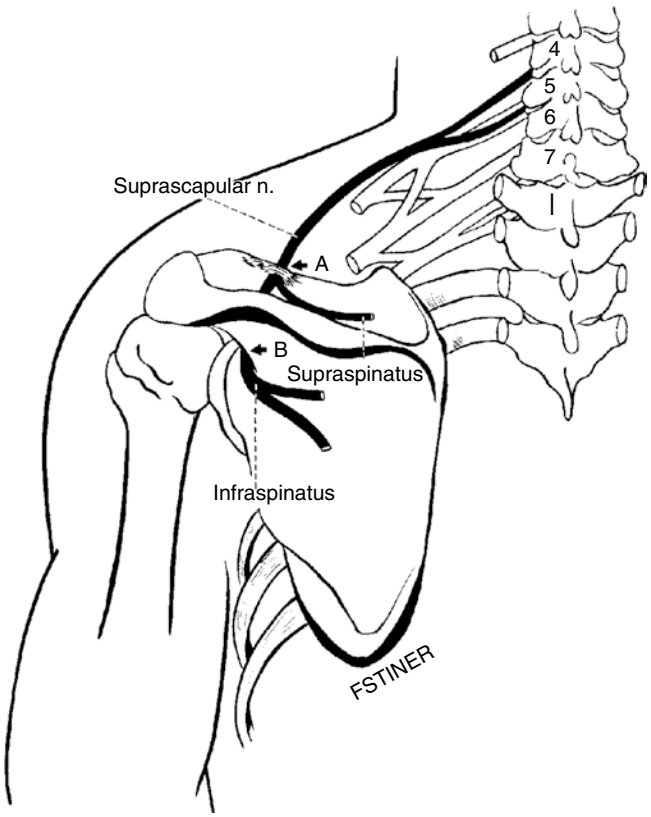

Fig. 40.13 Anatomy of the suprascapular nerve. The suprascapular nerve originates from the upper trunk of the brachial plexus. The nerve first runs under the suprascapular notch (*A*) to innervate the supraspinatus muscle. Sensory fibers are then given to the shoulder joint before the nerve wraps around the spinoglenoid notch (*B*) to supply the infraspinatus muscle (Adapted from Haymaker and Woodhal [102]. With permission)

Suprascapular Neuropathy

Anatomy (Fig. 40.13)

The suprascapular nerve arises off the upper trunk of the brachial plexus, receiving innervation from the C5 and C6 roots. The nerve runs posteriorly under the trapezius, passing through the suprascapular notch of the scapula to enter the supraspinous fossa. The suprascapular notch is U-shaped, located along the superior border of the scapula, and covered by the transverse scapular ligament. The suprascapular nerve supplies motor fibers to the supraspinatus muscle before proceeding laterally to supply deep sensory fibers to the glenoacromial and acromioclavicular joints. It then wraps around the spinoglenoid notch of the scapular spine to enter the infraspinous fossa where it supplies motor fibers to the infraspinatus muscle. The suprascapular nerve usually carries no cutaneous sensory fibers, although rare anomalous innervations have been reported whereby the suprascapular nerve carries cutaneous sensation to the proximal lateral arm, the area usually supplied by the axillary nerve.

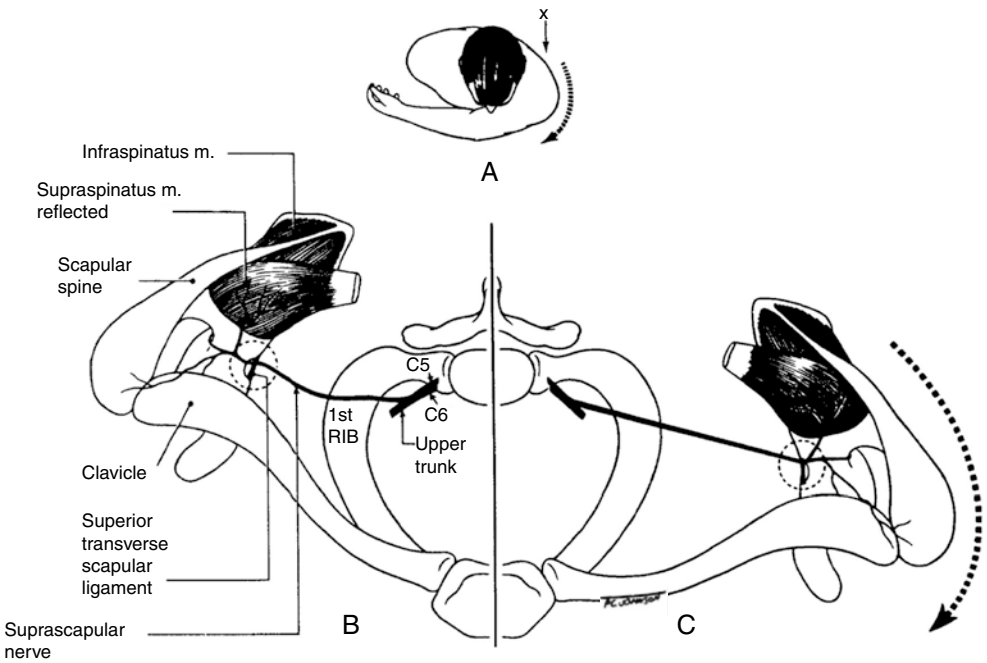

Fig. 40.14 Suprascapular neuropathy. Suprascapular neuropathy may occur from repetitive protraction of the scapular and tethering of the nerve between the suprascapular notch and the upper trunk of the brachial plexus. Coronal view of the suprascapular nerve from above: (*B*) normal position, (*C*) nerve stretch produced by arm posture in (*A*) (From Kopell and Thompson [106]. By permission of Surgery, Gynecology & Obstetrics, now known as the Journal of the American College of Surgeons)

Etiology and Pathogenesis

Suprascapular entrapment most commonly occurs at the suprascapular notch, under the transverse scapular ligament [1, 5, 68–71]. Less frequently, the nerve can also be entrapped distally at the spinoglenoid notch [72, 73]. The suprascapular nerve is relatively immobile both at its origin at the upper trunk and at the suprascapular notch. As both the shoulder and scapula are quite mobile, movement, especially repetitive movement, results in stretch and nerve injury (Fig. 40.14) [71].

Rare cases of suprascapular nerve entrapment have also been reported secondary to a variety of mass lesions, including ganglion cysts, sarcomas, and metastatic carcinomas. In addition, certain activities, professions, and positions are associated with suprascapular entrapment. For example, suprascapular neuropathy has been reported as a consequence of positioning during surgical procedures, whereby patients are placed in a knee-chest position with the scapula protracted. Weight lifting has been implicated in several reports as a provocative factor in suprascapular entrapment, likely as a consequence of repetitive movement of the scapular, especially during lifts that involve shoulder abduction and protraction [5, 68]. Several other professions are at risk for suprascapular entrapment. These include professional volleyball players, baseball pitchers, and dancers where the clinical and EDX findings most often suggest a distal lesion at the spinoglenoid notch [72].

In addition, suprascapular neuropathy, which is sometimes confused clinically with a rotator cuff injury, may also accompany a rotator cuff injury. First, one might initially assume that both would have a common traumatic etiology. However, it is also possible that suprascapular neuropathy may actually occur as a result of a rotator cuff tear, usually a large and full thickness tear. Following a rotator cuff tear, there may be medial retraction of the tendon to the supraspinatus and infraspinatus muscles. This then may result in increased tension of the suprascapular nerve both at the suprascapular notch and the spinoglenoid notch [74]. Finally, the suprascapular nerve may be involved selectively or with other proximal upper limb nerves during an attack of neuralgic amyotrophy.

Clinical Presentation

Symptoms and signs depend on the site of nerve entrapment [1]. At the most common site of compression, the suprascapular notch, shoulder pain may be prominent. The pain is typically described as deep and boring, occurring along the superior aspect of the scapula and radiating to the shoulder, but usually no more distally. The pain may be exacerbated by shoulder movements, especially adduction of the extended arm. This movement results in protraction of the scapula, which increases the nerve tethering between the upper trunk and the suprascapular notch. Occasionally, the suprascapular notch may be tender to palpation. Weakness involves shoulder abduction and external rotation. Atrophy may be recognized, especially over the infraspinatus muscle, which is not covered by the trapezius muscle.

If the entrapment occurs distally at the spinoglenoid notch, the syndrome is isolated to atrophy and weakness of the infraspinatus muscle. Pain is usually absent, since the deep sensory fibers to the shoulder joint have exited more proximally.

Differential Diagnosis

Several conditions may be confused with suprascapular neuropathy, including cervical radiculopathy, rotator cuff injury and other orthopedic conditions, and neuralgic amyotrophy [1]. In contrast to suprascapular neuropathy, a C5–C6 radiculopathy may have radiating pain from the neck into the arm and is associated with sensory abnormalities in the lateral arm, forearm, and thumb. Often, the biceps and brachioradialis tendon reflexes will be depressed or absent.

Orthopedic conditions, especially rotator cuff injuries, may be difficult to differentiate clinically from suprascapular neuropathy. Although weakness should not be present, pain often prevents full muscle activation. Exacerbation of pain by palpation (other than at the suprascapular notch) or by passive shoulder movement (other than abduction and protraction of the shoulder) is unusual for suprascapular entrapment.

Lastly, neuralgic amyotrophy often presents with severe proximal arm and shoulder pain and later weakness and, in some cases, primarily involves the suprascapular nerve.

Evaluation and Diagnosis

Patients with suspected suprascapular neuropathies should undergo EDX and imaging studies. EDX studies can demonstrate abnormalities of the suprascapular-innervated muscles and exclude cervical radiculopathy or brachial plexopathy [1]. Since the suprascapular nerve has no cutaneous distribution, there is no corresponding sensory nerve to be recorded. However, sensory nerve studies (i.e., lateral antebrachial, median, and radial sensory nerves) are helpful in excluding an upper trunk brachial plexopathy. Motor conductions can be performed with technical difficulties, stimulating Erb's point and recording with either a surface or monopolar needle electrode over either the supraspinatus or infraspinatus muscles [1, 70]. Comparing amplitude side to side can give an estimate of the amount of axonal loss present. However, these studies generally do not increase the yield over conventional electromyography in terms of localizing the lesion. Typically, the pathophysiology of suprascapular neuropathies is axonal loss.

During needle EMG, both the supraspinatus and infraspinatus muscles should be studied. In lesions at the suprascapular notch, both are abnormal. However, with spinoglenoid lesions, only the infraspinatus is involved. If either of these muscles is abnormal, it is essential to sample other C5–C6-innervated muscles (e.g., deltoid, biceps, brachioradialis), as well as the cervical paraspinal muscles, to exclude a cervical radiculopathy or more widespread brachial plexus lesion.

In addition, patients with suspected suprascapular neuropathy should undergo MRI of the shoulder. Ganglion cysts are easily demonstrable as well as other mass lesions which can affect the suprascapular nerve [73]. In patients which suprascapular neuropathy at the suprascapular notch, imaging will be normal, although atrophy of the supra- and infraspinatus muscles may be present.

Management and Prognosis

Therapy of suprascapular neuropathy is usually surgical, with the exception of those cases resulting from neuralgic amyotrophy [5, 68]. In cases of repetitive trauma (e.g., weight lifting), avoidance of the activity, physical therapy, and observation are indicated before consideration of surgical release. Unless a cyst or other mass lesion is present in the spinoglenoid notch on imaging, the site of entrapment is usually at the suprascapular notch. Surgical release of the suprascapular ligament usually results in excellent recovery.

Axillary Neuropathy

Anatomy (Fig. 40.15)

Along with the radial nerve, the axillary nerve originates from the termination of the posterior cord of the brachial plexus [1]. The axillary nerve is composed primarily of

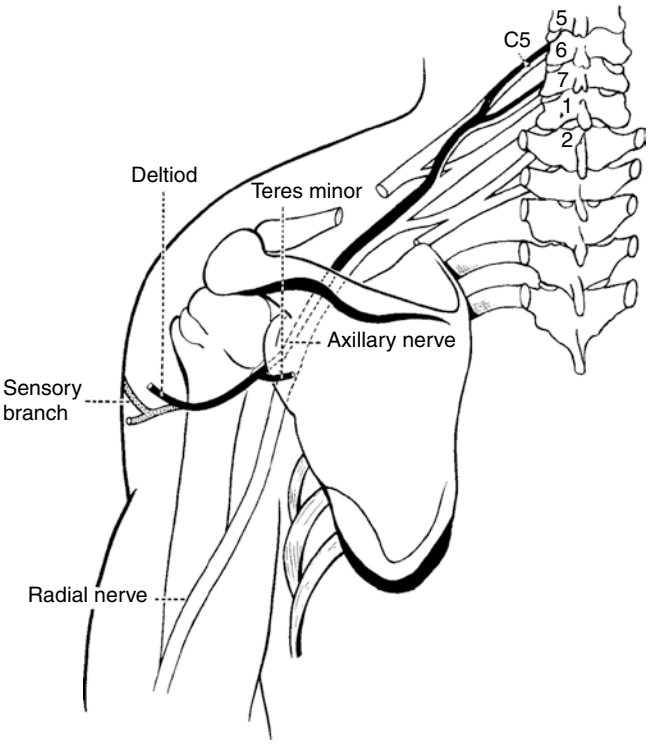

Fig. 40.15 Anatomy of the axillary nerve. The axillary nerve originates from the posterior cord of the brachial plexus. The nerve innervates the teres minor and deltoid muscles as well supplies sensation to the lateral shoulder (Adapted from Haymaker and Woodhal [102]. With permission)

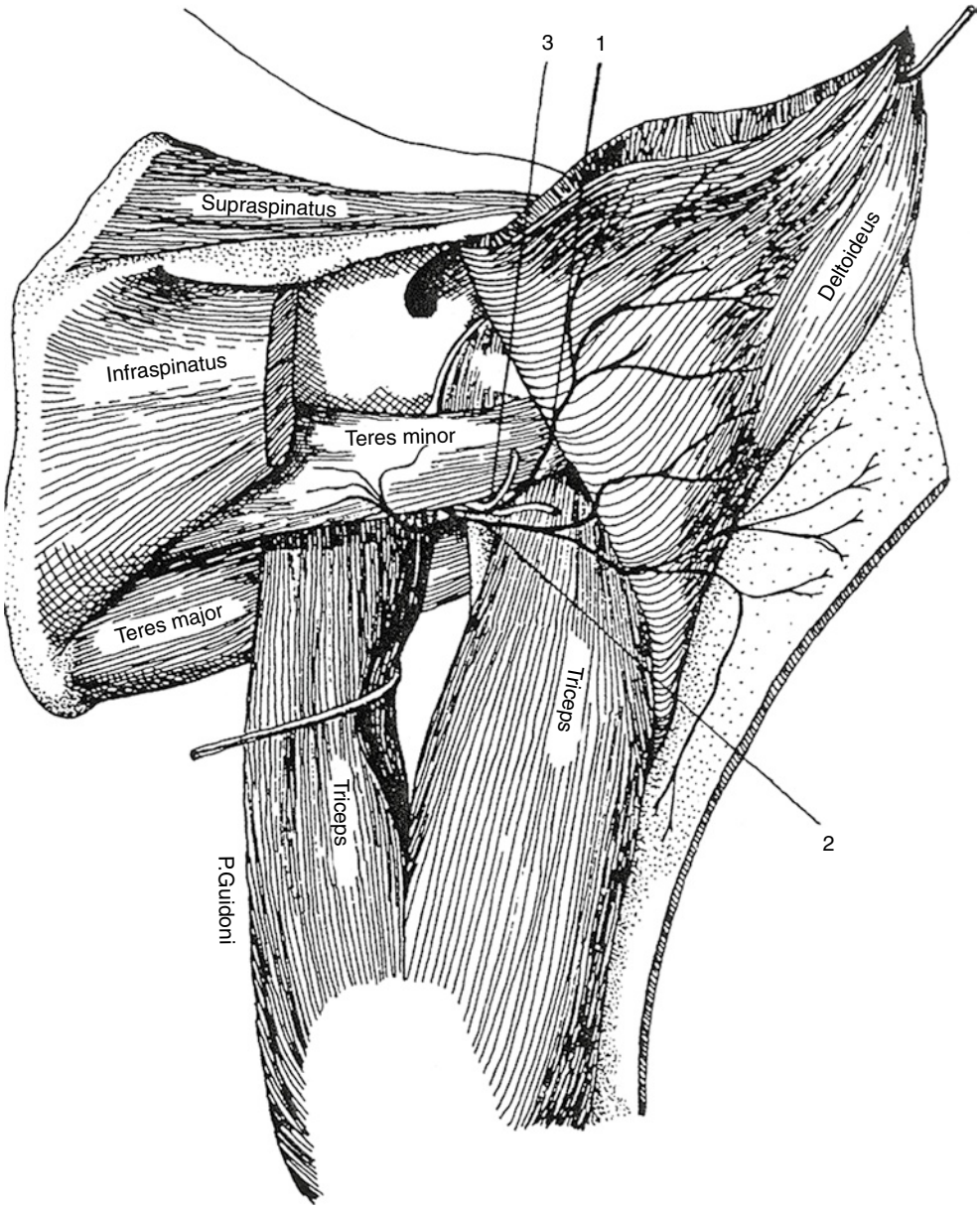

Fig. 40.16 Posterior view of the quadrilateral space: anterior (*1*) and posterior (*2*) branches of the circumflex nerve and circumflex artery (*3*) (From Paladini et al. [107]. With permission)

C5–C6 fibers, running through the upper trunk and posterior cord of the plexus. The nerve leaves the axilla through the quadrangular space, formed by the humerus, teres minor, teres major, and long head of the triceps muscles (Fig. 40.16). Muscular innervation is supplied to the teres minor and deltoid muscles, which aid in shoulder external rotation and abduction, respectively. A small cutaneous sensory branch supplies an oval-shaped area over the lateral shoulder.

Etiology and Pathogenesis

Axillary neuropathies typically result from trauma, especially dislocation of the shoulder and fracture of the humerus [5, 76, 77], and surgical positioning [78, 79]. Rare cases of entrapment in the quadrangular space have been reported, but are exceptional [80–84].

Clinical Presentation

Patients with axillary neuropathies have a well-defined circular area of numbness over the lateral shoulder, along with partial weakness of shoulder abduction and external rotation. The degree of weakness varies from patient to patient. The weakness is only partial, since other muscles also contribute to shoulder external rotation (i.e., the infraspinatus) and abduction (i.e., the supraspinatus).

Differential Diagnosis

Axillary neuropathy may be confused with suprascapular neuropathy, C5–C6 radiculopathy, neuralgic amyotrophy, and local orthopedic conditions. Key physical exam findings include sensory loss over the lateral shoulder (not present in suprascapular neuropathy) and intact biceps and brachioradialis reflexes (may be depressed in C5–C6 radiculopathy). Orthopedic conditions, especially rotator cuff injuries, may be difficult to differentiate clinically from axillary neuropathy. Although weakness should not be present, pain often prevents full muscle activation. Similar to its involvement of the suprascapular neuropathy, neuralgic amyotrophy may present with severe proximal arm and shoulder pain and later weakness and, in some cases, primarily involves the axillary nerve.

Evaluation and Diagnosis

X-ray of the shoulder and humerus should be performed in traumatic cases to help exclude fracture and shoulder dislocation. EDX studies should be delayed for several weeks when they can better define the lesion anatomy and assess the amount of axonal loss. From a localization point of view, the major goals of EDX testing are to demonstrate abnormalities of axillary-innervated muscles and rule out cervical radiculopathy or brachial plexopathy [1]. There is no routine sensory conduction study available for the axillary nerve. However, as the axillary nerve originates from the posterior cord and upper trunk, sensory nerves that run through the posterior cord and upper trunk should be studied. These include the radial and lateral antebrachial cutaneous sensory nerves and the median sensory nerve, especially when recording the thumb. Abnormalities of any of these sensory studies suggest a more widespread brachial plexopathy.

Axillary motor nerve conduction studies can be performed stimulating the axilla and Erb's point and recording with a monopolar needle or preferably a surface electrode over the deltoid [74]. CMAP amplitude can be compared both from side to side to assess the amount of axonal loss and between the axilla and Erb's point on the symptomatic side to look for conduction block. However, these studies can be technically difficult to perform, especially obtaining supramaximal stimulation in obese patients. Since these are usually axonal loss lesions, motor studies are best used to assess axonal loss by comparing the symptomatic to asymptomatic side and thus generally do not increase the yield of localizing the lesion beyond what is obtained from routine needle EMG.

In axillary neuropathies, needle EMG is used to demonstrate denervation and/or reinnervation in the two axillary-innervated muscles, the deltoid and teres minor. All three heads of the deltoid are easily accessible to needle EMG; the teres minor is considerably more difficult to sample. If abnormalities are found in any of these muscles, other muscles innervated by the upper trunk and posterior cord should be studied to ensure that the abnormalities found in the axillary-innervated muscles are not part of a more widespread brachial plexus or cervical root lesion.

Management and Prognosis

In traumatic cases of axillary neuropathy, observation and physical therapy are the first in order while awaiting signs of reinnervation and recovery. Much of the action of axillary-innervated muscles can be subserved by suprascapular-innervated muscles. In cases where a complete laceration of the nerve is likely clinically and in those who had not had any recovery over 6 months, surgical exploration and nerve grafting should be considered.

Musculocutaneous Neuropathy

Anatomy (Fig. 40.17)

The musculocutaneous nerve arises directly from the lateral cord of the brachial plexus [1]. In the upper arm, it pierces the coracobrachialis muscle to run in the fascia between the biceps and brachialis muscles. It innervates all three of these elbow flexor muscles, including the biceps, brachialis, and coracobrachialis. The terminal extension of the nerve past the elbow is the musculocutaneous sensory or lateral antebrachial cutaneous branch. In the region of the elbow, it runs deep to the brachial fascia and over the brachialis muscle with the biceps tendon medial and the brachioradialis lateral. In the forearm, the nerve becomes subcutaneous and separates into two terminal divisions (anterior and posterior) to supply sensation to the lateral half of the forearm. The posterior branch may form anastomoses with either the radial sensory nerve or posterior cutaneous nerve of the forearm. The anterior branch may rarely anastomose with the median sensory fibers.

Etiology and Pathogenesis

Isolated musculocutaneous neuropathies are rare. More commonly, they occur as part of more widespread traumatic lesions of the shoulder and upper arm, especially fractures of the proximal humerus [5, 77]. Musculocutaneous neuropathy has been associated with positioning during general

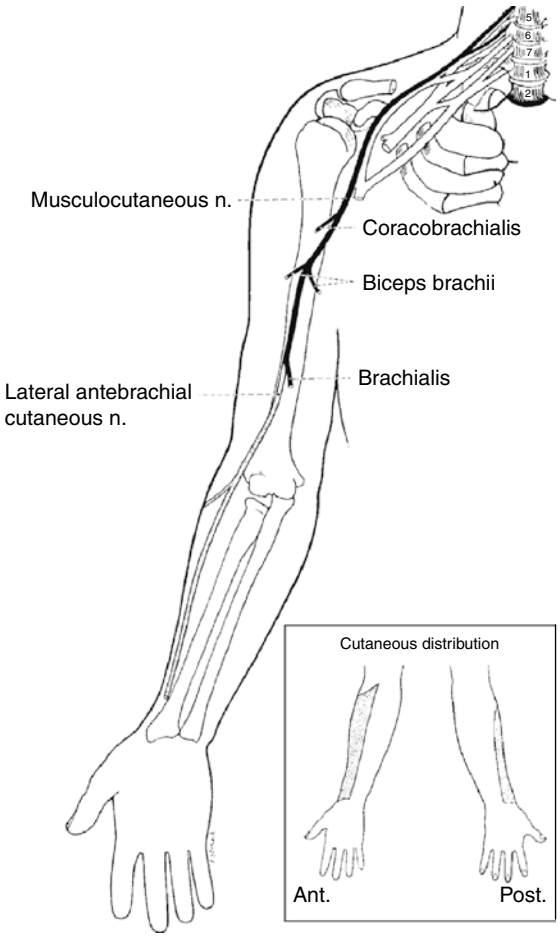

Fig. 40.17 Anatomy of the musculocutaneous nerve. The musculocutaneous nerve originates from the lateral cord trunk of the brachial plexus. The nerve innervates the biceps, brachialis, and coracobrachialis muscles. It then continues past the elbow as a pure sensory nerve, the lateral antebrachial cutaneous nerve, to supply sensation to the lateral forearm (From Haymaker and Woodhal [102]. With permission)

anesthesia and peripheral nerve tumors [85]. Some cases have occurred after strenuous upper extremity exercise without apparent cause, included weight lifting, football throwing, rowing, and carrying heavy textile rolls on the shoulder with the arm curled over the roll [86–88]. Various mechanisms have been proposed for these exercise-related cases. Bony tumors, including benign humeral exostoses, have resulted to mononeuropathies through direct impingement [89]. Often, in these later cases, symptoms were preceded by upper extremity exercise.

In addition, the musculocutaneous sensory (lateral antebrachial) nerve can be entrapped in isolation [90]. It occurs at the elbow where the nerve becomes entrapped between the biceps tendon/fascia and brachialis muscles. This neuropathy may also occur from a hyperextension injury of the elbow, including during sports-related activities such as tennis or following intravenous cannulation in the antecubital fossa.

Clinical Presentation

Clinically, musculocutaneous neuropathies result in weakness of elbow flexion, an absent biceps reflex, and sensory loss in the lateral forearm. In isolated involvement of the musculocutaneous (lateral antebrachial) sensory nerve, patients report worsening pain and/or paresthesias when the arm is pronated and extended. This position increases the pressure on the nerve at the elbow site. Examination in these cases shows isolated altered sensation in the lateral forearm, with normal muscle strength and reflexes. There may be tenderness to palpation over the nerve at the elbow.

Differential Diagnosis

The differential diagnosis of musculocutaneous neuropathies includes lesions of the lateral cord and upper trunk of the brachial plexus and the more common C5–C6 radiculopathies. Although less common than suprascapular and axillary neuropathies, neuralgic amyotrophy can present with prominent involvement of the musculocutaneous nerve as well. In addition, rupture of the biceps tendon may present with apparent weakness of arm flexion and mimic a musculocutaneous neuropathy. However, in tendon rupture, there is no sensory loss, and typically the biceps muscle is retracted, and there is bulging in the upper arm.

Evaluation and Diagnosis

Imaging is necessary in traumatic cases. X-ray of the shoulder and humerus should be performed in traumatic cases to help exclude fracture and shoulder dislocation. EDX studies can also be helpful but are best delayed for several weeks when they can better define the lesion anatomy and assess the amount of axonal loss. From a localization point of view, the major goals of EDX testing are to demonstrate abnormalities of musculocutaneous-innervated muscles and rule out cervical radiculopathy or brachial plexopathy [1]. The most important nerve conduction study to perform is the lateral antebrachial cutaneous sensory study. Musculocutaneous neuropathies, both distal and proximal, result in abnormal lateral antebrachial SNAPs.

Similar to axillary motor studies, musculocutaneous motor nerve conduction studies can be performed stimulating the axilla and Erb's point and recording with either a monopolar needle or preferably a surface electrode over the biceps [75]. The CMAP amplitude can be compared both from side to side to assess the amount of axonal loss and between the axilla and Erb's point to look for a conduction block. In contrast to the sensory studies, these motor studies are more technically difficult, especially obtaining supramaximal stimulation in obese patients. They are best used to assess the degree of axonal loss by comparing the

symptomatic to asymptomatic side. Similar to axillary and suprascapular neuropathies, musculocutaneous neuropathies are usually axonal loss lesions. Accordingly, motor studies generally do not increase the yield of localization over performing the needle EMG alone.

In distal musculocutaneous sensory neuropathies at the elbow, the needle EMG is normal. In proximal lesions, EMG demonstrates denervation and/or reinnervation with decreased recruitment of MUAPs in the biceps. The brachialis and coracobrachialis can also be sampled, but are more difficult than the biceps and offer little additional information. If abnormalities are found in the biceps, it is essential that other upper trunk- and lateral cord-innervated muscles are studied to ensure that the abnormalities found are not part of a more widespread brachial plexus lesion or C5–C6 radiculopathy.

Management and Prognosis

In traumatic cases of musculocutaneous neuropathy, observation is first in order looking for reinnervation. In cases where a complete laceration of the nerve is likely clinically and in those who had not had any recovery over 6 months, surgical exploration and nerve grafting should be considered.

In cases of isolated distal musculocutaneous sensory neuropathy, treatment usually involves time, splinting, and analgesics in the hope that if the lesion is neurapraxic, it will recover [75]. If unsuccessful, steroid injection adjacent to the nerve is often attempted. Ultimately, surgery decompression and partial resection of the biceps fascia are required.

Long Thoracic Neuropathy

Anatomy (Fig. 40.18)

The long thoracic nerve arises directly from the C5–C6–C7 roots, before the brachial plexus proper. The nerve runs inferiorly to innervate only one muscle, the serratus anterior. Anatomically, the serratus anterior muscle is considered as having an upper portion of the muscle, supplied by C5–C6 fibers, and a lower portion, supplied by C7 fibers. The upper portion is responsible principally for scapular protraction (i.e., pulling the scapula forward over the rib cage) and the lower portion for scapular stabilization. Protraction is the movement of the scapula forward along the chest wall. The serratus anterior arises from the first eight to ten thoracic ribs and inserts on the costal margin of the scapula.

Etiology and Pathogenesis

Long thoracic nerve palsies may occur as part of a more widespread traumatic lesion affecting the cervical roots [5].

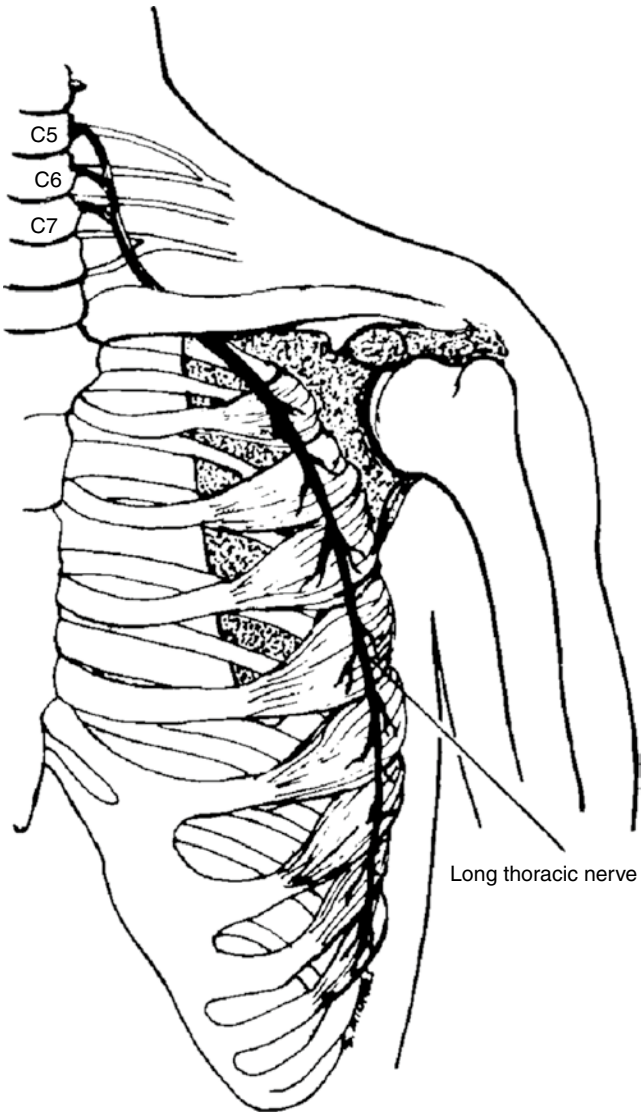

Fig. 40.18 Anatomy of the long thoracic nerve. The long thoracic nerve originates directly from the C5, C6, and C7 roots, proximal to the brachial plexus proper. It runs inferiorly to supply the serratus anterior muscle. There is no cutaneous sensory innervation (From Fisher [78]. With permission)

Although isolated long thoracic palsies have also been reported as a consequence of external compression and stretch, many result from neuralgic amyotrophy (see Chap. 46). Indeed, in some attacks of neuralgic amyotrophy, the long thoracic nerve is affected in isolation. Patients describe severe pain in the shoulder region that last several days to weeks. As the pain abates, patients note difficulty with shoulder movement.

Clinical Presentation

Weakness or paralysis of the serratus anterior characteristically results in winging of the scapula. Winging from serratus anterior dysfunction becomes most pronounced when

the arm is extended in front of the body. As the serratus anterior is a shoulder stabilizer, other shoulder muscles may also appear weak, including the deltoid, supraspinatus, and infraspinatus. However, if these muscles are tested with the examiner's hand pressed against the scapula or in the recumbent position, much of the "weakness" disappears. As the long thoracic nerve has no cutaneous distribution, there is no area of altered sensation or numbness.

Differential Diagnosis

Apparent winging of the scapula can occur with weakness of the serratus anterior, rhomboids, and/or trapezius muscles [77]. Winging from serratus anterior weakness results as the scapula is displaced medially and superiorly with the inferior angle rotated toward the midline, and the vertebral border of the scapula becomes prominent as it no longer is opposed to the thoracic cage. The winging becomes more prominent as the patient attempts to push forward against resistance. In winging from weakness of the rhomboids, the scapula moves the opposite direction, farther from the midline of the back as the rhomboids normally draw the scapula toward the back. In weakness of the trapezius, winging is not as pronounced as that of the serratus anterior. A decreased shoulder shrug is easily apparent when looking at the patient from the back.

In addition, scapular winging can be a prominent part of some inherited myopathies, especially facioscapulohumeral (FSH) muscular dystrophy where weakness usually involves other muscle groups including the facial muscles, biceps and triceps, wrist extensors, and ankle dorsiflexors.

Evaluation and Diagnosis

EDX studies can be helpful in both the diagnosis and prognosis of long thoracic neuropathies [1]. Unfortunately, there is no reliable way to study the long thoracic nerve with nerve conductions. In order to look for evidence of a more widespread brachial plexus lesion, sensory conductions should be performed, studying especially those nerves that travel through the upper and middle trunks, which have the same root innervation as the long thoracic nerve. These studies include the lateral antebrachial cutaneous, median, and radial sensory nerves.

The EDX evaluation relies on the needle EMG. In long thoracic nerve palsy, abnormalities are limited to the serratus anterior muscle. Other C5–C6–C7-innervated limb muscles should be sampled to exclude a radiculopathy or brachial plexopathy. In addition, the cervical paraspinal muscles should be checked as well, to help exclude a more proximal lesion at the roots.

Management and Prognosis

As most long thoracic neuropathies occur as part of neuralgic amyotrophy, management and prognosis of isolated long thoracic palsies is similar to that of neuralgic amyotrophy [91]. As the underlying etiology is unknown, there is no proven therapy that alters prognosis. Some patients are prescribed a short course of steroids, similar to their use in Bell's palsy, if recognized during the acute painful part of the presentation. Results with steroids are mixed; some patients report decreased pain. Otherwise, treatment is largely supportive. Analgesics, including narcotics, are often needed early on to treat pain. Physical therapy, especially range of motion and light exercise, is essential. Although most patients with neuralgic amyotrophy make a good recovery, the time to recovery is usually months to years. During that time, prevention of contractures, especially around the shoulder, is important in ensuring a good functional outcome. Overall, the long-term prognosis in neuralgic amyotrophy is excellent with 36 %, 75–80 %, and 90 % recovering by 1, 2, and 3 years, respectively. Rare patients have reported continued improvement up to 6–8 years after the event.

In patients with an obvious penetrating trauma or iatrogenic injury, early exploration with neurolysis, direct repair, or nerve grafting should be considered. Otherwise patients should be observed for clinical and EDX signs of recovery. In patients who fail to recover and have disabling symptoms, surgical therapy, including muscle transposition or scapula fixation, can be considered. Surgical options for patients with serratus anterior palsy include scapulothoracic fusions and dynamic muscle transfers [92]. Scapulothoracic fusions are generally regarded as salvage procedures after failure of other surgical techniques. Fusion of the scapula to the thorax eliminates scapular winging but also eliminates scapular motion. Dynamic muscle transfers consistently have shown the best results for correction of scapular winging and restoration of function in patients with serratus anterior palsy because of long thoracic nerve injury with the current preferred treatment being transfer of the sternal head of pectoralis major to the inferior angle of the scapula extended [92].

Spinal Accessory Neuropathy

Anatomy (Fig. 40.19)

The spinal accessory nerve is a pure motor nerve, with no cutaneous sensory fibers. The spinal accessory nerve is derived from C1 to C4 cervical levels. The nerve ascends through the foramen magnum, to return through the jugular foramen. It first supplies motor innervation to the sternocleidomastoid muscle and then runs superficially in the posterior cervical triangle to innervate the trapezius muscle.

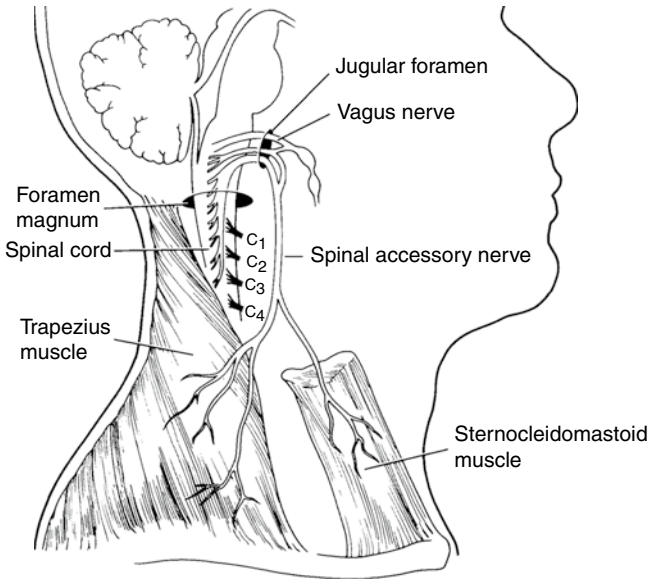

Fig. 40.19 Anatomy of the spinal accessory nerve. The spinal accessory nerve originates from C1 to C4 roots, ascending through the foramen magnum then to return via the jugular foramen. The nerve first innervates the sternocleidomastoid muscle before running over the posterior cervical triangle to innervate the trapezius muscle. There is no cutaneous sensory innervation (From Spence [108]. Reprinted by permission)

The trapezius is the major suspensory muscle of the shoulder. The upper fibers of the trapezius elevate the scapula and rotate its lateral angle upward, the intermediate fibers adduct and retract the scapula, and the lower fibers depress and rotate the scapula downward.

Etiology and Pathogenesis

Often, spinal accessory palsies occur in the region of the posterior cervical triangle, resulting in isolated weakness of the trapezius. This may occur from stretch, external compression (e.g., golf bag), but most commonly following local surgical procedures [93–95]. Carotid endarterectomy and cervical lymph node biopsy are the most common procedures that injure the spinal accessory nerve [96–99].

Clinical Presentation

In distal spinal accessory palsies, atrophy and weakness of the trapezius occur, resulting in a shoulder drop [1]. The destabilized scapula moves downward from the weight of the limb. It also moves laterally away from the spine as a result of the unopposed action of the serratus anterior. In this posture, the head of the humerus cannot articulate properly with the glenoid, resulting in impaired shoulder abduction. Mild scapular winging may also be seen, especially during attempted arm abduction. Indeed, an intact trapezius is needed for proper shoulder fixation and essentially all movements around the shoulder. A destabilized shoulder from trapezius weakness often results in apparent weakness of other shoulder movements as well. Thus, it is not uncommon for patients with a spinal accessory neuropathy to be misdiagnosed clinically as a brachial plexopathy or other proximal neuropathy, in addition to primary orthopedic problems of the shoulder. Indeed, patients with a spinal accessory neuropathy commonly go many months before the correct diagnosis is reached. Adding to the confusion is that pain and paresthesias may occur, presumably from traction on the brachial plexus as a result of the dropped shoulder. The dropped shoulder can also cause similar symptoms on a vascular basis, from compression of the axillary artery, resulting in pain and paresthesias [100].

In the less common proximal lesions of the spinal accessory nerve, weakness of the sternocleidomastoid muscle also occurs, in addition to trapezius weakness. This manifests as weakness of neck flexion as well as contralateral turning of the head and neck.

Differential Diagnosis

The diagnosis is straightforward when there is a history of local compression or if the patient has had a recent local surgical procedure. Otherwise, one must consider skull-based pathology and involvement of the lower cranial nerves. The scapular winging should be differentiated from those due to rhomboid and serratus anterior weakness (see above).

Evaluation and Diagnosis

EDX studies can confirm the presence of an isolated spinal accessory neuropathy and help assess prognosis in the traumatic cases [1]. Motor studies can be performed with surface recording electrodes over the upper trapezius. The CMAP from the upper trapezius can be compared to the contralateral side. Since the posterior sternocleidomastoid is the only easily accessible stimulation site, the major use of this study is to measure the distal CMAP amplitude and compare it to the contralateral side, to estimate the amount of axonal loss.

As the spinal accessory nerve carries no sensory fibers, there is no corresponding sensory nerve study to perform. However, in those patients who appear to have shoulder weakness from poor fixation, it is advisable to assess the sensory nerves that travel through the upper trunk of the brachial plexus. These studies, including the lateral antebrachial cutaneous, radial, and median SNAPS, should be sampled bilaterally to help exclude a more widespread lesion affecting the upper plexus.

Needle EMG can be used to assess the trapezius (upper, middle, and lower fibers) as well as the sternocleidomastoid muscles. If the trapezius is severely atrophied, it is easy to inadvertently pass through this muscle with the needle and actually be sampling underlying muscles (e.g., supraspinatus, infraspinatus, rhomboids). Along with checking the spinal accessory-innervated muscles, needle EMG should be used to sample other proximal muscles, especially those that control the shoulder. Since spinal accessory neuropathies may result in apparent weakness of the shoulder, it is essential to confirm that other shoulder girdle muscles are normal on needle EMG.

Management and Prognosis

In cases caused by external compression, avoidance of the activity is first indicated. Physical therapy can be of benefit to build up adjacent shoulder stabilizing muscles. In cases caused by stretch or those following lymph node biopsy where laceration is likely, management is more problematic [99]. Similar to other traumatic neuropathies, if no recovery has been noted either clinically or by needle EMG at 6 months, surgical exploration and possible nerve grafting can be considered. In addition, muscle transfer procedures may be considered to substitute for the loss function of the trapezius [101].

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Compressive and Entrapment Neuropathies of the Lower Extremity

41

Bashar Katirji

The Fibular (Peroneal) Nerve

Anatomy

The peroneal nerve was recently renamed as the fibular nerve by the Federative Committee on Anatomic Terminology to eliminate confusion between the terms peroneal and perineal nerves. The common fibular nerve (formerly known as the common peroneal nerve and lateral popliteal nerve) and the tibial nerve (formerly known as the posterior tibial nerve and medial popliteal nerve) form the sciatic nerve. Both nerves share a common sheath within the sciatic nerve but never exchange fascicles [1]. The first branch of the common fibular nerve is a motor branch that usually exits near to the gluteal fold and innervates the short head of biceps femoris. The tibial nerve innervates the rest of the hamstring muscles. The common fibular and tibial nerves separate completely in the upper popliteal fossa or slightly above that, with significant individual variability.

In the popliteal fossa, the common fibular nerve gives off two branches, the lateral cutaneous nerve of the calf, which innervates the skin over the upper third of the lateral aspect of the leg (Fig. 41.1), and the fibular communicating nerve which joins the sural nerve. The common fibular nerve then descends and curves around the anterolateral aspects of the fibular head and neck. After the fibular nerve gives off a small articular branch to the proximal tibiofibular joint, the common fibular nerve winds around the fibular neck and passes through the "fibular tunnel"; this is formed between the tendinous edge of the peroneus longus muscle and the fibula [1, 2]. Near that point, the common fibular nerve divides into its terminal branches, the deep and superficial fibular nerves.

The deep fibular nerve (formerly named deep peroneal nerve or anterior tibial nerve) is primarily motor. It passes through the proximal lateral compartment of the leg to enter the anterior compartment, where it innervates the tibialis anterior, extensor hallucis longus, peroneus tertius, and extensor digitorum longus. Slightly proximal to the ankle joint, the deep fibular nerve passes under the extensor retinaculum and then divides into a lateral motor branch which innervates the extensor digitorum brevis, and a medial sensory branch which becomes subcutaneous in midfoot and supplies the skin of the web space between the first and second toes (Fig. 41.2).

The superficial fibular nerve is predominantly sensory. It traverses usually the lateral compartment, where its gives motor branches to the peroneus longus and brevis. Less commonly, it passes through the lateral compartment or both the anterior and lateral compartments [3]. In the distal leg, the nerve, now a purely sensory nerve called the superficial fibular sensory nerve, pierces the crural fascia approximately 10 cm proximal to the lateral malleolus, to become subcutaneous [4, 5]. Soon after, it divides into a small medial cutaneous and a larger intermediate cutaneous nerve and innervates the skin of the lower two thirds of the lateral aspect of the leg and the dorsum of the foot (except for the first web space) (see Fig. 41.1).

The accessory deep peroneal nerve is a common anomaly occurring in 19–28 % of the general population, based on electrophysiological studies, and in up to 67 %, based on anatomical studies, with a likely autosomal dominant mode of inheritance [6–8]. When present, it arises as a motor branch of superficial fibular nerve, usually a continuation of the muscular branch that innervates the peroneus brevis muscle. The accessory deep fibular nerve traverses along the posterior aspect of the peroneus brevis muscle and then, accompanied by peroneus brevis tendon, passes behind the lateral malleolus near the sural nerve to reach the foot (Fig. 41.3). There, it sends branches to the lateral part of

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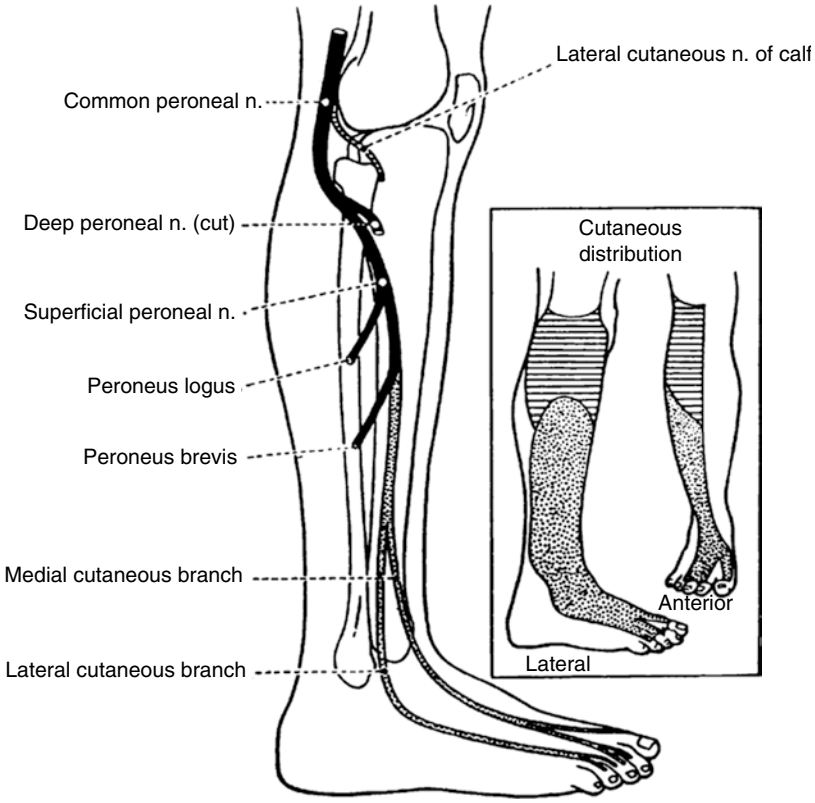

Fig. 41.1 The common and superficial fibular (peroneal) nerve with their terminal branches and cutaneous innervation (From Haymaker and Woodhall [393]. With permission)

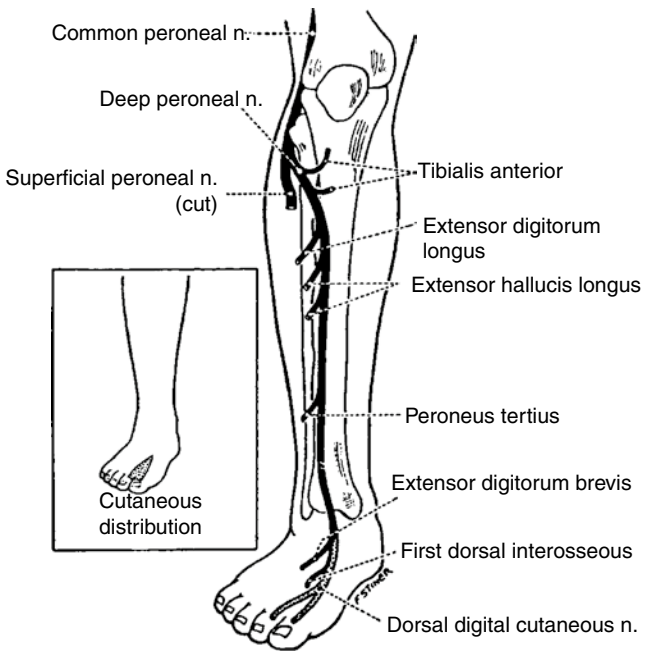

Fig. 41.2 The deep fibular (peroneal) nerve and its terminal branches and cutaneous innervation (From Haymaker and Woodhall [393]. With permission)

extensor digitorum brevis, ankle joint, and ligaments. Rarely, the extensor digitorum brevis receives complete innervation through the accessory deep fibular nerve [9–11].

Common Fibular (Peroneal) Mononeuropathy at the Fibular Neck

Etiology and Pathogenesis

Common fibular mononeuropathies around the fibular neck are usually caused by external nerve compression or by knee trauma (Table 41.1) [12–14]. In compressive lesions, the common fibular nerve is often trapped between an external object or internal structure and the fibular neck. Typically, the deep fibular branch is more severely affected than the superficial branch. This phenomenon is related to the topographical arrangement of the common fibular nerve around the fibular neck, where the exiting fascicles, forming the superficial branch, are placed laterally while the deep fibular nerve is located medially in direct contact with the fibular bone [15]. Occasionally, the lesion at the fibular neck is restricted to the deep fibular nerve (see below) [14, 15].

Intraoperative compression is the most common cause of acute fibular mononeuropathies at the fibular neck [12, 14]. This occurs during anesthesia for surgical procedures in which the fibular nerve is distant from the surgical field, such as during coronary bypass artery grafting or craniotomy. The fibular nerve becomes compressed due to malpositioning of legs and failure to properly pad the knees. Weight loss, due to a concurrent illness or with dieting, is another common precipitating factor of fibular nerve compression at the fibular neck [14, 16–19]. Loss of subcutaneous fat padding around

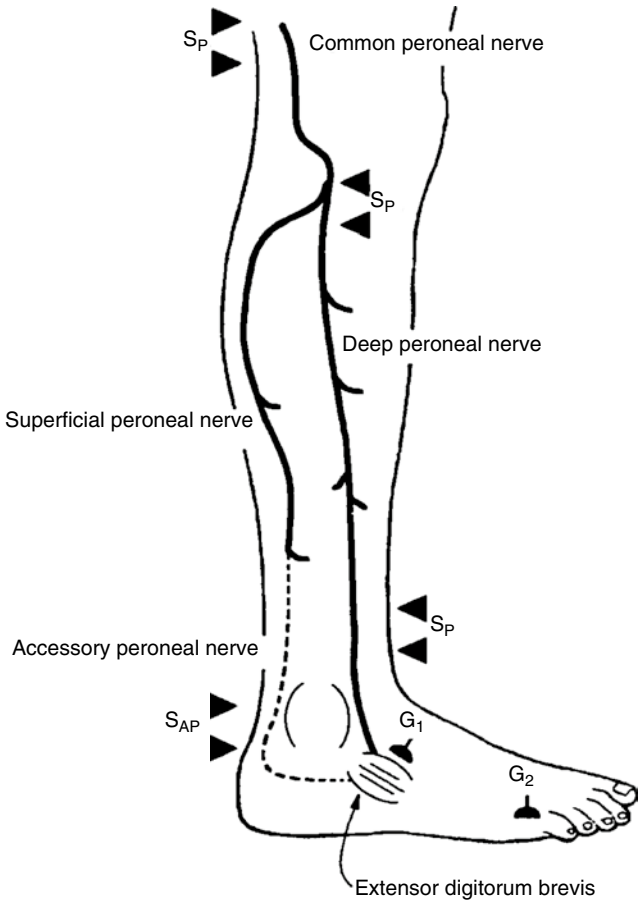

Fig. 41.3 The accessory deep fibular (peroneal) nerve (S_P, stimulation, fibular nerve; S_{AP}, stimulation, accessory fibular nerve; G1, active recording; G2, reference recording) (From Preston and Shapiro [394]. With permission)

Table 41.1 Causes of common fibular nerve lesions at the fibular neck

Compression
During anesthesia
Weight loss
Habitual leg crossing[a]
Prolonged hospitalization[a]
Prolonged bed rest[a]
Anorexia nervosa[a]
Coma
Diabetes mellitus
Peripheral polyneuropathy
Prolonged squatting
Yoga
Crop harvesting "strawberry pickers"
Childbirth
Military training
Iatrogenic
Above or below knee cast
Ankle-foot orthosis
Pneumatic compression device
Antithrombotic stocking
Bandage
Strap
Lithotomy position with stirrups
Intrauterine (with breech presentation)
Trauma
Blunt
Fibular fracture
Tibial plateau fracture
Knee joint ligament rupture
Knee dislocation
Superior tibiofibular joint dislocation
Inversion/plantar flexion ankle sprain
Open
Laceration
Gunshot wound
Animal bite
Iatrogenic
Conventional knee surgery
Knee joint replacement
Arthroscopic knee surgery
Mass lesion
Extrinsic
Osteochondroma
Giant cell tumor
Baker's cyst
Hematoma
Pseudoaneurysm
Extraneural cyst
Intrinsic
Intraneural ganglion cyst
Schwannoma
Neurofibroma
Neurogenic sarcoma
"Focal hypertrophic neuropathy"
Infection
Leprosy
Entrapment
"Fibular tunnel syndrome"

[a]Usually with weight loss

the common fibular nerve, rendering it exposed to the fibular bone, is the likely cause of compression in these patients. A reduction in the peroneal nerve transverse cross-sectional area has been reported on ultrasonography in these patients. The nerve appeared thinner and its ultrasonic reflectivity was lower [20]. Weight loss is often overlooked by treating physicians who may be unaware of this precipitating factor. Habitual leg crossing is also an important risk factor [21], but this is invariably associated with another risk factor, particularly weight loss [14]. Prolonged hospitalization, bed rest, or coma, particularly when associated with weight loss, is not uncommon causes of fibular nerve compression at the fibular

neck. This is likely precipitated by poor patient positioning resulting in leg compression against firm mattresses and bed rails or, merely, prolonged external rotation in a "frog-leg position." Diabetes mellitus, with or without a peripheral polyneuropathy, is a likely independent risk factor for developing common fibular nerve lesions around the fibular neck [14, 22]. Although it was reported in only one patient of 380 diabetics studied in a cross-sectional population study [23], a series of 103 patients with peroneal neuropathy at the fibular head found that 8 % were diabetics [14]. Patients with underlying peripheral polyneuropathy in general have also a higher incidence of such a lesion. Iatrogenic compression by external devices applying pressure on the fibular nerve against the fibular neck may cause fibular mononeuropathy. These include above and below knee casts, ankle-foot orthoses, pneumatic compression devices, and antithrombotic stockings, bandages, and straps [24–28].

Prolonged squatting, such as during crop harvesting ("strawberry pickers fibular palsy"), Yoga meditation, or childbirth, is associated with common fibular nerve lesions at the fibular neck [29–35]. The exact site of fibular nerve compression during squatting is not well understood. Aided by weight of the body, the common fibular nerve may be stretched around the fibular neck or compressed between the biceps femoris tendon and the lateral head of the gastrocnemius muscle. Lithotomy positioning, particularly with the use of stirrups, for hysterectomy, prostatectomy, or vaginal delivery, is another cause of fibular nerve compression at the fibular neck.

Intrapartum fibular neuropathy in the setting of normal childbirth is rare. It is usually compressive across the fibular neck. This may occur bilaterally. It may be caused by the stirrups during lithotomy positioning which is used less commonly during childbirth. Squatting during labor, which is common in certain countries but rarely in the United States, may result in compressive fibular neuropathy at the knee, particularly when labor is prolonged [33, 35]. Finally, direct pressure on the nerve across the fibular neck may occur while the knees are grasped by the patient or assistants to keep her hips and knees forcibly flexed [36, 37]. This has been referred to as "pushing palsy" [36]. Nurses and obstetricians must be aware of potential fibular nerve injury during labor, and women should be instructed to avoid maintaining positions that result in prolonged, uninterrupted pressure on the fibular nerves by frequently varying their position during childbirth. It is also not clear whether reported patients with postpartum foot drop following vaginal delivery may actually represent cases of intrapartum lumbosacral plexopathy due to compression of the lumbosacral trunk by the fetal head in the pelvis [38, 39].

Direct nerve trauma is the second most common cause of common fibular mononeuropathies at the fibular neck. This includes blunt or open trauma, as well as surgical nerve injury. Blunt trauma is often associated with vehicular accidents or sport injuries leading to soft tissue injuries such as ligamental ruptures of the knee joint, tibiofibular fracture with or without a coexisting fibular head fracture, knee dislocation, or dislocation of the superior tibiofibular joint [40, 41]. Open injuries are usually due to lacerations (by knives, chainsaws, broken glass, etc.), gunshot wounds, or animal bites. Iatrogenic fibular nerve lesions around the fibular neck are common following surgical procedures in which the fibular nerve is in or near the operative field, such as with conventional knee surgery as well as knee arthroscopy [42–44]. Finally, stretch injuries of the common fibular nerve or to one of its terminal branches may occur following inversion ankle sprains [45–47]. This is likely caused by traction and compression of the common peroneal nerve as it winds around the neck of the fibula and possible compression by hematoma. This may be more common than suspected and may account for the persistent weakness of ankle and the increased risk of recurrent ankle sprains in patients with prior ankle inversion injuries [48].

Intraneural ganglia of the fibular nerve causing fibular neuropathy and foot drop are increasingly diagnosed but remain under-recognized despite that fibular intraneural ganglion is the most common type of intraneural ganglia. These are mucinous cysts which originate from the superior tibiofibular joint after disruption of its capsule, allowing dissection of the synovial fluid along the articular branch of the fibular nerve reaching the epineurium of the nerve [49]. In 40 % of cases, there is a residual pedicle connecting to the joint which may explain the high (10–20 %) recurrence rate. Patients with fibular nerve lesions who have no precipitating factors (such as weight loss or immobility) and who exhibit knee pain, neuropathic leg pain, and fluctuating foot weakness should be suspected as harboring intraneural fibular ganglia. Pain and fluctuating foot weakness are good predictors for the presence of intraneural fibular ganglion [50]. A palpable mass at the fibular neck is only detected in only about ½ of the patients. On neurological examination, there is a preferential involvement of the deep fibular nerve and with predominant tibialis anterior weakness, since the tibialis anterior branch is consistently involved while other muscular branches are less affected [51]. Imaging of the knee by MRI with fat suppression images or ultrasound is necessary to visualize the lesion.

Rare causes of fibular nerve lesions around the fibular neck include extrinsic masses such as osteochondromas which are more common in children and adolescents and usually arise from the proximal fibula and often compress the deep more than the superficial fibular nerve [52]. Baker's cysts, hematomas, and pseudoaneurysms are other mass lesions associated with such lesions [53]. Intrinsic nerve sheath tumors, including schwannomas, neurofibromas, and neurogenic sarcomas, are relatively rare [52, 53]. Leprous

neuritis is accompanied by significant thickening of the epineurium which results in fibular nerve injury [54].

In contrast to the carpal tunnel and cubital tunnel syndromes, chronic fibular nerve entrapment at the fibular tunnel is extremely rare [2]. This seems to occur mainly in athletes, particularly runners, and overlap with the exertional form of the anterior compartment of the leg (see below) [55, 56].

Common fibular mononeuropathies in children are similar to those of adults with compression and trauma as the leading causes [57]. Weight loss, sometimes associated with anorexia nervosa, iatrogenic lesions, such as with casts or following tibial osteotomies, and bone tumors, such as osteochondromas, are more common etiologies of common fibular nerve lesions than in adults [52, 57, 58]. Neonatal fibular nerve injuries are uncommon, usually associated with breech presentations and malpositioning but may have a prenatal onset likely from intrauterine stretching of the infant's fibular nerve [59, 60]. The prognosis is usually good, since most cases are due to neurapraxia despite that significant axonal loss may dominate in few cases [59, 60].

Idiopathic cases of fibular nerve lesions at the fibular neck constitute about 10–15 % of case series [61]. These cases do not have any of the known precipitating risk factors and do not have any identifiable mass lesion such as intraneural ganglion.

Clinical Presentation

Fibular mononeuropathy is the most common compressive mononeuropathy in the lower extremity [12, 14, 15, 29]. All age groups are equally affected but the disorder is almost three times more common in men [61]. Most fibular nerve lesions are unilateral and affect the right and the left side equally. Bilateral lesions are seen in less than 10 % of all the cases [13, 14, 61]. By far, lesions of the common fibular nerve at the fibular neck are the commonest, while selective proximal deep and high common fibular nerve lesions occur in a small percentage.

Common fibular mononeuropathy at the fibular neck is a frequent cause of acute foot drop, which may be complete or partial. In some instances, the foot drop develops gradually over days or even weeks. Though the foot drop is often acute in compressive lesions, the onset of foot drop may be subacute, or cannot be determined [12, 14, 57]. In general, postoperative compression and direct trauma to the fibular nerve have a well-defined history of an acute foot drop, while cases associated with weight loss or prolonged hospitalization often present in a gradual fashion or their onset may not be ascertained (Fig. 41.4).

Foot drop may cause the toes to get trapped or causes the patient to fall. Also, patients may inadvertently sprain or fracture their foot or ankle. Subjective numbness, mostly on the dorsum of foot, but occasionally extending into the lower

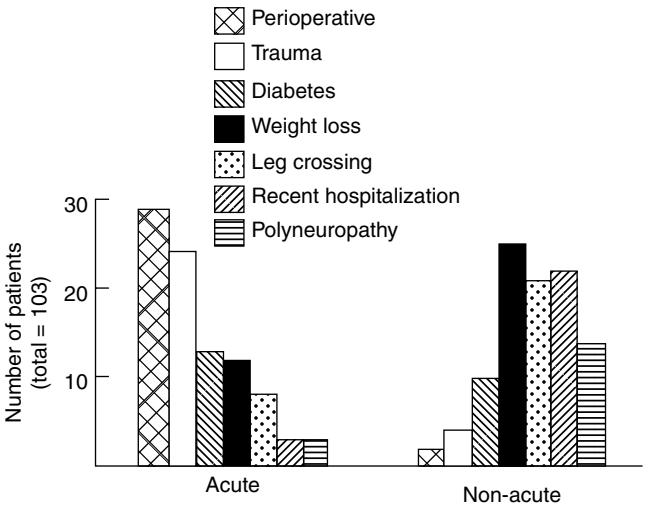

Fig. 41.4 Predisposing factors in 103 patients with fibular mononeuropathies. Note the difference between lesions of acute versus non-acute onset (From Katirji and Wilbourn [14]. With permission)

lateral leg, is common. In high (proximal) fibular lesions, the sensory loss in the lateral leg may extend into the knee (see section "Differential Diagnosis"). Most patients with lesions at the fibular neck have a mild deep, boring pain around the knee or in the leg, except for patients with intraneural ganglia who may have more pronounced pain [50]. A steppage gait with significant foot drop is evident in 2/3 of the patients with significant disability [61], since the patient has to raise the leg in order to avoid striking the foot and toes on the ground.

The neurological findings are restricted to weakness and sensory loss in the distribution of the common fibular nerve. In most cases, weakness of ankle and toe dorsiflexion dominates, while ankle eversion is relatively stronger, since the superficial fibular nerve is often less damaged than the deep fibular nerve. In contrast, ankle inversion, toe flexion, and plantar flexion are spared. Also, knee flexion and extension and hip abduction, adduction, and extension are normal. Deep tendon reflexes are normal. Hypoesthesia or hyperesthesia to touch and pain is common and limited to the lower two thirds of the lateral leg and dorsum of foot. In some patients, Tinel's sign may be elicited by percussion of the common fibular nerve around the fibular neck.

Ankle inversion may be difficult to assess in patients with complete or severe foot drop. An apparent weakness of ankle inversion often results in incorrect diagnoses, such as sciatic mononeuropathy or L5 radiculopathy, which may lead to unnecessary investigations and therapies [14]. Ankle inversion strength is best evaluated with the foot slightly dorsiflexed. In patient with significant foot drop, the ankle should be dorsiflexed passively to around 90°, before asking the patient to invert the foot.

Athletes, particularly runners, may have transient sensory symptoms or foot weakness after exercise, which may be attributed to the fibular tunnel syndrome [55, 56]. Often, the neurological examination in these patients is normal except for possible Tinel's sign at the fibular head.

Differential Diagnosis

The differential diagnosis of common fibular mononeuropathy at the fibular neck is similar to that of foot drop. Foot drop is defined as severe weakness of ankle dorsiflexion with intact plantar flexion and is a common presentation in neurological practice. It should be distinguished from a flail foot in which there is no or minimal ankle or foot movement in all directions, including severe weakness of ankle dorsiflexion, plantar flexion, and intrinsic foot muscles. In contrast to a flail foot, voluntary movement at or distal to the ankle occurs in foot drop due to intact plantar flexion and intrinsic foot muscles. Many patients with peripheral polyneuropathy, such as Charcot-Marie-Tooth disease, are often mislabeled as having bilateral foot drop, while careful examination reveals foot and ankle weakness in all direction, compatible with bilateral flail foot.

Unilateral foot drop may be due to an upper or lower motor neuron lesion (Table 41.2). Lower motor neuron lesions, causing unilateral foot drop and often confused with common or deep fibular mononeuropathy, include sciatic mononeuropathy (especially when affecting the common fibular nerve predominantly), lumbosacral plexopathy (particularly when involving the lumbosacral trunk lesion), or lumbar radiculopathy (particularly L5 radiculopathy and, less commonly, L4 radiculopathy). Table 41.3 reveals the useful diagnostic features of these disorders [62]. In general, radicular pain and positive straight leg test (Lasègue test) are common in L5 radiculopathy, may be present in sciatic nerve lesions, and are not seen in or plantar flexion, or absent/depressed ankle jerks are findings which are inconsistent with fibular nerve lesion. Establishing the diagnosis of fibular mononeuropathy may be based on clinical grounds in many cases, but often requires electrodiagnostic (EDX) studies for diagnostic as well as prognostic reasons (Table 41.4).

Bilateral fibular nerve palsies resulting in bilateral foot drop are more challenging to diagnose and much less common than unilateral cases [13, 14, 29, 61]. They often mimic generalized neuromuscular disorders such as peripheral polyneuropathies, myopathies, or motor neuron diseases (Table 41.5).

Table 41.2 Causes of unilateral foot drop

Deep fibular mononeuropathy
Common fibular mononeuropathy
Anterior compartmental syndrome of the leg
Sciatic mononeuropathy
Lumbosacral plexopathy[a]
L5 radiculopathy
L4 radiculopathy
Multifocal motor neuropathy
Amyotrophic lateral sclerosis
Poliomyelitis and postpoliomyelitis syndrome
Cortical or subcortical parasagittal cerebral lesion

[a]Particularly when the lumbosacral trunk is involved

Evaluation and Diagnosis

Electrodiagnostic Studies

The EDX studies in patients with foot drop and suspected fibular mononeuropathy are extremely useful. The evaluation is aided by the anatomy of the common fibular nerve and its branches which are accessible to multiple nerve conduction studies (NCSs) and to needle electromyography (EMG). The objectives of the EDX studies in evaluating such patients are the following:

1. To confirm that the foot drop is due to a common or deep fibular mononeuropathy and exclude other causes of foot drop such as L5 radiculopathy and sciatic mononeuropathy
2. To localize the site of the fibular nerve lesion (fibular neck, upper thigh, or selective deep branch)
3. To define the primary pathophysiological mechanism of injury (demyelinating versus axonal versus mixed)

Table 41.3 The differential diagnosis of common causes of foot drop: Clinical

	Fibular neuropathy at the fibular head	L5 radiculopathy	Lumbar plexopathy (lumbosacral trunk)	Sciatic neuropathy (mainly fibular)
Common causes	Compression (weight loss, perioperative), trauma, intraneural ganglion	Disc herniation, spinal stenosis	Pelvic surgery, hematoma, prolonged labor	Hip surgery, injection injury, coma
Ankle inversion	Normal	Weak	Weak	Normal or mildly weak
Toe flexion	Normal	Weak	Weak	Normal or mildly weak
Plantar flexion	Normal	Normal	Normal	Normal or mildly weak
Ankle Jerk	Normal	Normal (unless with S1)	Normal (unless with S1)	Normal or depressed
Sensory loss distribution	Fibular nerve distribution only	Poorly demarcated, predominantly big toe	Well demarcated to L5 dermatome	Fibular nerve distribution plus lateral cutaneous of calf and sole (tibial)
Pain	Rare, deep	Common, radicular	Common, can be radicular	Can be severe

Table 41.4 The differential diagnosis of common causes of foot drop: Electrodiagnosis

	Fibular neuropathy at the fibular head	L5 radiculopathy	Lumbar plexopathy (lumbosacral trunk)	Sciatic neuropathy (mainly or exclusively fibular)
Fibular motor study to EDB and/or Tib ant	Low amplitude or conduction block across fib head or both	Usually normal but can be low in amplitude	Low in amplitude	Low in amplitude
Superficial Fibular sensory study	Low or absent[a]	Normal	Low or absent	Low or absent
Sural sensory study	Normal	Normal	Normal or low amp	Normal or low amp
Fibular muscles[b]	Abnormal	Abnormal	Abnormal	Abnormal
Tibial L5 muscles[c]	Normal	Usually abnormal	Usually abnormal	Normal or abnormal
Other L5 muscles[d]	Normal	Normal or abnormal	Normal or abnormal	Normal
Biceps femoris (SH)	Normal	Usually normal	Usually normal	Abnormal
Paraspinal fibrillations	Absent	May be absent	Absent	Absent

Source: Adapted from Katirji [62]. With permission
[a]May be normal in purely demyelinating lesions or lesion of the deep fibular nerve only
[b]Below knee (tibialis anterior (Tib Ant), extensor digitorum longus, extensor digitorum brevis (EDB), extensor hallucis, ± peroneus longus), SH, short head
[c]Tibialis posterior and flexor digitorum longus
[d]Gluteus medius and tensor fascia lata

Table 41.5 Causes of bilateral causes of foot drop

Myopathies
Distal myopathies
Scapuloperoneal muscular dystrophy
Facioscapulohumeral muscular dystrophy
Myotonic dystrophy
Neuropathies
Multifocal motor neuropathy with conduction block
Chronic inflammatory demyelinating polyneuropathy
Bilateral fibular mononeuropathies
Bilateral sciatic mononeuropathies[a]
Bilateral lumbosacral plexopathies[a]
Radiculopathies
Bilateral L5 radiculopathies
Conus medullaris lesion
Anterior horn cell disorders
Amyotrophic lateral sclerosis
Poliomyelitis and the postpoliomyelitis syndrome
Cerebral lesions
Bilateral cortical or subcortical parasagittal lesions

[a]Extremely rare causes

4. To predict the prognosis and expected course of recovery
5. To assess the presence and extent of reinnervation (in axonal loss lesions)

Nerve Conduction Studies

Sensory and motor fibular NCS are essential in the EDX evaluation of patients with foot drop or suspected fibular mononeuropathy. These studies should include the following:

1. *Superficial fibular sensory NCS* is extremely important in assessing patients with foot drop or with suspected fibular mononeuropathy. The superficial fibular SNAP is easy to obtain and is not more technically demanding than the sural SNAP [63, 64]. The superficial fibular SNAP is evaluated in the leg, distal to the frequent site of common fibular nerve compression at the fibular neck. It is low in amplitude or absent when there is significant axonal loss, but remains normal in purely demyelinating common fibular nerve lesions at the fibular neck, in deep fibular mononeuropathies, and in L5 radiculopathies. Occasional patients with definite L5 radiculopathy may have low-amplitude or absent superficial fibular SNAP [65].
2. *Fibular motor NCS, recording the extensor digitorum brevis (EDB)*, is a commonly utilized motor NCS. It is routinely applied for the study of the integrity of the fibular nerve and its motor fibers during assessment of all patients subjected to an EDX evaluation of the lower extremity. In patients with suspected fibular mononeuropathies, particular attention should be made to the compound muscle action potential (CMAP) after stimulating the deep fibular nerve at the ankle and the common fibular nerve below the fibular neck and at the popliteal fossa.

   Fibular motor NCS, recording EDB, is easy to perform, familiar to all electromyographers, and has well-established normal values. Its major disadvantage is that the EDB muscle may be asymptomatically atrophic and chronically denervated in isolation, possibly due to local trauma or the use of tight shoes. This results in low-amplitude fibular CMAP recording EDB, which may erroneously suggest the presence of an axon-loss fibular nerve or an L5 root lesion. In these instances, the denervation is restricted to the EDB, and all other fibular nerve and L5-root-innervated muscles are normal.

   Partial innervation of the EDB by the accessory deep fibular nerve is a common anomaly, occurring in 19–28 % of the population (Figs. 41.3 and 41.5) [4, 7]. When present, the fibular motor CMAP is higher while stimulating the

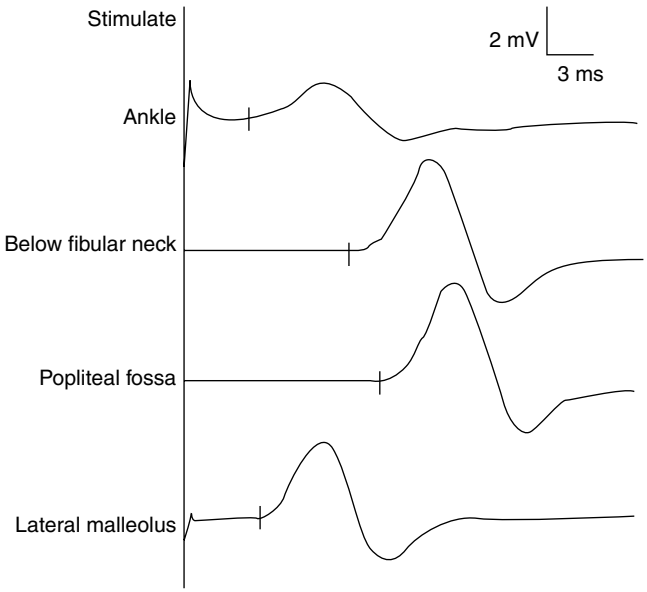

Fig. 41.5 Nerve conduction studies in the presence of an accessory deep fibular nerve (From Preston and Shapiro [394]. With permission)

knee compared to ankle stimulation. Stimulation of the accessory deep fibular nerve behind the lateral malleolus results in a CMAP, which accounts for most of the difference in fibular CMAP amplitudes with distal and proximal stimulation. Rarely, the EDB is totally innervated by the accessory deep fibular nerve, resulting in absent fibular CMAP, recording the EDB, following ankle stimulation [9–11]. To avoid a misdiagnosis of fibular mononeuropathy, a proximal stimulation of the fibular nerve at the knee should always be done, and if a motor response is recorded, then stimulation of the accessory deep fibular nerve behind the lateral malleolus should follow.

3. *Fibular motor NCS recording tibialis anterior* is extremely important in patients with foot drop and fibular mononeuropathy [13, 14, 66]. The tibialis anterior is the principal dorsiflexor of the ankle and is the most clinically relevant muscle in patients with foot drop. Evaluating the motor fibers destined to the tibialis anterior is far more pertinent than the EDB in predicting the outcome of foot drop in patients with fibular nerve lesions. Also, since the EDB is not uncommonly atrophic and denervated in isolation, low-amplitude CMAP, recording EDB, may erroneously suggest that the fibular lesion is axonal and severe. In fact, fascicular involvement of the common fibular nerve at the fibular neck is not uncommon [15]. This is sometimes manifested by low-amplitude or absent fibular CMAPs, recording EDB, and normal distal fibular CMAP, recording tibialis anterior, with a conduction block across the fibular neck. In these situations, the fibular motor NCS, recording tibialis anterior, helps establishing the extent of demyelination and axonal loss of motor fiber destined to this muscle. This assessment is extremely helpful prognostically, since conduction block due to segmental demyelination carries an excellent prognosis for recovery, while axonal lesions have a protracted course.

Table 41.6 Electrodiagnostic strategy in patients with foot drop or suspected fibular mononeuropathy

Nerve conduction studies
Bilaterally
Superficial fibular sensory studies
Fibular motor conduction studies recording EDB stimulating at the ankle, below the fibular head and behind the knee (lateral popliteal fossa)
Fibular motor conduction studies recording tibialis anterior below the fibular head and behind the knee (lateral popliteal fossa)
On the symptomatic side[a]
Sural sensory study
Tibial motor study
Needle EMG
At least two deep fibular-innervated muscles (tibialis anterior, extensor hallucis, extensor digitorum brevis, and longus)
At least one superficial fibular-innervated muscle (peroneus longus and brevis)
The short head of biceps femoris[b]
At least two L5-innervated muscles (e.g., tibialis posterior, flexor digitorum profundus, gluteus medius, or tensor fascia lata) and one L4-innervated muscle (e.g., vastus lateralis), preferably with the corresponding lumbar paraspinal muscles
At least one tibial-innervated muscle (e.g., medial head of gastrocnemius)

Source: Adapted from Katirji [13]. With permission
[a]These should be done bilaterally, if there is any suspicion of a proximal (high) fibular nerve lesion (sciatic neuropathy affecting the fibular nerve predominantly or exclusively)
[b]Mandatory in axon-loss fibular mononeuropathies

The fibular motor and sensory NCS should be performed bilaterally, for comparison and accurate estimation of distal fibular CMAPs and SNAPs (Table 41.6). The sural sensory and tibial motor NCS should be studied on the symptomatic side and bilaterally when there is a suspicion of a sciatic nerve lesion or a proximal (high) common fibular mononeuropathy. The tibial H-reflexes, done bilaterally, assess the integrity of the tibial component of the sciatic nerve.

Needle EMG

At least two deep fibular-innervated muscles (such as tibialis anterior and extensor hallucis longus) and one superficial fibular-innervated muscle (such as peroneus longus) should be sampled. In axon-loss common fibular mononeuropathies, which are unlocalizable by NCS, sampling the short head of biceps femoris is required to exclude a proximal common fibular lesion, i.e., a sciatic neuropathy affecting the fibular nerve predominantly or exclusively [44].

Sampling non-fibular muscles is also essential. This includes muscles innervated by the L5 root such as the tibialis

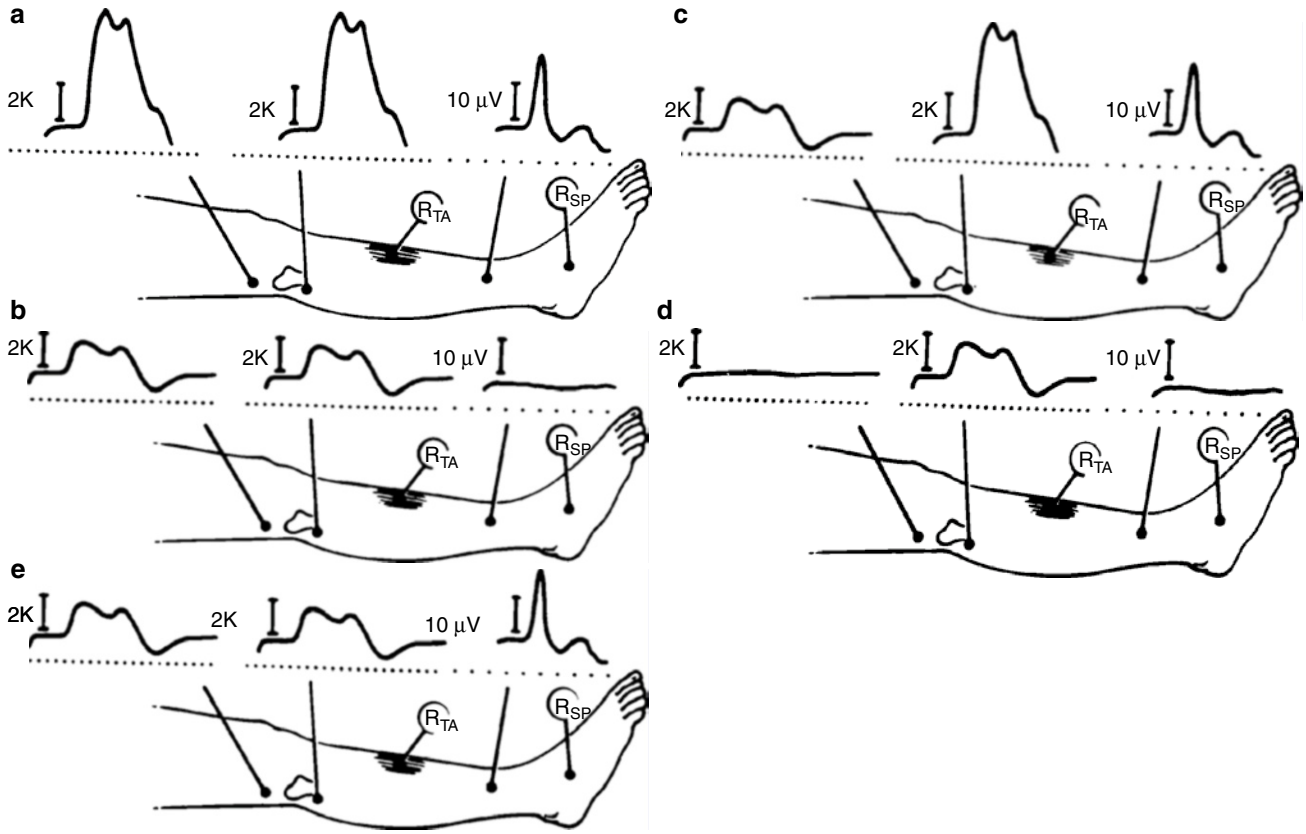

Fig. 41.6 Diagrams of the nerve conduction studies in fibular mononeuropathies (RTA, recording tibialis anterior CMAP; RSP, recording superficial fibular SNAP; proximal latencies are not shown to scale). (**a**) Normal, (**b**) partial "pure" axonal loss, (**c**) partial "pure" demyelinative conduction block, (**d**) mixed axonal loss and demyelinative conduction block, and (**e**) deep fibular axonal loss (From Katirji and Wilbourn [14]. With permission)

posterior, flexor digitorum longus, tensor fascia lata, or gluteus medius and the tibial nerve such as the medial gastrocnemius, flexor digitorum longus, tibialis posterior, and long head biceps femoris. These muscles are normal in common fibular nerve lesions, but abnormal in L5 radiculopathy or lumbosacral plexopathy.

Electrodiagnostic Findings in Fibular Mononeuropathies

The EDX findings in fibular mononeuropathies often conform to one of the following patterns (Fig. 41.6 and Table 41.7) [12–15, 61]:

1. *Demyelinative common fibular nerve lesions across the fibular neck* constitute about 20–30 % of all fibular mononeuropathies. In patients with weight loss or prolonged abnormal posture (such as squatting), 50–70 % have purely demyelinative conduction blocks. These lesions present, solely, with partial or complete conduction block across the fibular neck. On NCS, the distal fibular CMAPs (recording EDB and tibialis anterior) and superficial fibular SNAP are normal. However, there is a significant (>20–50 %) drop in CMAP amplitude and/or area, consistent with conduction block across the fibular neck (Fig. 41.6c). The primary pathology of these common fibular nerve lesions is segmental demyelination, which carries excellent prognosis with expected recovery in 2 to 3 months provided the cause of compression is eliminated. Care should be taken into account for the time required for Wallerian degeneration, since "axonal conduction block" may occur when NCSs are performed less than 10 days following the onset of acute axonal lesions (see below).

   In contrast to the carpal tunnel syndrome and ulnar mononeuropathy across the elbow, isolated focal slowing across the fibular neck is not a common feature of fibular mononeuropathy, seen in less than 5 % of the cases [13, 14, 61]. When present it is almost always associated with a localized conduction block. It is also occasionally encountered in patients recovering from fibular nerve lesions across the fibular neck.
2. *Axon-loss fibular nerve lesions* are characterized by low-amplitude or absent distal and proximal fibular CMAPs, recording EDB and tibialis anterior. The fibular motor conduction velocities are normal in mild and moderate lesions, but may be slightly reduced diffusely, without focal slowing, in severe lesion. In general, complete axon-loss fibular nerve injuries are slow to improve since they

Table 41.7 Electrophysiological patterns of fibular mononeuropathies

Pattern	Site of lesion	Frequency	Superficial fibular SNAP	Distal fibular CMAPs[c]	Conduction block at fibular head	Focal slowing across the fibular head	Needle EMG of peroneus longus	Needle EMG of biceps femoris (short head)	Prognosis for recovery
Conduction block	Fibular head	20–30 %	Normal	Normal	Present	Rare	Abnormal	Normal	Excellent
Axonal loss	Mid-thigh and fibular head[a]	15–20 %	Usually absent	Low amplitude or absent	Absent	Absent	Abnormal	Normal	Protracted
	Deep fibular	5–8 %	Normal	Low amplitude or absent	Absent	Absent	Normal	Normal	Fair
	Proximal[b]	<5 %	Usually absent	Low amplitude or absent	Absent	Absent	Abnormal	Abnormal	Very poor
Mixed	Fibular head	30–40 %	Low amplitude or absent	Low amplitude	Present	Rare	Abnormal	Normal	Biphasic

Source: Adapted with revisions from Katirji [13]. With permission
[a]Usually around the fibular head
[b]High, proximal to the gluteal fold
[c]Recoding tibialis anterior and EDB

are dependent on proximal to distal reinnervation, while partial lesions recover faster due to sprouting.

Axon-loss fibular lesions are poorly localized by NCS and often require a detailed needle EMG for better characterization. Based on location, they may be subdivided into three types:

a. *Axon-loss common fibular nerve lesions* constitute about 15–20 % of all fibular mononeuropathies. In contrast, axon-loss lesions constitute about 60 % of patients with fibular nerve lesions due to local trauma [61]. Pure axon-loss lesions are not easily localized by EDX studies due to the absence of focal slowing or conduction block. Though they are often labeled by EDX studies as located between mid-thigh and fibular neck or at/proximal to fibular neck, most of these lesions are actually at the fibular neck, as often supported by the clinical history (such as following knee surgery, fracture, laceration). These lesions are characterized by axon-loss pattern on motor NCS (i.e., low-amplitude or absent fibular CMAPs recording EDB and tibialis anterior) with low-amplitude or absent superficial fibular SNAP (Fig. 41.6b). On needle EMG, there are often fibrillation potentials and decreased number of rapidly firing MUAPS in all common fibular-innervated muscles below the knee with normal short head of biceps femoris. Sensory NCS of the lateral cutaneous nerve of the calf is a promising, yet not proven, study which may help better in localizing these lesions distal to the popliteal fossa [67].

b. *Axon-loss common fibular nerve lesions located proximal to the gluteal fold* share the same NCS abnormalities as distal axon-loss common fibular mononeuropathies (Fig. 41.6b). However, these lesions are associated with denervation of the short head of biceps femoris. They have very poor prognosis, but are, fortunately, extremely rare accounting for less than 5 % of all fibular mononeuropathies [14, 68].

Selective proximal common fibular mononeuropathies in the upper thigh are essentially sciatic nerve lesions affecting the common fibular nerve exclusively. More typically, sciatic nerve lesions are associated with tibial nerve injury. This usually results in low-amplitude or absent sural SNAP, delayed or absent H-reflex, or mild denervation in the tibial-innervated muscles (such as the medial gastrocnemius, flexor digitorum longus, tibialis posterior, or abductor hallucis).

c. *Axon-loss proximal deep fibular nerve lesions* are less frequent than common fibular mononeuropathies and constitute about 5–8 % of all fibular nerve lesions [13, 14, 61]. However, these isolated deep fibular nerve lesions constitute about 1/3 of all the traumatic cases [61] and are the typical lesions seen with intraneural fibular ganglia [50, 51]. The distal fibular CMAPs, recording EDB and tibialis anterior, are low in amplitude and/or area with normal superficial fibular SNAP (Fig. 41.6e). The fibular motor conduction velocities are often normal but may be minimally and diffusely reduced without focal slowing. The superficial fibular SNAP and needle EMG of peroneus longus and brevis are normal. Since this NCS pattern is identical to that of moderate or severe L5 radiculopathy, needle EMG of other L5-innervated muscles helps to distinguish a deep fibular nerve lesion from an L5 radiculopathy. Tested muscles should include muscles innervated by the L5 root via the tibial nerve (flexor digitorum longus or tibialis posterior) and the gluteal nerves (tensor fascia lata, gluteus medius, or gluteus maximus), as well as the lumbar paraspinal muscles.

3. *Mixed common fibular nerve lesions (demyelinative across the fibular neck with axon loss)* are common and constitute 30–40 % of all fibular nerve lesions at the fibular neck. They are characterized by a low amplitude and/or area of the distal fibular CMAPs, recording EDB and/or tibialis anterior, with partial or complete conduction block across the fibular neck (Fig. 41.6d). The superficial fibular SNAP is low in amplitude or absent. The findings often reflect a fascicular nerve injury with different pathophysiological processes involving fibers directed to the EDB versus tibialis anterior [14, 15, 67]. For example, it is not uncommon to find conduction block across the fibular neck (consistent with segmental demyelination) while recording the tibialis anterior and low-amplitude distal and proximal fibular CMAPs (consistent with axonal loss) while recording the EDB. Fibular motor conduction velocities are usually normal, and, rarely, there is an accompanying focal slowing. Recovery of the neurological deficit in these cases is usually biphasic; the first phase is due to remyelination and is relatively rapid occurring over 6–8 weeks, while the second phase is due to reinnervation and sprouting and is more protracted extending into months or years.

Clinico-Electrodiagnostic Correlations in Fibular Mononeuropathies

When assessing mononeuropathies in general, the distal CMAP amplitude is the best quantitative parameter in the evaluation of the presence and extent of axonal loss. This applies also to fibular mononeuropathy, where low-amplitude distal CMAPs are the best evidence for the presence of motor axonal loss. Though a low or absent superficial fibular SNAP indicates sensory axonal loss, this rarely results in disability. Hence, axon-loss and mixed fibular mononeuropathies should be restricted to lesions with low-amplitude distal fibular CMAPs. These nerve injuries are often associated with protracted improvement.

In contrast to the distal CMAP amplitudes, fibrillation potentials, which are sensitive evidence of recent motor axonal loss, are poor quantitative measures of the extent of

motor axonal loss. In fibular nerve lesions, fibrillation potentials are detected in all cases regardless of the primary pathophysiological process, provided the needle EMG is done at least three weeks after the onset of foot drop [14]. In fact, fibrillation potentials are seen in "purely" demyelinating fibular nerve lesions, manifesting with conduction block and normal distal fibular CMAPs. This finding is best explained by the loss of few "clinically irrelevant" motor axons in the midst of significant demyelination. Patients with fibular nerve lesions, normal distal fibular CMAPs, and "purely" demyelinating conduction blocks recover quickly, despite the presence or absence of fibrillation potentials.

Based on a strict criterion of low-amplitude distal fibular CMAP, a clinically significant axonal loss is present in about 70–80 % of all cases of fibular mononeuropathies [13, 14, 57, 61]. This includes cases of pure axon-loss as well as mixed lesions and occurs independent of its mode of onset (i.e., in acute, subacute, or undetermined onset lesions). In fibular nerve lesions due to trauma, about 60 % of cases have exclusive axonal damage [61]. In patients with weight loss or prolonged hospitalization/bedridden, conduction block is present in 50–70 % of the cases [61]. In perioperative cases or fibular nerve lesions caused by iatrogenic compression (such as casting), the fibular nerve lesions are equally divided between pure demyelination (conduction block) and mixed damage [14, 61]. This finding is in contrast to the common belief that acute perioperative compressive fibular lesions are due to neurapraxia (i.e., segmental demyelination) and should recover rapidly.

Timing of Electrodiagnostic Studies in Fibular Mononeuropathies

Sequential EDX studies are often indicated in patients with acute fibular mononeuropathies. In acute fibular nerve lesions at the fibular neck, examined within few days of the onset of foot drop, it is often possible to localize the lesion by demonstrating a conduction block pattern. However, this is not always consistent with segmental demyelination, since the distal axons are excitable after an axon-loss fibular nerve lesion until Wallerian degeneration is completed 7–11 days later. Serial NCS of axon-loss fibular mononeuropathy reveals that the distal CMAP decreases steadily to reach their nadir in 5–6 days and the SNAP in 10–11 days following the injury (Fig. 41.7) [62, 69]. Thus, a repeat NCS, after 10–11 days from the onset of an acute fibular nerve lesion, is often necessary to establish the primary pathology and prognosis. If conduction block persists, then the fibular lesion is demyelinating and has a relatively good prognosis. However, in axonal loss lesions, the distal fibular CMAPs decrease, to reach values very similar to the proximal CMAPs, and the superficial fibular SNAP, studied distal to the lesion, is often low in amplitude or absent. In mixed lesions, a combination of the above findings occurs (see Fig. 41.6).

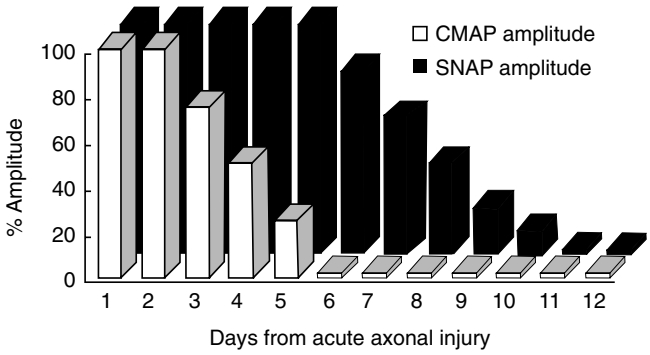

Fig. 41.7 Distal sensory nerve action potentials (SNAP) and compound muscle action potential (CMAP) after acute axonal nerve injury (From Katirji [62]. With permission)

Conduction block across the fibular neck detected in the early days of foot drop is extremely helpful in localization, particularly in closed nerve injury or compression, where the exact site of lesion is not clear based on clinical grounds. This explains the importance of obtaining NCS in the first few days of symptoms though these findings are not useful prognostically. If the lesion is due to axonal loss and the NCSs are performed after the completion of Wallerian degeneration (i.e., after 7–11 days), finding low or absent distal and proximal fibular CMAPs does not allow a precise localization of the injury site. In these cases, needle EMG often assists in localizing the lesion to a nerve segment rather than to a well-defined point along the nerve. In acute fibular nerve lesions, fibrillation potentials appear in affected muscles at about the second week first in proximally situated muscles, such as tibialis anterior and peroneus longus, and then more distally, such as extensor hallucis longus and extensor digitorum brevis. Fibrillation potentials become widespread in all denervated muscles after three weeks, and they are most profuse at about 4–6 weeks after axonal injury. They will ultimately decrease due to either reinnervation or fatty degeneration of muscle fibers.

In complete axon-loss fibular lesion, follow-up EDX studies are often necessary in attempt to detect evidence of early reinnervation, even before it becomes evident clinically. In these cases, the early signs of reinnervation often manifest by recording nascent MUAPs, which are rapid firing, low amplitude, short duration, and polyphasic in morphology. Also, sequential EDX studies are often necessary following surgical interventions such as neurolysis or nerve repair [69, 70].

Imaging Studies

Imaging studies are increasing utilized in the diagnosis of the causes of fibular nerve lesions around the fibular neck. Plain X-rays may be useful in revealing bony abnormalities, bony tumors, and dislocations. Ultrasonography of the popliteal fossa or fibular neck region may help identifying cystic lesions such as Baker's cysts, intraneural ganglion cysts, or

aneurysms [50, 71, 72]. MRI is effective in visualizing soft tissue masses, cysts, intraneural ganglia, or intrinsic nerve tumors [50, 73–75]. Intraneural ganglia were detected by ultrasound in 5 of 28 (18 %) consecutive fibular nerve lesions and by MRI in 6 of 10 (60 %) consecutive patients with non-traumatic fibular nerve lesions [72, 74].

Treatment, Management, and Prognosis

Fibular nerve injury may result in significant disability mostly due to foot drop, which may not recover completely or in a timely manner, particularly when axonal loss is severe. Ankle-foot orthosis (AFO), to improve gait and prevent ankle contractures and sprains, is indicated when the foot drop is profound, axonal, or expected to have a protracted course [76]. Active foot exercises and passive range of movements are useful. Patients with significant weight loss should be warned about leg crossing and should wear protective knee pads, properly placed over the fibular head and neck to prevent recurrent external compression.

Patients with axon-loss fibular nerve lesions around the fibular neck should be observed for 4 to 6 months to allow for improvement by spontaneous reinnervation [70]. Restoration of ankle dorsiflexion is a realistic goal for those with severe axon-loss fibular nerve injuries. In contrast to proximal axon-loss peripheral nerve lesions (such as brachial plexopathies and sciatic mononeuropathies), fibular nerve lesions around the fibular neck reinnervate relatively quick since the lesion site (fibular neck) is not far removed from the main target muscle (i.e., tibialis anterior). In general, partial lesions recover faster due to sprouting, while complete lesions reinnervate only by proximal to distal axonal growth only, which usually proceeds at a rate of 1 mm/day. Severe lesions often require sequential EDX examination to look for early evidence of reinnervation and follow its progression. Needle EMG of the tibialis anterior and/or peroneus longus may reveal fast-firing, low-amplitude, short-duration, and polyphasic MUAPs ("nascent" MUAPs) as the first sign of reinnervation.

Surgical intervention on the fibular nerve is appropriate in certain situations with relatively good outcome [53, 70, 77, 78]:

1. When the nerve is lacerated and visibly discontinuous. This repair could be done, usually by end-to-end anastomosis, at the time of laceration suturing (primary repair) or at a later date if local infection is feared (secondary repair).
2. In severe axonal lesions, particularly those associated with closed or open trauma, when there is no clinical or EMG evidence for reinnervation in the tibialis anterior or peroneus longus despite four to six months from injury. Intraoperative EDX evaluation is useful for optimal results [53, 70, 77]. Neurolysis, nerve cable grafting, or end-to-end repair, done in a timely fashion, often results in satisfactory outcome [53, 70, 77].
3. In slowly progressive fibular neuropathies, when a mass lesion, nerve tumor, synovial cyst, or intraneural ganglion is suspected. In these patients, preoperative EDX studies combined with MRI may delineate the nature of the lesion and guide the surgical procedure.
4. Rarely, in patients with chronic persistent conduction block, or in athletes with possible "fibular tunnel syndrome" who do not respond to conservative therapy, fibular nerve exploration, and neurolysis, might be of help.
5. Patients with leprous fibular neuritis may respond to neurolysis of the thickened epineurium in the popliteal fossa and near the fibular neck [79]. Pain is often relieved while the foot drop may not respond.

Apart from nerve lacerations or gunshot injuries, which usually results in axonal injury, clinical assessment often cannot predict the prognosis in common fibular mononeuropathy. For example, patients with acute perioperative compressive nerve lesions at the fibular neck, which were traditionally considered benign, have a high likelihood of harboring axon loss which carries relatively poor prognosis [13, 14]. The EDX evaluation is essential in the planning of management and prognostication of fibular nerve lesions. It distinguishes lesions with a predominant segmental demyelination from those with extensive axonal loss. Compressive fibular neuropathies at the fibular neck due to demyelinative conduction block often have good prognosis with spontaneous recovery in 2 to 3 months as long as further compression is prevented. However, the prognosis of axon-loss fibular lesions is less promising and variable since it is dependent on its extent (partial or complete) and the degree of disruption of supporting nerve elements (i.e., endoneurium, perineurium, and epineurium) [1]. In general, gunshot and stretch injuries, and proximal (high) fibular nerve lesions carry a grave prognosis. In a longitudinal prospective study of fibular nerve lesions, greater muscle strength of tibialis anterior and higher fibular nerve conduction velocity at baseline were seen to be good prognostic factors in patients who were treated conservatively with no surgical intervention [12, 61, 73].

Deep Peroneal Mononeuropathy at the Fibular Neck

Etiology and Pathogenesis

Although fibular nerve lesions at the fibular neck often affect the deep fibular nerve predominantly, occasionally the deep fibular nerve is selectively injured [10]. In general, causes of deep fibular mononeuropathies at the fibular neck are the same as those leading to common fibular nerve lesions at the fibular neck (see above). However, certain causes have a predilection to the deep fibular nerve. These include intraneural

ganglion cysts [50, 51, 72], inversion ankle sprains of the foot [46, 80], osteochondromas [52], and following arthroscopic knee surgery [42].

Clinical Manifestations

Selective deep fibular mononeuropathies near the fibular neck are much less frequent than common fibular mononeuropathies, constituting about 5–8 % of all fibular nerve lesions [13, 14, 61]. However, these isolated deep fibular nerve lesions constitute about 1/3 of the traumatic cases [61]. They result in foot drop, but the weakness is restricted to foot dorsiflexion and toe extension, while ankle eversion remains normal. Also, the sensory manifestations are absent or minimal and limited to the first web space on the dorsum of the foot. Occasionally, the deep fibular lesion is more distal in the leg (such as with traction injury associated with ankle sprain), resulting in selective weakness of toe extension with normal foot dorsiflexion.

Differential Diagnosis

An L5 radiculopathy may mimic a deep fibular nerve lesion at the fibular head, since both entities may cause foot dorsiflexion weakness. However, as with a common fibular lesion, ankle inversion, toe flexion and hip abduction are normal in deep fibular mononeuropathy while often weak in L5 radiculopathy.

The anterior compartmental syndrome of the leg may be confused with a selective deep fibular mononeuropathy. By definition, compartmental syndrome is a state of emergency in which increase pressure within a limited space (compartment) in a limb compromises the perfusion, circulation, and function of the contents of that space [81]. Anterior compartmental syndrome of the leg occurs mainly following limb trauma (crush, contusion, fractures) or spontaneous bleeding into the compartment, but it may follow strenuous exercise such as running. The anterior compartment of the leg contains the deep fibular nerve and all its innervated muscles (tibialis anterior, extensor hallucis longus, and extensor digitorum longus) except the extensor digitorum brevis (EDB) which lies outside (distal) to the compartment.

Anterior compartmental syndrome of the leg is the most common compartmental syndrome in the lower extremity (see Chap. 37). Ischemia or necrosis of compartmental muscles results in weakness of foot and toe dorsiflexion. If there is concomitant deep fibular nerve ischemia, the EDB becomes weak and denervated, sometimes with hypesthesia in the distribution of the deep fibular nerve (the dorsal first web space). In these situations, anterior compartmental syndrome of the leg may be difficult to distinguish from a primary deep fibular nerve lesion, particularly when associated with trauma (such fibular fracture). However, characteristic findings of anterior compartmental syndrome of the leg, not present in primary deep fibular mononeuropathy, include the following [81]:

- Limb pain, often severe and out of proportion to what is anticipated from the clinical situation (such a tibial fracture). This may peak after a time interval from the primary etiological event (usually 1 to 3 days).
- Pain on flexion of toes and plantar flexion of ankle, which lead to stretch of the anterior compartmental muscles of the leg.
- Tenseness of the anterior compartmental fascia and, occasionally, focal herniation of muscle into the subcutaneous tissue.

The diagnosis of anterior compartmental syndrome of the leg requires a high degree of suspicion in patients at risk (i.e., trauma, fracture, crush, etc.). When suspected, tissue pressure measurement is of a great value in confirming the diagnosis. A tissue pressure above 60 mm Hg is diagnostic, although muscle and nerve tolerance to ischemia may be reduced by additional factors such as arterial occlusion, limb elevation, or hypotension.

Evaluation and Diagnosis

The EDX studies recommended in patients with suspected deep fibular mononeuropathy are similar to those required for patients with foot drop or common fibular mononeuropathy (see Table 41.6). The findings are generally compatible with an axon-loss or mixed proximal deep fibular lesion near the fibular neck. In pure axon-loss lesions, not associated with conduction block across the fibular neck, the NCS imitates a moderate or severe L5 radiculopathy: the fibular CMAPs, recording EDB and tibialis anterior, are low in amplitude with normal superficial fibular SNAP (Fig. 41.6e). In severe and complete axon-loss lesions, the fibular CMAP recording EDB is absent; however, the fibular CMAP recording tibialis anterior is low in amplitude but always recordable due to volume conduction from the normal neighboring peroneus muscles which remain intact. In partial axon-loss lesions, the fibular motor conduction velocities are often normal but may be minimally decreased without focal slowing. Needle EMG of peroneus longus and brevis is normal, while all deep fibular-innervated muscles reveal neurogenic changes. Also, needle EMG of other L5-innervated muscles (flexor digitorum longus, tibialis posterior, tensor fascia lata, gluteus medius, or gluteus maximus) is normal and helps to distinguish a deep fibular nerve lesion from an L5 radiculopathy.

The EDX studies are of little diagnostic value in the acute evaluation of the anterior compartmental syndrome of the leg. Often, they are performed after the acute phase to confirm or estimate the extent of injury. The superficial fibular SNAP and needle EMG of the peroneus longus and brevis are usually normal. On motor NCS, the fibular CMAP recording tibialis anterior is often absent or low in amplitude early in the illness due to muscle ischemia and necrosis. In contrast, stimulation of the fibular nerve at the ankle,

below the fibular neck, and behind the knee, recording EDB, results in normal CMAP when ischemia is restricted to muscles of the anterior compartment of the leg. This combination (normal CMAP recording EDB with absent or very low-amplitude CMAP recording tibialis anterior) is characteristic for the anterior compartment syndrome of the leg and uncommon in patients with common or deep fibular mononeuropathies [13–15]. However, when the compartmental syndrome is accompanied by deep fibular nerve ischemia (and equally in primary axon-loss deep fibular nerve lesions), the fibular CMAPs, recording EDB and tibialis anterior, are equally low in amplitude or absent following distal and proximal nerve stimulations.

Needle EMG of the anterior compartment muscles (all deep fibular-innervated muscles) reveals decreased insertional activity and no or very few MUAPs due to muscle fiber degeneration. In contrast, the EDB either is normal or shows fibrillations with no or few MUAPs, depending on whether the deep fibular nerve is intact or affected.

Treatment, Management, and Prognosis

The treatment of deep fibular nerve lesions at the fibular neck is similar to that of common fibular mononeuropathy (see above). In the anterior compartmental syndrome, a high index of suspicion, rapid diagnosis, and surgical intervention (fasciotomy) is warranted [81]. When treatment is delayed, severe muscle necrosis and permanent limb contractures occur resulting in severe disability.

Common Fibular Mononeuropathy at the Hip (Sciatic Mononeuropathy Affecting the Fibular Division Selectively)

Etiology and Pathogenesis

Partial lesions of the sciatic nerve at the hip usually affect the lateral division (fibular division) more than the adjacent medial division (tibial division) [1]. On rare occasions, the common fibular nerve is the only nerve injured leaving the tibial nerve completely intact [68]. As outlined earlier, though these two nerves form the sciatic nerve and share a common sheath, they are separate from the outset and do not exchange fascicles.

The greater vulnerability of the fibular division of the sciatic nerve to physical injury occurs with a variety of causes of sciatic nerve lesions including hip trauma, hip joint replacement, and gluteal injection. This is related to two reasons [1]:

1. The difference in the fascicular pattern of the perineurium among these two nerves in the upper thigh: the fibular nerve has fewer and larger fascicles with limited supportive tissue, while the tibial nerve is composed of many cushioning fascicles, well placed between the elastic epineurial tissues. This renders the fibular division of the sciatic nerve more susceptible to external pressure.
2. The anatomical course of the common fibular and tibial nerves: the fibular nerve is taut and secured at the sciatic notch and fibular neck, while the tibial nerve is loosely fixed posteriorly. Hence, traction of the sciatic nerve in the upper thigh (such as during total hip replacement) results in more extensive stretch injury to the fibular nerve than the tibial nerve.

Causes of high common fibular mononeuropathies are similar to sciatic nerve lesions in general (see below, the sciatic nerve) [68, 82–84]. This includes total hip replacement, hip fracture or dislocation, femoral fracture, gluteal injection, gluteal compartment syndrome, gunshot or knife wound, and acute compression during coma, drug overdose, prolonged sitting, or intensive care unit hospitalization (see below).

Clinical Presentation

High common fibular lesions manifest with findings similar to common fibular mononeuropathies at the fibular neck. However, these lesions are sometimes accompanied by subtle manifestations of tibial nerve involvement such as severe foot pain, absent/depressed ankle jerk, weak ankle inversion, or sensory loss in the sole.

Differential Diagnosis

A proximal (high) common fibular mononeuropathy often presents a diagnostic challenge since it imitates a common fibular nerve compression at the fibular neck. Although the clinical history is useful (such as following a gluteal injection or gunshot wound), it may be also misleading. For example, following a total hip replacement, a foot drop may be due to an iatrogenic sciatic nerve lesion (affecting mainly the fibular nerve) or a fibular nerve compression at the fibular neck due to leg malpositioning during anesthesia.

Perhaps, the best clinical way to establish that a common fibular lesion is proximal is by looking for subtle signs of tibial nerve involvement, such as weak ankle inversion, sensory loss in the sole, or absent/depressed ankle jerk. These findings are inconsistent with a common fibular mononeuropathy at the fibular neck. Despite this, distinguishing patients with axon-loss sciatic nerve lesions affecting exclusively the fibular component (i.e., proximal or high common fibular mononeuropathy) from a distal axon-loss common fibular mononeuropathy at the fibular neck remains clinically difficult (see Tables 41.3 and 41.4) [68]. The only useful clinical sign is detecting sensory loss in the upper lateral third of the leg, corresponding to the territory of the lateral cutaneous nerve of the calf, which originates from the common fibular nerve proximal to the fibular head (see Fig. 41.1). In practical terms, these lesions are only diagnosed accurately after a detailed EDX testing.

Evaluation and Diagnosis

When the tibial component of the sciatic nerve is slightly involved, the EDX study reveals additional findings, such as asymmetrically low (or sometimes absent) sural SNAP amplitude, borderline or low tibial CMAP amplitude, asymmetrically abnormal H-reflex, or minimal neurogenic changes in tibial-innervated muscles (such as gastrocnemius, tibialis posterior, or flexor digitorum longus).

The NCSs in proximal (high) common fibular nerve lesion are identical to an axon-loss common fibular mononeuropathy and do not distinguish it from a distal lesion at the fibular neck. However, needle EMG of the short head of biceps femoris, the only hamstring muscle innervated by the common fibular nerve, reveals signs of denervation. This muscle cannot be evaluated satisfactorily in isolation on manual muscle testing nor palpated during such testing because of its location deep to the long head. Its function is often concealed by the other more powerful tibial-innervated hamstring muscles (semitendinosus, semimembranosus, and long head of biceps femoris). However, the short head of biceps femoris is easily accessible to needle EMG. As a rule, this muscle should be sampled in all patients presenting with a foot drop, but in particular in patients with axon-loss common fibular mononeuropathies, where accurate localization is often dependent on this muscle.

Treatment, Management, and Prognosis

The treatment of a patient with high proximal fibular mononeuropathy is similar to patients with sciatic nerve lesions. Most lesions are managed conservatively with ankle-foot orthosis, pain management, and physical therapy. Rarely, severe lesions may be treated surgically, but the outcome of these patients is often poor.

Deep Fibular Mononeuropathy at the Ankle (Anterior Tarsal Tunnel Syndrome)

Etiology

Lesion of the distal segment of the deep fibular nerve on the dorsum of the ankle is sometimes referred to as the anterior tarsal tunnel syndrome, a term coined by Marinacci in 1968 [85]. However, the anterior tarsal tunnel is not a true anatomic tunnel, in contrast to the carpal tunnel or medial tarsal tunnel. Its floor is the fascia overlying the talus and navicular, and its roof is the inferior extensor retinaculum (Fig. 41.8).

Causes of the anterior tunnel syndrome include direct contusion to the dorsum of the ankle, chronic pressure from shoe rims or straps, ganglion cyst, pes cavus, talonavicular osteophyte, or fractures, dislocations, or sprains of the ankle [86–90]. Unusual positioning of the foot, such as with marked foot plantar flexion accompanied by dorsiflexion of the toes (e.g., with wearing high-heeled shoes) or extreme inversion of the foot (e.g., with spasticity or dystonia), is also associated with this syndrome [88].

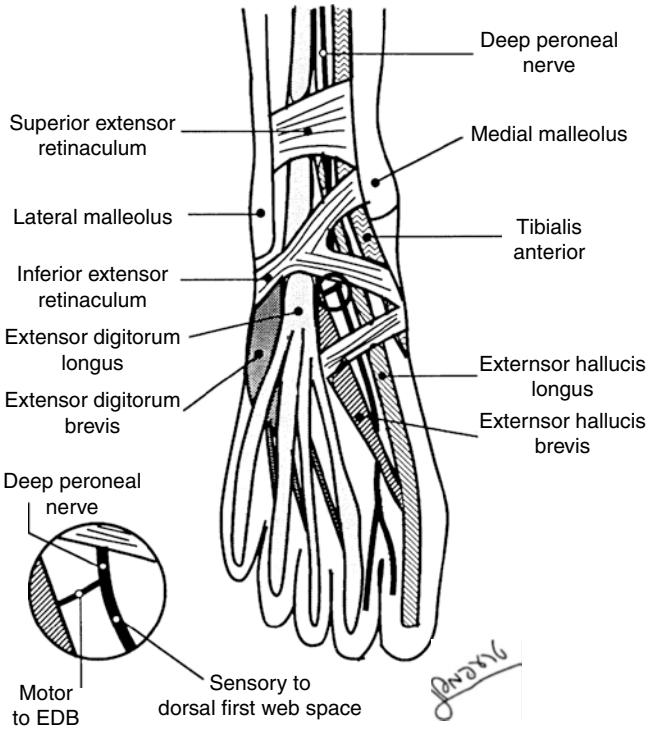

Fig. 41.8 Anatomy of the deep fibular nerve at the ankle and foot (dorsal view of ankle and foot) (From Dawson et al. [395]. With permission)

Clinical Presentation

The anterior tarsal tunnel syndrome is often asymptomatic, detected incidentally during EDX testing of the lower limbs for other symptoms such as lumbosacral radiculopathies. This has raised many questions as to the true existence of this entity.

In the symptomatic patients, the syndrome is slightly more common in women, probably related to the use of high-heeled shoes. It may be unilateral or bilateral. There is often numbness and paresthesias limited to the web space between the first and second toes. Ankle and foot pain, worse at night, are common, while foot weakness is not part of the syndrome. On examination, there is diminished sensation in the web space between the first and second toes (i.e., in the region innervated by the terminal portion of the deep fibular nerve) as well as wasting of the EDB muscle. In almost all the patients, the findings are sensory and motor since the bifurcation of the deep peroneal nerve into its medial terminal sensory branch (to the first web) and lateral terminal motor branch (to the EDB muscle) occurs underneath the extensor retinaculum in the majority of patients [91]. In contrast to EDB atrophy, weakness of the EDB is difficult to

assess due to the more powerful other toe dorsiflexors, i.e., the extensor hallucis longus and extensor digitorum longus. At times, a Tinel's sign over the deep fibular nerve at the ankle may be elicited.

Evaluation and Diagnosis

The EDX findings in the anterior tarsal tunnel syndrome are limited to prolongation of fibular motor distal latency recording EDB, with a normal proximal conduction velocity, and long-duration, high-amplitude, and polyphasic MUAP changes, usually with fibrillation potentials, in the EDB muscle [86, 87]. The fibular CMAP recording EDB is often low in amplitude, while the CMAP recording tibialis anterior and the superficial fibular SNAP are always normal. Similarly, needle EMG of common fibular- and L5- or S1-innervated muscles is normal. The findings may be unilateral or bilateral.

In asymptomatic patients, it may be difficult to separate the above findings from the common occurrence of denervation of the EDB, with or without slowing of fibular motor distal latency [87]. It is advised that the diagnosis of anterior tarsal tunnel syndrome be reserved to patient with typical clinical manifestations and EDX findings.

Treatment

Shoe modifications, avoiding high-heel or tight shoes, and correcting ankle malposition (e.g., by bracing) are often helpful. Corticosteroid injections are also useful [89]. Occasionally, surgical exploration may be necessary to remove a ganglion cyst or an osteophyte, or to simply divide the extensor retinaculum [88–90].

Superficial Fibular Mononeuropathy

Etiology

It is extremely rare for fibular nerve lesions at the fibular neck to affect the superficial fibular nerve only, without greater damage to the deep fibular nerve [13–15]. Superficial fibular mononeuropathies are usually due to nerve entrapment in the distal leg or ankle. The sites of these lesions are located distal to the motor branches to the peroneus longus and brevis; the symptoms are purely sensory including pain. A common site of entrapment is at the facial defect, 10 cm above the lateral malleolus, where the nerve becomes superficial. Most reported cases have been in athletes, and common precipitating events include long marches, tight boots, or direct blunt trauma [92–94]. Rarely, tumors such as lipomas or neuromas, or herniation of muscle through the facial defect may entrap the superficial fibular nerve. Near the ankle, superficial fibular nerve injuries may be due to tight shoes or ski boots, neuromas, acute contusions of the nerve, or iatrogenic (such as during ankle arthroscopy or needle insertion) [4, 92, 95–97].

Clinical Presentation

Lesions to the superficial fibular nerve in the distal leg are uncommon. They manifest with sensory loss in the lower lateral third of the leg and dorsum of foot, excluding the first web space. Pain in the distal anterolateral leg is common. Both numbness and pain may be worse with walking or running. Tenderness of the leg or swelling or both may be evident. Occasionally, Tinel's sign may be induced there.

Ankle pain with or without numbness over the dorsum of the foot is the only manifestation of superficial fibular lesions at the ankle. The pain is variable and may be present at rest or with exercise. Symptoms may worsen with ankle plantar flexion or inversion. Tinel's sign may be present.

Evaluation and Diagnosis

The EDX studies in patients with superficial fibular mononeuropathy in the distal leg often reveal an absent or low-amplitude superficial fibular SNAP, with or without a delay in its distal latency [93]. In contrast, fibular motor NCS and needle EMG of all fibular-innervated muscles, including the peroneus longus and brevis, are normal.

With ankle lesions, the SNAP abnormalities are less consistent, partially since most superficial fibular sensory nerve techniques are performed proximal to these lesions, with stimulation in the distal leg and recording at the ankle [63, 64].

Plain foot X-rays or MRI may reveal the potential causes such as mass lesion, osteophyte formation, or bony deformity. A diagnostic nerve block is also useful in confirming the source of symptoms.

Treatment, Management, and Prognosis

Distal leg and ankle lesions of the superficial fibular nerve may respond to change of foot wear, use of a removable cast boot, or night splinting in neutral position. Nonsteroidal anti-inflammatory agents or local corticosteroid injection may be helpful. Nonresponders may require surgical exploration with fasciotomy, neurolysis, or both.

Many patients with superficial fibular sensory mononeuropathy have persistent chronic foot pain and causalgia [93, 94]. Ankle lesions are particularly notorious in resisting treatment and resulting in chronic pain and disability.

The Sciatic Nerve

Anatomy

Originating from the L4, L5, S1, and S2 roots, the sciatic nerve is formed from the lumbosacral plexus after the exit of the superior and inferior gluteal nerves. It is composed of a lateral division, named the common fibular nerve (formerly the common peroneal nerve or the lateral popliteal nerve), and a medial division named the tibial nerve (formerly the medial popliteal nerve).

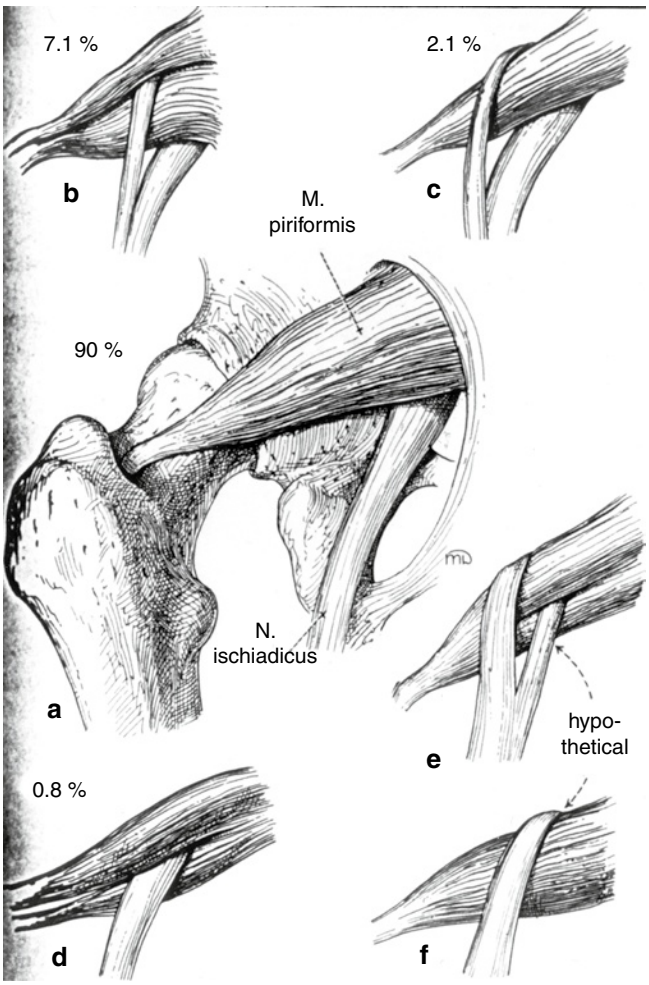

Fig. 41.9 Anatomic relationships of the sciatic nerve to the piriformis muscle. (**a**) the entire sciatic nerve passes underneath the piriformis muscle, (**b**) the fibular division pierces the piriformis muscle while the tibial exits underneath it, (**c**) the fibular division only exits above the muscle, (**d**) the entire sciatic nerve pierces the muscle, (**e**) and (**f**) hypothetical variations (Adapted from Beaton [99])

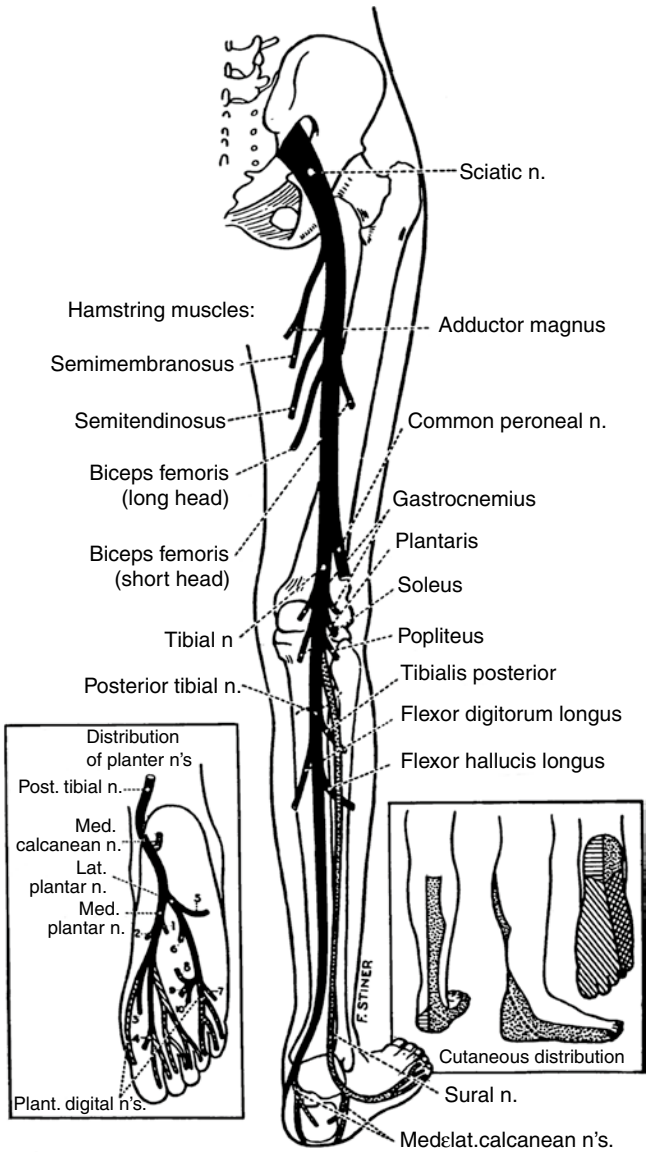

Fig. 41.10 The sciatic nerve and tibial nerves with motor and sensory branches (From Haymaker and Woodhall [393]. With permission)

Though enclosed in a common sheath, these two nerves are separate from the outset and do not exchange any fascicles [1].

The sciatic nerve leaves the pelvis via the sciatic notch, where the nerve has a close relation with the piriformis muscle, a flat pyramidal muscle, which originates from the front of the sacrum, the gluteal surface of the ilium, and the anterior capsule of the sacroiliac joint. The piriformis muscle leaves the pelvis via the greater sciatic foramen and inserts into the upper border of the greater trochanter, along with the obturator internus, gemelli, and quadratus femoris. All four muscles are external rotators of the hip. With the hip in the flexed position (such as while sitting), the piriformis is an abductor of the hip.

The interrelation between the piriformis and sciatic nerve anomalies is variable with a reported prevalence of "anomalies" ranging from 10 % to 30 % of individuals, but more realistically at about 16 % [98, 99]. Usually, the sciatic nerve passes underneath the piriformis muscle (Fig. 41.9). However, sometimes the fibular division only passes through or above the piriformis muscle, and, less frequently, the entire sciatic nerve pierces the piriformis muscle, or the nerve passes through the muscles or above it.

In the thigh, the tibial component of the sciatic nerve innervates most hamstring muscles (semitendinosus, semimembranosus, and long head of biceps femoris) and supplies a branch to the adductor magnus, while the common fibular component innervates the short head of biceps femoris only (Fig. 41.10). Usually, the common fibular and tibial nerves physically separate near mid-thigh or the upper popliteal fossa, but there is significant individual variability [1]. The common fibular nerve travels laterally and sweeps around the fibular head to travel in the anterior leg, while the tibial nerve continues posteriorly in the midline to enter the calf.

Table 41.8 Causes of sciatic mononeuropathy at the hip or thigh

Hip surgery or trauma
Total hip joint replacement
Hip fracture or dislocation
Femur fracture
Acute compression
Coma
Drug overdose
Intensive care unit
Prolonged sitting
Toilet seat
Lotus positioning
Surgical procedures
Open injury
Gunshot
Knife
Gluteal compartmental syndrome
Anticoagulation
Hemophilia
Rupture iliac artery aneurysm
Postoperative
Intramuscular gluteal injection
Endometriosis
Infarction
Vasculitis
Iliac artery occlusion
Arterial bypass surgery
Idiopathic
"Piriformis syndrome"

Sciatic Mononeuropathy at the Hip or Thigh

Etiology and Pathogenesis

Among the lower extremity mononeuropathies, sciatic nerve lesions at the hip are second in frequency only to fibular mononeuropathies. The sciatic nerve is predisposed to injury due to its close proximity to the hip joint and its relatively long course from the sciatic notch to the upper popliteal fossa. Since at least World War I, it has been known that partial sciatic nerve injuries usually affect the lateral division (common fibular nerve) more severely than the medial division (tibial nerve) [1]. This occurs independent of the causation of the sciatic nerve lesion. The greater vulnerability of the fibular division is due to the difference in the fascicular pattern and cushioning effect of the epineurium and the difference in the anatomical course between these two nerves (see above, the fibular nerve).

Hip replacement, dislocation, and fracture are the most common causes of sciatic nerve lesions at the hip (Table 41.8) [82–84, 100, 101]. Total hip joint replacement is a leading cause of such lesions, and sciatic mononeuropathy is the most common neurologic complication of total hip arthroplasty [100–102]. The estimated incidence of sciatic nerve lesion following total hip replacement is about 1–3 % [100, 101], although EDX studies may detect electrophysiological signs of sciatic nerve damage in as many as 70 % of patients [102]. The risk of sciatic nerve injury is higher in women, with procedures requiring limb lengthening, in patients with congenital hip dislocation or developmental dysplasia or undergoing total hip revisions [100, 101]. The sciatic nerve injury is often noted in the immediate postoperative period and is due to direct intraoperative stretch injury. Rarely, it is due to hemorrhage, prosthetic dislocation, migrating trochanteric wire, or leaking cement (methyl methacrylate) used in the arthroplasty [103, 104]. Occasionally, the onset is delayed for several years, usually due to prosthetic dislocation, osseous formation, or migrating trochanteric wire [104, 105]. Hip fracture or dislocation, or femur fracture, may also result in sciatic nerve injury, which may also occur during closed reduction or internal fixation [68, 82–84].

External compression of the sciatic nerve is the second common cause of sciatic nerve lesions at the hip. This occurs usually in the setting of unattended coma (such as with drug overdose) or coma associated with poor positioning (such as in the intensive care unit) [82, 106]. In many of these patients, the sciatic nerve injury is part of a gluteal or posterior thigh compartmental syndrome [106, 107]. Prolonged sitting, such as in "toilet seat" and "lotus" sciatic neuropathies or operative positioning in the sitting position, such as with craniotomy, may by itself cause sciatic compression [108–110]. Mass lesions in the buttock or thigh, such as malignant or benign tumors, persistent sciatic artery, vascular malformations (angioma, venous or arteriovenous malformation), or enlargement of the lesser trochanter (possibly from frequent sitting on hard benches), may compress the sciatic nerve [68, 84, 111–116].

Open sciatic nerve injuries are usually caused by gunshot wounds, knifes, or other sharp objects. Hemorrhage with the gluteal compartment is sometimes associated with sciatic nerve lesions. This may occur during anticoagulant therapy, in patients with hemophilia or Ehlers-Danlos syndrome, following hip surgery or due to rupture of an iliac artery aneurysm [100, 101, 106, 107]. Intramuscular gluteal injections, not administered properly in the upper outer quadrant of the buttock particularly in thin patients or children, may damage the sciatic nerve or its fibular component exclusively [68, 117–120]. This often occurs soon after the injection of a large quantity of a neurotoxic drug but may be delayed following repeated injections or due to fibrosis [120].

Sciatic mononeuropathies as a manifestation of endometriosis are an uncommon condition typically caused by pelvic endometriosis affecting the lumbosacral plexus or proximal sciatic nerve [121–123]. Menstruating women may have cyclic radicular pain ("catamenial sciatica") which waxes and wanes with the menstrual cycle. The majority of patients have cyclical radicular pain, but occasionally the patient develops fluctuating foot drop and signs of overt

Table 41.9 Differential diagnosis between fibular neuropathy at fibular head and sciatic neuropathy affecting predominantly the common fibular nerve

Symptom/sign	Sciatic nerve lesion affecting predominantly the common fibular nerve	Common fibular nerve lesion at the fibular head
Foot pain	Common	Rare
Radicular pain "Sciatica"	Common	Absent
Straight leg raise "Lasègue test"	Positive	Negative
Ankle jerk	Often depressed or absent	Normal
Ankle inversion	Often weak	Normal
Toes flexion	Often weak	Normal
Plantar flexion	May be weak	Normal
Tinel's sign at fibular neck	Negative	Common
Sensory loss	May extend into upper third of lateral leg[a] or sole[b]	Distal two thirds of lateral leg and dorsum of foot

Source: Adapted from Katirji [13]. With permission
[a]Distribution of lateral cutaneous nerve of the calf
[b]Tibial nerve distribution

sciatic mononeuropathy [123]. Typically, the symptoms start few days before menstruation and stop after menses end. With progression of disease, the manifestations of endometriosis become more constant, though often worse during menses.

Ischemic injuries to sciatic nerve may be due to small vessel disease, as with vasculitis involving the vasa nervorum, or large vessel disease, as with iliac or femoral artery occlusion [82, 84, 124, 125]. Similar injuries were described in patients with cardiac surgery, usually with intra-aortic balloon pump therapy with a catheter placed through the ipsilateral femoral artery [126, 127]. It is not clear whether the injury in the latter patients is due to selective sciatic nerve ischemia or to a distal axonopathy due to watershed ischemia of the lower limb (i.e., monomelic ischemic neuropathy) [128, 129].

Sciatic nerve lesions in children are rare and traumatic and iatrogenic causes constitute about 50 % of the cases [84, 124]. Less frequent causes include tumors, extrinsic compression and immobilization, and vascular causes [125]. In about 15–20 % of patients with sciatic nerve lesions, particularly children and young adults may develop a slowly progressive idiopathic sciatic mononeuropathy. These cases have evidence of axonal loss on EDX testing. No cause is identified despite imaging studies and surgical exploration [84, 130, 131].

Clinical Presentation

Sciatic mononeuropathy presents with weakness, pain, and sensory loss [82, 84, 105]. The foot weakness commonly manifests as a foot drop, since the fibular component is usually more affected than the tibial. Though weakness of tibialis anterior dominates the picture, careful examination often detects weakness of hamstrings (knee flexion), gastrocnemius (plantar flexion), or tibialis posterior (ankle inversion). Occasionally, sciatic nerve lesions in the hip are essentially pure high common fibular lesions, manifesting similar to common fibular lesions at the fibular neck (see above, the fibular nerve) [68]. In contrast, severe sciatic nerve lesions are associated with a flail foot (i.e., weak foot and ankle in all directions) and hamstring weakness.

Foot pain and dysesthesia are common symptoms of sciatic nerve injuries. This may give rise to diagnostic confusion since the site of pain is distant from the site of the lesion in the hip or thigh. Not infrequently, signs of complex regional pain syndrome (allodynia with skin, nail, and bone dystrophic changes) become dominant and disabling.

The ankle jerk is usually asymmetrically depressed or absent, a useful clinical clue in patients with mild sciatic lesions. Sensory loss and dysesthesia of the sole and dorsum of the foot and lateral leg are common.

Differential Diagnosis

Severe or complete sciatic nerve lesions pose little difficulty in diagnosis since the weakness involves all muscles along the knee, often with the hamstrings. Also, the sensory loss below the knee spans both the fibular and tibial distributions while sparing the medial leg (saphenous nerve distribution). In contrast, partial sciatic nerve lesions, which usually present with foot drop, may be difficult to differentiate from fibular mononeuropathy, lumbosacral radiculopathy, and lumbosacral plexopathy (see Table 41.3). There are clinical hints which are useful in distinguishing a sciatic mononeuropathy from fibular nerve lesion at the fibular neck (Table 41.9). Lumbosacral radiculopathies, particularly when the L5 and S1 roots are involved, may mimic partial sciatic nerve lesions. The lack of back pain and well-demarcated sensory loss favors a sciatic lesion. Lumbosacral plexopathies, particularly those involving the lumbosacral trunk mainly, are often mislabeled as a sciatic mononeuropathy. These lesions are often due to pelvic fracture, hematoma, or fetal head compression during a labor in women with short stature or delivering large babies [38, 39].

Sciatic nerve lesions may be difficult to separate from acute ischemic monomelic mononeuropathy, since all muscles below the knee are innervated by the sciatic nerve (see Chap. 37) [128, 129]. A history of large vessel compromise in the involved limb is common in ischemic monomelic neuropathy. In sciatic nerve lesions, there is usually preservation of saphenous sensory territory, while the sensory loss in ischemic monomelic neuropathy is diffuse in the involved leg with a stocking glove distribution.

In sciatic nerve lesions, particularly when partial or presenting with foot drop, EDX studies are often necessary for final confirmation and exclusion of all the above lesions (see Table 41.4).

Evaluation and Diagnosis

Electrodiagnostic Studies

The EDX findings in sciatic mononeuropathy parallel the clinical manifestations. Often, the EDX study unveils involvement of the tibial nerve which could not be detected clinically despite careful neurological examination. The EDX examination often confirms the presence of axon-loss sciatic mononeuropathy and helps to exclude a common fibular nerve lesion around the fibular neck, a lumbosacral radiculopathy or plexopathy. It is not uncommon for the NCS to suggest that the lesion is an axon-loss common fibular mononeuropathy, since the fibular nerve is often affected more severely than the tibial nerve. Helpful clues for the presence of a sciatic nerve lesion on nerve conduction studies include an asymmetrically low or absent sural SNAP or H-reflex, or an asymmetrically low-amplitude M-response recording soleus/gastrocnemius (recorded during H-reflex testing), or tibial CMAP recording abductor hallucis. Therefore, it is highly recommended that the contralateral H-reflex, M-response, sural sensory and tibial motor nerve conduction studies be done in all patients with foot drop, especially when a sciatic nerve lesion is considered.

It is important to recall that the sural nerve is formed by the medial sural cutaneous nerve, which originates from the tibial nerve in the popliteal fossa, and fibular (peroneal) communicating nerve (also called the lateral sural nerve), which originates from the common fibular nerve in the popliteal fossa. These two branches join in the calf to form the sural nerve. This fibular communicating nerve is present in 40–84 % of dissected cadavers and contributes to about 30–40 % of the antidromic sural SNAP (stimulating at the calf and recording at the ankle) with minimal side-to-side difference [132]. Thus, an abnormally low-amplitude sural SNAP does not automatically indicate involvement of the tibial nerve.

The needle EMG is frequently necessary to confirm that the foot drop is a sciatic nerve lesion. The common fibular-innervated muscles are usually significantly denervated. Among tibial-innervated muscles, those located below the knee, such as the abductor hallucis, flexor digitorum longus, and gastrocnemius (medial and lateral heads), are most useful by revealing fibrillation potentials and neurogenic changes. This is especially important when the lesion is relatively chronic and the hamstrings were allowed to reinnervate. The hamstring muscles innervated by the tibial nerve (semitendinosus, semimembranosus, and long head of biceps femoris) may also reveal fibrillation potentials, decreased recruitment, and large MUAPs. The short head of biceps femoris, innervated by the common fibular nerve, is frequently much more affected than the other hamstrings. Finally, one may occasionally find neurogenic changes in the thigh adductors, particularly in severe sciatic nerve injuries, since the adductor magnus receives dual innervation from the sciatic as well as the obturator nerves. The needle EMG in these cases is not complete unless the glutei, tensor fascia lata, and lumbar paraspinal muscles are sampled to exclude a lumbosacral plexopathy or radiculopathy.

On rare occasions, the common fibular component of the sciatic nerve is selectively injured in the hip or thigh (see above, the fibular nerve) [68]. In these occasions, the H-reflex, and sural sensory and tibial motor conduction studies, as well as all tibial-innervated muscles above and below the knee are normal. These lesions are purely axonal and mimic a common fibular mononeuropathy at the fibular neck. Thus, sampling the short head of biceps femoris is mandatory in all patients with fibular mononeuropathy, especially those axonal ones which could not be localized by NCS due to the lack of conduction block or focal slowing.

Ancillary Testing

Plain X-rays of the hip is useful in the diagnosis of hip dislocation or fracture. CT of the pelvis and gluteal compartment, urgently in patient with possible compartmental syndromes, may reveal a hematoma or significant compartmental swelling. MRI is also useful in the diagnosis of endometriosis or nerve tumor as a cause of sciatic mononeuropathy [133].

Treatment, Management, and Prognosis

Patients with gluteal compartmental syndrome should undergo emergency surgical decompression. Surgical intervention is required for patients with hip fracture, dislocation, or prosthetic hip dislocation. Surgical exploration and neurolysis or surgical repair with sutures or grafts is also indicated for patients with sciatic nerve lesions due to lacerations, gunshot wounds, and hip replacement [134, 135]. Surgical management should be guided by intraoperative nerve action potential recordings. Partial or complete surgical excision should be attempted in sciatic neurogenic tumors [113]. Patients with mild manifestations of sciatic mononeuropathy due to endometriosis may respond to pharmacologic suppression of the ovarian cycle [122, 123]. Those with severe symptoms require surgical resection of endometrial foci and adhesions. When the above fails, particularly when reproduction is not an issue, a permanent

cure may be accomplished by surgical menopause through bilateral oophorectomy.

Most symptomatic sciatic nerve lesions require pain management. Anticonvulsants, such as gabapentin or pregabalin, and antidepressants, such as duloxetine or tricyclics, are the drugs of choice. This, coupled with physical therapy and ankle-foot orthosis for foot drop, often assists patients in ambulation.

The prognosis of sciatic nerve lesions is generally guarded. At least 1/2 of patients with sciatic nerve lesions following total hip arthroplasty recover completely, while 15 % have a poor outcome with significant weakness, pain, and sensory loss [100, 101]. In general, patients with severe lesions have significant residual weakness, while partial lesions may improve significantly due to reinnervation. Many patients are left with chronic foot pain and signs of complex regional pain syndrome.

The Piriformis Syndrome

Etiology and Pathogenesis

The piriformis syndrome is an ill-defined and controversial entity. It is proposed that leg pain ("sciatica") may be caused by compression of the sciatic nerve at the pelvic outlet by the piriformis muscle. In 1928, Yeoman was the first to refer to the piriformis muscle as a possible cause of sciatic nerve entrapment [136]. He suggested that periarthritis of the anterior sacroiliac ligament may extend into the piriformis muscle and the adjacent sciatic nerve. Later in 1947, Robinson coined the term "piriformis syndrome" and set six criteria for diagnosis: history of trauma to the buttock, pain in the buttock extending to the leg, worsening of pain by stooping or lifting, palpable and tender sausage-shaped mass over the piriformis muscle, positive Lasègue sign, and possible gluteal atrophy [137]. The piriformis syndrome was popularized in the thirties and forties based on the close relation between the sciatic nerve and the piriformis muscle, but has become less known since the advances of radiological techniques (myelography, CT, and MRI) that have demonstrated that many patients with sciatica harbor a lumbosacral radiculopathy due to nerve root compression within the spinal canal. The lack of objective clinical findings and confirming investigations has increased the controversies and severely compromised the credibility of this syndrome [138, 139]. Also, despite the high incidence of anomalous relationship between the sciatic nerve and the piriformis muscle, the prevalence of these anomalies in patients is not significantly different treated with surgical intervention for in piriformis syndrome are compared to the general population. This suggests that the anatomical variation may not be as important in the pathogenesis of this syndrome [98, 99].

There is a recent resurgence of interest in the piriformis muscle in an attempt to explain the cause of sciatica and buttock pain in patients with no demonstrable nerve root compression on imaging studies [140]. Currently, there is a great controversy among physicians as to the frequency and, even, existence of this syndrome [138, 139]. The piriformis syndrome is likely a very rare cause of leg pain and sciatica, and only a small number of such patients have "true" piriformis syndrome. Typically, these are women with a history of trivial trauma to the buttock, who have exquisite buttock tenderness near the sciatic notch, and EDX findings of a mild axon-loss sciatic mononeuropathy, with or without an inferior gluteal mononeuropathy. At operation most of these patients have an anomalous band (or vessel), in the region of the piriformis muscle, compressing the sciatic nerve [141, 142]. This suggests that in these selected cases of sciatic neuropathy at the sciatic notch, the piriformis muscle plays no role in pathogenesis and is likely a mere innocent bystander.

Clinical Presentation

The piriformis syndrome is up to six times more common in women than men. Often patients complain of buttock pain and tenderness that may (or may not) radiate down the thigh and lower leg. Most patients are aware of point tenderness in the buttock which is usually near the sciatic notch. The pain is worse with prolonged sitting (such as while driving or biking), during bending at the waist, or during an activity that requires hip adduction and internal rotation (such as cross-country skiing). It is often much relieved with standing or walking. Dyspareunia in women or pain with bowel movements are not uncommon symptoms. Back pain is usually absent or minimal. Paresthesias of the buttock and/or in a patchy sciatic nerve distribution are not uncommon. There is usually no objective weakness. A history of buttock trauma is common in most patients with the piriformis syndrome. Prolonged sitting on hard surfaces may also trigger this syndrome (hence the terms "wallet neuritis" and "hip pocket neuropathy").

The absence of physical signs is considered an essential criterion for the diagnosis, which is also a major criticism for the existence of the piriformis syndrome. In contrast to other causes of sciatic neuropathy, the piriformis syndrome is not associated with weakness, reflex changes, or definitive sensory loss.

Reproduction of sciatica upon deep palpation in the sciatic notch or upon rectal or pelvic examination is common and considered by some as diagnostic [140, 143]. Patients with piriformis syndrome tend to walk with their leg externally rotated. This is sometimes seen when the patient is in a supine position (positive piriformis sign). A positive Trendelenburg test in which the patient stands on the asymptomatic foot and the buttock of the unsupported foot falls (rather than rise) may be present. This suggests weak gluteal

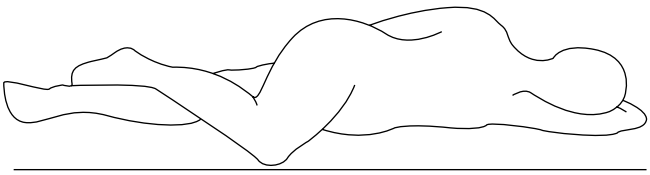

Fig. 41.11 The FAIR test (*f*lexion, *a*dduction, and *i*nternal *r*otation) in the diagnosis of the piriformis syndrome

muscles, as seen in few patients with the piriformis syndrome. More rarely, there may be mild wasting of the buttock (gluteus maximus) due to concomitant entrapment of the inferior gluteal nerve.

Many proponents of the piriformis syndrome rely on the presence of positive test maneuvers in the bedside diagnosis of the piriformis syndrome [140]. These may be divided into two categories: one in which passive stretching of the piriformis muscle and the other in which active contraction (with resistance) of the piriformis muscle occur. Pain in the affected buttock (and sometimes thigh) during the maneuver is considered a positive test.

- *Freiberg test.* Passive forceful internal rotation of the extended thigh at the hip while the patient is lying reproduces the pain. Unfortunately, this test may be positive in other disorders around the hip joint and buttock.
- *Pace test.* Resisted abduction of the thigh induces buttock pain. This is usually done while the patient is in the sitting position, but may be difficult to do because of pain induced by sitting.
- *Beatty test.* An alternative method to the Pace test. It is done with the patient lying with the painful side up, and the painful leg semi-flexed, and the knee resting on the table [143]. Deep buttock pain is produced when the patient lifts (abducts the thigh) and holds the knee several inches off the table. In herniated lumbar discs, the maneuver often produces lumbar and leg pain but not deep buttock pain, while in primary hip abnormalities, pain was often produced in the trochanteric area but not in the buttock.
- *Flexion, adduction, and internal rotation (FAIR) test.* The patient lies on the unaffected side, bends the knee of the affected leg to a 90° angle and catching the foot behind the calf of the affected leg, and swings the affected leg over the healthy one until the knee touches the examining table (Fig. 41.11). The FAIR maneuver often reproduces the buttock pain and sciatica. The FAIR test correlates well with patients with true piriformis syndrome and is a better predictor of successful physical therapy and surgery [144].

More recently, criteria for the diagnosis have been proposed. Fishman proposed the following criteria: (1) positive Lasègue sign at 45°, (2) tenderness at the sciatic notch, (3) increased pain in the sciatic distribution with the thigh in the FAIR position, and (4) EDX studies that exclude myopathy or neuropathy [138, 144].

Differential Diagnosis

Buttock pain and tenderness with or without back pain are common symptoms and may be caused by a variety of disorders including lumbosacral radiculopathy, bursitis, and hip joint disease. In all of these entities, referred pain down the thigh and tenderness in the buttock is possible. Also, many of the maneuvers used in the diagnosis of the piriformis syndrome are nonspecific, subjective, and often positive in a variety of disorders of the hip and buttock.

The major differential diagnosis of patients with suspected piriformis syndrome is a lumbosacral radiculopathy, particularly an L5 or S1 radiculopathy. Sciatica is a common symptom of radiculopathies and is often associated with low back pain. In contrast to the piriformis syndrome, the pain in lumbosacral radiculopathy is often worse with standing or walking. Finally, pain with sitting and exquisite tenderness in the sciatic notch is rare in lumbosacral radiculopathies.

Evaluation and Diagnosis

The piriformis syndrome is a clinical diagnosis often supported by the patient's history and few of the findings on the clinical examination. EDX and imaging studies are useful, mostly in excluding other entities such as lumbar spine disease or mass lesions compressing the sciatic nerve.

Electrodiagnostic Studies

In the majority of cases of piriformis syndrome, the EDX studies (NCS and needle EMG) are normal, which has kept the controversy around this syndrome active. The sural sensory and fibular and tibial motor nerve conduction studies, as well as the F waves and H-reflexes, are normal and symmetrical [145]. Chang et al. found significant slowing of the sciatic motor nerve conduction velocity in the gluteal segment of the sciatic nerve with magnetic stimulation of the L5, but not S1, nerve root [145]. Fishman and colleagues found also that the H-reflex, done at rest and during the FAIR maneuver, displays an asymmetrical delay in latency during the FAIR test in patients with the piriformis syndrome [144, 146]. On needle EMG, reports of rare cases have revealed denervation changes on needle EMG of the hamstring muscles and gastrocnemius. These patients often have fibrous band or aberrant artery compressing the sciatic nerve in the region of the piriformis muscle [141, 142, 145].

Imaging

Imaging of the spine is essential in excluding lumbar radiculopathy as the causation of leg pain. Imaging of the sciatic notch is helpful in excluding a tumor or hematoma. MRI of the sciatic notch may show hypertrophy of the piriformis in patients with suspected piriformis syndrome [147, 148]. MRI also often shows the relation between the sciatic nerve and piriformis muscle and its anomalies [147]. Occasionally, MRI have helped in identifying abnormal vessels or bands in

the region of the piriformis muscle, though these MRI findings (bands, vessels, hypertrophy of piriformis) are equally common in asymptomatic subjects or on the asymptomatic sides of patients.

Diagnostic Nerve Block

Relief of symptoms by a nerve block with corticosteroids or lidocaine in the region of the sciatic notch is considered a diagnostic confirmation of the piriformis syndrome. However, opponents of this syndrome argue that pain relief from corticosteroid injection is not a proof that the sciatic nerve is compressed by the piriformis muscle. Patients with distal nerve or proximal root lesions (such as lumbosacral radiculopathies) often get pain relief by sciatic nerve blocks.

Management, Treatment, and Prognosis

Therapy of the pain syndrome in patients with the piriformis syndrome includes one of the following methods:

Conservative therapy. This should be the initial treatment and is aimed at relaxing the tight piriformis muscle. As a home program, the patient is instructed to perform prolonged stretching of the piriformis muscle by flexion, adduction, and internal rotation of the symptomatic hip. This could be done in the supine and standing positions. The patient should hold the leg in the stretched position for 5 s and gradually increase to 60 s [149, 150]. Moist heat or ultrasound prior to stretching is often useful.

Corticosteroid and lidocaine injection. Injection into the piriformis muscle with corticosteroids with or without lidocaine preferably done under imaging (CT or MRI) guidance has been advocated. This has been reported to be effective in almost 2/3 of the patients, particularly those with a positive FAIR test. The muscle may be injected through the sciatic notch, from the perineum, or through the vagina.

Botulinum toxin. Botulinum toxin type A (Botox or Dysport) or type B (Myobloc) is injected usually with CT guidance into the piriformis muscle. Several trials demonstrated better efficacy with botulinum toxin-A over both placebo and corticosteroid with lidocaine [140, 151–154]. The effects persist for up to 3 months. If done with piriformis stretching therapy, there is usually a reduction in the need for repeated injections.

Surgery. Surgical exploration of the sciatic nerve in the region of the piriformis muscle should be reserved to patients who have failed conservative or injection therapies [140–142]. Section of the piriformis muscle is the most popular advocated procedure, but its value is uncertain. Abnormal bands or vessels constricting the sciatic nerve in the buttock, if encountered, should also be removed (Fig. 41.12). The success rate of surgery is unknown but failures have been reported [155]. Fishman et al. reported that 68 % of carefully selected patients with the piriformis syndrome showed a 50 % or greater improvement in pain at a mean follow-up of 16 months [144]. Surgical release should be considered a treatment of last resort, since it could be hazardous since it may lead to debilitating sciatic nerve injury [156].

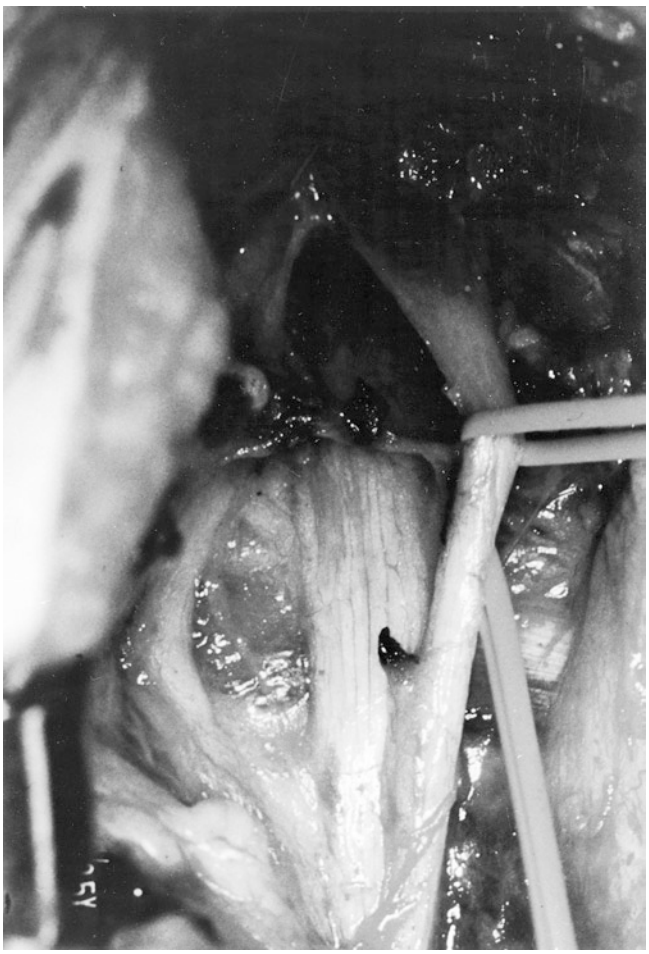

Fig. 41.12 Intraoperative findings in a patient with the piriformis syndrome, revealing a compressive band over the tibial component of the sciatic nerve. The fibular component is pulled away and the piriformis muscle has been divided (Courtesy of Drs. Henry H. Bohlman and Cheryl A. Petersilge)

The prognosis of patients with the piriformis syndrome is unknown because of its controversial nature. Good outcome has been reported in patients treated with botulinum toxin injection with piriformis stretching [152]. Surgical intervention is useful in about 50 % of the patients [144], particularly those with abnormal EMG findings or with compressive bands or vessels [142, 157].

The Tibial Nerve

Anatomy

The tibial component of the sciatic nerve innervates all of the hamstring muscles except the short head of the biceps femoris which is supplied by the common fibular nerve. The tibial nerve

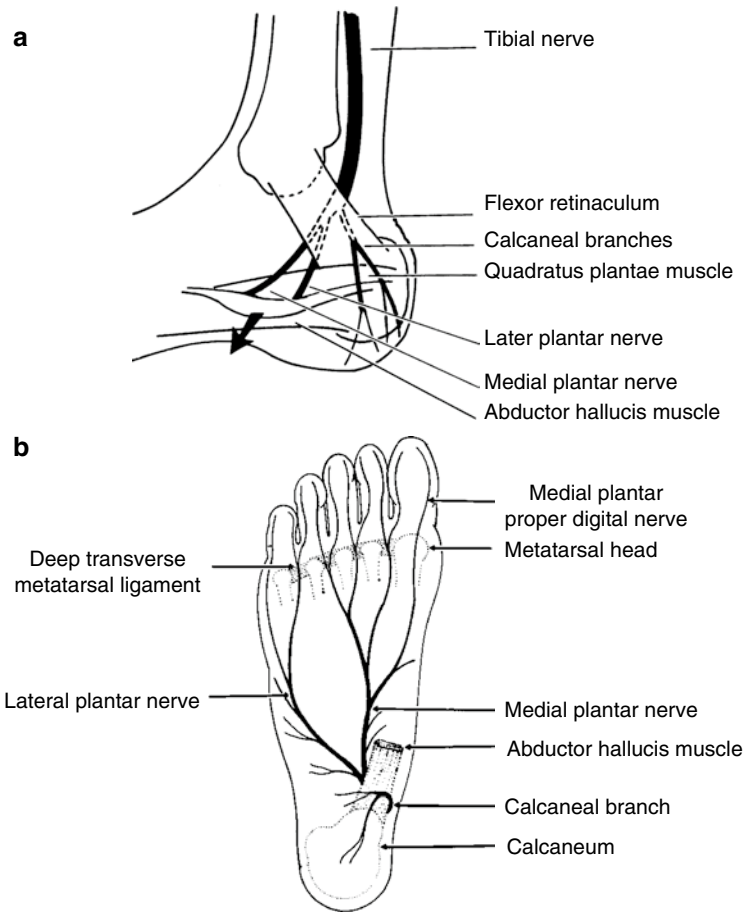

Fig. 41.13 The course of the distal tibial nerve and its terminal branches. (**a**) Medial view and (**b**) plantar view (From Dyck and Thomas [396] and Stewart [397]. With permission)

(sometimes referred to as the posterior tibial nerve [158]) separates completely from the common fibular nerve in the upper popliteal fossa (see sciatic nerve). Soon, it gives off its first branch, the sural nerve, a purely sensory nerve which innervates the skin over lateral aspect of the lower leg and foot including the little toe. In 80 % of individuals, the sural sensory nerve is joined by a sensory branch, referred to as the sural communicating nerve, fibular communicating nerve, or the lateral sural nerve (with the main sural nerve as the medial sural nerve), which originates from the common fibular nerve in the popliteal fossa. Then, the sural nerve runs between the Achilles tendon and lateral malleolus and innervates the lateral side of the ankle and lateral border of the sole up to the base of the fifth toe.

In the upper calf, the tibial nerve dips underneath a tendinous arch of soleus muscle, the fibromuscular soleal sling, and innervates the gastrocnemius, soleus, tibialis posterior, flexor digitorum profundus, and flexor hallucis longus (see Fig. 41.10). Beyond the soleus arcade, the tibial nerve is sometimes referred to as the posterior tibial nerve.

At the ankle, the tibial nerve passes posterior to the medial malleolus and through the tarsal tunnel (also called medial tarsal tunnel) to enter the foot. The tarsal tunnel is roofed by the laciniate ligament (flexor retinaculum) which extends between the medial malleolus and the calcaneus. It contains,

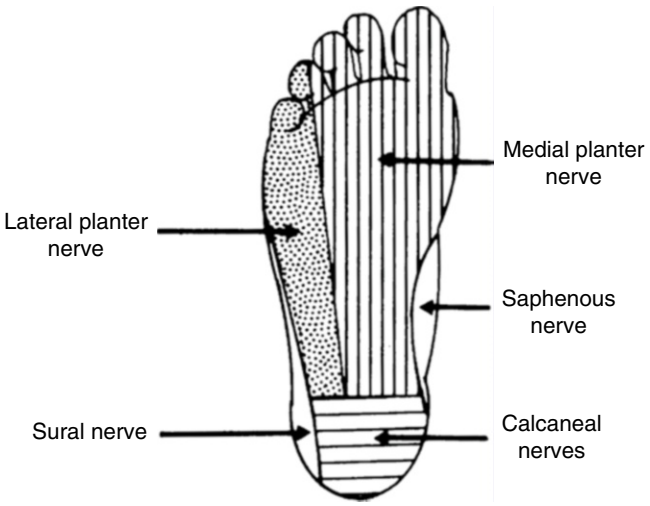

Fig. 41.14 Cutaneous innervation of the sole of the foot (From Dyck and Thomas [396]. With permission)

in addition to the tibial nerve, the posterior tibial artery and the tibialis posterior, flexor digitorum longus, and flexor hallucis longus tendons. There or slightly distal to that point, the tibial nerve divides into its three terminal branches (Figs. 41.13 and 41.14) [159]: (1) the calcaneal branch, a

purely sensory nerve, that innervates the skin of the sole of the heel; (2) the medial plantar nerve which innervates the abductor hallucis, flexor digitorum brevis, and flexor hallucis brevis in addition to the skin of the medial sole and, at least, the medial three toes; and (3) the lateral plantar nerve which innervates the abductor digiti quinti pedis, flexor digiti quinti pedis, adductor hallucis, and the interossei in addition to the skin of the lateral sole and two lateral toes.

The interdigital nerves are sensory branches which arise from the medial and lateral plantar nerves. Similar to the digital branches in the hand, each interdigital nerve in the foot innervates the skin on the sole of two opposing toes. Exceptions are the medial plantar proper digital nerve and lateral plantar proper digital nerve which innervates the medial side of the great toe and the lateral side of the little toe, respectively. Before entering the toes, the interdigital nerves cross over the metatarsal heads and the deep transverse metatarsal ligaments which connect the metatarsal heads (Fig. 41.13).

Proximal Tibial Mononeuropathy

Tibial nerve lesions proximal to the ankle are rare and most are located near the popliteal fossa. The nerve may be compressed by a Baker's cyst [160, 161], intraneural ganglion (likely originating from the superior tibiofibular ganglion cyst) [162, 163], a hematoma [164], or a fibrous band or the aponeurotic arch of the soleus muscle ("soleal sling syndrome") [165–168]. The proximal tibial nerve may also be injured during surgical procedures involving the knee [169, 170]. Nerve sheath tumors, including schwannomas and neurofibromas, may arise in the tibial nerve near the popliteal fossa [171, 172].

Clinically, these lesions often present with foot pain and numbness and pose a diagnostic challenge since they may mimic a tarsal tunnel syndrome [172]. This may be aggravated, particularly in patients with nerve compression by the tendinous arch of the soleus, by passive ankle dorsiflexion, and, sometimes, by active dorsiflexion or plantar flexion. Tenderness in the popliteal fossa and upper calf and a positive Tinel's sign on percussion of the tibial nerve in the lower popliteal fossa are common and useful localizing signs [165]. Weakness of plantar flexion, toe flexion, and ankle inversion with absent ankle jerk is not common, but, when present, helps to guide the clinician away from the tarsal tunnel. Also, sometimes the sensory loss not only involves the foot but extends into the lateral border of the foot (sural nerve distribution).

The EDX studies of tibial nerve lesions in the popliteal fossa may be normal or reveal evidence of an axon-loss proximal tibial mononeuropathy. The tibial CMAPs, recording abductor hallucis and abductor digiti minimi pedis, are low or absent. There is no accompanying focal slowing across the ankle as seen in some patients with the tarsal tunnel syndrome. Tibial distal latencies and proximal conduction velocities are normal or diffusely borderline or slow. The sural SNAP may be normal, low, or absent depending on whether the lesion is distal or proximal to the takeoff of the nerve in the popliteal fossa. Needle EMG may reveal denervation usually in the intrinsic muscles of the foot, but, at times, in both heads of gastrocnemius, soleus, tibialis posterior, or flexor digitorum longus. In contrast, the fibular NCSs and needle EMG of the hamstrings and all common fibular-innervated muscles are normal unless there is a concomitant fibular nerve palsy [164]. The EDX examination may have difficulty distinguishing these lesions from S1/S2 radiculopathies when the sural SNAP is normal or from tarsal tunnel syndrome when the proximal tibial nerve lesion is fascicular resulting in sparing of the gastrocnemius and soleus muscles. Detecting denervation in the gluteus maximus, gluteus medius, and lumbar paraspinal muscles confirms an S1/S2 radiculopathy. Focal slowing of the tibial motor distal latencies or mixed plantar latencies is a useful distinguishing EDX feature, but unfortunately not a common, localizing finding in the tarsal tunnel syndrome (see below).

The treatment of tibial nerve lesions in the popliteal fossa is often surgical. Removing the cystic lesion, nerve sheath tumor, or hematoma is often indicated. Division of the tendinous arch of the soleus muscle with neurolysis of the tibial nerve often leads to relief of pain and improvement of muscle strength in more than half of the patients [165, 168].

Tarsal Tunnel Syndrome

Etiology and Pathogenesis

Tarsal tunnel syndrome (TTS) was first described by Keck in 1962 [173]. Its true incidence is unknown, though it is an uncommon entrapment mononeuropathy. TTS is not as well understood as its counterpart in the hand, the carpal tunnel syndrome [174]. TTS is sometimes referred to as the medial tarsal tunnel syndrome, to distinguish it from the anterior tarsal tunnel syndrome which is an entrapment of the terminal segment of the deep fibular nerve under the extensor retinaculum in the dorsum of the foot (see fibular nerve above).

TTS is caused by compression of the tibial nerve or any of its three terminal branches under the flexor retinaculum [85, 174, 175]. The disorder is insidious in onset, more common in women and is usually unilateral. Bilateral TTS is rare accounting for less 10–20 % of cases. Most cases of TTS are idiopathic with no clear precipitating cause (Table 41.10). Ankle trauma, particularly sprains and fractures, is the second most common cause of TTS [175]. The trauma is usually remote and often sports related, and the entrapment is due to fibrosis or bony changes within the tarsal tunnel space. Athletes, including runners, joggers, and dancers, are

Table 41.10 Causes of tarsal tunnel syndrome

Idiopathic
Ankle trauma
Sprains
Fractures
Ankle tenosynovitis or arthritis
Mass lesion
Ganglion
Varicose veins
Schwannoma
Lipoma
Biomechanical causes
Heel varus
Heel valgus
Ill-fitted shoes
Systemic illness
Rheumatoid arthritis
Diabetes mellitus
Acromegaly
Systemic lupus erythematosus
Hypothyroidism
Hyperlipidemia

particularly at high risk for developing TTS [176, 177]. Arthritis and tenosynovitis of the ankle may be associated with TTS [178, 179]. Rheumatoid arthritis is the most common systemic disorders associated with TTS. The prevalence of TTS in patients with rheumatoid arthritis is about 5 % [178, 179], while, based on electrophysiological criteria, TTS may be present in up to 15 % of patients with rheumatoid arthritis [179]. Other systemic disorders, including diabetes mellitus, acromegaly, hypothyroidism, systemic lupus erythematosus, and hyperlipidemia, may be associated with TTS [180, 181]. Finally, biomechanical causes, such as ill-fitting foot wear or heel varus and valgus deformity, may precipitate TTS [85, 173, 175]. Hypertrophic or anomalous abductor hallucis mass lesion within the tarsal tunnel (ganglion, lipoma, schwannoma) or varicose veins occupying the tarsal tunnel space are not uncommon findings on MRI or on surgical exploration for TTS [182–185]. Tibial nerve lesions at the ankle may be iatrogenic, such as after ankle arthroscopy [186, 187].

Clinical Presentation

The most common symptoms of TTS are burning pain and numbness in the sole of the foot and heel. The pain may worsen, or occur only, after prolonged standing, walking, jogging, or running. Occasionally, the pain radiates proximally to the calf. Subjective weakness or imbalance is extremely rare. The neurological examination reveals sensory impairment in the sole in the distribution of one or all of the terminal tibial branches (medial plantar, lateral plantar, or calcaneal). In 40 % of patients, the heel is spared when the calcaneal branch takes off before the flexor retinaculum, while in 25 % of patients, the sensory loss involves all three terminal branches territory. In 25 % of TTS patients, the sensory loss is only in the medial plantar nerve distribution, while in 10 % it follows the lateral plantar nerve selectively. The sensory manifestations may be triggered or exaggerated by foot eversion. Tinel's sign, induced by percussion of the tibial nerve at the flexor retinaculum (behind the medial malleolus), is present in most patients [175, 188]. Muscle wasting in the sole is rare. Weakness is usually not detected since the long toe flexors are intact. The ankle jerk and sensation of the dorsum and lateral foot are normal.

Differential Diagnosis

TTS may be difficult to distinguish from other common orthopedic, rheumatological, and neurological conditions particularly in patients with a prior history of foot or ankle trauma. Plantar fasciitis, stress fracture, arthritis, or bursitis causes foot pain. However, the pain in these latter conditions is usually worse in the morning, improves with walking, and is not associated with paresthesia or Tinel's phenomenon. Complex regional pain syndrome, with or without ankle trauma, leads to severe foot burning pain, but is often associated with swelling, skin trophic changes, and poorly localized dysesthesia.

Proximal tibial mononeuropathy particularly when caused by nerve compression by the tendinous arch of the soleus muscle (the soleal sling syndrome) [165, 168], or a sciatic mononeuropathy affecting the tibial component particularly when due to nerve sheath tumors [172], often presents with indolent symptoms that may mimic TTS. These lesions may present with foot pain and numbness, but they are often associated with calf weakness or atrophy and absent or depressed ankle jerk, findings not consistent with TTS. An S1 or S2 radiculopathy, in isolation or as a component of lumbar spinal canal stenosis, may result in foot numbness or pain which is often worse with walking or standing. However, there is usually low back and posterior thigh pain ("sciatica"), depressed or absent ankle jerk, or weakness of gastrocnemius or glutei muscles.

A particularly troublesome task is distinguishing patients with TTS from those with early sensory peripheral polyneuropathy, particularly in the elderly. A useful feature is that TTS is rarely bilateral while peripheral polyneuropathy often affects both feet. Also, the sensory loss in polyneuropathy usually involves both the sole and dorsum of foot and is rarely associated with Tinel's sign at the flexor retinaculum.

Lesions of the medial or lateral plantar nerves at the tarsal tunnel may mimic selective lesions of these nerves within the sole of the foot. Causes of *medial plantar mononeuropathy* distal to the tarsal tunnel include trauma, jogging, bunion surgery, foot deformities (such as pes cavus), arthritis or synovial cyst of the first metatarsophalangeal joint, schwannoma, or entrapment at the abductor tunnel [189–192]. The

clinical manifestations and the EDX findings are indistinguishable from TTS affecting the medial plantar nerve selectively. A careful history and a Tinel's sign distal to the tarsal tunnel are useful features. *Lateral plantar mononeuropathy* distal to the ankle is extremely rare and is also indistinguishable from TTS affecting the lateral plantar nerve selectively. These lesions are usually due to fracture, trauma, or a schwannoma [193, 194].

TTS affecting the medial plantar nerve selectively should be distinguished from *Joplin's neuroma* [195–197]. This is due to selective lesion to the medial plantar proper digital nerve to the great toe, which innervates the skin on the medial aspect of the great toe. Joplin's neuroma is often caused by trauma, bunion, callus, or biomechanical imbalances such as using tight or ill-fitting shoes. There is usually perineural fibrosis on pathological examination. The symptoms include pain and numbness in the medial great toe and, occasionally, Tinel's sign by percussion of the first metatarsophalangeal joint. Abnormality of the sensory NCS of the medial plantar proper digital nerve, using near-nerve recording at the ankle with surface stimulation at the great toe, was described but is not popular [198].

Evaluation and Diagnosis

The diagnosis of TTS is often made on clinical grounds with supports from ancillary testing such as EDX studies, plain X-rays, tomogram, bone scan, and MRI. Careful clinical evaluation of the ankle and foot is essential, and EDX studies are often necessary for correct diagnosis.

Electrodiagnostic Studies

Several EDX techniques are used to assess for TTS. Most of these involve assessing sensory or motor nerve fibers that traverse the medial or the lateral plantar nerves. The following are the most commonly utilized studies in patients with suspected TTS:

1. *Tibial motor NCSs recording from the abductor hallucis (medial plantar motor NCS) and the abductor digiti quinti pedis (lateral plantar motor NCS).* These are the first NCSs described to diagnose TTS [173]. Prolonged medial and/or lateral plantar distal latencies, using absolute values or by comparing to the contralateral asymptomatic limb, are considered diagnostic. Although these studies are easy to perform, they are not sensitive since they only assess tibial motor fibers; only about half of symptomatic limbs have abnormal tibial motor latencies [199].

2. *Mixed medial and lateral plantar NCSs.* These are the most widely employed studies for the evaluation of TTS [200, 201]. Mixed nerve action potentials of the medial and lateral plantar nerves are obtained by percutaneous (surface) stimulation of the medial and lateral plantar nerves on the sole of the foot while recording with surface electrodes over the tibial nerve posterior to the medial malleolus. These studies are the counterparts of the median and ulnar palmar mixed studies performed for the evaluation of carpal tunnel syndrome. Asymmetrical slowing of latency of the medial or lateral (or both) mixed nerve action potentials is considered abnormal. Another likely significant, though poorly localizing, abnormality is absent mixed plantar responses on the symptomatic side. Although this test is more sensitive than the tibial motor distal latencies (abnormal in about 2/3 of symptomatic limbs), it is plagued by many technical problems. It may be technically difficult to elicit these potentials in subjects with foot calluses on the plantar surface of the foot, ankle edema, foot deformities, or even in normal adults over 45 years of age.

3. *Medial and lateral plantar SNAPs.* NCS techniques for assessing solely the sensory fibers of the medial and lateral plantar nerves are reported. The orthodromic techniques consist of stimulating the first and fifth toes while recording from the tibial nerve proximal to the flexor retinaculum [188]. Antidromic studies stimulating the ankle and recording the toes are also possible. A variation of the orthodromic sensory NCS technique includes recording via needle electrode placed close to the tibial nerve and proximal to the flexor retinaculum [202]. Unfortunately, with any of these NCS procedures, the elicited SNAPs are extremely low in amplitude in normal subjects and require signal averaging. Moreover, in some healthy individuals, the responses cannot be evoked. As with the other plantar NCS techniques, prolonged latencies are sought. A possibly significant finding is absent SNAPs on the symptomatic side. This study is sensitive, reported to abnormal in over 90 % of symptomatic limbs [188, 199, 203]. The plantar SNAPs have not gained wide popularity.

Needle EMG examination of the muscles of the sole (such as abductor hallucis and abductor digiti quinti pedis) may be abnormal with TTS if axon loss has occurred. Also, MUAP loss, chronic neurogenic MUAP changes, and fibrillation potentials in various combinations may be found. A complicating factor is that these muscles are painful, difficult to activate, and may show denervation changes in asymptomatic patients, especially in the older age group, probably due to external trauma to the nerves and muscles of the foot [204].

An important task of the EDX studies is to differentiate TTS from peripheral polyneuropathy or S1/S2 radiculopathy, since all three entities result in abnormal tibial motor conduction studies and denervation of intrinsic muscles (Table 41.11). Distinguishing these three disorders is very difficult in the elderly patients in whom lower extremity SNAPs and H-reflexes are often absent.

The effect of surgical decompression of TTS on EDX studies has not been well studied. Improvement of EDX abnormalities has been noted postoperatively in about half of the patients with some residual findings [205, 206]. Thus,

Table 41.11 Electrophysiological differentiation of tarsal tunnel syndrome

	Tarsal tunnel syndrome	Chronic S1/S2 radiculopathy	Peripheral polyneuropathy
Nerve conduction studies			
Sural sensory study	Normal	Normal	Abnormal
Fibular motor study	Normal	Normal or low amplitude	Abnormal
Tibial motor study	Low amplitude and/or slow latency	Normal or low amplitude	Low amplitude and/or slow latency
Motor conduction velocities	Normal	Normal or slowed	Slowed
Plantar mixed nerve conduction studies	Slow latency or absent	Normal	Slow latency or absent
H-reflex	Normal	Abnormal	Abnormal
Upper extremity conductions	Normal	Normal	May be abnormal
Needle EMG			
AH/ADQP	Denervated	Denervated	Denervated
EDB	Normal	Denervated	Denervated
Medial gastrocnemius	Normal	Denervated	Denervated
Tibialis anterior	Normal	Normal	Denervated
Paraspinal muscles	Normal	Normal or fibrillations	Normal or fibrillations
Symmetry of findings	Asymmetrical[a]	Asymmetrical[a]	Symmetrical

Source: Adapted from Katirji [398]. With permission
[a]When bilateral, AH = abductor hallucis, ADQP = abductor digiti quinti pedis, EDB = extensor digitorum brevis

caution should be taken when interpreting the EDX abnormalities after surgery.

Imaging Studies

X-rays of the foot may reveal other causes of foot pain such as a bony spur, ankle or foot deformity, bony prominence from talocalcaneal coalition, or degenerative arthritis. MRI of the ankle is useful in identifying mass lesions within the tarsal tunnel such as ganglion cysts, dilated varicose veins, flexor hallucis longus tenosynovitis, fibrosis, or nerve sheath tumors [207, 208]. High-resolution MR neurography has recently shown promise in detecting focal nerve fibrosis in 90 % of patients [209].

Treatment, Management, and Prognosis

Conservative treatment should be initiated in all patients first. Sources of pressure, such as ill-fitting shoes, should be identified and eliminated. Other helpful measures include minimizing insole or lateral foot wedge. Nonsteroidal anti-inflammatory agents or local injection with long-acting corticosteroids may be also useful in alleviating tenosynovitis or arthritis.

Only a small proportion of patients requires surgical release of the flexor retinaculum. Satisfactory results are variable, ranging from 40 % to 90 % [206, 210–214]. Good results are achieved by selecting patients with documented entrapment who failed conservative treatment or those with identifiable space occupying lesions. Cases associated with foot comorbidities such as ankle trauma or deformities and patients with long duration of symptoms and longer tibial motor nerve conduction latencies have a poorer outcome [206, 210, 213]. Although, most patients improve with minimal sequelae, some may not or go on to develop chronic pain syndromes and features of complex regional pain syndrome.

Interdigital Neuropathy (Morton's Neuroma)

Etiology and Pathogenesis

Morton's neuroma (Morton's metatarsalgia) should be more correctly termed as *interdigital neuropathy* between the third and fourth toes. It is not a true neuroma. Interdigital neuropathies of the web space between the other toes may also occur. Morton's neuroma is caused by compression or entrapment of the interdigital nerve, against the deep transverse metatarsal ligament (Fig. 41.13b). Chronic repetitive compression of the interdigital nerve between the metatarsal heads is a likely mechanism, with hyperextension of the metatarsophalangeal joints being an exacerbating posture and resulting in angulation of the interdigital nerves. Most cases of Morton's neuromas are associated with fixed hyperextension of the metatarsophalangeal joints, which may be congenital or associated with wearing high heels or prolonged squatting. Rheumatoid arthritis, dystonia, and spasticity may also result in fixed hyperextension of these joints with subsequent development of interdigital neuropathies. At surgery, there is often a fibrous nodule of the interdigital nerve near the

metatarsal head which contains nerve fibers with varying degrees of demyelination.

Clinical Presentation

Morton's neuroma is a common source of forefoot pain [215, 216]. Middle-aged women comprise about 3/4 of patients. Foot pain particularly near the arch and the third and fourth toes is the most common presentation. The pain may radiate proximally to the ankle and calf. The pain is often lancinating, worse with weight bearing and relieved by rest. Numbness is not uncommon, often involving two adjoining toes. Involvement of the other interdigital nerves is less common.

The neurological examination reveals numbness in an interdigital nerve distribution. There is no weakness and the rest of the examination is normal. The most sensitive and specific clinical test is the *web space compression test:* while holding the dorsal and plantar aspect of the metatarsal head with the thumb and index fingers, a squeeze may reproduce the symptoms [217, 218]. Occasionally, a Tinel's sign may be also reproduced there.

Differential Diagnosis

Morton's neuroma may mimic other causes of foot pain, such as plantar fasciitis, bursitis, or arthritis. Tarsal tunnel syndrome may involve one plantar nerve only resulting in restricted numbness mimicking Morton's neuroma. However, palpation of the metatarsal heads does not usually reproduce the symptoms. It may be difficult to distinguish interdigital neuropathy from metatarsal joint disease, where the head itself (and not the space between two heads) is tender. Sensory loss and Tinel's signs are usually absent.

Evaluation and Diagnosis

The diagnosis of Morton's neuroma requires a high degree of suspicion, particularly when predisposing factors are present. Evaluation of the foot for deformities, congenital anomalies, or muscle imbalance is important. Web space compression and reproduction of the symptoms is an extremely useful sign [217, 218]. Local anesthetic block may be used as a diagnostic tool, but has no effect on surgical outcome. MRI scan and ultrasonography of the foot are the diagnostic studies of choice with conflicting results on their relative sensitivities [217–219]. MRI is very useful in showing the neuroma and excluding other cause of compressive nerve lesions, but may show neuroma in asymptomatic patients also [218]. Ultrasonography of the foot often shows an ovoid, hypoechoic mass oriented parallel to the long axis of the metatarsal bones. EDX studies are of value, in excluding other peripheral nerve causes of foot pain, such a lumbosacral radiculopathy or TTS. Sensory NCSs of the interdigital nerves, including near-nerve needle and signal averaging techniques, were described, are difficult to evoke, and, hence, have not been widely used [220, 221].

Treatment and Prognosis

Conservative treatment is often useful in alleviating the symptoms and is the first line of therapy [222]. Avoidance of high heels, changing to flat wear, and modification of shoes are often useful. Orthotic inserts or pads may prevent the repetitive compression on the interdigital nerve. Repeated corticosteroid injection may relieve the symptoms in more than half of patients and should be attempted before surgery [223]. Alcohol injection of Morton's neuroma has also been advocated with a high success rate [224]. Surgical neurolysis of the interdigital nerve often results in complete relief of symptoms and is the treatment of choice for many patients [225, 226]. Surgical excision of the neuroma is preferred by others and is indicated for patients who fail neurolysis [226–228]. Failure of neurolysis or neurectomy with persistent pain is reported in 5–10 % of patients [227, 228].

Sural Mononeuropathy

The sural nerve may be damaged at the ankle or calf. Less commonly, the lesion is at the popliteal fossa. Common causes include trauma including fractures, sprains, and lacerations. Mechanical compressions against hard ridges such as while sitting with crossed ankles, wearing tight high-topped boots, or elastic stockings were reported. Less common structural causes include schwannoma, ganglionic cysts, thrombophlebitis, bone tumor, neuroma, or Baker's cyst. Iatrogenic lesions of the sural nerve may follow vein stripping, ankle liposuction, ankle or knee arthroscopy, gastrocnemius muscle biopsy, and a variety of popliteal fossa surgical procedures [229–231].

The sural nerve is often used for nerve grafting and for diagnostic nerve biopsy. Immediate postoperative complications following this procedure, including infections or delayed wound healing, occur in up to 20 % of patients, particularly those with peripheral neuropathy or diabetes mellitus [232, 233]. Numbness and dysesthesia in sural sensory distribution occur in about half of the patient, decreasing over the next few years to a small area of hypesthesia [232, 233]. Delayed persistent pain (sural neuralgia) occurs in up to 30 % of patients and may be due to a neuroma formation [233]. An anterior fascicular sural nerve biopsy which preserves lateral heel sensation has been advocated with a reduction in the incidence of chronic foot pain [234].

The symptoms of sural mononeuropathy include pain and paresthesias in the lateral ankle and foot. Tinel's sign may be elicited along its course. The neurological examination reveals well-demarcated sensory loss in the sural nerve distribution with normal strength and reflexes. The sensory loss associated with sural neuropathy may mimic an S1 radiculopathy. However, lesions of the S1 root often results in absent or depressed ankle jerk with variable weakness of plantar flexion.

With EDX testing, sural nerve SNAP is usually absent or low in amplitude, while all other lower extremity NCSs and needle EMG are normal. In contrast, the SNAP in S1 radiculopathy is normal and there is often denervation in the gastrocnemius and other S1-innervated muscles. It should be noted that the sural SNAP may be difficult to evoke in the elderly or with ankle edema.

The treatment of sural mononeuropathy is directed toward the cause, such as removal of a mass lesion. Changing foot gear often improves the compressive symptoms. Patients with sural neuralgia may be treated with anticonvulsants, such as gabapentin and pregabalin, or antidepressants, such duloxetine and amitriptyline. Patients with a neuroma may respond to nerve excision and transposition of stump into bone or muscle.

The Femoral Nerve

Anatomy

The femoral nerve is formed by the combination of the posterior divisions of the ventral rami of L2, L3, and L4 spinal roots. The anterior divisions of the same roots form the obturator nerve. The femoral nerve, also called the anterior crural nerve, is a relatively short nerve. Soon after its formation in the pelvis, it innervates to the psoas muscle which receives additional separate branches from the L3 and L4 roots directly. The femoral nerve passes between the psoas and iliacus muscles and is covered by the tight iliacus fascia, which forms the roof of the iliacus compartment. The iliopsoas muscle and femoral nerve are the main constituents of this compartment.

The femoral nerve emerges from the iliacus compartment after passing underneath the rigid inguinal ligament in the groin. About 4–5 cm, before crossing the inguinal ligament, it innervates the iliacus muscle. Soon after passing underneath the ligament, the femoral nerve branches widely into (1) terminal motor branches to all four heads of the quadriceps (rectus femoris, vastus lateralis, vastus intermedius, and vastus lateralis) and sartorius muscles, and (2) three terminal sensory branches, the medial and intermediate cutaneous nerve of the thigh which innervate the skin of the anterior thigh, and the saphenous sensory nerve (Fig. 41.15).

The saphenous nerve travels the thigh, lateral to the femoral artery, by passing posteromedially from the femoral triangle through the subsartorial (Hunter's or adductor) canal. It gives off the infrapatellar branch that innervates the skin over the anterior surface of the patella. About 10 cm proximal and medial to the knee, the saphenous nerve becomes subcutaneous by piercing the fascia between the sartorius and gracilis muscles. Then, it crosses a bursa at the upper medial end of the tibia (pes anserinus bursa). In the lower third of the leg, it divides into two terminal branches to innervate the skin of the medial surface of the knee, medial leg, medial malleolus, and a small area of the medial arch of the foot (Fig. 41.15).

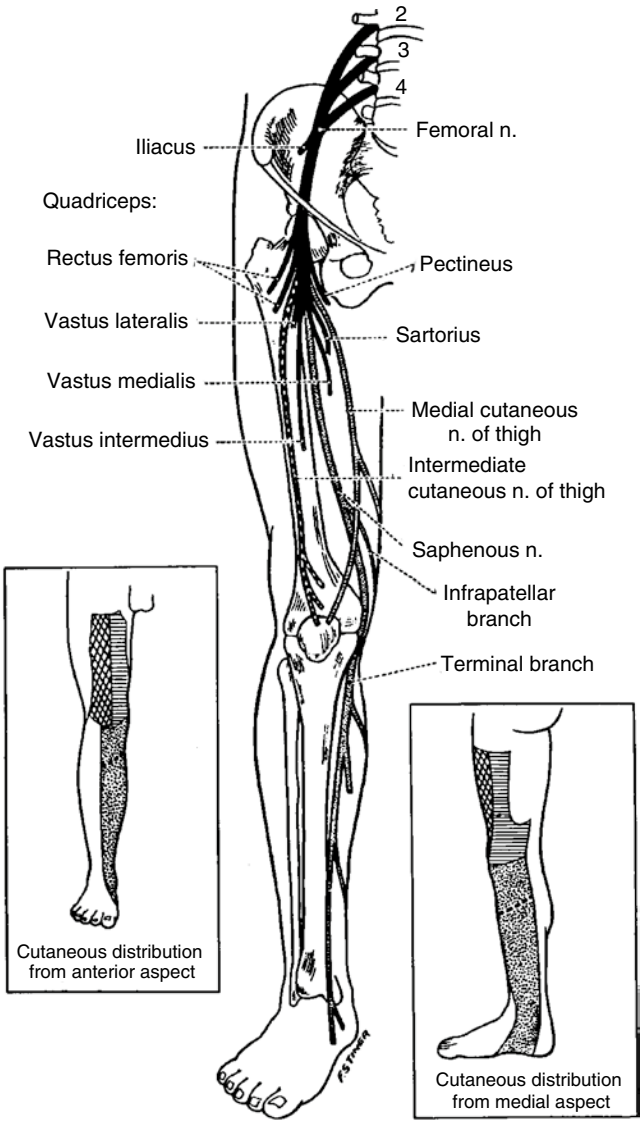

Fig. 41.15 The femoral nerve and its terminal motor and sensory branches and cutaneous distribution. The patterns of the cutaneous nerves are duplicated in the inserts. The broken line in the inserts represents the boundaries between the infrapatellar and terminal branches of the saphenous nerve (From Haymaker and Woodhall [393]. With permission)

Femoral Mononeuropathy

Etiology and Pathogenesis

Because of its short course, the main trunk of the femoral nerve is usually injured at one of the two sites: the retroperitoneal pelvic space or the inguinal ligament

Table 41.12 Common causes of femoral mononeuropathy

1. Compression in pelvis
By retractor blade during pelvic surgery
(Abdominal hysterectomy, radical prostatectomy, renal transplantation, etc.)
By iliacus or psoas retroperitoneal hematoma
(Anticoagulation (systemic or subcutaneous abdominal heparin), hemophilia, coagulopathy, ruptured abdominal aneurysm, femoral artery catheterization)
By pelvic mass (lymphadenopathy, tumor, abscess, cyst, aortic or iliac aneurysm)
2. Compression in the inguinal region
By inguinal ligament during lithotomy position
(Vaginal delivery, laparoscopy, vaginal hysterectomy, urological procedures)
By inguinal hematoma
(Femoral artery catheterization such as for coronary angiography)
During total hip replacement
By inguinal mass (e.g., lymphadenopathy)
3. Stretch injury (hyperextension, dancing, Yoga)
4. Others (radiation, laceration, misplaced injection)

Source: Adapted from Katirji [398]. With permission

(Table 41.12). Most femoral mononeuropathies are iatrogenic, occurring during intra-abdominal, intrapelvic, inguinal, or hip surgical or diagnostic procedures. The nerve injury often results from direct nerve trauma or poor leg positioning during the procedure but may be due to a compressive hematoma.

Iatrogenic nerve injury during pelvic surgical procedures is the most common cause of femoral mononeuropathy. This may occur following a variety of procedures including abdominal hysterectomy, radical prostatectomy, renal transplantation, colectomy, proctectomy, inguinal herniorrhaphy, lumbar sympathectomy, appendectomy, tubal ligation, abdominal aortic repair, and a variety of other intra-abdominal vascular, urological, or gynecological operations [235–245]. During these surgical procedures, the lateral blade of the retractor compresses the intrapelvic portion of the femoral nerve against the pelvic wall. Most cases occur following the use of self-retracting blades compared to the handheld blades [239, 245]. With an incidence of 7–11 % in patients undergoing abdominal hysterectomy; avoiding using retractors during gynecological operations decrease this incidence of femoral nerve injury by 93 % [245]. The incidence of femoral neuropathy after renal transplantation is about 2–3 % [236, 237]. In addition to retractor injury, femoral nerve ischemia is a possible mechanism since the incidence correlates with selection of iliac artery anastomosis and the duration of the arterial anastomosis [236]. In addition to possible ischemia, the postoperative femoral nerve lesions may be caused by postoperative retroperitoneal hematoma or inadvertent laceration or suturing of nerve [235, 246]. Stapling of the femoral nerve may also occur following laparoscopic inguinal hernia repair [241, 242, 247].

Femoral mononeuropathy may occur during surgical procedures of the hip joint [100, 102, 248–250]. Total hip replacement may result in iatrogenic femoral nerve injury in 0.1 to 2.4 % of patients [250]. The femoral injury is considered to be due to misplacement of the anterior acetabular retractors during the procedure, but recent experimental studies suggested that it is likely due to the incorrect use of instruments or implants (e.g., screws, cement, acetabular cup) [251]. Regardless of exact cause, these lesions are most frequent in revisions, anterolateral approach, and complicated reconstructions [248].

Acute hemorrhage in the iliacus compartment may lead to a compartmental syndrome which results in iliopsoas muscle or femoral nerve ischemia or both. Occasionally, the hematoma is large and extends into the psoas muscle or retroperitoneal space leading to a more extensive injury of the lumbar plexus or entire lumbosacral plexus. These hematomas may be a complication of anticoagulant therapy (heparin or warfarin), hemophilia or other blood dyscrasias, ruptured abdominal aortic aneurysm, pelvic operations, or traumatic rupture of the iliopsoas muscle [252–254]. Iatrogenic hemorrhage may occur following femoral artery (and less commonly femoral vein) catheterization for a variety of reasons, including coronary, cerebral, and aortic angiography [254, 255]. The prevalence of retroperitoneal hemorrhage is about 0.5 % of femoral artery cannulation for cardiac catheterization, but is probably on the rise, particularly with the increase use of thrombolytic agents. About a third of these hemorrhages result in femoral nerve injury or a lumbar plexopathy [254, 255].

Compression of the femoral nerve may occur at the inguinal ligament during lithotomy positioning for a variety of procedures. This often follows prolonged lithotomy positioning, particularly with extreme hip flexion and external rotation [256, 257]. The nerve is often kinked under the inguinal ligament but may also be stretched by excessive hip abduction and external rotation. These lesions are often associated with vaginal delivery and are likely underestimated since most are mild and recover rapidly. The reported incidence has declined, possibly due to the increased use of cesarean section and/or increased awareness of this complication, from about 4.7 % to about 2.8/100,000 deliveries (0.00028 %) [258]. Femoral mononeuropathy due to lithotomy positioning may also occur with other procedures including vaginal hysterectomy, prostatectomy, and laparoscopy [243, 259–261].

Pelvic mass lesions, other than hematomas, may also compress the femoral nerve. These include lymphadenopathy, abscess, cyst, enlarged iliac or aortic aneurysm, or tumor such as lymphoma and primary malignancy of colon, rectum, or ilium. Femoral nerve tumors, such as neurofibromas,

schwannomas, and neurogenic sarcoma, are relatively rare [262, 263].

Femoral nerve traumatic stretch may occur with hyperextension of the hip, such as in dancers, or with prolonged squatting such as during Yoga exercise [264, 265]. Selective injury of the motor branch to the vastus lateralis may also occur in athletes [266]. Femoral nerve injury may result from penetrating gunshot and stab wounds, lacerations, and contusions injuries associated with pelvic fractures.

A discussion of femoral neuropathy is incomplete without referring to the so-called diabetic femoral neuropathy. Earlier clinical reports suggested that selective femoral neuropathy may be a complication of diabetes mellitus. However, it is now clear that this is a misnomer. Diabetic patients actually have more extensive subacute peripheral nerve disease involving the lumbosacral plexus and spinal roots consistent with diabetic radiculoplexopathy, also known as diabetic amyotrophy or diabetic proximal neuropathy (see Chap. 31) [267, 268]. Although the brunt of weakness in these patients often falls on the quadriceps muscle, mimicking selective femoral nerve injuries, careful clinical and needle EDX examination reveal more widespread involvement of thigh adductors and sometimes foot dorsiflexors, muscles not innervated by the femoral nerve [269]. Despite the current knowledge, the term diabetic femoral neuropathy, unfortunately, has not completely vanished [270].

Clinical Presentation

Most cases of femoral mononeuropathies are unilateral, while bilateral lesions may occur, particularly after lithotomy positioning [244, 256, 264]. The clinical presentation of femoral nerve lesions is often acute, with thigh weakness and anterior thigh and leg numbness. Patients frequently complain that their leg buckles underneath them which may lead to falls. Acutely, groin or thigh pain is usually mild, while a deep delayed pain and hyperesthesia are not uncommon. An exception to this is in patients with retroperitoneal hematomas, who often complain of severe acute pain in the back, abdomen, groin, buttock, or anterior thigh and tend to keep their hip flexed.

The neurological examination reveals weakness of knee extension (quadriceps) with absent or depressed knee jerk. Thigh adduction and ankle dorsiflexion are, however, normal. Hip flexion (iliopsoas) is usually weak when the lesion is intrapelvic (such as during pelvic surgery), but spared when the lesion is at the inguinal region (such as during lithotomy positioning). Sometimes, it is difficult to examine hip flexion accurately because of groin or abdominal pain such as following recent pelvic surgery, vaginal delivery, or with iliacus hematoma. Hypesthesia over the anterior thigh and medial calf is common. A positive reversed straight leg test (pain in anterior thigh with extension of hip) may occur in femoral nerve lesion, particularly when associated with iliacus or retroperitoneal hematoma.

Differential Diagnosis

Quadriceps weakness with absent/depressed knee jerk and sensory manifestations in anterior thigh are manifestations shared not only by femoral neuropathy but also by an upper lumbar (L2, L3, and L4) radiculopathy (such as with disc herniation) and lumbar plexopathy (such as with diabetic amyotrophy). Careful examination of the thigh adductors, innervated by the L2, L3, and L4 roots via the obturator nerve, is extremely important, since weakness of these muscles is inconsistent with a femoral neuropathy and points to a lesion proximal to the femoral nerve. Also, weakness of ankle dorsiflexion (tibialis anterior), innervated by the L4 and L5 roots via the common fibular nerve, is highly suggestive of an L4 radiculopathy or lumbar plexopathy. Back and buttock pain and a positive reversed straight leg are common in upper lumbar radiculopathy, but may occur with lumbar plexopathy and femoral mononeuropathy, particularly when due to retroperitoneal hematoma or mass.

Sensory loss in the anterior thigh due to femoral neuropathy may occasionally be confused with meralgia paresthetica (lesion of the lateral femoral cutaneous nerve). This is particularly true in mild femoral nerve lesion when weakness of thigh muscles or depressed knee jerk may not be present. The sensory loss in meralgia paresthetica is lateral, does not extend beyond the knee, and rarely crosses the anterior midline of the thigh. In contrast, the sensory loss in femoral nerve lesions is anterior and often extends beyond the knee to include the medial leg (saphenous distribution).

Evaluation and Diagnosis

Since the majority of femoral nerve lesions are iatrogenic, a detailed history is extremely important. Acute quadriceps weakness, anterior thigh numbness, and depressed-absent knee jerk following abdominal surgery, particularly when using self-retractors, are highly suggestive of an intrapelvic femoral neuropathy. Similar manifestations, particularly when associated with severe pain and occurring in the setting of anticoagulation, coagulopathy, femoral vessel catheterization, or trauma, should raise the question of a femoral nerve injury due to an iliacus or retroperitoneal hematoma. Unilateral or bilateral quadriceps weakness following vaginal delivery, urological procedures, or laparoscopy, particularly when the iliacus muscle function is preserved, is often diagnostic of a femoral nerve compression at the inguinal ligament.

Electrodiagnostic Studies

The EDX testing in a patient with suspected femoral neuropathy is extremely useful in (1) confirming the presence of a selective femoral mononeuropathy, (2) excluding a lumbar plexopathy and radiculopathy, (3) localizing the site of femoral nerve injury, and (4) predicting the prognosis by assessing the primarily pathophysiological process (segmental demyelination or axonal loss).

The saphenous SNAP evaluates the postganglionic L4 sensory fibers and plays an important role in the differential diagnosis of femoral nerve lesions. It is often absent in femoral neuropathy and lumbar plexopathy but normal in L4 radiculopathy since the root lesion is intraspinal, i.e., proximal to the dorsal root ganglion. Rarely, the saphenous SNAP is normal in "purely" demyelinating femoral mononeuropathies where there is no Wallerian degeneration which is usually complete in 10–11 days in sensory fibers. The saphenous SNAPs should be studied bilaterally for comparison, since these potentials may be difficult to obtain in the elderly and obese patients and in patients with leg edema.

Femoral motor conduction studies are important in the assessment of the primary pathophysiological process and prognostication of femoral mononeuropathy [256, 271]. In contrast to many peripheral nerves, the femoral nerve may be only stimulated in the groin, allowing evaluation of a distal CMAP only. A femoral CMAP amplitude and/or area, obtained after 4 to 5 days from injury (the time needed for completion of Wallerian degeneration of motor axons), reflects, semiquantitatively, the primary pathophysiological process and predicts the prognosis. If the femoral CMAP amplitude and/or area is low or absent, in the presence of moderate or severe impairment of recruitment of quadriceps MUAPs, the lesion is primarily axonal. The prognosis is relatively protracted since it will depend on sprouting and reinnervation. Patients with CMAP amplitude more than 50 % of the contralateral side improve within 1 year, while fewer than half of the patients with a CMAP less than 50 % of the contralateral side improve [271]. In contrast, when the femoral CMAP amplitude and/or area is normal despite significant reduction of MUAP recruitment, the lesion is primarily demyelinating and the prognosis is excellent since it is dependent on remyelination. All patients with such findings recover in 6–8 weeks.

Needle EMG is essential in all patients with femoral mononeuropathy in order to localize the site of femoral nerve lesion and exclude a lumbar radiculopathy or plexopathy. Fibrillation potentials and decreased recruitment of MUAPs of quadriceps are common in all three entities. However, these changes are present in the thigh adductors (L2/L3/L4 – obturator nerve) only in patients with upper lumbar radiculopathy or plexopathy. Also, in L4 radiculopathy, similar neurogenic changes may be present in the tibialis anterior (L4/L5 – common fibular nerve). Since the branch to the iliacus muscle originates 4–5 cm above the inguinal ligament, sampling this muscle determines whether the femoral nerve lesion is distal (i.e., around the inguinal ligament) or proximal (i.e., intrapelvic). Fibrillation potentials are a poor quantitative measure of the extent of this axonal loss since they are identified whenever axonal loss occurs, even if minimal. Thus, these potentials identify the presence of axonal loss but do quantitate its extent, and are therefore, by themselves, poor indicators of the extent of peripheral nerve injury. The amplitude and/or area of the femoral CMAP is the best quantitative measure of motor axonal loss.

Imaging Studies

In patients with acute femoral mononeuropathy and severe pain, particularly in the setting of anticoagulation, coagulopathy, or femoral vessel catheterization, a retroperitoneal hematoma should be considered and confirmed (or excluded) urgently by a CT scan of the pelvis. CT or MRI of the pelvis is also useful in patients with suspected pelvic mass lesion or femoral nerve tumor.

Treatment, Management, and Prognosis

Most patients with femoral mononeuropathy are treated conservatively waiting for spontaneous remyelination and reinnervation. A knee-ankle-foot or knee only orthosis is helpful for patients with severe weakness of the quadriceps to assist in walking and prevent falls [272]. Anticonvulsants or antidepressants may be used for the delayed pain and hyperesthesia associated with femoral nerve lesions.

Hematoma evacuation in patients with iliacus or retroperitoneal hematoma at the time of the development of femoral neuropathy shortens the recovery period and results in rapid return of neurological function [252, 253]. Ideally, hematoma evacuation should occur as soon as it is detected and before signs of severe femoral nerve injury occur. Without operative treatment, the neurological deficit persists with a protracted leg weakness.

Compared to other peripheral nerve injuries, femoral mononeuropathy carries a relatively good prognosis due to its short length, even when the lesion is due to axonal loss. The quadriceps, which is the most clinically relevant muscle, is proximal and relatively near the injury sites at the inguinal ligament or in the pelvis. These optimal conditions often lead to effective sprouting and reinnervation in axonal loss lesions. As outlined, the femoral CMAP amplitude is the best estimate of the extent of axonal loss and is the only independent factor influencing prognosis [256, 271]. Demyelinating femoral nerve lesions often recover in 2 to 3 months by remyelination, whereas axonal lesions require one or more years. In general, compressive femoral mononeuropathies at the inguinal ligament following childbirth or laparoscopy tend to be demyelinating and recover rapidly, while lesions caused by iliacus hematomas are axonal with a more protracted recovery.

Prevention of iatrogenic femoral nerve lesions is essential. Eliminating retractors, particularly self-retractors, during pelvic surgery decreases the incidence of these lesions [239]. Compression at the inguinal ligament may be prevented by avoiding prolonged lithotomy positioning and extreme hip flexion and external rotation.

Saphenous Mononeuropathy

Saphenous mononeuropathies are usually iatrogenic occurring after vascular or orthopedic operations. Saphenous nerve damage occurs in up to 40 % of patients undergoing stripping of the long saphenous varicose vein, but only 6–7 % of patients have persistent and disabling sensory loss [273–276]. Also, harvesting the long saphenous vein for a coronary artery bypass is often complicated by damage to the saphenous nerve [277–279]. About 10 % of patients undergoing arterial operations in the thigh, such as superficial femoral thromboendarterectomies or femoropopliteal bypass grafts, develop saphenous mononeuropathy [280, 281]. Surgical operations on the knee, including meniscectomies and arthroscopic procedures, may injure the saphenous nerve or its infrapatellar branch [282–284]. Entrapment of the saphenous nerve may occur as it exits the subsartorial (adductor or Hunter) canal or by pes anserine bursitis [285–287]. The infrapatellar branch may be entrapped behind the sartorius tendon or injured with acute or repetitive medial knee trauma [288]. Schwannomas of the saphenous nerve or its infrapatellar branch are described [289].

Patients with saphenous mononeuropathy often complain of paresthesias or hyperesthesias of medial leg that may extend into the medial arch of the foot. Knee pain is common and may be the presenting symptom [288]. Leg pain with allodynia is also common and is sometimes referred to "saphenous neuralgia" [279, 281]. Selective infrapatellar branch entrapment often causes anterior, anteromedial, or anterolateral knee pain with minimal sensory loss confined to small patch below the knee. In entrapment of the saphenous nerve, tenderness or Tinel's sign may be elicited on percussion of the saphenous nerve at its subsartorial exits, four finger breadths above the medial condyle of the femur.

On EDX studies saphenous SNAP is the most important study. This study is technically difficult, especially in the elderly and obese patients [290, 291]. The study should be obtained bilaterally and a proximal technique should be done if the more common distal response could not be evoked bilaterally [290, 291]. Saphenous nerve lesions should be differentiated from L4 radiculopathy, lumbar plexopathy, or femoral mononeuropathy, and the EDX studies are useful in confirmation. Muscle strength and needle EMG of quadriceps, iliacus, and thigh adductors are normal in patients with saphenous mononeuropathy. Saphenous SNAP is often absent or low in amplitude in patients with saphenous or femoral nerve lesions but normal in L4 radiculopathy (see femoral nerve). The pain in patients with infrapatellar branch lesions mimics various pathology of the knee joint which should always be excluded.

Treatment of patients with saphenous nerve lesions depends on its causation. The circumference of the saphenous sensory loss becomes smaller with time in iatrogenic lesions [273, 274]. Topical lidocaine or capsaicin creams are fairly effective [292]. Saphenous nerve blocks may alleviate the symptoms in patients with entrapment at the subsartorial canal. Decompression of the saphenous nerve at this canal or the infrapatellar branch near the sartorius tendon may resolve the symptoms in patients with definite nerve entrapment.

Prevention of iatrogenic lesions is accomplished by a meticulous knowledge of the anatomy of the saphenous nerve and its infrapatellar branch [284, 293, 294]. During saphenous vein harvest, the most vulnerable area, which is the inferior third of the leg, should be avoided [293]. Saphenous nerve injury during stripping of varicose veins is significantly reduced by removal of only the femoral part of the vein or by downward (rather than upward) stripping of the long saphenous vein [275, 276].

The Lateral Femoral Cutaneous Nerve

Anatomy

The lateral femoral cutaneous nerve (lateral cutaneous nerve of the thigh, LFCN) is formed from sensory fibers originating from the ventral rami of L2 and L3 spinal roots (Fig. 41.16). The nerve travels within the lower abdominal muscles and crosses the iliacus muscle. The LFCN leaves the pelvis by passing underneath or within the inguinal ligament, 1.5 cm medial to its lateral insertion at the anterior superior iliac spine in 60 % of subjects. In 20 % each, the nerve exits the pelvis at or lateral to the anterior superior iliac spine [295, 296]. The LFCN, then, changes its direction from a horizontal to a vertical course and pierces the fascia lata a short distance below the inguinal ligament. Soon after, the LFCN divides into its terminal branches in the leg to innervate the skin of the lateral thigh. Although the sensory territory of the nerve is slightly variable between individuals, it does not extend beyond the knee and seldom across the anterior or posterior midline of the thigh.

Etiology and Pathogenesis

Mononeuropathy of the LFCN is the most common pure sensory mononeuropathy in the lower extremity. It is often referred to as *meralgia paresthetica* (Greek: mèros = thigh and algo = pain) or the Bernhardt-Roth syndrome. Meralgia paresthetica is often due to entrapment of the LFCN under or through the inguinal ligament where it is engulfed by multiple layers of fascia. This was confirmed histologically by the presence of focal demyelination, Wallerian degeneration, and internodal swellings at that site [297].

The majority of cases of meralgia paresthetica are idiopathic, though the disorder is frequently associated with pregnancy, diabetes mellitus, advancing age, and obesity [298–302]. The incidence rate of meralgia paresthetica is

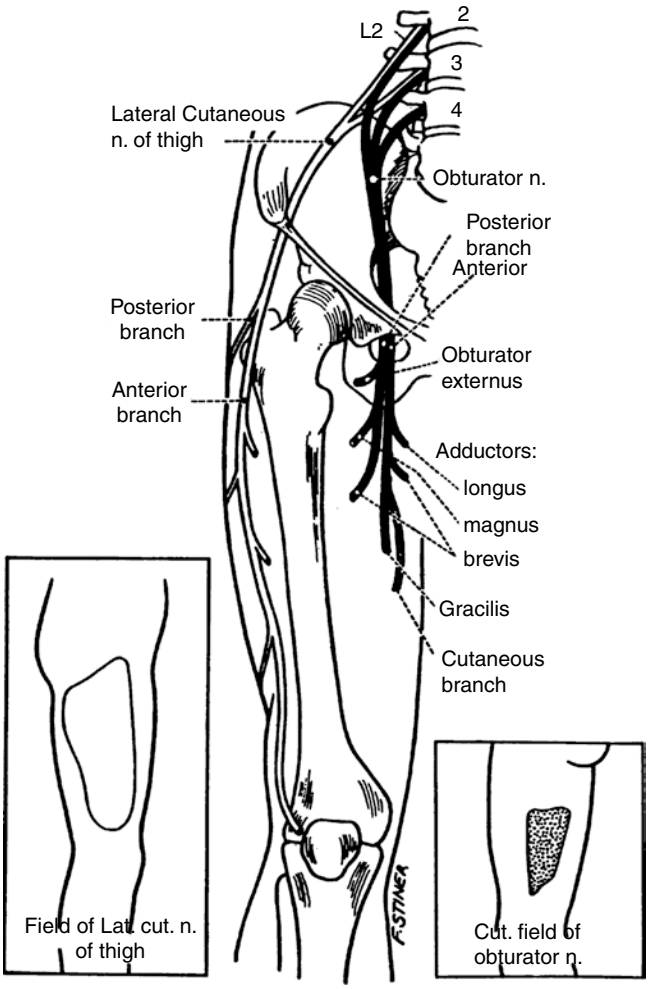

Fig. 41.16 The lateral cutaneous of the thigh and obturator nerves (From Haymaker and Woodhall [393]. With permission)

32.6 per 100,000 patient years and in the diabetic population 247 per 100,000 patient years (7½ times the general population). The association with diabetes is independent of body weight [298, 299]. It often manifests between the ages of 55 and 65 years. Compression of the nerve at the inguinal ligament may occur during occupational activities, such as wearing large tool belts, leaning against a tool bench or gymnastic bars, or simply by wearing tight clothing, low-cut trousers, body armor wears, or large pagers [303–306]. Iatrogenic lesions are described following iliac bone graft, misplaced injection, hip surgery, or pelvic surgery such as renal transplantation, gastric bypass, and laparoscopic herniorrhaphy [307–309]. Meralgia paresthetica may occur during anesthesia in the prone position such as for thoracolumbar spine surgery [310]. Although intrapelvic retractor injury explains many of the postoperative meralgia paresthetica, prolonged postoperative hip flexion following abdominal surgery or prolonged "frog-leg" positioning during vein harvesting for coronary artery bypass or during the relaxed postanesthesia period may explain some of these nerve lesions [311, 312]. Blunt trauma, such as avulsion fracture of the anterior superior iliac spine or seat belt trauma, or laceration may occasionally cause a lesion of the LFCN [313–315]. A pelvic or bone mass such as abdominal aortic aneurysm or metastatic tumor to the iliac crest may present with manifestations of a mononeuropathy of the LFCN [316–318].

Clinical Presentation

Almost all patients present with numbness and pain (hence the appropriate term meralgia paresthetica). The paresthesias may be unpleasant and annoying, often described to correlate with a trouser pocket area. Deep pain is rare while burning and stinging are common. Hyperesthesia and, sometimes, allodynia may occur. The symptoms may worsen with standing, walking, or turning in bed or improve with hip flexion. Despite transient symptoms, the neurological examination often detects a well-circumscribed area of sensory loss to touch and pin prick in the distribution of the LFCN, in its entirety, in a smaller area within the center of its territory, or in one of its terminal branches. In the majority of the patients, the sensory loss is in the lateral aspect of the thigh, but in 20 % the sensory loss extends or is exclusively in the anterior thigh [300]. Alopecia restricted to the area of sensory loss has been described [319].

Differential Diagnosis

Meralgia paresthetica may be confused with an upper lumbar radiculopathy, particularly L2 or L3 radiculopathy, a femoral mononeuropathy, or lumbar plexopathy. The sensory impairment in L2 or L3 radiculopathy is not well circumscribed, and there is often deep seated back, buttock, and groin pain. In femoral neuropathy and lumbar plexopathy, the numbness often involves the anterior thigh and does not respect the anterior thigh midline, often extending medially in the thigh and leg. Also, lower extremity weakness or depressed knee jerk often excludes meralgia paresthetica. Because of fluctuating pain, particularly if worsened by standing and walking, this disorder may be mistaken for lumbar spinal stenosis. However, the symptoms in spinal stenosis are often bilateral, the sensory manifestations not well demarcated, and there may be associated weakness or reflex changes.

Evaluation and Diagnosis

The diagnosis of meralgia paresthetica is straightforward to most neurologists, although it may be elusive to other physicians in more than 50 % of the patients [300]. Often, the patient is able to outline the exact area of sensory loss, which often correlates with the cutaneous distribution of the LFCN or one of its branches. A detailed history may reveal the precipitating cause such as weight gain or wearing tight pants. Imaging is often unnecessary except if an abdominal mass is suspected. Then, a CT scan of the pelvis is indicated.

EDX testing in meralgia paresthetica is important in excluding lumbar radiculopathy and plexopathy. SNAP of the LFCN

may be recorded antidromically or orthodromically, but may be absent in healthy subjects, particularly in women and obese individuals, or on the asymptomatic side in symptomatic individuals. Stimulating 4 cm distal rather than 1 cm medial to the anterior superior iliac spine evokes a response in 90 % of healthy subjects [320]. In patients with meralgia paresthetica, asymmetrically low-amplitude (at least half of the contralateral) or absent SNAP on the symptomatic side is the most specific EDX finding [300]. Somatosensory evoked potentials (SEP) of the LFCN are also possible. Dermatomal SEP (stimulating the lateral thigh) is more diagnostic than segmental SEP (stimulating the lateral femoral cutaneous nerve near the anterior superior iliac spine) [321, 322]. Absolute lateral femoral cutaneous SEP latency, absent response, and amplitude reduction (>50 % compared with the contralateral response) are considered diagnostic findings [323]. Comparison of the ipsilateral dermatomal SEP to the commonly studied tibial SEP is also useful in confirming the diagnosis of meralgia paresthetica with high sensitivity and specificity [324].

Treatment and Prognosis

Meralgia paresthetica is often a self-limiting disease with resolution of symptoms with time in the majority of patients. Pregnant women resolve after delivery and obese patients improve with weight loss. In diabetic patient, there is a tendency for slow improvement, though residual sensory loss in a smaller territory may persist for few years. Addressing compressive elements such as tight clothing or large belts is essential. Recurrence may occur with subsequent pregnancies or in diabetics.

Treatment should be initiated if neuropathic pain is intolerable. Antidepressants (such as tricyclics and duloxetine), anticonvulsants (such as carbamazepine, pregabalin, and gabapentin), or local treatment (such as capsaicin or lidocaine patch or cream) is often useful. Steroid injections may be helpful in resistant cases and are used as a prognostic indicator for the outcome of surgery [325]. Surgical decompression of the LFCN is indicated in patients with persistent pain and no precipitating risk factor [325–328]. Children tend to be more resistant to conservative treatment than adults and more often are treated surgically [329]. Neurolysis, decompression, and sectioning of the nerve (neurectomy) are all effective with 90–95 % success rate [325–328]. It should be noted that obesity has a poor outcome in general [328], and neither the lateral femoral SNAP nor the SEP has a predictive value on the outcome of meralgia paresthetica [330].

The Ilioinguinal Nerve

The ilioinguinal nerve originates from L1 spinal root, passes next to the lateral border of the psoas muscle, and follows the abdominal wall similar to an intercostal nerve. When the ilioinguinal nerve passes medial to the anterior superior iliac spine, it pierces the transverse and internal oblique muscles and runs along the inguinal canal with the genital branch of genitofemoral nerve and spermatic cord in men and the round ligament in women. The ilioinguinal nerve innervates the lower abdominal muscles and a strip of skin along the inguinal ligament to the base of penis and scrotum in men or labium majus in women (Fig. 41.17).

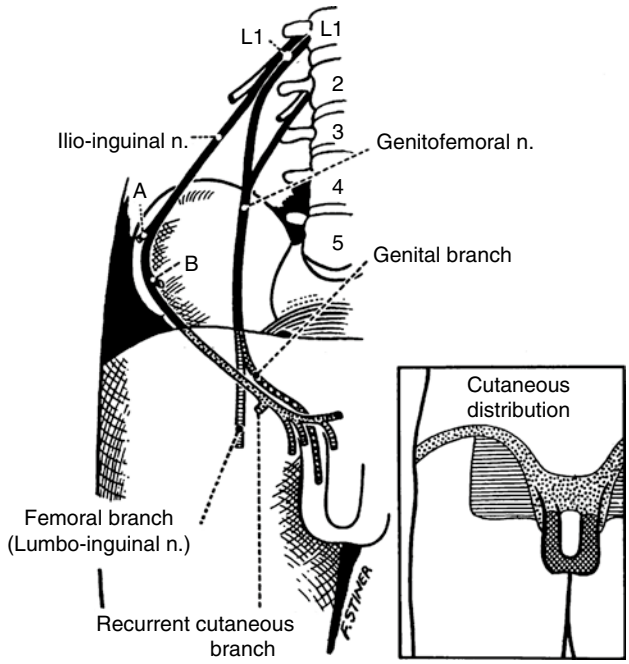

Fig. 41.17 The ilioinguinal and genitofemoral nerves. A and B are motor branches to the abdominal muscles (From Haymaker and Woodhall [393]. With permission)

Lesions of the ilioinguinal nerve are usually caused by iatrogenic nerve damage, trauma, or entrapment. Laparoscopic or open hernia repair is the most common cause of ilioinguinal nerve lesions [331, 332]. Chronic inguinal neuralgia after herniorrhaphy is likely caused by the entrapment of the sensory nerve in the scar tissue formed by the polypropylene mesh [333]. Other surgical operations, such as appendectomy, bladder suspension, iliac bone grafting, and gynecologic operations using the transverse (Pfannenstiel) incisions, may also injure the ilioinguinal nerve [334]. A blow to the lower abdomen may cause damage to the nerve. Entrapment of the ilioinguinal nerve may occur at the abdominal outlet medial to the anterior superior iliac spine.

Patients with ilioinguinal mononeuropathy often complain of burning pain in the lower abdomen radiating to the upper thigh and into the scrotum or labium majus. Sensory loss in the ilioinguinal nerve distribution is also common. The pain or sensory symptoms may worsen with extension of the hip, and the patients may be only comfortable in the flexed position. Tinel's sign may be induced by tapping the lower abdomen. A well-circumscribed trigger point medial and below the anterior superior iliac spine may be present in patients with entrapment of the ilioinguinal nerve. Bulging

of the lower abdominal wall, due to weakness of transverse and internal oblique muscles, may occur in severe lesions.

Ilioinguinal mononeuropathy should be differentiated from adjacent sensory mononeuropathies of the groin including iliohypogastric and genitofemoral nerve lesions (see below). Concomitant iatrogenic injuries of two or more of these nerves are common. High lumbar radiculopathies, such as L1 or L2 radiculopathy, cause groin pain and numbness and may be associated with ilioinguinal nerve lesions that may be mistaken as a frank hernia. Often, diagnostic nerve block is needed for confirmation [331, 334]. EDX studies, particularly the sensory nerve conduction studies, are not popular for technical reasons. However, needle EMG of lower abdominal muscles may reveal denervation [335]. Needle EMG of the upper lumbar paraspinal muscles is useful in excluding a high lumbar radiculopathy.

Treatment of ilioinguinal nerve lesion is often surgical. Nerve blocks may offer transient relief but are more important diagnostically. Surgical exploration with neurectomy (nerve section) is advocated with good results in over 3/4 of patients [336, 337]. Pulsed radiofrequency lesioning of the ilioinguinal nerve is also an alternate method [338]. Prevention of ilioinguinal nerve injury during abdominal operations is essential. In inguinal hernia repair, the ilioinguinal nerve should be displaced from the spermatic cord, and, in appendectomy, the incision should be more than 3 cm from the anterior superior iliac spine [339, 340]. There is a continuous debate as to whether division of the ilioinguinal nerve during inguinal hernia repair reduces the incidence of ilioinguinal nerve injury and chronic groin pain/neuralgia [341–343].

The Iliohypogastric Nerve

The iliohypogastric nerve originates from the L1 spinal root with occasional contribution from the T12 root. The nerve crosses the psoas and the quadratus lumborum muscles and the lower border of the kidney. Near the iliac crest, the iliohypogastric nerve passes through the transverse and internal oblique abdominal muscle after giving them off small motor branches. It then divides into two cutaneous terminal branches: a lateral branch which innervates a small strip of skin in the upper lateral buttock and an anterior branch which innervates a small area of skin above the pubis symphysis.

Isolated lesions of the iliohypogastric nerve are extremely rare and usually iatrogenic. More often the nerve is injured along with the ilioinguinal nerve because of their close anatomic relationship. Most cases occur after appendectomy, hernia repair, abdominoplasty, nephrectomy, or gynecologic surgery using the transverse (Pfannenstiel) incisions [337, 344]. Entrapment of the iliohypogastric nerve has not been described.

The clinical manifestations of iliohypogastric nerve lesions include pain above the symphysis and sensory loss in a small area above the symphysis. Bulging of abdominal wall is rare, often seen when there is concomitant involvement of the ilioinguinal nerve.

Iliohypogastric nerve lesions should be differentiated from other proximal sensory mononeuropathies around the groin, including ilioinguinal and genitofemoral nerves, and from L1 or L2 radiculopathy. Diagnostic nerve block is useful in confirmation of diagnosis. Nerve conduction studies of the iliohypogastric nerve have not been described. Needle EMG of lower abdominal muscles may reveal denervation, particularly when associated with ilioinguinal nerve lesion [335].

Neurectomy is the treatment of choice and is effective in the majority of patients, with the minority continuing to have pain in the groin [337]. Prevention of surgical trauma of the hypogastric nerve is advocated. Abdominal incisions (such as Pfannenstiel's suprapubic incision or lower paramedian incision) should pass at least 5 cm above to the inguinal ligament, and the nerve should be displaced carefully downward during oblique lumbar incisions, such as for nephrectomy [339]. Division of the iliohypogastric, ilioinguinal, or genitofemoral nerves during inguinal hernia does not always reduce the incidence of chronic inguinal neuralgia [340].

The Genitofemoral Nerve

The genitofemoral nerve is formed from the L1 and L2 spinal roots. It then passes through the psoas muscle and travels, vertically and retroperitoneal, along its lateral edge to reach the inguinal ligament. There, it divides into femoral and genital branches. The femoral branch passes under the inguinal ligament and innervates a small area of skin on the anterior aspect of the thigh. The genital branch travels medially, with the ilioinguinal nerve, to supply the cremasteric muscle and shares, with that nerve, the sensory supply of the scrotum or labium majus (Fig. 41.17).

The genitofemoral nerve may be injured mostly during appendectomy, but also following inguinal herniorrhaphy, laparoscopic varicocele ligation, nephrectomy, cesarean section, or blunt abdominal trauma [331, 345, 346]. Some cases are delayed, caused by adhesions and scarring. Because of proximity, damage of the genital branch often occurs with injuries of the ilioinguinal nerve at the inguinal ligament. Tumors and spontaneous genitofemoral neuralgia are exceedingly rare.

Clinically, genitofemoral neuralgia presents with pain and paresthesias in the medial inguinal area and scrotum or labium majus. The symptoms overlap significantly with ilioinguinal mononeuropathy such that some authors lump these

injuries into a common term, *"inguinal neuralgia"* [334, 347]. On examination there may be sensory loss in the genitofemoral distribution, often overlapping with the ilioinguinal distribution. Absent or diminished cremasteric reflex may occur on the affected side.

Genitofemoral mononeuropathy should be distinguished from ilioinguinal nerve lesion or L1 or L2 radiculopathy. Diagnostic nerve blocks are often necessary in patients with suspected ilioinguinal neuralgia. It is often useful to block first the ilioinguinal nerve at the lateral end of the inguinal ligament. If the symptoms are not relieved, then paravertebral blocks of L1 and L2 (genitofemoral nerve) should be attempted. Electrophysiological studies include motor conduction latency to the cremasteric muscle, needle EMG of the cremasteric muscle, and the cremasteric reflex [348, 349]. Delayed motor latencies have been reported in children with inguinal hernia [349]. These studies remain unpopular because of technical difficulties.

Once the diagnosis is made, neurectomy is effective in the majority of patients, which could be performed via laparoscopy [331, 337, 350]. Treatment of neuropathic pain with anticonvulsants or antidepressants is a useful adjunctive therapy [351].

The Posterior Femoral Cutaneous Nerve

The posterior femoral cutaneous nerve (posterior cutaneous nerve of the thigh, PFCN) arises from the S1 to S3 spinal roots. It exits the pelvis, with the inferior gluteal nerve, through the greater sciatic notch under the piriformis muscle, and enters the thigh near the sciatic nerve at the lower border of the gluteus maximus (Fig. 41.18). The PFCN innervates the skin of the lower buttock, posterior thigh, popliteal fossa, and proximal third of the calf. It also gives off branches to the perineum and scrotum in men or labium majus in women.

Lesions of the PFCN are rare [352–355]. Intramuscular injections in the buttock are the most common iatrogenic cause. Lacerations or gunshot wounds may selectively injure the PFCN, but often there is a concomitant lesion of the inferior gluteal nerve or sciatic nerve or both. Compression of the nerve by prolonged pressure on the buttock may occur during gymnastic exercises or long bicycle riding [355]. Pelvic mass lesions, such as colorectal tumors or venous malformations, and gluteal hematomas may cause mononeuropathy of the PFCN.

Paresthesias in the lower buttock and posterior thigh are the predominant features. Burning or throbbing pain may accompany the sensory symptoms and often radiates to the perineum, scrotum, or labium majus. The pain may be worse in the sitting or lying positions.

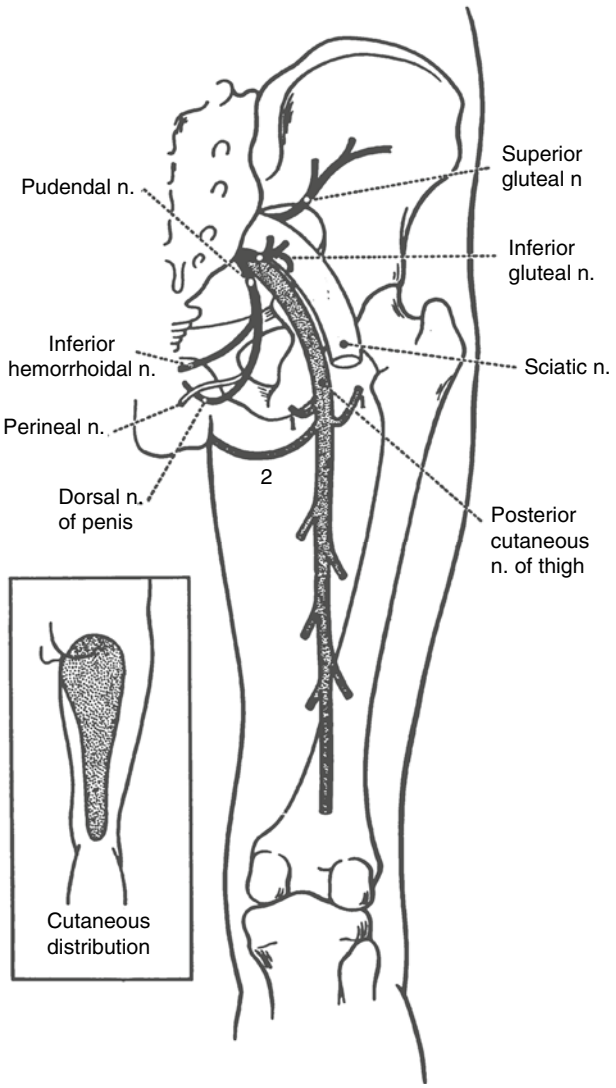

Fig. 41.18 The posterior cutaneous nerve of the thigh and its relation to the gluteal sciatic nerves (From Haymaker and Woodhall [393]. With permission)

A lumbosacral radiculopathy, particularly S1 or S2 radiculopathy, or a sacral plexopathy may mimic a lesion of the PFCN. Depressed or absent ankle jerk and calf or hamstring muscle weakness or atrophy help to exclude a PFCN lesion as a cause of posterior thigh pain ("sciatica") or numbness.

The diagnosis of mononeuropathy of the PFCN relies on a detailed history and typical sensory findings. CT or MRI of the pelvis is indicated if there is a suspicion of a pelvic mass such a colorectal cancer. SNAP of the PFCN is useful in confirming the findings, particularly when compared to the asymptomatic side [354, 356, 357].

The management of mononeuropathy of the PFCN is often conservative except with mass lesions which are often removed surgically. Avoiding pressure on the buttock and proper padding of bicycle seats are recommended.

The Obturator Nerve

The obturator nerve derives its fibers from the ventral divisions of L2, L3, and L4 spinal roots (the femoral nerve originates from the dorsal divisions of the same roots). The obturator nerve passes along the medial edge of the psoas muscle and over the sacroiliac joint before it reaches the obturator canal. The obturator nerve divides into an anterior and posterior branches, usually at the obturator canal, but sometimes proximal or distal to it [358], to innervate the thigh adductors, i.e., the adductor longus, adductor brevis, and adductor magnus (the latter receives additional innervation from the sciatic nerve). The obturator nerve also innervates a small area of skin in the inner thigh (see Fig. 41.16).

Obturator nerve lesions often accompany femoral mononeuropathies as a component of a lumbar plexopathy. Isolated obturator mononeuropathy may be a manifestation of obturator hernia, endometriosis, or a new or recurrent pelvic malignancy [359–363]. Pelvic trauma, particularly when associated with pelvic fractures, may injure the obturator nerve. Iatrogenic lesions occur during hip surgery or replacement, often caused by retractor blade injury, cement extrusion, or fixation screws [100, 102, 364, 365]. Genitourinary procedures and abdominal operations, such as aortofemoral bypass, oophorectomy, or laparoscopic pelvic lymphadenectomy, may also be associated with obturator nerve injury [366–372]. Vaginal delivery, particularly when forceps are used, may also damage the obturator nerve [373]. True entrapment of the obturator nerve by a thick fascia overlying the short adductor muscle is described in athletes [374]. Mass lesions, such as synovial cysts or schwannomas, ganglion cysts, or lipomatosis of the obturator nerve, have been described, but are rare [375–379].

The clinical presentations of obturator mononeuropathies are variable. Neuralgic pain in the medial thigh, worse with exercise, sometimes referred to as obturator neuralgia, is not uncommon particularly in athletes or patients with obturator hernia [360, 363, 372, 374, 380]. Numbness in the medial thigh is common, while subjective weakness and gait impairment are rare. In few patients, obturator nerve injury is only detected on clinical or EDX examination. The neurological findings are limited to weakness of thigh adduction, sometimes associated with sensory loss in the medial thigh. Circumduction of the weak leg, due to abnormal hip abduction, may result in a wide-based gait.

Obturator mononeuropathy may be mistaken as a lumbar radiculopathy, such as an L4 or L3 radiculopathy, or lumbar plexopathy, such as a diabetic amyotrophy. A radiculopathy or plexopathy is distinguished by the presence of quadriceps weakness, iliopsoas weakness, or depressed/absent knee jerk. Disorders of the symphysis or pubis may have referred pain in the medial thigh mimicking an obturator nerve lesion.

The diagnosis of obturator nerve lesions is straightforward when the typical findings are present. Patients with pain and subtle neurologic findings pose a problem in diagnosis. The needle EMG component of EDX studies is most useful since there is no motor or sensory conduction studies techniques available for the obturator nerve [363, 372, 381]. Needle EMG reveals fibrillation potentials, large MUAPs recruited rapidly, or both in the thigh adductors only. In contrast, needle EMG of the quadriceps, iliacus, and lumbar paraspinal muscles is normal. Patients with obturator mononeuropathy and no history of pelvic or hip surgery, or pelvic trauma, should undergo a pelvic CT or MRI to exclude pelvic malignancy [362].

Treatment of obturator nerve lesions depends on the cause and the patient's symptomatology. Correcting an obturator hernia is essential since the mortality from intestinal obstruction is high. Weakness and sensory loss improves in most patients. In those with disabling pain, obturator nerve blocks may be useful [382]. Surgical excision of the obturator nerve may also relieve the pain. The outcome of obturator neuropathy is good in the majority of patients [372, 381].

The Gluteal Nerves

The superior gluteal nerve originates from the L4, L5, and S1 spinal roots and exits the pelvis through the suprapiriform foramen. It then passes through the gluteus medius and minimus and innervates both muscles, before ending in the tensor fascia lata muscle. The inferior gluteal nerve originates from the L5, S1, and S2 spinal roots and exits the pelvis underneath the piriformis in close association with the sciatic nerve and the posterior femoral cutaneous nerve (Fig. 41.18). The inferior gluteal nerve innervates the gluteus maximus only.

Lesions of the gluteal nerves are rare and most are iatrogenic. Superior gluteal nerve injuries may occur with intramuscular injections [383]. This may result in lesions before or after the nerve supplies the gluteus medius and minimus muscles. Pelvic trauma may result in isolated superior gluteal nerve injuries [384]. The inferior gluteal nerve and the accompanying posterior femoral cutaneous nerve may be compressed by intrapelvic masses such as colorectal malignancy, or large iliac artery aneurysm [385, 386]. Both gluteal nerves may be injured after total hip replacement, irrespective of the approach (lateral or posterior) [387–390]. In fact, subclinical gluteal neuropathies are detected by needle EMG in about 3/4 of patients undergoing hip replacement [387]. Endometriosis has been described as a cause of superior luteal neuropathy [391]. Finally, the superior gluteal nerve may be entrapped by the anterior superior tendinous fibers of the piriformis muscle [392], while the inferior gluteal nerve may be compressed, with the sciatic nerve, as it passes under the piriformis muscle (see section "Piriformis Syndrome" above).

Weakness of abduction of the affected hip with a waddling gait is the main manifestation of a superior gluteal mononeuropathy. When the patient is asked to stand on one leg, there is a pelvic tilt toward the healthy side (Trendelenburg sign). Atrophy of buttock with weakness of hip extension is the common feature of inferior gluteal nerve lesions.

Gluteal mononeuropathies are difficult to diagnose without EDX confirmations. Close inspection and examination of the buttock is essential. Disorders of hip joint often mimic these lesions and should always be excluded. EDX studies are limited to needle EMG since the gluteal nerves are not accessible to nerve conduction studies. Fibrillations and loss of MUAPs in the tensor fascia lata and gluteus medius are features of superior gluteal nerve lesions. At times, the gluteus medius is spared when the lesion is distal such as with intramuscular injections. Isolated denervation of the gluteus maximus is the only finding in inferior gluteal mononeuropathy, although abnormal posterior femoral cutaneous SNAP or findings of sciatic nerve involvement may coexist. The EDX findings in gluteal mononeuropathies should be distinguished from L5 and S1 radiculopathy, where denervational changes are often more prominent in distal L5- or S1-innervated muscles such as the tibialis anterior or medial gastrocnemius, respectively.

Treatment of gluteal nerve lesions depends on its causations. Since these lesions are proximal, most partial lesions improve significantly without intervention. Nerve block may be useful in entrapments, and surgical intervention is rarely necessary [392].

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Cranial Nerve Palsies

42

Vita Grynova Kesner and Christina Fournier

Introduction

The enumeration and naming of the cranial nerves represent a curious example of evolution in anatomical classification. The earliest classification was recorded by Galen during the second century A.D., and it included 7 pairs: optic (I); oculomotor (II); trigeminal (III); motor root of trigeminal (IV); facial and auditory (V); glossopharyngeal, vagus, and accessory (VI); and hypoglossal (VII) [1]. Progress in both anatomy and physiology resulted in numerous revisions of the nomenclature of cranial nerves. The current classification of 12 cranial nerves was developed by Soemmerring in 1778 as part of a doctoral thesis in medicine: olfactory (I), optic (II), oculomotor (III), trochlear (IV), trigeminal (V), abducens (VI), facial (VII), vestibulocochlear or acoustic(VIII), glossopharyngeal (IX), vagus (X), spinal accessory (XI), and hypoglossal (XII).

Trigeminal Nerve

Neuroanatomy

The fifth or trigeminal nerve is the largest cranial nerve and functions as a mixed motor and sensory nerve. Its fibers exit through the ventral surface of the mid-pons. The large trigeminal (gasserian) ganglion is positioned in the tip of the petrous bone, where the nerve divides into its three sensory divisions – ophthalmic, maxillary, and mandibular. These branches exit the skull through the superior orbital fissure, foramen rotundum, and foramen ovale, respectively. The motor fibers of the trigeminal nerve form a separate fascicle, which passes underneath the gasserian ganglion, merges with the mandibular division, and terminates in the muscles of mastication (Figs. 42.1 and 42.2).

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Trigeminal Neuralgia ("Tic Douloureux")

The incidence of trigeminal neuralgia (TN) is approximately 4–5 in 100,000 [2]. TN manifests as episodes of severe unilateral paroxysmal facial pain, often described as stabbing, shock-like, or electrical in the distribution of one or more branches of the trigeminal nerve. The typical pain is lancinating or shooting. Atypical facial pain is usually constant and aching, burning, throbbing, or stinging. The most common pain location is along the nasolabial fold, innervated by the maxillary branch. It is followed in frequency by symptoms along the lower jaw, in the area of the mandibular branch, and the least common pain location is around the eye and forehead, areas innervated by the ophthalmic branch. Painful episodes may have a duration as brief as a few seconds or extend to several minutes in a continuous crescendo. They are often triggered by chewing, swallowing, talking, or light tactile stimuli. Patients may lose considerable weight due to impaired nutrition.

Classic TN should not be associated with any clinically evident neurologic deficits and can be either idiopathic or associated with vascular compression of cranial nerve V [3]. When a vascular source is identified, often an arterial loop from the superior cerebellar artery compresses the trigeminal nerve's sensory roots. Less often, vascular compression can occur from branches of the internal carotid artery, basilar artery, a primitive trigeminal artery, or rarely from an arteriovenous malformation or saccular aneurysm.

Symptomatic TN is due to a structural lesion other than vascular compression [3]. Demyelination of the proximal portion of the trigeminal sensory nerve root and ephaptic spread of excitation can cause TN in patients with multiple sclerosis [4]. Two to four percent of patients with TN have multiple sclerosis, and one to five percent of patients with

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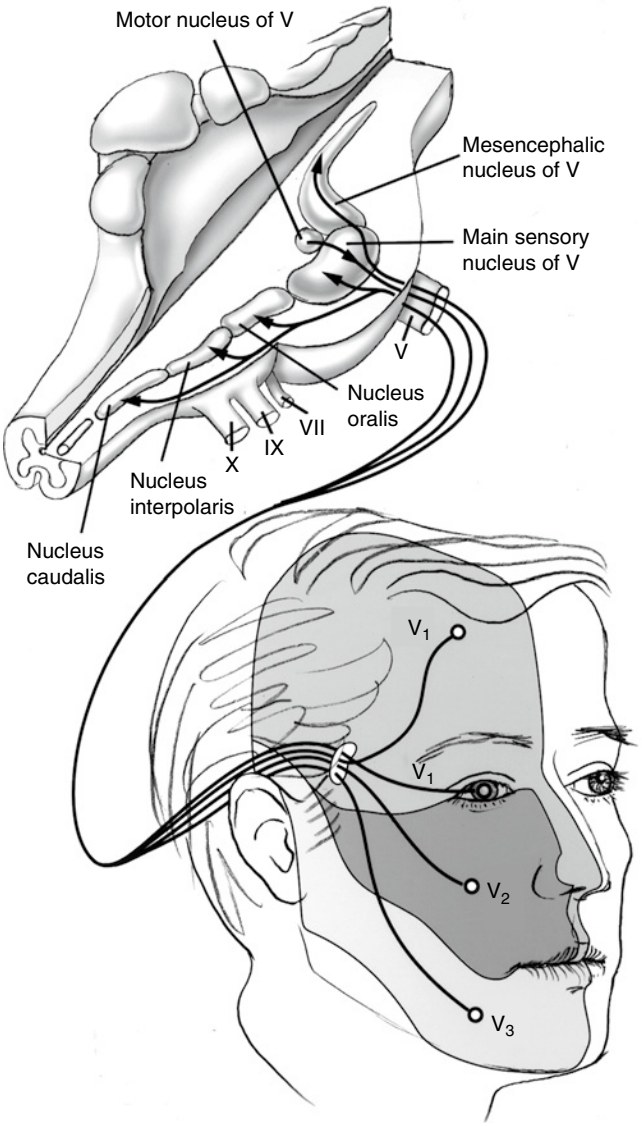

Fig. 42.1 The multiple subdivisions of the trigeminal nuclei occupy a significant rostrocaudal extent in the midbrain, pons, and medulla. Each branch of the trigeminal nerve (*V1* ophthalmic, *V2* maxillary, and *V3* mandibular) innervates a distinct area of the face, as indicated by the different shaded areas in the illustration. Note that the cornea is supplied by the ophthalmic division

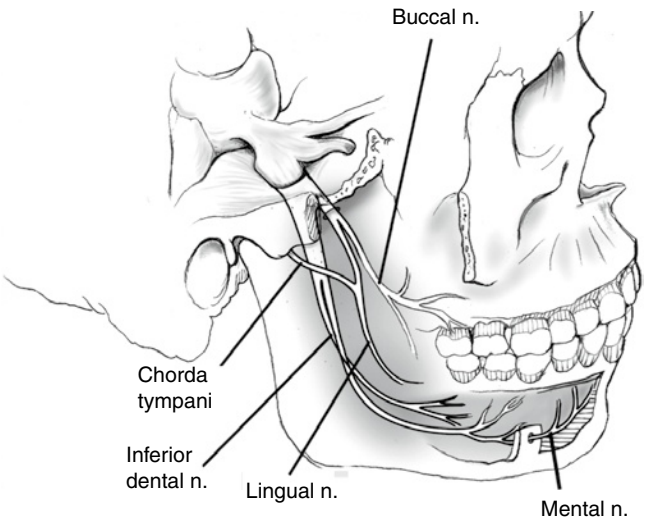

Fig. 42.2 Branches of the mandibular division of the trigeminal nerve

multiple sclerosis will develop trigeminal neuralgia, although the symptoms of multiple sclerosis often precede the onset of TN [5]. Cerebellopontine angle tumors, schwannomas of the trigeminal or vestibular nerve, meningiomas, and arachnoid cysts can less commonly cause trigeminal neuralgia. Younger patient's age, the presence of sensory deficits, or bilateral symptoms are thought to increase the risk of symptomatic TN.

Imaging in patients with TN identifies structural causes in up to 15 % of patients and should be pursued for evaluation. MRI of the skull base with gadolinium is preferred, and angiography can be helpful in the appropriate clinical context. Measurement of the blink reflexes, in which the latency and amplitude of ipsilateral and contralateral facial muscle contractions are recorded following the stimulation of the supraorbital branch of the trigeminal nerve, identifies symptomatic TN with a sensitivity of 59–100 % and specificity of 93–100 % [6]. With symptomatic trigeminal neuralgia, the ipsilateral R1 and R2 responses and contralateral R2 response are delayed or absent with ipsilateral trigeminal stimulation, while all three responses are normal with contralateral stimulation.

Medical treatment of TN usually involves anticonvulsant medications. Carbamazepine or oxacarbamazepine are effective in 60–80 % of patients and are recommended as first line treatment. Typical doses used include carbamazepine 200–1,200 mg/day or oxacarbamazepine 600–1,800 mg/day. Other medications including gabapentin, phenytoin, clonazepam, baclofen, lamotrigine, and valproate have been tried with variable success [7].

In patients who are refractory to medical treatment, several surgical options have been utilized including percutaneous Gasserian lesions, gamma knife surgery, and microvascular decompression. Methods of percutaneous Gasserian lesions include radiofrequency thermocoagulation, glycerol rhizotomy, and balloon compression. Although variance is noted between different publications, long-term satisfactory pain control in ablative Gasserian ganglion procedures and gamma knife is about 50 % [8]. Microvascular decompression may be superior to other procedures, with 70 % of patients being free of pain after 10 years [9]. The presence of typical lancinating pain (versus atypical and constant) is the only significant and independent predictor of outcome following microvascular decompression in patients with TN [10]. In this procedure, surgeons perform a suboccipital craniotomy, dissect the offending arterial loop, and separate the loop from the trigeminal root with Teflon. The mortality rate of this procedure is 0.2–0.4 %, and morbidity

varies based on institutional experience and volume. Other complications include aseptic meningitis, hearing loss, CSF leaks, infarcts, and hematomas.

Trigeminal Sensory Neuropathy

This is an uncommon clinical condition that results in facial paresthesias in the distribution of the fifth cranial nerve. The diagnosis of idiopathic trigeminal neuropathy can be made only after evaluation and exclusion of other causes, including drug intoxication from drugs such as oxaliplatin, trichloroethylene, and hydroxystilbamidine. Isolated chronic trigeminal sensory neuropathy may be a manifestation of connective tissue disorders such as Sjögren's syndrome, systemic lupus erythematosus, scleroderma, or mixed connective tissue disease. It is frequently bilateral and is not confined to individual nerve branches [11]. It affects patients of all age groups, independent of the etiology. Although a number of series report a benign course without other associated neurological defects and preserved corneal reflexes [12], other series describe frequent associations with tumors of the cerebellopontine angle, skull base, nasopharyngeal region, multiple sclerosis, or vasculitis [13]. Furthermore, sensory deficits in the face should always elicit inquiries about previous facial skin cancer because of the well-known tendency of squamous cell carcinomas to infiltrate along the perineurial sheathing of the cutaneous nerves [14]. Treatment with corticosteroids has limited efficacy in this condition.

Numb Chin and Numb Cheek Syndromes

Persistent numbness in the lower lip and chin (*numb chin syndrome*) may result from lesions of the mental nerve or the mandibular division of the fifth cranial nerve. This is also referred to as *mental neuropathy* and is often seen with metastatic cancer; it may be part of disease progression in advanced cases or the initial manifestation of a relapse in patients with known systemic cancer. Sometimes, it is the first symptom of an underlying malignancy. This occurs classically with nasopharyngeal carcinoma but is in fact most common with metastatic breast cancer, lymphoma, prostatic cancer, and lung cancer [15]. In more than half of the patients, this is due to invasion of the mandible and infiltration of the inferior alveolar nerve. In the rest, it is due to lesions of the base of the skull or leptomeningeal seeding [15]. Hence, the work-up should include imaging of the mandible by orthopantomogram or CT, and if negative, imaging of brain, base of skull, and CSF analysis. The prognosis is poor with a very high mortality in 6–12 months [15, 16]. In elderly patients with mandibular atrophy, impingement of the mental nerve at the mental foramen has been described [17] (Fig. 42.2).

On the other hand, numbness in the malar region (*numb cheek syndrome*) may be the initial manifestation of epithelial tumors (e.g., basal or squamous cell carcinomas of the face) or associated with incompletely treated neoplasms. Thus, persistent or progressive sensory deficits in the maxillary or mandibular divisions require thorough neuroimaging studies, laryngologic surgical evaluation, and careful clinical follow-up, as some neoplasms may initially be too small for detection.

Herpes Virus Infections

Infection by the herpes zoster virus is probably the most common lesion affecting the trigeminal ganglion. The ophthalmic division is involved in a ratio of 4:1 compared to lesions to the maxillary or the mandibular divisions. Clinically, patients describe a relatively rapid onset, with severe, constant, and disabling facial pain. Small vesicles often appear along the forehead and the eyebrow between the third and fifth days, followed by pronounced facial edema.

In contrast, infection caused by the herpes simplex virus (HSV), which results from persistent presence of HSV in the trigeminal ganglion, has a more indolent course. It affects all three trigeminal divisions equally and manifests as lifetime recurring episodes of mucous membrane lesions in the oral cavity and, most commonly, as "cold sores" in the lips.

Facial Nerve

Neuroanatomy

The seventh or facial nerve is a mixed motor and sensory nerve. It innervates the muscles of facial expression, the salivary and lacrimal glands, and the mucous membrane of the oral and nasal cavities. In addition, it conveys taste sensation from the anterior two-thirds of the tongue via the lingual and chorda tympani nerves and provides tactile sensation to a small but distinct area in the posterior external auditory canal (Hitzelberger's sign). The motor fibers originate in the facial nucleus located in the pons, sweep medially around the nucleus of the abducens nerve, and exit the ventral surface of the pons in the cerebellopontine angle. The facial nerve, along with the nervus intermedius and vestibulocochlear nerves, then passes from the brainstem into the temporal bone through the inner acoustic meatus. The seventh cranial nerve follows a tortuous course within the facial canal of the temporal bone exiting the skull through the stylomastoid foramen to supply the muscles of facial expression. The facial nerve also supplies the submandibular and sublingual glands (Fig. 42.3).

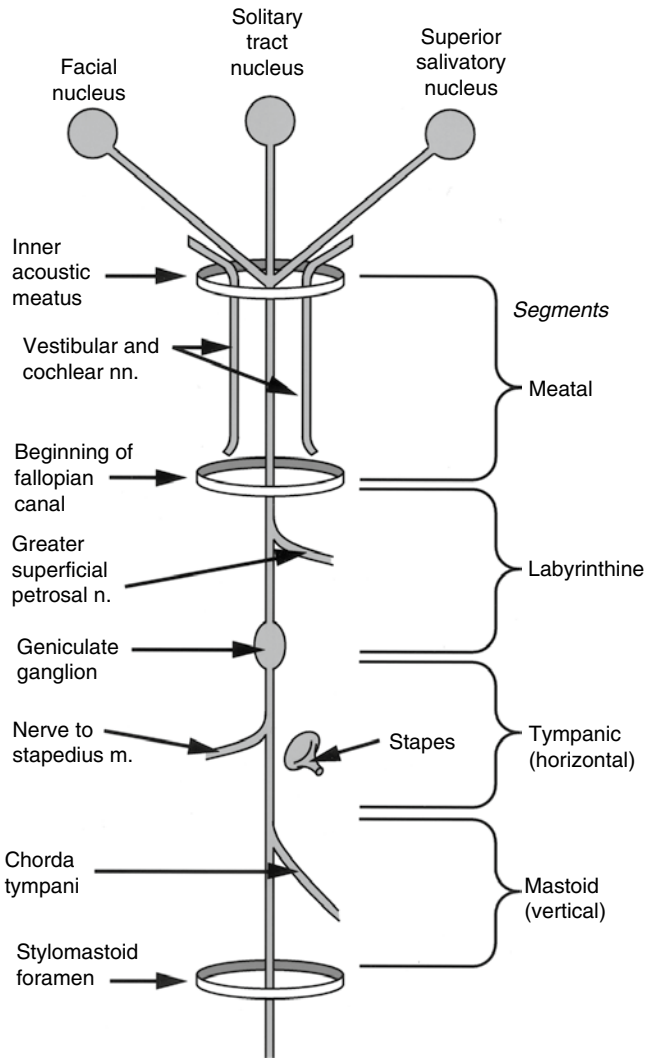

Fig. 42.3 The facial nerve contains fibers from the facial, solitary tract, and superior salivatory nuclei. It exits the skull through the inner acoustic meatus, in conjunction with the vestibular and cochlear nerves. Within each designated segment (labyrinthine, tympanic, and mastoid) of its complex trajectory, the facial nerve gives off a branch that can help in the clinical identification of the site of lesion

Given the close proximity of the genu of the facial nerve and the nucleus of the abducens nerve within the pons, facial palsies secondary to intrapontine lesions are almost always also associated with gaze or sixth nerve impairment, thus distinguishing them from more peripheral lesions. The anatomical branching pattern of the facial nerve sometimes allows for the localization of the lesion in the temporal bone (Fig. 42.3) [18]. Lesions of the most distal mastoid (vertical) segment affect the chorda tympani nerve, thus impairing taste sensation in the ipsilateral anterior two-thirds of the tongue. Lesions involving the tympanic (horizontal) segment within the middle ear result also in hyperacusis due to damage to the nerve to the stapedius muscle. Lesions of the most proximal labyrinthine segment result also in impaired ipsilateral lacrimation because of the involvement of the greater superficial petrosal nerve. Distal lesions of the facial nerve may affect individual motor branches, thus causing focal paresis of individual facial mimetic muscles. Such lesions can usually be confirmed by needle electromyographic examination.

Bell's Palsy

Idiopathic facial nerve palsy, or Bell's palsy (BP), is the most common lesion of the seventh cranial nerve. Clinically, patients frequently describe a dull pain in or behind the ipsilateral ear, suggestive of an ear infection as the initial manifestation. This is thought to be due to dysfunction of the sensory supply to portions of the external ear canal. A peripheral-type facial paralysis quickly follows and usually achieves maximum impairment in 48–72 h. In addition to facial paresis, patients may also describe impairment of taste and hyperacusis.

The site of injury to the facial nerve in BP is often in the proximal (and most narrow) portion of the facial canal [19]. The initial lesion is inflammatory in nature, causes segmental demyelination of motor axons, and disrupts the conduction of electric impulses. More severe lesions will result in direct injury to the axons, which can be detected on facial motor nerve conduction studies: there is a significant decrease of amplitude in the compound motor action potential (CMAP) recording the facial muscles in the involved side. The facial CMAP, performed after 7–10 days from the onset of facial weakness (time to complete Wallerian degeneration if any), has an important prognostic value [20]: If the CMAP of the involved side is 30 % or greater of that on the normal side, 84 % of the patients will have complete recovery. However, when the CMAP is 25 % or less of the normal side, there is an 88 % chance of incomplete recovery. In a small percentage of patients, delayed recovery with axonal loss can lead to aberrant regeneration of the remaining motor fibers.

The most common neurological sequelae of aberrant facial nerve regeneration results in synkinesis or contraction of the lower facial muscles on the previously involved side whenever there is an eye blink. Two very uncommon examples of abnormal regeneration patterns are so-called crocodile tears, i.e., lacrimation of the ipsilateral eye during chewing, and Marin-Amat syndrome, or "jaw-winking," manifested as closure of the ipsilateral eyelid when the jaw opens.

Although BP was classically defined as a unilateral peripheral facial palsy of unknown etiology, many studies support an association of acute facial palsy with herpes simplex virus (HSV). Latent HSV type-1 is isolated in the majority of the geniculate ganglia from autopsy samples [21]. Furthermore, HSV-1 genome was detected in 79 % of facial nerve endoneurial fluid in patients with BP, but not in normal

controls [22]. Others propose an immune etiology to BP, and in fact, recent studies suggest that treatment of BP with steroids alone provides the most benefit for facial muscle recovery and is superior to immunotherapy with antiviral medications. Treatment with both steroids and antiviral medications has not been clearly shown to confer additional benefit over treatment with steroids alone [23].

Herpes zoster infection of the geniculate ganglion (*Ramsay-Hunt syndrome, herpes zoster oticus with facial palsy*) is also increasingly recognized as a cause of facial palsy. Its incidence is 5/100,000 of the United States population with higher incidence in subjects older than 60 years. With zoster infections, in addition to pain, tinnitus, and decreased hearing, the appearance of vesicles in the external auditory canal and soft palate is characteristic [24]. Antibody titers against varicella-zoster virus (VZV) provide a useful adjuvant to the clinical diagnosis of Ramsay-Hunt syndrome. In a prospective study of 43 patients with facial nerve palsy, 75 % of patients with typical vesicular lesions (8 of 12) presented with antibody titers >1/10. In contrast, only 29 % (9 of 31) of patients without vesicular lesions presented with such high titers [25]. Oral antiviral agents are effective in patients with herpes zoster infection in general, by speeding up rash healing and decreasing pain duration. Although corticosteroids are mostly helpful in reducing the acute pain and the incidence of postherpetic neuralgia, their use in the Ramsay-Hunt syndrome remains anecdotal with no available controlled trials [26].

Bilateral Facial Palsy

Bilateral and simultaneous facial weakness (facial diplegia) is an uncommon event and often a diagnostic challenge. Although Guillain-Barré syndrome (GBS) is associated with facial diplegia in up to 60 % of the cases, bilateral facial weakness is a dominant neurological finding in the atypical forms of GBS such as the descending or the pharyngeal-cervical-brachial forms. Another rare GBS variant is characterized by facial diplegia only but is often associated with distal limb paresthesias, abnormal limb nerve conduction studies, and positive serology for a recent cytomegalovirus infection [27]. Neurosarcoidosis and accidental or intentional ingestion of the toxin, ethylene glycol ("antifreeze"), may also cause facial diplegia. The combination of facial diplegia, aseptic meningitis, and a slightly erythematous indurated face resembling painless cellulitis should trigger an investigation for Lyme disease. In Keane's seminal review of bilateral facial palsies, the most common cause was bilateral idiopathic BP (10 of 43 patients), followed closely by brainstem tumors (9 patients) and Guillain-Barre syndrome (5 patients) [28]. Less common causes of bilateral facial palsy include malignant lymphoma [29] and gelsolin-related familial amyloidosis, an autosomal dominant condition also associated with corneal lattice dystrophy and a generalized polyneuropathy [30].

Congenital Disorders

Unilateral or bilateral facial palsies in neonates are usually due to traumatic injuries versus congenital abnormalities. Traumatic facial nerve damage is usually associated with difficult forceps delivery and presents with periauricular ecchymosis, hemotympanum, and facial swelling. In contrast, congenital facial disorders often present with other systemic stigmata, e.g., microtia, external auditory atresia, limb deformity, or hypoplasia of the pectoral muscle. In particular, Möbius syndrome, which results from bilateral hypogenesis or agenesis of the nucleus of the sixth and seventh cranial nerves, is often associated with limb abnormalities. In the cardiofacial (Cayler's) syndrome ("asymmetric crying facies"), the neonate exhibits facial asymmetry when crying but not at rest. The cause of this motor deficit is isolated weakness of the depressor anguli oris and depressor labii inferioris [31].

Glossopharyngeal Nerve

Neuroanatomy

The ninth cranial or glossopharyngeal nerve receives contribution from several brainstem nuclear complexes (tractus solitarius [gustatory nucleus], nucleus ambiguus, inferior salivatory nucleus). Distinct subsets of the glossopharyngeal nerve fibers emerge from the medulla between the VIII and X cranial nerves. The nerve leaves the skull through the jugular foramen and reaches the lateral wall of the pharynx by following the inferior border of the stylopharyngeus muscle.

Isolated lesions of the IX nerve are very uncommon. Thus, multiple syndromes are described involving combined injuries to the nucleus or the peripheral fibers of the glossopharyngeal nerve and the other three lower cranial nerves (vagus, spinal accessory, and hypoglossal). However, isolated lesions of the glossopharyngeal nerve can manifest as slight difficulties with swallowing due to weakness of the stylopharyngeus muscle, taste disturbance in the posterior third of the tongue, reduced or absent gag reflex, or decreased parotid gland secretion.

Glossopharyngeal Neuralgia

Glossopharyngeal neuralgia is a relatively rare neuralgia which presents as severe, sharp, and lancinating pain located in the lateral portion of the throat or tonsillar region, producing extreme discomfort. The pain often is referred to the

ipsilateral ear and external auditory canal. Trigger zones are usually located in the posterior and lateral pharyngeal and tonsillar fossa. Thus, talking, chewing, or swallowing can initiate the pain. Autonomic dysfunction (salivation, lacrimation, bradycardia, and syncope) may be associated with glossopharyngeal neuralgia. This condition may be idiopathic or secondary to a local structural lesion, such as a tumor of the peripheral nerve or a cerebellopontine angle tumor. Other reported causes include enlarged tortuous vertebral or posterior cerebellar arteries, oropharyngeal carcinoma, paratonsillar abscess, or elongated styloid process. Patients often lose considerable weight before treatment is initiated.

Treatment is targeted toward the underlying cause of secondary neuralgias. Medical treatment is similar to that of trigeminal neuralgia, and carbamazepine has been used as the initial line of treatment. Stereotactic radiosurgery and neurosurgical intervention may be effective in medically refractory cases [32, 33]. Surgical exploration often reveals aberrant vessels across the nerve, neurofibromas, or cholesteatomas adjacent to the nerve. The overall immediate success rate exceeded 90 % in patients treated with microvascular decompression, and long-term patient outcomes were best for typical glossopharyngeal neuralgia with pain restricted to the throat and palate. Nerve sectioning can be curative [34].

Glomus Jugulare Tumors

These are highly vascular erosive tumors that arise from the chemoreceptor cells in proximity to the jugular foramen. Their clinical manifestations result from compression of the adjacent IX, X, and XI cranial nerves. Patients often present with difficulties in swallowing, hoarseness in voice, and pulsatile tinnitus followed by conductive hearing loss. Patients may also present with symptoms of increased intracranial pressure due to compression of the jugular vein which results in impairing venous drainage. Treatment options for glomus jugulare tumors include subtotal resection with or without adjuvant postoperative radiosurgery, gross-total resection, or stereotactic radiosurgery alone [35].

Vagus Nerve

Neuroanatomy

The tenth cranial or vagus nerve has the longest and most widely distributed extracranial trajectory of all cranial nerves. The brainstem nuclear connections are similar to those of the glossopharyngeal nerve. The motor fibers originate from the nucleus ambiguus and the dorsal motor nucleus of the vagus. The sensory fibers are collected mostly at the jugular and the nodose ganglia. The vagus nerve, as do the glossopharyngeal and spinal accessory cranial nerves, exits the cranial vault through the jugular foramen.

Lesions of the vagus nerve lead to weakness of the palate and pharynx. Unilateral lesions cause defective elevation of the palate during phonation with deviation of the uvula to the contralateral side. Bilateral lesions result in nasal speech, nasal regurgitation with swallowing, and snoring. Pharyngeal paralysis results in varying degrees of dysphagia.

Clinically, two branches of the vagus nerve are of particular importance. The *superior laryngeal nerve* originates in the proximity of the nodose ganglion, and its branches innervate the cricothyroid and the inferior pharyngeal constrictor muscles, as well as the mucosa of the larynx and the various laryngeal glands. The *recurrent laryngeal nerve* controls all the intrinsic muscles of the larynx responsible for vocalizations. The right and left recurrent laryngeal nerves have different courses: On the right side, the nerve descends caudally with the main vagal trunk, loops underneath the subclavian artery, and redirects rostrally to innervate the larynx. The left recurrent laryngeal nerve loops underneath the aortic arch, thus following a longer course, and is therefore more vulnerable to lesions along its trajectory. The recurrent laryngeal nerves may be damaged by carcinoma of the thyroid, tumors of the mediastinum and lung, trauma, or iatrogenically in procedures such as thyroidectomy. Recurrent laryngeal neuropathy may also be a rare manifestation of idiopathic brachial plexopathy.

Recurrent laryngeal and superior laryngeal nerve lesions can be minimally symptomatic or lead to persistent hoarseness and dyspnea. They can also cause autonomic dysfunction with impairment of esophageal, gastric, and intestinal motility, as well as vagal cardiac activity. Intraoperative nerve monitoring has been utilized in attempts to reduce the risk of recurrent laryngeal nerve injury, but the benefits of these techniques remain uncertain [36].

Brainstem Lesions

Because of significant crossover of the supranuclear pathways to the nucleus ambiguus, only bilateral lesions are of clinical significance. Patients with such lesions, which can be caused by motor neuron disease, poliomyelitis, or primary brainstem tumors, have a pseudo-bulbar clinical presentation manifested as dysphagia and dysarthria.

Nuclear or intramedullary lesions can result from vascular infarcts (lateral medullary or Wallenberg syndrome), neoplasias, inflammatory lesions, syringobulbia, motor neuron disease, or poliomyelitis. Infranuclear lesions often occur as the vagus nerve exits the skull through the jugular foramen and are often associated with lesions of the glossopharyngeal and spinal accessory nerves. Peripheral lesions affecting the recurrent laryngeal nerve, usually the most common type of neurogenic laryngeal dysfunction, can result from trauma, surgical procedures in the neck region, and tumors of the

mediastinum and lung. Patients with acute unilateral injury to the recurrent laryngeal nerve often complain of difficulties in coughing forcefully ("bovine cough") and a hoarse voice.

Extramedullary Lesions

Posterior fossa or jugular foramen tumors can cause compression of the vagus nerve. Vagus nerve damage can also result from carotid artery aneurysm or dissection. Inflammatory and infectious processes responsible, such as sarcoidosis, Lyme disease, and Guillain-Barre syndrome, can affect the vagus nerve in conjunction with other cranial and peripheral neuropathies. Toxic causes and nutritional causes, such as alcohol-induced neuropathy, Beriberi or thiamine deficiency [37], and vincristine-induced nerve toxicity, have been implicated as causes of vagus neuropathies [38].

Spinal Accessory Nerve

Neuroanatomy

The eleventh or spinal accessory nerve is a purely motor cranial nerve and is composed of a smaller cranial part ("accessory" to the vagus nerve) and a larger spinal portion (C2-C6 ventral roots). The cranial part of the XI cranial nerve, in conjunction with the vagus and glossopharyngeal nerves, innervates muscles of the pharynx and larynx. The larger spinal portion innervates the sternocleidomastoid and upper portions of the trapezius muscles. The lower portions of the trapezius receive innervation from the ventral ramus of spinal roots C2-4.

Clinical Syndromes

A great diversity of lesions can injure the nerve fibers of the spinal accessory nerve, because the nerve follows a long course in the spinal canal, inside the cranial vault, and peripherally. Intraspinal lesions can result from motor neuron disease, poliomyelitis, syringomyelia, tumors, and external cervical trauma. Intracranially, masses such as meningiomas and neuromas may damage the neurons or the axons by direct compression. Arguably the most common type of lesion occurs in the periphery, between the jugular foramen and the nerve terminations in the trapezius muscle. Iatrogenic lesions, such as those resulting from radical neck dissections or lymph node biopsies in the neck region, are very common causes of injury (Fig. 42.4). Surgical exploration and nerve repair can be effective in the restoration of function in cases of nerve transection, and early operative intervention yields the best functional results [39]. Other etiologies include carotid endarterectomy [40], coronary artery bypass surgery, radiation damage, shoulder

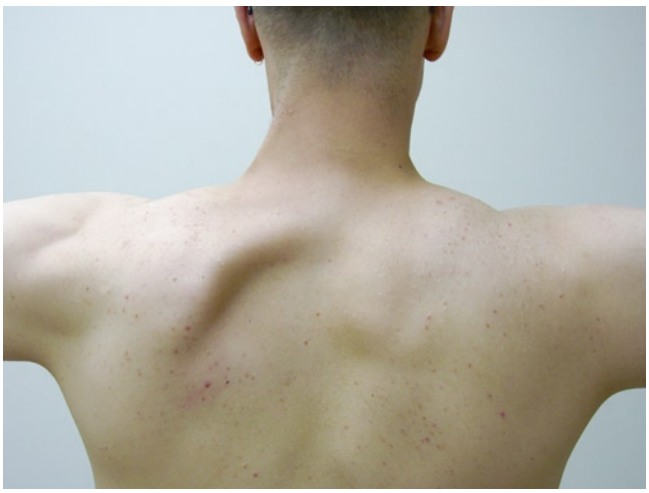

Fig. 42.4 Left spinal accessory nerve lesion resulting in scapular winging following scalene nerve biopsy (Courtesy of Dr. Bashar Katirji)

dislocation, blunt trauma, and stretch and biting injuries [41]. In Vernet's syndrome, the spinal accessory nerve is injured in conjunction with the glossopharyngeal and vagus nerves as these three cranial nerves pass through the jugular foramen (Fig. 42.5). Neuralgic amyotrophy with involvement of cranial nerves IX, X, XI, and XII has been reported [42]. In addition, isolated unexplained lesions of cranial nerve XI can occur with spontaneous recovery. Motor nerve conduction studies of the spinal accessory nerve, particularly when asymmetry is noted in latency and amplitude with a unilateral lesion, and electromyography of the trapezius or sternocleidomastoid can be useful in confirming the diagnosis for CN XI lesions.

Patients with lesions of the spinal accessory nerve proximal to the branching point to the sternocleidomastoid muscle have weakness in turning the head toward the unaffected side. Furthermore, attempts of neck flexion in the supine position may show a head deviation to the affected side. Lesions of the motor branches to the trapezius muscle result in significant wasting of muscle mass, and the affected shoulder is notably lower than the healthy counterpart. At rest the scapula is displaced laterally, with the inferior angle rotated medially. Scapular winging is further accentuated by attempted abduction of the arm. In contrast, in scapular winging associated with weakness of the serratus anterior muscle, which can result from injuries to the long thoracic nerve, the scapula is displaced medially, and winging is accentuated by forward flexion or protraction against resistance.

Clinical Anatomy of the Jugular Foramen

There is a unique anatomical relationship between the last four cranial nerves (glossopharyngeal, vagus, spinal accessory, and hypoglossal) and the jugular foramen (JF) which

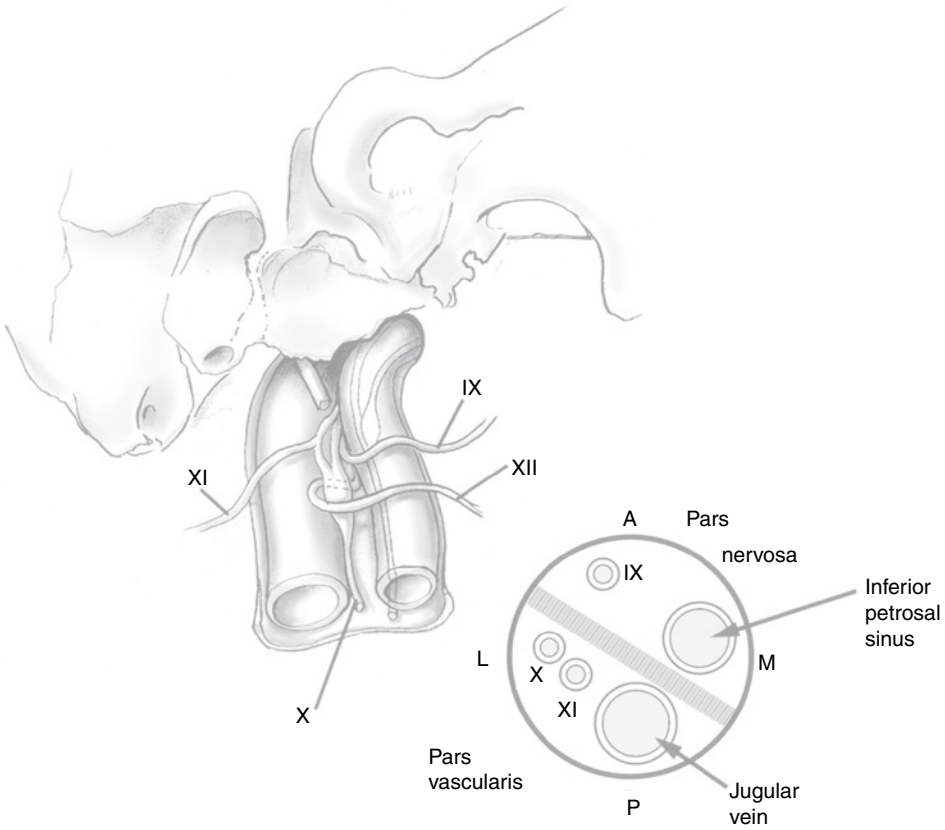

Fig. 42.5 Regional anatomy of jugular foramen and associated cranial nerves

explains the observed clinical syndromes (Table 42.1). Thus, a more detailed examination of this anatomical region is warranted (Fig. 42.5). Three cranial nerves (IX, X, and XI) exit the base of the skull through the JF. The hypoglossal nerve passes through the hypoglossal canal, which lies immediately medial to the JF. The JF is divided in two compartments by a fibrous or bony septum: *pars nervosa* (anteromedial) and *pars vascularis* (posterolateral). Despite the nomenclature, only the glossopharyngeal nerve goes through the smaller pars nervosa together with the inferior petrosal sinus. The pars vascularis contains the vagus and the accessory nerves, as well as the jugular vein.

The close proximity of the last four cranial nerves often results in combined nerve lesions. Clinical presentations of such lesions generally include hoarseness or loss of voice strength, nasal speech, and difficulties in swallowing.

The *Vernet's syndrome* manifests as deficits of the cranial nerves (IX, X, XI) that traverse the jugular foramen. Sparing of the hypoglossal nerve and the cervical sympathetic chain often suggests the intracranial nature of the lesion causing this syndrome. In contrast, all four lower cranial nerves are impaired in the *Collet-Sicard syndrome* (Table 42.1). Although an intracranial lesion can result in this combination of cranial nerve deficits, a more parsimonious explanation is an extracranial lesion just outside of the jugular foramen affecting the nerves that pass through the JF (IX, X, XI) and the nearby hypoglossal nerve as it exits through the separate hypoglossal canal. An intracranial lesion extensive enough to cause a Collet-Sicard syndrome would very likely distort the lower brainstem and the cerebellum, thus causing pyramidal and cerebellar signs. The inclusion of a Horner's syndrome to the impairment of the last four cranial nerves constitutes the clinical presentation of the *Villaret's syndrome*. This always indicates an extracranial lesion, usually in the area of the posterior nasopharynx, as it affects the sympathetic chain, which

Table 42.1 Brainstem lesions and clinical syndromes

Syndromes	Cranial nerve involvement	Clinical presentation
Tolosa-Hunt	III,IV,V,VI	Multiple cranial nerve palsies
Millard-Gubler	VI,VII	VI and VII palsies and contralateral hemiplegia
Foville's	VI,VII	VI and VII palsies, contralateral hemiplegia, and gaze palsy to the side of the lesion
Vernet's	IX,X,XI	Ageusia (1/3 posterior tongue); paralysis of vocal cords, palate, and pharynx; paralysis of trapezius and sternocleidomastoid
Schmidt's	X,XI	Paralysis of soft palate, pharynx, and larynx; paresis of ipsilateral trapezius and sternocleidomastoid
Tapia's	X,XII	Paresis of pharynx and larynx; paralysis and atrophy of tongue
Jackson's	X,XI,XII	Paresis of pharynx and larynx; paresis and atrophy of tongue; paresis of ipsilateral trapezius and sternocleidomastoid
Collet-Sicard	IX,X,XI,XII	Anesthesia of palate; paresis of vocal cords and palate; weakness of trapezius and sternocleidomastoid; paresis and atrophy of tongue; hemianesthesia of pharynx and larynx
Villaret's	IX,X,XI,XII, and cervical sympathetic	Same as above plus Horner's syndrome

does not traverse the jugular foramen, and the extracranial portion of the lower cranial nerves.

Hypoglossal Nerve

Neuroanatomy

The twelfth or hypoglossal nerve is a purely motor nerve that controls the extrinsic and intrinsic muscles of the tongue. The hypoglossal nucleus is located in the floor of the fourth ventricle, close to the midline, and the fibers traverse the cross-section of the caudal medulla before exiting through the ventral surface of the brainstem, between the pyramidal tract and the olivary eminence. The nerve leaves the skull base through the hypoglossal canal and courses briefly with the IX, X, and XI cranial nerves before it separates at the mastoid level and innervates the tongue. A unilateral lesion of the hypoglossal nerve results in ipsilateral paresis and wasting of the tongue.

Clinical Syndromes

A common cause of isolated hypoglossal nerve damage occurs as a complication of carotid endarterectomies [43], particularly due to variability in location between the hypoglossal nerve and the carotid bifurcation [44]. However, peripheral lesions may also result from radiation therapy, local tumor (e.g., salivary gland neoplasm), carotid artery aneurysm and dissection, internal jugular vein cannulation, glomus jugulare resection, and trauma to the face (Fig. 42.6). Clinically, patients with unilateral injuries to the hypoglossal nerve have unilateral atrophy of the tongue and mild difficulties manipulating food. The tongue deviates toward the side of the lesion due to the unopposed action of the healthy contralateral genioglossus muscle (see Fig. 42.6). There is tremendous difficulty moving the tongue from side to side. However, only with bilateral nerve injuries will patients encounter significant difficulties in swallowing, talking, and respiration, because the tongue falls backward and obstructs the upper airways.

Motor neuron disease, poliomyelitis, syringomyelia, tumors [45], and infarcts may cause lesions to the neurons of the hypoglossal nucleus. An infarct may assume the presentation of the medial medullary syndrome [46] (i.e., ipsilateral tongue paresis associated with a contralateral corticospinal tract lesion causing paresis of the arm and leg and medial lemniscus involvement leading to diminished proprioceptive and tactile sensation). Basilar meningitis or intracranial metastases can occasionally affect CN XII but most commonly will do so in conjunction with other lower cranial nerve lesions. Hypoglossal nerve palsy has also been reported in association with infectious mononucleosis [47] and due to subluxation of the odontoid process with rheumatoid arthritis [48].

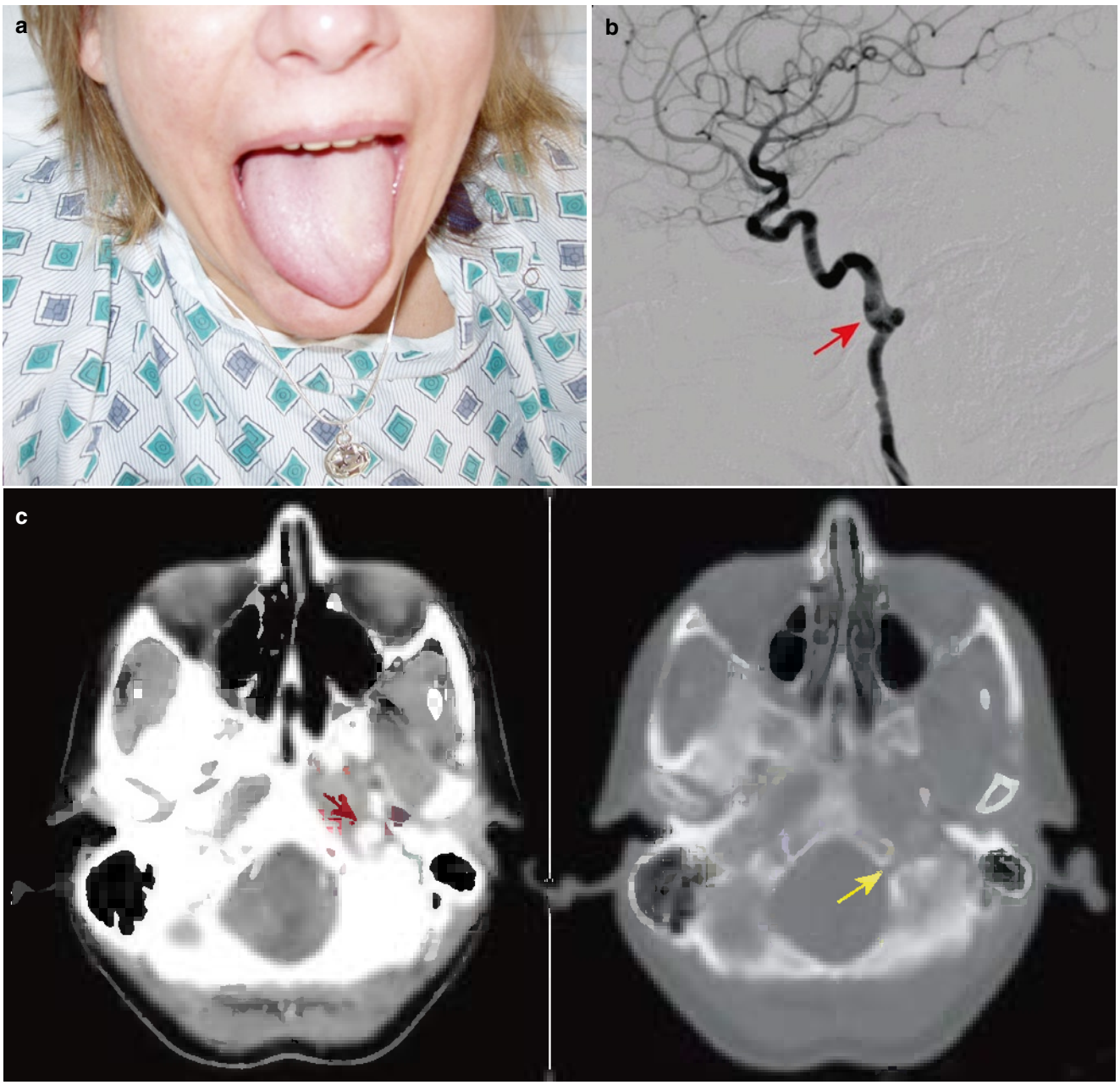

Fig. 42.6 Acute left hypoglossal nerve lesion with tongue deviation to the left (**a**) in a patient with carotid artery dissection and aneurysm as shown by angiography (**b**, *red arrow*) and CT scanning of skull base (**c**) (*red arrow* aneurysm, *yellow arrow* hypoglossal canal) (Courtesy of Dr. Bashar Katirji)

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Peripheral Nerve Tumors

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Peripheral nerve tumors encompass neoplasms originating in peripheral nerves and those originating from tissues extrinsic to the peripheral nerves with consequent neural compression. Although much less common than nerve entrapment or nerve injuries, these peripheral nerve tumors are not rare, as several thousand cases are diagnosed annually [1–4]. Physicians undertaking the management of these lesions must have experience with the anatomy of the area involved by the tumor as well as a fundamental understanding of the internal structure of the involved nerve itself [5, 6]. Surgical resection is the treatment for most peripheral nerve tumors and can be quite complex with the risk of serious neurologic deficit. The pathologic diagnosis of these lesions can be difficult as well, and misinterpreted histology can result in incorrect treatment and serious disability. Physicians who are not comfortable in the diagnosis and treatment of these lesions should refer peripheral nerve tumors to a medical center with surgeons and pathologists with experience in such cases in order to maximize patient satisfaction and good outcomes.

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Diagnosis

Peripheral nerve tumors have a broad and complex range of histopathology. The differential diagnosis of a mass or pain encompasses a wide range of etiologies, and peripheral nerve tumor is frequently overlooked. Commonly encountered neoplasms, such as schwannomas, neurofibromas, plexiform neurofibromas, and neurogenic sarcomas, have classic clinical presentations and characteristic gross and microscopic features [7]. The prototypically clinical presentation of a peripheral nerve tumor is a mass which can be mobilized perpendicular to the course of the nerve but not longitudinal to the nerve (Fig. 43.1a) [8]. Patients may also report induced paresthesia in the nerve distribution upon percussion of the nerve by the examiner. Once a peripheral nerve tumor is suspected, it is imperative to seek out evidence of other nerve tumors and von Recklinghausen's disease (neurofibromatosis 1-NF1). Though MRI is not particularly helpful in managing patients with nerve injuries, MRI together with computed tomographic (CT) scanning is most useful in delineating the true extent of the tumor or identifying additional lesions diagnostic of NF1 (Fig. 43.1b). Angiography and myelography are occasionally required to fully evaluate complex lesions [9]. Any tumor located in close proximity to the spine should have the medial extent of the tumor carefully defined by such studies. Unfortunately, no imaging modality can conclusively differentiate schwannoma from neurofibroma or malignant versus benign peripheral nerve tumors with certainty. The diagnosis depends on histopathological evaluation of tumor tissue.

Once the diagnosis of a peripheral nerve tumor is made on clinical grounds, the clinician cannot determine at that point whether the diagnosis is a schwannoma, a neurofibroma, or a malignant nerve tumor. Depending on the physician's experience with nerve tumors, it may be best to refer a patient to an appropriate medical center with experience in managing these complex patients where a definitive diagnosis can be made and, if necessary, definitive surgery can be performed. A partial or suboptimal resection may lead to clinical worsening.

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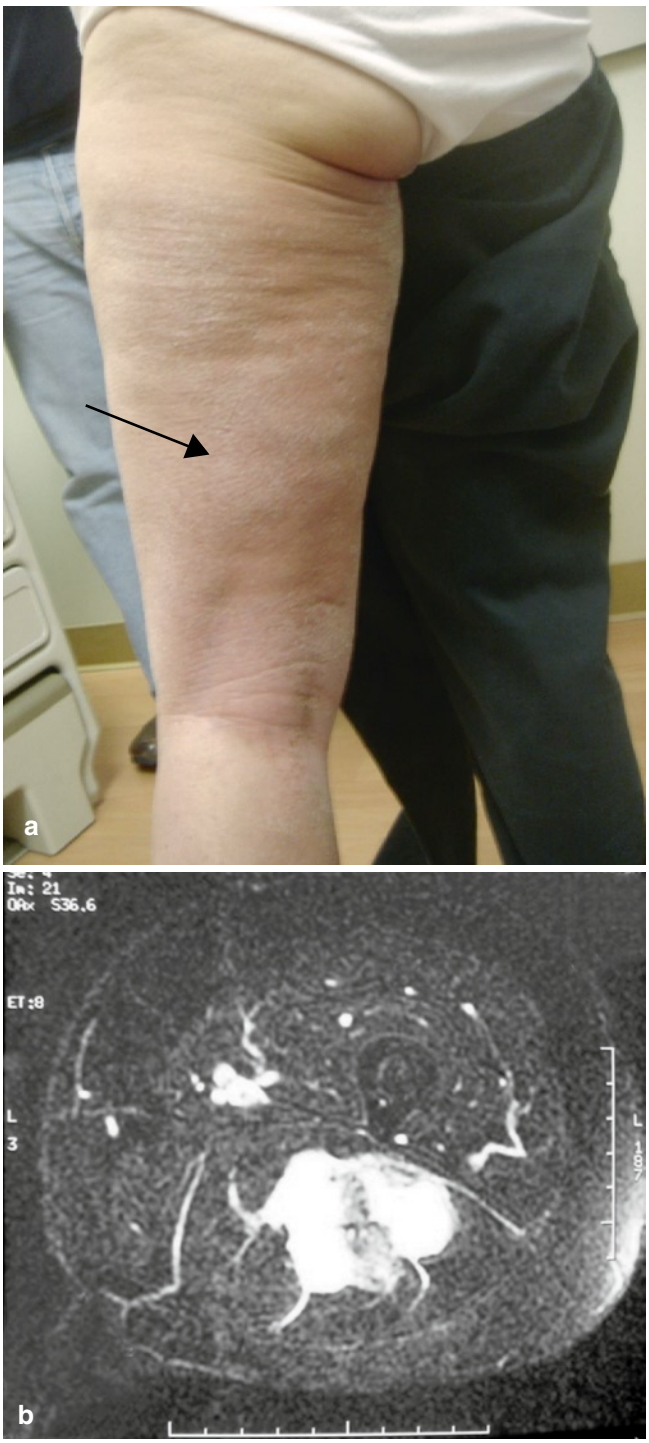

Fig. 43.1 (**a**) Photo of a patient showing left posterior sciatic nerve mass (*arrow*) and (**b**) axial MRI scan showing a left sciatic nerve schwannoma

Peripheral nerve tumors may be classified into benign and malignant tumors. The benign tumors may further be divided into those that are of neural sheath origin and those that involve the peripheral nerves but are not of neural sheath origin. Malignant tumors can be categorized as those of neural sheath origin, including neurogenic sarcomas, and malignancies of non-neural origin compressing or directly involving nerve by either direct extension or metastasis.

Benign Neural Sheath Tumors

Schwannomas

Schwannomas are the most common benign neural sheath tumor. The incidence of schwannomas is higher in females than males for reasons not fully understood [10]. The typical presentation of a schwannoma is a painless but palpable mass which may occur throughout the upper or lower extremities (Tables 43.1, 43.2, and 43.3). Percussing over the mass usually generates paresthesias in the distribution of the affected nerve (Tinel's sign). In one series of 85 schwannomas, all patients but one had a Tinel's sign [11]. Rarely, a schwannoma may present with a neurologic deficit or abnormal electrodiagnostic studies [12]. If the patient presents after a biopsy or an attempted resection of a schwannoma, symptoms then are more likely to be pain, paresthesias, neurologic deficit, or a combination of these symptoms. Occasionally, schwannomas can develop in patients with NF1 although neurofibromas are the most likely diagnosis in this population [13]. Schwannomatosis has recently been proposed as a separate syndrome in patients with multiple schwannomas but no stigmata of NF2 such as vestibular schwannomas[14]. Symptomatic tumors should be removed, provided that the patient is an acceptable surgical candidate.

Schwannomas most likely originate from Schwann cells, but the exact origin of these tumors has previously been disputed [15–17]. Histopathology reveals a tumor composed only of Schwann cells without fibroblasts or perineural cells. The tumor consists of two distinct cellular patterns. Antoni A tissue is characterized by hypercellular compact elongated cells which may demonstrate Verocay bodies made up of alternating parallel rows of tumor cells forming palisading region. Antoni B tissue is characterized by loosely arranged, hypocellular regions (Figs. 43.2 and 43.3). Lipid-laden cells may be found in either Antoni A or B tissue. The vasculature of schwannomas is often thickened, hyalinized, and may even be thrombosed. The compact Antoni type A tissue of a schwannoma must be differentiated from the less compact and more myxomatous matrix of a neurofibroma. Antoni type B tissue has a somewhat loose stroma and may be distinguished from a neurofibroma by mucopolysaccharide stain. Schwannoma matrix does not stain for mucopolysaccharide but neurofibroma matrix does. Schwannomas will demonstrate strong S 100 positivity and frequently also show positivity for podoplanin, calretinin, and SOX 10 [18–21].

Schwannomas are well encapsulated and displace adjacent nerve fascicles laterally. Larger schwannomas tend to stretch and elongate the fascicles but do so at such a slow rate

Table 43.1 Location of benign neural sheath tumors of the brachial plexus

	Schwannoma	NF	NF-NF1	Totals
Supraclavicular brachial plexus	46	46	22	114
Infraclavicular brachial plexus	15	16	9	40
Axillary nerve	5	6	5	16
Musculocutaneous nerve	4	2	1	7
Other	4	2	0	6
Totals	74	72	37	183

NF Neurofibroma, *NF-NF1* Neurofibroma in patient with neurofibromatosis 1

Table 43.2 Location of benign neural sheath tumors of the upper extremity

	Schwannoma	NF	NF-NF1	Totals
Median nerve				
Arm	9	11	5	25
Elbow/forearm	5	7	3	15
Wrist	7	3	3	13
Ulnar nerve				
Arm	7	11	8	26
Elbow/forearm	2	8	3	13
Wrist/hand	1	3	4	8
Radial nerve				
Arm	8	3	3	14
Elbow	2	2	2	6
PIN/SSR	2	1	2	5
Totals	43	49	33	125

NF Neurofibroma, *NF-NF1* Neurofibroma in patient with von Recklinghausen disease, *PIN* Posterior interosseous nerve, *SSR* Superficial sensory radial nerve

Table 43.3 Location of benign neural sheath tumors in the lower extremity

	Schwannoma	NF	NF-NF1	Totals
Pelvic plexus	11	12	11	34
Femoral nerve	8	8	3	19
Sciatic nerve				
Buttock	6	5	4	15
Thigh	16	11	6	33
Tibial nerve	14	7	5	26
Fibular (peroneal) nerve	8	6	4	18
Saphenous nerve	2	1	0	3
Sural nerve	1	0	2	3
Obturator nerve	3	1	1	5
Totals	69	51	36	156

NF Neurofibroma, *NF-NF1* Neurofibroma in patient with von Recklinghausen disease

that neurological function is typically preserved [10]. Generally, one or two nerve fascicles enter the tumor proximally and emerge distally. Electrical stimulation across these fascicles does not produce a nerve action potential (NAP); thus, surgical resection is therefore possible without interrupting functional nerve fibers. Operative removal is usually indicated based upon expectant improvement of pain, improvement or stabilization of motor symptoms [9], or to prevent the tumor from enlarging to the point at which such symptoms would develop. MRI can provide information regarding the relationship of the tumor to the surrounding structures [22, 23] but has not been reliably able to distinguish between schwannomas and neurofibromas [11].

Operative Procedure

The patient is positioned so that the involved limb's response to electrophysiologic stimulation can be observed (Fig. 43.4). The anesthesia providers should be instructed to avoid muscle relaxant medications. Surgical exposure includes nerve and related structures both proximal and distal to the lesion itself (Fig. 43.5). Exposure may be limited if resecting a schwannoma involving the pelvic plexus or the proximal spinal nerve level of the brachial plexus where exposure either proximal or distal to the lesion may be difficult. The schwannoma is usually found surrounded by nerve fascicles [16]. As a schwannoma increases in size, it may bulge out of the nerve in a concentric manner, leaving fascicles asymmetrically arrayed

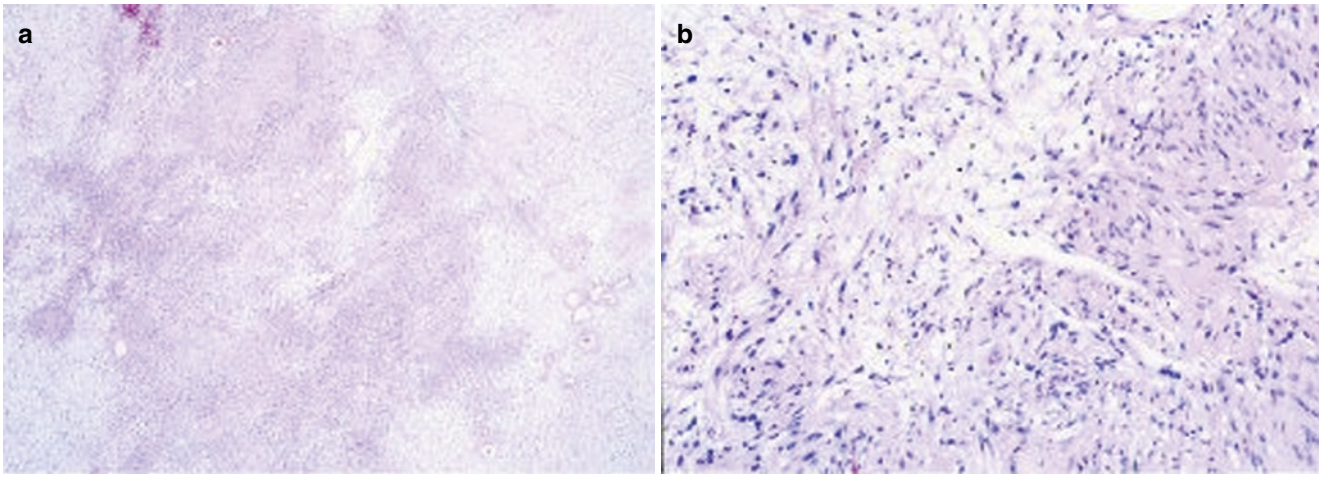

Fig. 43.2 Schwannoma: low-power view (**a**) showing compact (Antoni A) and loose (Antoni B) type areas. (**b**) High-power view showing Antoni A (spindle-shaped cells in left upper corner) and Antoni B type (pale loose stroma and more stellate-shaped cells in *right lower corner*)

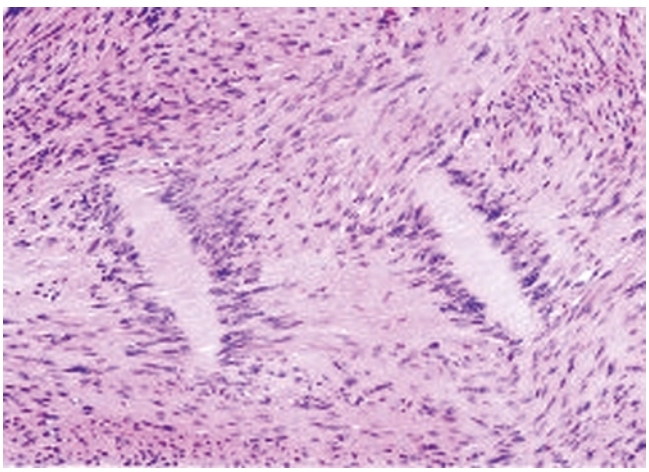

Fig. 43.3 Verocay bodies: regimented/palisaded, spindle-shaped nuclei and intervening nuclear free zones

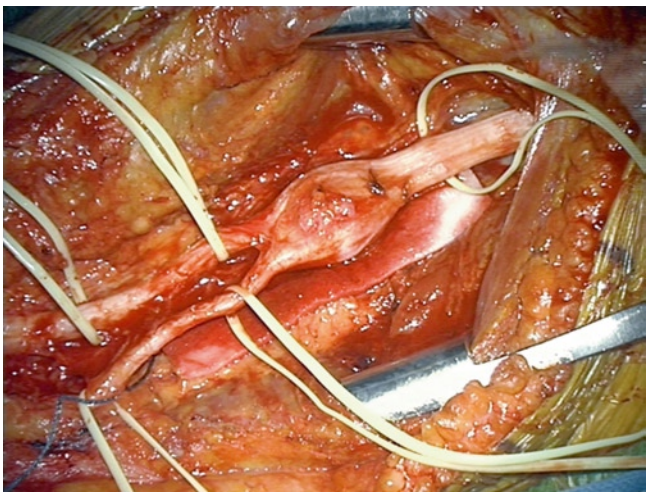

Fig. 43.5 Surgical exposure of right sciatic schwannoma with both proximal and distal anatomy exposed

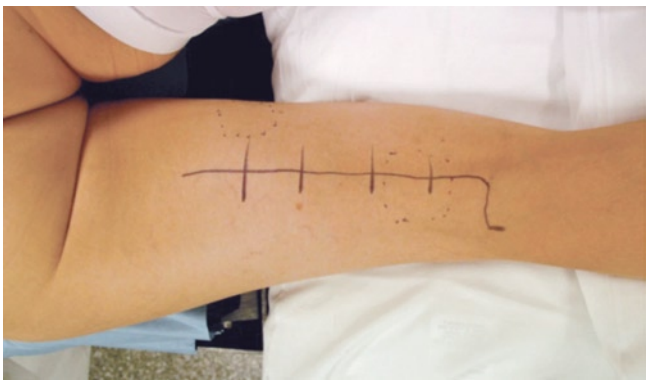

Fig. 43.4 Positioning and incision for left sciatic nerve tumor resection. Note leg is positioned to allow observation of motor response upon stimulation

around the tumor itself. Schwannomas are encapsulated; thus, by dissecting longitudinally along the mass, the fascicles can then be gently dissected away from the tumor capsule (Fig. 43.5). Further dissection at the proximal and distal poles of the tumor usually reveals a relatively small nerve fascicle entering and leaving the tumor. When these fascicles are stimulated across the tumor, no NAP is conducted yielding a flat recording [11]. Stimulation of the proximal or, rarely, distal tumor fascicle alone may generate muscle contraction in the distribution of the nerve. This is the result of retrograde stimulation of healthy fascicles not of conduction across the fascicles entering the tumor. The entering and exiting nerve fascicles are divided which allows the en bloc removal of the tumor with its capsule intact as a single mass (Fig. 43.6). When unable to perform an en bloc resection, the capsule of

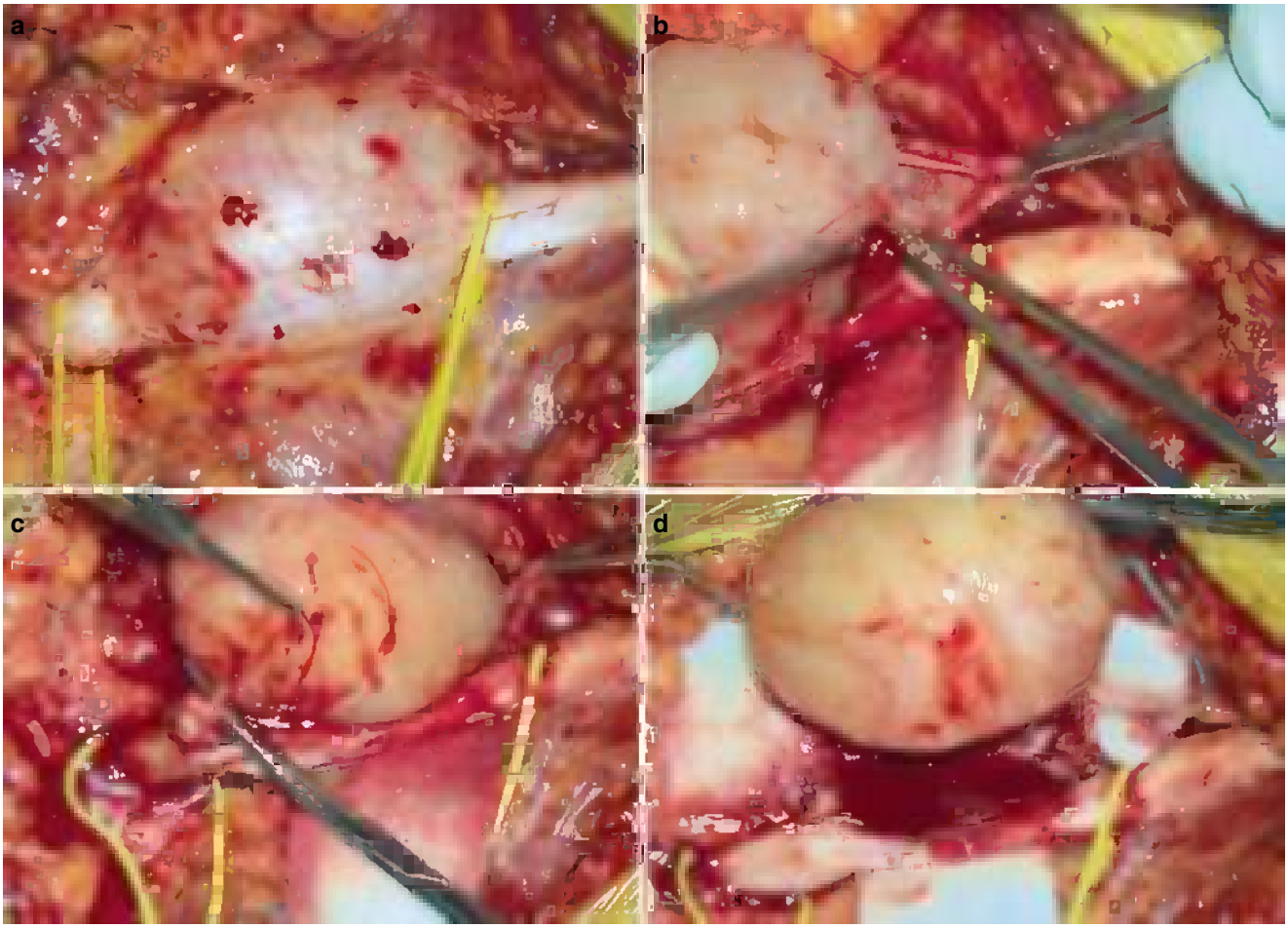

Fig. 43.6 Surgical resection of sciatic nerve schwannoma. (**a**) Dissection of tumor with proximal and distal involved nerve, (**b**) dissection along longitudinal axis of nerve, (**c**) continuation of dissection, and (**d**) removal of tumor en bloc with capsule intact

the schwannoma can be opened longitudinally, and its relatively soft, usually homogenous, sometimes cystic contents can be evacuated. Following internal debulking of the tumor, the capsule can be gently dissected away from the fascicles. If this method is utilized, it should be done thoroughly to reduce the incidence of recurrence. Large schwannomas may extend beyond the immediate nerve tissue making resection more difficult and increasing the possibility of recurrence [24]. Following careful resection, the presenting symptoms of schwannomas usually resolve. Eighty-seven percent of patients had improved or stable motor function in one series, and 85 % of patients who presented with pain had either total or partial resolution of this symptom [11].

Solitary Neurofibromas

Local or radicular pain is more likely to occur as a presenting symptom with solitary neurofibromas than with schwannomas [16]. In one large series, pain was associated with neurofibromas in 47 % of cases versus 31 % of schwannoma cases [11]. Solitary neurofibromas are less common than neurofibromas associated with NF1. As with schwannomas, these tumors can generally be displaced perpendicular to the course of the nerve of origin but not longitudinally. A neurologic deficit is slightly more likely to be present at the time of presentation than with a schwannoma but is greatly increased in neurofibroma patients who have had a prior biopsy or attempted but incomplete removal [25]. Solitary neurofibromas produce symptoms due to local axonal compression and are likely to be fusiform rather than plexiform in non-NF1 patients [10]. Tinel's sign is present in most cases; one series of 197 neurofibromas reported a positive test in all patients [11].

For unclear reasons, solitary neurofibromas are found more frequently on the right side of the body than the left [10]. As with schwannomas, neurofibromas can occur throughout the upper or lower extremities (Tables 43.1, 43.2, and 43.3), but unlike schwannomas, they are more likely to arise from the motor portion of the nerve than the sensory

portion [10]. The female predominance of neurofibromas is even greater than that of schwannomas by mechanisms that are not well understood [10].

Neurofibromas originate from cells believed to be more primitive than a Schwann cell, likely arising from the perineural fibroblast [26]. Compared to a schwannoma, the tumor's histological background is less compact and more myxomatous, contains mast cells and lymphocytes, and stains more positively with a mucopolysaccharide stain, such as Alcian blue (Figs. 43.7 and 43.8). The myxo-collagenous background of a neurofibroma also usually stains intensely with a reticulum stain as opposed to a schwannomas where this is not seen. Fewer Schwann cells are present in neurofibromas than schwannomas and are mixed together with distorted myelinated and unmyelinated axons. The vasculature in neurofibromas is less likely to be thickened and hyalinized than in schwannomas. Neurofibromas can occur as a localized mass or can involve longer segments of nerves. No histologic difference exists between a solitary neurofibroma and one associated with NF1. Unlike schwannomas, neurofibromas involve the entire cross-section of the nerve, resulting in the absence of cleavage planes between normal nerve and tumor. This makes gross total resection of the tumor without removal of normal nerve impossible.

The optimal management for neurofibromas is guided by patient symptoms. Patients without symptoms with known neurofibromas can be managed expectantly with observation. Resection of neurofibromas is reserved for tumors causing pain, progressive neurologic deficits, or those in which the diagnosis is uncertain or malignancy is suspected. MRIs are useful to define the anatomic location and extent of the tumor [23]. In cases where the neurofibroma is on a proximal nerve, imaging studies of the spine should be performed to assess for intraspinal tumor extension [27].

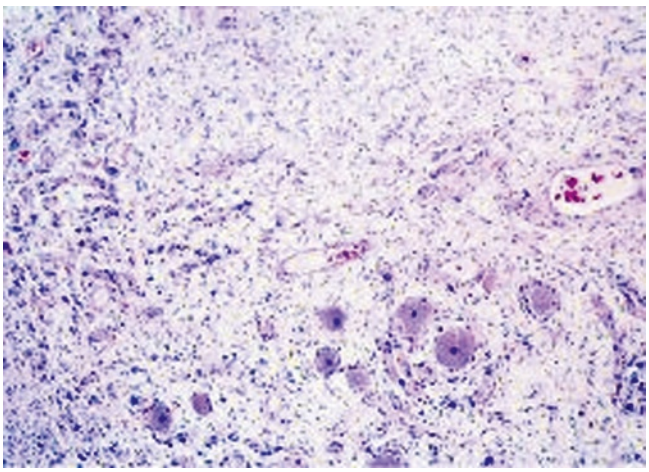

Fig. 43.7 Neurofibroma involving dorsal root ganglion: neoplasm composed of Schwann, perineurial-like and fibroblastic cells (neurons surrounded by satellite cells are residual from the infiltrated dorsal root ganglion)

Operative Procedure

The initial surgical approach is similar to that for a schwannoma. In most cases, the nerve fascicles are "basketted" around the main tumor mass and must be carefully dissected away. Neurofibromas usually have a capsule which is often more adherent to the central mass of the tumor than a schwannoma. The key steps for removal of a neurofibroma include dissecting out the fascicles at both ends of the tumor. If solitary, the fascicle entering and leaving the neurofibroma is larger than that seen in a comparable sized schwannoma. In other lesions, several fascicles approach and leave the tumor. It is more efficacious at times to section an entering or leaving fascicle or fascicles at one or the other pole and then gently elevate the mass away from the tumor and dissect beneath it to clear the mass away from the fascicles and the capsule left on the underside. NAP recording obtained across the tumor by stimulating the entering fascicle(s) is usually flat, indicating nonconducting fascicles that can be sectioned just as in a

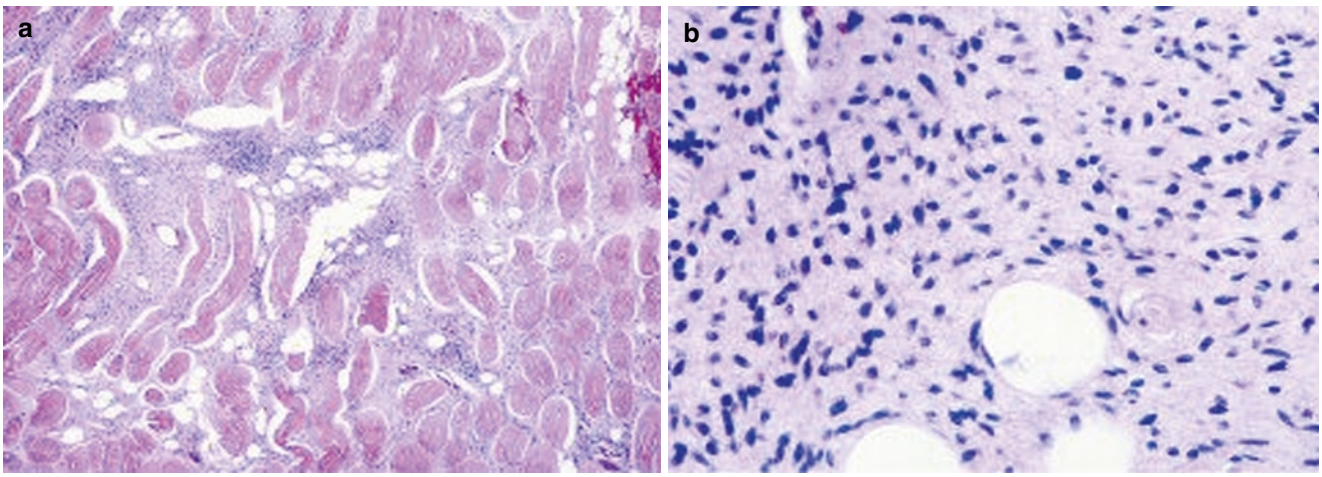

Fig. 43.8 Diffuse neurofibroma (**a**) low-power view and (**b**) high-power view. There is a disordered proliferation of relatively small spindle to stellate-shaped tumor cells, infiltrating adipose tissue and skeletal muscle

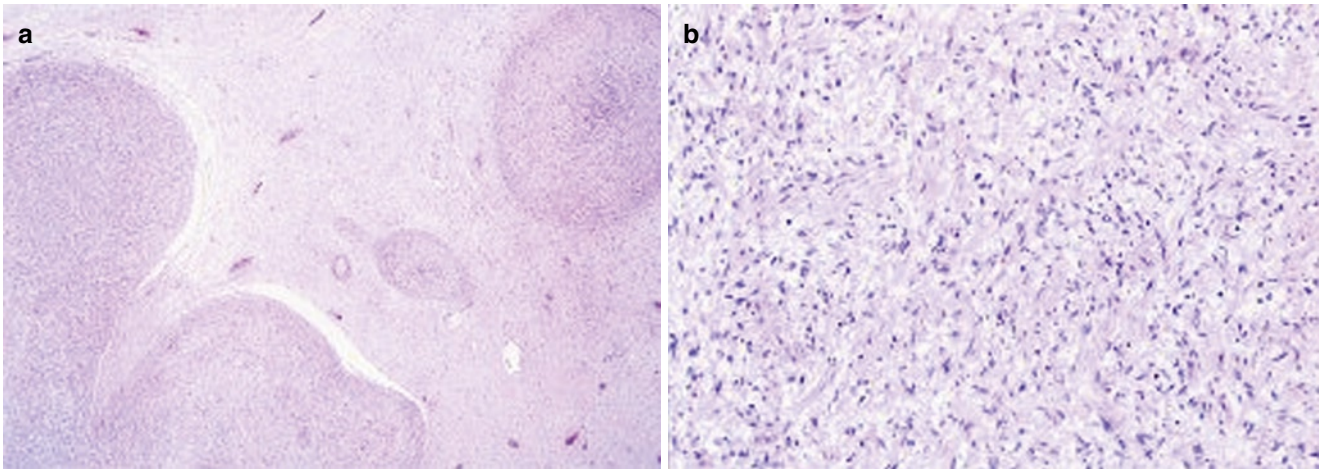

Fig. 43.9 Plexiform schwannoma, low-power view (**a**): multiple, well-circumscribed tumor nodules involving dermis. (**b**) High-power view showing well-circumscribed tumor nest, spindle cells arranged in a typical fascicles and palisades

schwannoma [11]. NAP recording after the mass is removed can be used to confirm maintenance of most function just as in a schwannoma. Occasionally, the neurofibroma requires partial graft repair after resection, particularly when loss of function is a concern or when functional fascicles were sacrificed to gain complete tumor resection. Donner et al. reviewed their series of 123 neurofibromas occurring in 121 patients without NF1, noting that 90 % had stable or improved motor function and 88 % had partial or complete resolution of pain [11].

Neurofibromas Associated with Neurofibromatosis 1 (NF1)

Neurofibromatosis 1 (NF1), also known as von Recklinghausen disease, is a phakomatosis defined in part by multiple neurofibromas. NF1 is inherited on chromosome 17 in an autosomal dominant pattern with full penetrance but variable expression. The overall incidence of NF1 is approximately one per 300 individuals, with many afflicted patients showing mild symptoms with limited number of tumors [2]. NF1-associated neurofibromas are more evenly divided between males and females and are seen equally on both sides of the body [10]. Additionally, NF1-associated neurofibromas are more likely to present at an earlier stage than solitary neurofibromas [10]. The range of neurofibromas in NF1 includes tumors in small cutaneous nerves to larger lesions in larger proximal nerves [10]. Most cases of NF1-associated solitary neurofibroma can be excised without serious deficit, even when the tumor involves a major nerve. The technique is the same as that for a non-NF1 neurofibroma described above. In NF1 patients, there is a 15 % risk of malignant degeneration of the neurofibroma [28, 29]; thus, every attempt should be made to remove all tumor fragments intraoperatively.

Patients with NF1-associated neurofibromas do not have as high a rate of resolution of symptoms as patients with sporadic neurofibromas due to the more difficult dissection of neurofibromas in patients with NF1. A series of 48 patients with NF1 who had neurofibromas resected noted that 83 % had stable or improved motor function and 74 % had partial or complete resolution of pain symptoms [11]. However, 16 % of patients experienced new but usually mild pain syndromes. Since neurofibromas in NF1 patients are more likely to be plexiform, the incidence of total resection is 60 % as compared to 80 % for solitary neurofibromas [11].

Plexiform Neurofibromas

Plexiform neurofibromas are histologically identical to solitary neurofibromas (Fig. 43.9) but involve a length of nerve in an interweaving fashion [11]. Plexiform tumor masses lack a capsule and can be both intrafascicular and extrafascicular. These tumors present an operative challenge, but resection is possible, though complete resection is generally not feasible without incurring a neurological deficit. Indications for surgery include symptomatic tumors involving sensory nerves or branches. Even an attempt at a partial resection of a plexiform tumor may lead to a neurological deficit. Nerve section, both proximal and distal to such a lesion and repair of the gap, which is usually lengthy, does not usually restore function [30, 31]. Decompression and debulking of the tumor may provide a benefit in patients with severe pain as a dominant symptom or with large tumors. In selected cases, it may be possible to reduce pain by decompressing a nerve through a neurolysis. Tumors involving less important sensory nerves or branches, such as antebrachial cutaneous, superficial sensory radial, sural, or saphenous nerves, can be removed in total, along with the nerve of origin.

Plexiform neurofibromas are very likely to be associated with NF1 but rarely may be also encountered as sporadic, solitary non-NF1 associated lesions. A sizable plexiform tumor

can be accompanied by hundreds of smaller neurofibromas involving the nerve of origin of the larger lesion. These associated tumors involve the nerve proximal to and distal to the large lesion and, occasionally, other nerves in the same limb, a syndrome called regionalized NF1, or neurofibromatosis type 5 [32]. Only a palliative operative procedure can be performed in these situations. If the plexiform tumor is large and firm, removal can be considered to ensure that malignant transformation is not present, a process that occurs in 5 % of plexiform neurofibromas, usually marked by significant pain and rapid growth [33]. Secondary operations for neural sheath tumors for which repair are necessary require frozen section biopsy of nerves or elements of origin to ensure that residual tumor is not incorporated in the repair.

In one series, nine patients with plexiform neurofibromas were treated either by partial excision ($n=5$), internal neurolysis with gross total excision ($n=1$), internal neurolysis with subtotal excision ($n=1$), or division of the nerve both proximal and distal to the tumor with nerve grafts ($n=2$) [13]. Tumors recurred in four patients with the time to symptomatic recurrence being 4–19 months. All four of these patients had worse motor exams, and three of the four developed new pain syndromes. MRI is useful in monitoring the rate of growth of plexiform neuromas as rapid growth and development of pain may herald malignant degeneration [34].

Neurothekeoma

Neurothekeomas are benign nerve sheath tumors that generally occur in the first three decades of life [35]. They are soft mobile tumors often based in the dermis. The cell of origin for these tumors was believed to occur in either the Schwann cell line or the perineural cell line, and tumor cells are often arranged in fascicles bounded by myxoid stroma. Recent investigations have shown that these tumors are positive for vimentin, CD10, NKI/C3, and at times focal reactivity for smooth muscle actin, yet are negative for S 100 and GFAP [36]. It is postulated that neurothekeomas may actually be of fibroblastic origin [36]. Treatment is symptomatic, with most neurothekeomas removed suspected to be schwannomas perioperatively. A gross total resection can almost always be performed with only rare recurrences.

Other Benign Peripheral Nerve Tumors

Several types of tumors occur less frequently than lesions of neural sheath origin but can be responsible for pain and, in some instances, loss of nerve function (Table 43.4). Some of these are favorable lesions as they tend to cause symptoms from nerve compression rather than originating within neural tissue [10]. On occasions, these lesions may be adherent to the epineurium making resection difficult and recurrence rate high [37]. The following is a discussion of the more common lesions.

Desmoids and Myositis Ossificans

Desmoids are lesions believed to arise from muscle and can involve soft tissue and compress, incorporate, or adhere to major nerves. They originate from a mesenchymal origin and are benign in the sense that they do not metastasize to other parts of the body, but they are rarely cured due to their invasiveness of soft tissue. Recurrence after a presumed gross total resection is common [4]. Desmoids are most common on the abdominal wall, but they can be present in the neck, shoulder, or extremities as well. Operative treatment involves a relatively wide exposure of the lesion and early identification of any nerve or nerves involved. The desmoid usually needs to be sharply dissected away from the nerve and involved epineurium usually requires resection. Both the firmness of these lesions and their adherence to nerves and vessels make removal without deficit difficult unless great care is taken during the dissection. As a result, recurrence is common. Desmoids are associated with patients with familial adenomatous polyposis, a condition caused by a mutation of the APC gene, and studies are showing that certain APC mutations will generate a desmoid phenotype [38, 39].

Myositis ossificans is a poorly defined disorder that may be related to previous trauma or surgery. It usually produces a firm to hard mass of tissue with calcification and, like a desmoid, can envelope contiguous soft tissues, including bone. Symptoms develop due to neural compression, vascular compression, or both. Removal of these masses can be technically difficult. Complete resection is rarely possible and usually not indicated as neurolysis of the nerve often dramatically improves symptoms.

Myoblastomas and Lymphangiomas

These two pathologic entities have similar behavior and somewhat similar appearance during surgery. Myoblastomas consist of plump and somewhat angular cells in a compact arrangement with acidophilic granules, whereas lymphangiomas have cells of a lymphoid nature. These tumors tend to spread as a sheet of tumorous tissue and are less likely to form a globular mass than are a desmoid tumor or a hemangioma [4, 32]. Both tumors can also become adherent to or envelope nerves leading to neurological symptoms. Treatment involves a wide surgical exposure to determine normal anatomy distal and proximal to the lesion prior to skeletonizing the involved nerve away from the lesion.

Table 43.4 Benign tumors of non-neural sheath origin involving peripheral nerve

Tumor type	No. of cases	Tumor type	No. of cases
Ganglion cysts		Vascular tumors/lesions	
Fibular (peroneal)	19	Hemangioma	
Femoral	1	Ulnar	3
Tibial	1	Fibular (peroneal)	1
Sciatic	2	Hemangiopericytoma	
Posterior interosseous nerve	1	Median	1
Ulnar (Guyon) canal	1	Brachial plexus	1
Median	2	Glomus tumor	
Suprascapular	3	Peroneal branch	2
Epidermoid cyst		Digital	1
Sciatic	1	Venous angioma	
Cystic hygroma		Median	1
Accessory	1	Tibial	1
Desmoid		Sciatic	1
Brachial plexus	6	Hemangioblastoma	
Median	1	Median	1
Radial	1	Triton tumor	
Fibular (peroneal)	1	Brachial plexus	2
Sciatic complex	1	Lymphangiomas	
Meningioma		Median/ulnar	1
Brachial plexus	2	Brachial plexus	1
Lipomas		Myositis ossificans	
Median	5	Radial	1
Posterior interosseous	2	Brachial plexus	1
Radial	2	Osteochondroma	
Ulnar	1	Radial	1
Musculocutaneous	1	Fibular (peroneal)	2
Sciatic	3	Brachial plexus	1
Ganglioneuroma		Hidradenitis	
Brachial plexus	3	Ulnar	1
Pelvic plexus	1	Median/ulnar	1
Myoblastoma or granular cell tumors			
Brachial plexus	2		

Lipomas and Lipohamartomas

Lipomas are fatty lesions that usually occur solely in the subcutaneous region thus rarely involve the major nerves. Rarely, a large lipoma envelops or compresses nerve, or originates deep to the subcutaneous tissues in a limb and thus compresses or entraps nerve producing neurologic symptoms [4]. Common sites include the forearm or popliteal region, with resultant posterior interosseous or fibular (peroneal) nerve palsy, respectively. Larger lipomas in the supraclavicular fossa can involve the brachial plexus, while those in the buttock, leg, or arm can potentially compress the median, sciatic, or ulnar nerves.

Lipohamartomas are also composed of fatty tissue and are intrinsic to nerve and usually involve the median nerve at the wrist or palmar levels [32]. When median nerve lesions present with pain and paresthesias, treatment is sectioning of both the transverse carpal ligament in the palm, its extension covering the nerve and the lipomatous mass at the wrist level. When serious loss of median function occurs, more extensive surgery consisting of internal neurolysis with reduction of the bulk of the tumor from around individual fascicles can be performed. More focal lipohamartomas can be treated with resection and repair.

Hemangiomas, Hemangiopericytomas, and Vascular Malformations

Vascular lesions including hemangioma, hemangiopericytomas, as well as aneurysms and arteriovenous fistulae, originate close to nerves and can compress or elevate them [40]. An operation for these lesions, especially if the nerve is involved, is never easy. Preoperative angiography is of some help in planning surgery. Intraoperatively, it is imperative to isolate vessels on the periphery of the lesion and ligate or clip them if they are not the major supply to the extremity. Nerves are carefully dissected away from the lesion while

protecting them as much as possible. Occasionally, a hemangioma, hemangioblastoma, venous aneurysm, or fistula directly involves nerve or appears to originate in it. If the clinical situation warrants proceeding with surgical resection, a careful interfascicular dissection is necessary for removal. Each fascicle or group of fascicles needs to be stripped of the abnormal vascular tissue to assure adequate resection of the vascular lesion.

Hemangiopericytomas, which usually arise in the mediastinum and secondarily involves the brachial plexus, can behave in a malignant fashion and metastasize to other sites, including, rarely, the brain. It cannot usually be removed entirely, and the surgeon must be content with a subtotal procedure to decompress the brachial plexus.

Ganglions and Epidermoid Cysts

Most ganglions arise from joints and at sites that do not usually involve nerves, such as the dorsum or the side of the wrist [41]. Occasionally, this tumor arises from a region of the wrist joint that compresses the thenar sensory branch of the median nerve, the ulnar palmar branch, or the main trunk of the median or ulnar nerves. Other sites where these ganglions are clearly of joint origin include the forearm, where they arise from the radioulnar joints and compress the posterior interosseous nerve; the knee, involving the fibular (peroneal) nerve [42]; the ankle, involving the posterior tibial nerve; and the hip, involving the sciatic nerve. Ganglions at the elbow level can involve radial and, less frequently, median and ulnar nerves, whereas those in the shoulder can involve the brachial plexus, particularly the suprascapular branch in the region of the scapular notch. Ganglion cysts usually present as a tender mass resulting in pain or paresthesias in the distribution of the nerve involved [10]. Occasionally, they result in a motor and sensory deficit or both. Another type of ganglion does not appear to have a connection with a joint, such as those found in the deep fibular (peroneal) nerve over the head of the fibula [43, 44]. It is likely that these lesions originate from the superior tibiofibular joint after disruption of its capsule, allowing dissection of the synovial fluid along the articular branch of the fibular nerve reaching the epineurium of the nerve. The previous connection with the joint is often then obliterated. Intraneural ganglia may extend great distances along the course of the nerve, such as the fibular (peroneal) division of the sciatic nerve, resulting in motor or sensory deficit [4].

Most localized lesions are resectable without serious loss of function. For ganglions extrinsic to nerve but compressing it, the surgeon must dissect around such lesions after carefully identifying, dissecting away, and protecting the involved nerve. The origin of the cystic lesion should be ligated or secured in some other fashion close to the joint to reduce recurrence. For intraneural ganglions, interfascicular dissection seems to work best because fascicles are cleared of the cyst and then its capsule. For larger lesions, it may be necessary to evacuate the synovial-like contents of the cysts and dissect the capsule away from the decompressed and split fascicles. Occasionally, larger lesions require several operations before they are obliterated.

Epidermoid cysts usually do not arise within nerve itself but may compress an adjacent nerve. Common locations for the epidermoid cysts involve the sciatic nerve close to the sciatic notch or behind the knee, involving the posterior tibial nerve [4]. These cysts can be resected as a solitary mass after performing neurolysis on and gently retracting involved nerves. Occasionally, a large lesion at the hip or pelvic level requires initial evacuation and then dissection of the capsule away from adjacent tissues, including nerves.

Hypertrophic Neuropathy or Onion-Whorl Disease

Hypertrophic neuropathy is a rare disease of unknown etiology and pathogenesis. Fascicles and individual nerve fibers become encased by connective tissue in a circular fashion, as if the endoneurium has proliferated. This results in a hypertrophic nerve with an "onion-whorl" appearance to its nerve fibers. Histologically, there is proliferation of perineural cells, endoneurial fibrosis, fibrotic replacement of the perineurium, and significant reduction in myelin [10].

Hypertrophic neuropathy primarily affects children or young adults with a predilection for the fibular (peroneal) nerve in the leg or the median nerve in the arm [45, 46]. Less commonly, it can also be found in the brachial plexus as well as the ulnar, radial, and sciatic nerves [4, 45, 47]. The lesion usually involves a lengthy segment of nerve resulting in a progressive loss of function. It does not spread to other nerves in the body. Some of its histologic features suggest either a contusive stretch injury or a chronically compressive etiology, but a history of significant trauma is usually absent, and no obvious entrapment or irritative environment is found on surgical exploration.

Pain or progressive loss of function warrants exploration. Function is usually partially spared distal to the lesion, and NAPs across the lesion are often present. External or external and internal neurolysis is usually performed. Manipulation of the lesion, particularly by internal neurolysis, may produce additional and even complete loss of function, despite the fact that neurolysis is less invasive than resection. An alternative is to proceed with resection, despite the attendant loss, and to replace the lost segment by grafts. Since the disease usually involves a significant segment of nerve, the grafts are likely to be long.

Table 43.5 Malignant neural sheath tumors

	No. of cases	NF1	Avg. F/U (month)	Deaths (%)
Neurogenic sarcomas				
Brachial plexus	14	4	50	29 %
Sciatic	6	1	17	0
Fibular (peroneal)	1	0	18	0
Tibial	1	1	30	0
Femoral	3	1	36	0
Ulnar	2	0	37	50 %
Fibrosarcoma				
Brachial plexus	2	0	39	0
Femoral	1	0	18	100 %
Neuroblastoma				
Sacral plexus	1	0	38	0
Totals	31	7	38	19 %

Avg. F/U average follow-up, *NF1* neurofibromatosis 1

Malignant Neural Sheath Tumors

Malignant neural sheath tumors (MNST) are a group of neoplasms consisting of malignant schwannomas and malignant neurofibromas, commonly grouped as neurogenic sarcoma and fibrosarcomas (Table 43.5) [27, 48]. The differentiation between malignant schwannomas and malignant neurofibromas can be difficult, a positive mucopolysaccharide stain favoring the latter. Histopathologic analysis reveals mitotic activity, cellular pleomorphism, necrosis, and hemorrhage in most cases (Figs. 43.10, 43.11, 43.12, and 43.13). Heterogeneous cell lines are present in 15 % of MNSTs and are generally found in patients with neurofibromatosis [48]. Approximately half of MNST arise in patients with NF1 [48] but can occur as solitary lesions in patients without NF1 [49]. Spontaneous malignant degeneration of solitary benign schwannomas is rare except in patients with NF1 [7]. Malignant degeneration of a plexiform neurofibroma in a patient with NF1 is not uncommon [18]. There is no gender preference in MNST and no specific laterality. Prior treatment with radiation therapy is a risk factor in the development of approximately 10 % of cases of MNST [48, 50]. MNST can be suspected if a mass increases rapidly in size and is associated with a progressive loss of function [51]. These lesions are often firmer than benign neural sheath tumors and are also relatively adherent to surrounding structures.

MNST usually manifests as pain with or without progressive loss of neurological function. Other common findings of MNST include a mass with irregular borders, a rapid increase in size, and a large size at presentation [10]. On rare occasion, patients with MNST present with metastasis to lung, bone, liver, or other organs [10]. MR imaging (Fig. 43.14a, b) is useful in defining the anatomy of the tumor as well as to screen for metastasis [22]. The 5-year survival for patients with MNST can approach 50 % but is much lower in patients with NF1 [52].

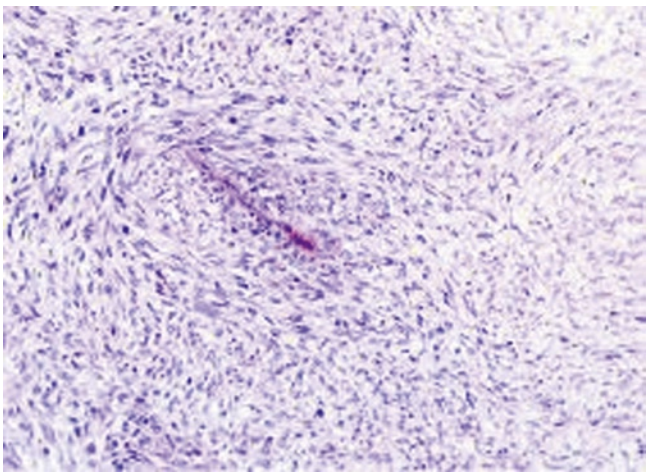

Fig. 43.10 Malignant neural sheath tumor, conventional: cellular (fibrosarcoma-like) spindle cell neoplasm with frequent mitoses and perivascular condensation of tumor cells

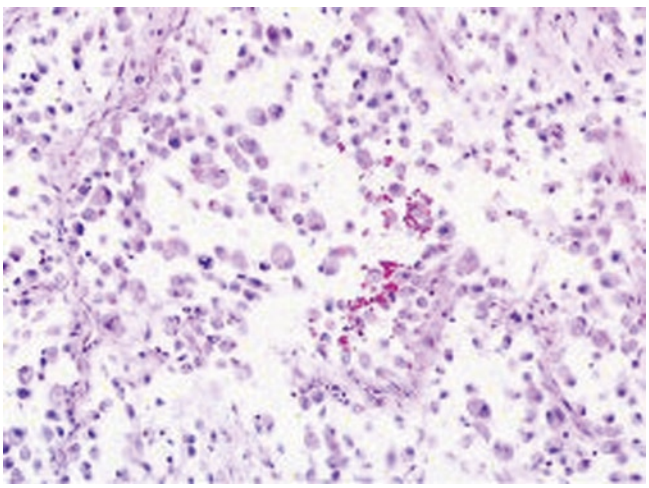

Fig. 43.11 Malignant neural sheath tumor, epithelioid: discohesive round to polygonal cells with well-defined cytoplasmic borders (epithelioid), embedded in a loose/myxoid stroma. Mitotic activity is high

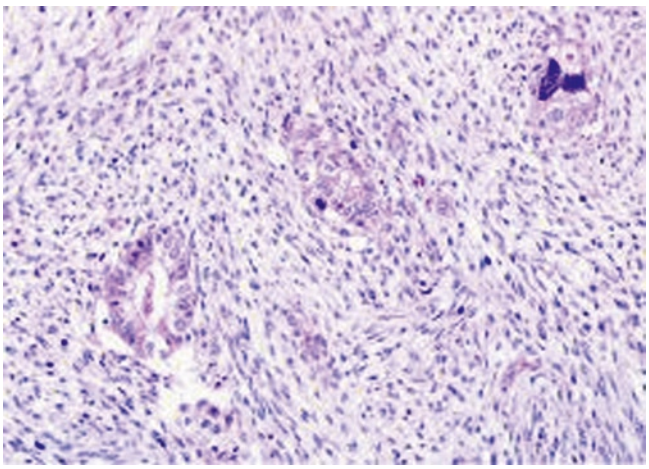

Fig. 43.12 Malignant neural sheath tumor, with divergent (epithelial) differentiation: spindle cell neoplasm with focal gland formation

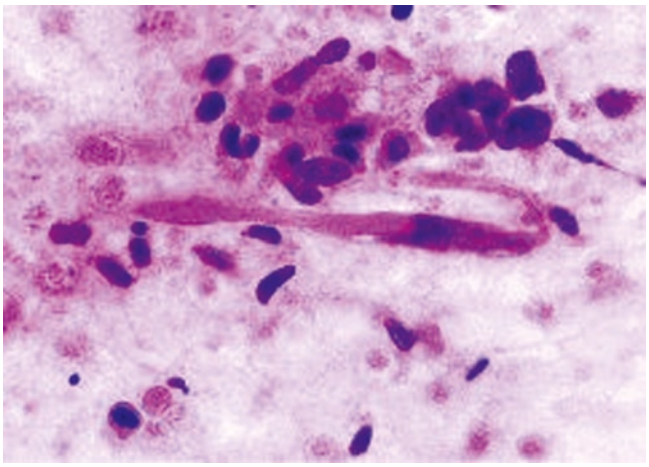

Fig. 43.13 Malignant neural sheath tumor, with divergent (rhabdomyosarcomatous) differentiation (high-power view of H and E stained smear): atypical elongated cell with eosinophilic cytoplasm myofibrillar bands

Despite preoperative symptoms and findings suggesting malignancy, the clinician cannot be certain of the diagnosis without a biopsy, which usually requires an operation. If prior biopsy was performed with a diagnosis of MNST, then a metastatic evaluation needs to be performed including a chest x-ray, CT or MR scan, abdominal CT, and bone scan. Following this and based on the extent of metastatic disease, options include the following:

1. Perform wide local resection, including removal of adjacent as well as adherent soft tissues (Fig. 43.15a, b). Resection should include a several-centimeter margin of entering and exiting nerve shown to be free of malignant changes on frozen and subsequent permanent sections. At that time, some surgical oncologists favor placement of tissue rods for irradiation locally, whereas others favor external radiation. Chemotherapy may also be added.
2. Amputate the limb well above the level of the lesion. Proximal upper limb lesions can also be managed by forequarter amputation of shoulder and arm above the level of the plexus or spinal nerves. Proximal lower limb lesions may require hip disarticulation with section of the proximal sciatic and femoral nerves.
3. Irradiate the limb with or without adjuvant chemotherapy in patients who refuse surgery beyond an attempt to remove the lesion or in patients with widely metastatic disease.

A critical step in managing these lesions is to obtain as thorough a neuropathologic examination of as much tissue as possible. As a result, further treatment depends heavily on the nature of the malignancy as determined by permanent sections. The recurrence rate is high, even after wide local excision and irradiation, but some patients survive beyond 5 years with proper management [53]. Although patients have died despite forequarter amputation or hip disarticulation when results for metastasis were negative, the largest percentage of survivors beyond 5 years is in this category [27].

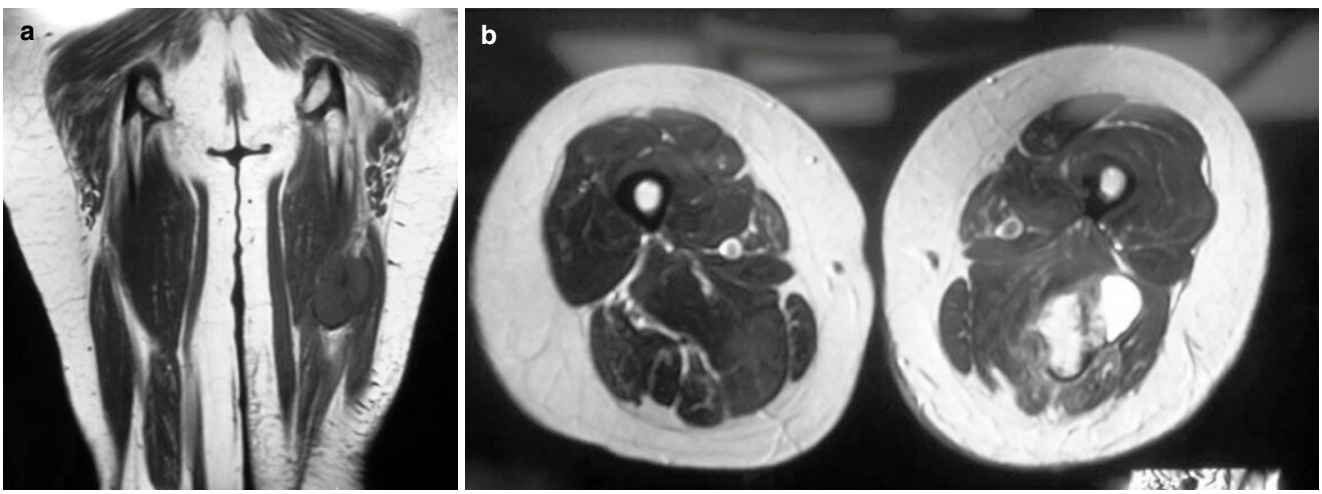

Fig. 43.14 MR imaging of malignant peripheral nerve sheath tumor of left sciatic nerve (**a**) coronal T1 pre-contrast image (**b**) axial T1 post-contrast image

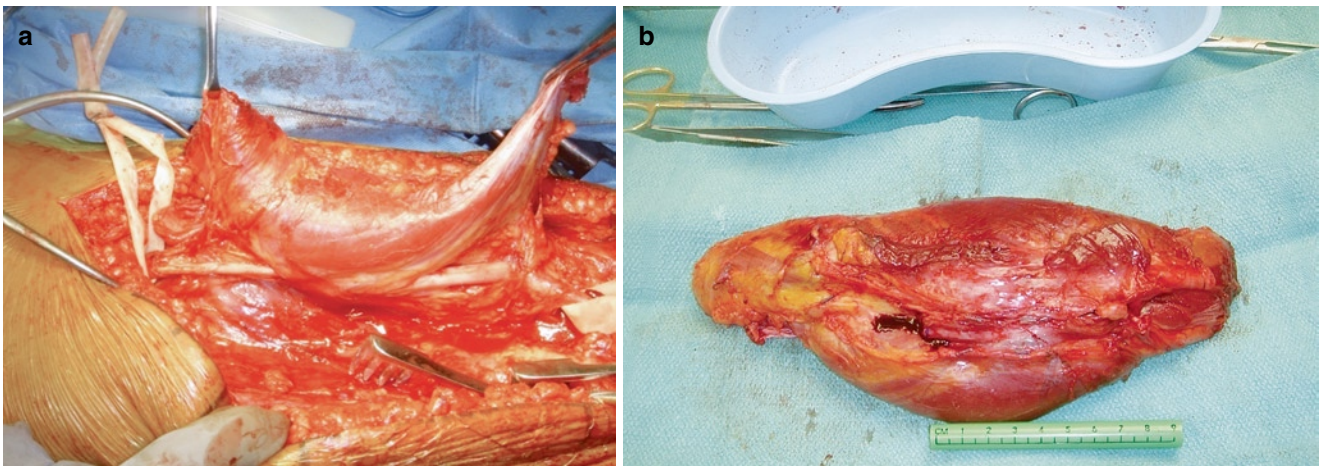

Fig. 43.15 Surgical resection of malignant peripheral nerve sheath tumor of sciatic nerve. (**a**) Note adherent biceps femoris to tumor and wide local resection to remove adjacent and adherent tissue. (**b**) Resected tumor with wide margin or tissue and visible proximal and distal stump of sciatic nerve

In recent years, however, limb-sparing procedures, including wide local resection, placement of x-ray rods, and sometimes external x-ray treatment, in conjunction with chemotherapy in carefully selected patients resulted in good to excellent survival rates [54–56]. Therefore, limb-sparing surgery is an accepted form of treatment in many patients with MNST.

Metastatic Carcinoma

This diverse group of tumors usually involves nerves by direct extension from the primary site. Occasionally, a malignancy may metastasize to nerve or tissues adjacent to it. Treatment plans must be individualized given the wide scope of variability in presentation and extent of involvement with each particular cancer. Breast carcinoma is the most common metastatic lesion involving nerve [4, 27]. Metastases to nerves have also been described with lung, melanoma, thymoma, pancreatic, and prostate cancer [8, 27, 57–59]. Most of these metastases occur in the brachial plexus. Metastasis located at an infraclavicular axillary level appears to present by direct extension, while metastasis located at the supraclavicular plexus is more likely with breast cancer disseminated through the lymph nodes. Most of these patients had prior mastectomy followed by irradiation, making differentiation between neoplastic plexopathy with metastatic breast cancer and radiation plexopathy more challenging (see Chap. 46) [60, 61].

If a mass is palpable or seen on scan in a patient with a history of breast cancer, then decompression of involved neural elements is reasonable. Unlike malignant neural sheath tumors, the nerve involved by metastasis can be treated with external neurolysis and careful removal of tumor from involved nerve. As much of the adjacent mass as possible is also removed. Metastases do not typically invade nerve beyond the epineural level, but exceptions exist. In cases of invasion of the neural elements by metastatic lesions, resection of the involved neural elements may be considered for pain control as a palliative procedure.

Metastatic lung cancer also commonly involves nerve and particularly the brachial plexus. Lung cancer may involve the brachial plexus by direct extension and most often produces a *Pancoast syndrome*. If pain is a severe problem, a posterior subscapular resection of the first rib and subtotal resection of the apical tumor to decompress the lower elements of the plexus may be performed as a palliative procedure. This procedure combined with cervical laminectomy for associated epidural metastatic disease is also palliative. Occasionally, a high contralateral open cervical cordotomy also helps control the pain associated with a Pancoast syndrome. The main focus for this palliative operation is adequate decompression of the compressed or entrapped nerve [62].

True metastatic disease involving nerve is seen with lymphoma, bladder cancer, and melanoma, although it is less common than breast or pulmonary cancer. With melanomas involving the plexus, removing the tumor from any epineural attachment has sufficed. The surgical procedure is then followed by local irradiation. A similar approach is also sufficient, at least for palliative purposes, for lymphoma.

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Cervical Radiculopathy

44

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Anatomy

The cervical spinal column is comprised of 7 vertebral bodies. The first (the atlas) is a ring of bone without a body; the second (the axis) has a bony process (the odontoid) that extends upward and around which the axis rotates. Neural foramina are formed between each pair of vertebral bodies and are bounded superiorly and inferiorly by pedicles, anteriorly by intervertebral disc and vertebral body, and posteriorly by facet joint (Fig. 44.1). Through the neural foramina pass the spinal nerve roots, recurrent meningeal nerves, and radicular blood vessels. The number designation of the exiting cervical spinal nerve root corresponds with the number of the vertebral body below it, except at the C7–T1 intervertebral level, where the exiting root is numbered C8.

The blood supply to spinal nerve roots is provided by a capillary network derived from the radicular arteries. In the rat, in the transitional region between the peripheral and central nervous system (the root entry zone), blood vessels are positioned on the surface of rootlets and in interradicular spaces, but not in rootlets themselves. The density of capillaries is very high in the ventral nerve root entry zone [1]. Distal to the rootlets in rats, at the proximal and distal root levels, ventral root capillary density is higher than at the dorsal roots [2].

The spinal canal is bounded posterolaterally by laminae and the ligamentum flavum, anterolaterally by pedicles, and anteriorly by intervertebral discs and vertebral bodies. The maximal anterior-posterior dimension of the canal at the C1–C3 levels ranges from 16 to 30 mm and at the C4–C7 levels from 14 to 23 mm. The diameter of the spinal cord at C1 is about 11 mm, at C2–C6 about 10 mm, and at C6–C7 about 7–9 mm. The cervical canal diameter is reduced by 2–3 mm with extension.

Facet joints are true synovial joints that link adjoining vertebral bodies, and provide spinal column directional stability during spine movement, based on the specific plane of the facet joint articulation. Facet joints are innervated by branches of the posterior primary ramus of the spinal nerve root. Spondylotic degenerative change at facet joints produces osteophyte formation that leads to neural foraminal and canal stenosis.

Intervertebral discs provide both support for the spinal column and mobility of the spine. Discs account for up to 30 % of the total height of the spinal column. They are composed of a gelatinous nucleus pulposus, surrounded by a containing ring of elastic collagen (the annulus fibrosus). The nucleus, which is about 90 % water, desiccates through life, fills with fibrous tissue, and loses its elasticity. Disc material and the ligamentum flavum do not contain nociceptors, but the posterior ligament, which lies next to the disc, does. This arrangement makes it most likely that disc herniation through the annulus fibrosus in itself does not produce pain, although the subsequent pressure on the posterior ligament and the nerve root does. In a clinical study of patients under local anesthesia, compression of a nerve root produced limb pain, while pressure on the disc produced pain in the neck and the medial border of the scapula. Intradiscal injection and electrical stimulation of the disc also suggested that neck pain was referred by a damaged outer annulus [3].

Historical Features of Cervical Radiculopathy

The association of arm pain with cervical disc protrusion and cervical spondylosis was not clear before the middle of the twentieth century. Arm pain was attributed to conditions such as neuritis, fibrositis, and scalenus anticus syndrome. Pathological reports in the early 1900s described cervical disc herniations as "chondromas," often associated with spinal cord compression. In 1934, Mixter and Barr reported disc

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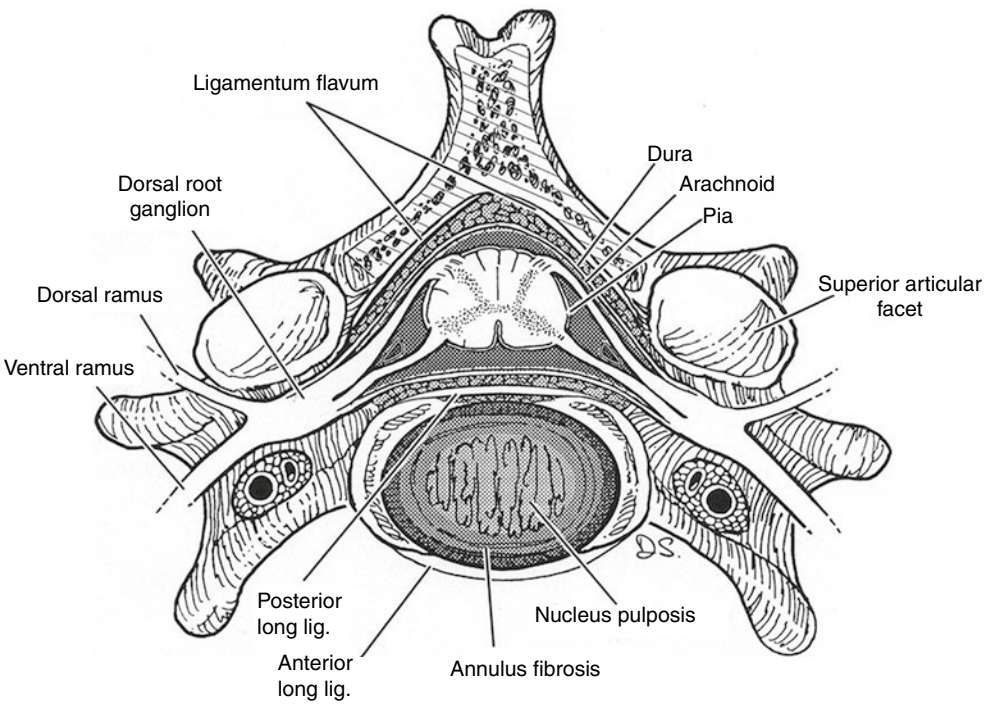

Fig. 44.1 Diagram of the cross section of the spine at the cervical level

herniation as the cause of sciatica in the lumbar region, but it was not until 1943 that Semmes and Murphey reported cervical disc herniation as the cause of radiculopathy in the absence of myelopathy. However, even into the 1950s it was commonplace for patients to undergo section of the scalenus anticus for treatment of symptoms that now would be recognized as classical cervical radiculopathy.

Risk Factors and Epidemiology of Cervical Radiculopathy

Research regarding risk factors in low back pain is much more plentiful than for acute neck pain. Factors strongly associated with low back pain such as prior back injury, age, and job satisfaction/emotional distress do not seem readily transferrable to acute neck pain. In one study, factors associated with acute neck pain included heavy lifting at work, cigarette smoking, and frequent diving from a diving board [4]. Risk factors for slow recovery from whiplash have been studied and include female gender, older age, having dependants, and not having full-time employment [5]. In an epidemiological study of cervical radiculopathy in Rochester, Minnesota, physical exertion or trauma preceded onset of radiculopathy in almost 15 % of their 561 patients, most often the result of snow shoveling in the winter and playing golf in the summer [6]. Motor vehicle accidents were responsible for radiculopathy due to spinal fracture, but not due to disc protrusion, and 41 % of patients had had prior lumbar radiculopathy, and 31 % had had prior cervical radiculopathy.

Cervical radiculopathy is a common condition with a male to female ratio of 1:7. In the Rochester study, the annual age-adjusted rate was 83.2 cases per 100,000, with a peak frequency of 202.9 per 100,000 per year for the 50–54-year age group [6]. The C7 root was involved in 46 % of cases, the C6 root in 17.6 %, and the other levels each in less than 10 % of cases. The cause of radiculopathy was disc protrusion in 22 % and spondylosis, disc, or both in 68 %. Surgical treatment was subsequently performed on 26 %, but at last follow-up, 90 % of all patients were asymptomatic or only mildly incapacitated by their radiculopathy. There are no studies that provide information about the factors on initial evaluation that predict prognosis.

Pathophysiology of Cervical Spondylosis

Pathology of Spondylosis

Spondylosis literally refers to a condition of the spine. In common medical parlance, it signifies age-related degenerative changes in the disc, the vertebral body, the facet joints, and points where they come in contact with each other in the spine. Damage to the nervous system occurs as the result of degenerative change at three main points: the disc, the uncovertebral joints, and the zygapophyseal (facet) joints. Resulting bony overgrowth (osteophytes) or disc herniation at these points may directly impinge on spinal nerve roots or the spinal cord, or their effect may be primarily to produce instability and misalignment of the spine that in turn produces

pain and neurological sequelae. It is not known whether changes in these different structures are causally interrelated or occur independently.

One school of thought suggests that the cascade of spondylotic changes is led by degenerative change in the nucleus pulposus of the disc. With age there is gradual narrowing of the disc space coincident with changes in disc proteoglycan composition. Later, cracks develop in the disc, and deposits of gas and calcification may form. Eventually the disc material becomes desiccated and friable. Age-related changes also occur in the annulus fibrosus, which becomes more fibrotic and less elastic. Fissures develop and calcium is deposited. As the disc shrinks and the intervertebral disc space narrows, the annulus tends to buckle out.

As the disc degenerates, changes are seen at the vertebral body end plates adjacent to the disc. The marrow undergoes fibrovascular change or fatty marrow replacement. Finally end-plate sclerosis develops. Osteophyte formation occurs at the margins of the vertebral bodies. What triggers osteophyte formation is unclear, although spinal movement at ligamentous attachment sites and loss of buffering tissues between bony surfaces likely play roles. Osteophyte production appears to slow as advancing spondylosis leads to decreasing spinal movement [7].

Uncovertebral joints are not true joints but may represent a slit in the intervertebral disc at the point where the uncinate process makes contact with the disc and vertebral body above. As disc substance decreases, there is more contact between the uncinate process and adjacent bone, leading to osteophyte formation (Fig. 44.2). At the cervical levels, dorsal protrusion of these osteophytes narrows the adjacent neural foramen (where spinal nerve roots exit); lateral protrusion may lead to impingement of the vertebral artery. These changes are greatest at the C5–6 and C6–7 levels, where cervical movement is greatest.

Facet joint degeneration may not be as directly related to the above spondylotic changes but often coexists. One study suggested that disc degeneration predominates at the lower cervical levels, while facet joint change predominates at the upper levels [8]. Disc degeneration is likely to put additional weight-bearing strains on facet joints, which are not weight-bearing structures. With unnatural movement of the spine, the synovial joint bears more structural burdens, degenerates, and develops osteophytes. These osteophytes grow into the posterior aspect of the neural foramen (Fig. 44.3).

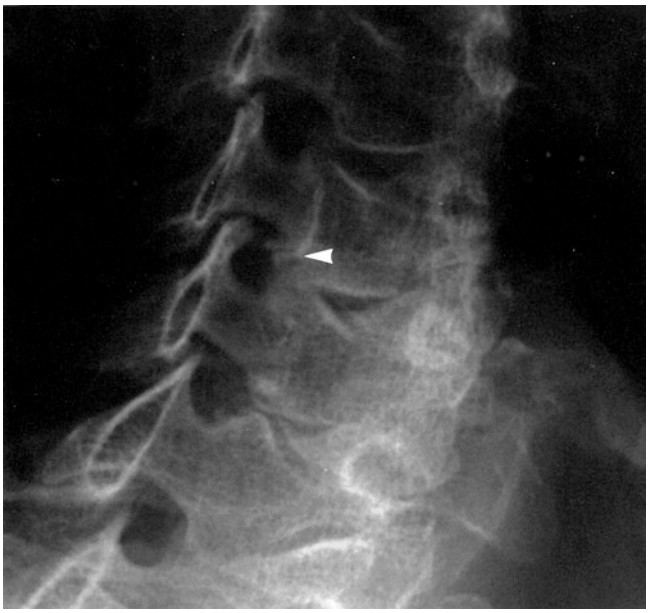

Fig. 44.2 Cervical radiograph demonstrating uncovertebral osteophyte encroaching into neural foramen (*arrow*)

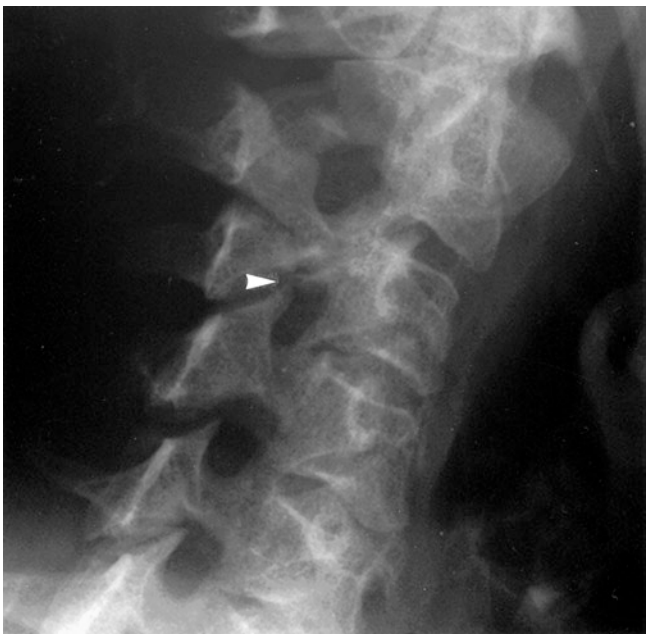

Fig. 44.3 Cervical radiograph demonstrating facet joint osteophyte encroaching into neural foramen (*arrow*)

Pathophysiological Mechanisms of Nerve and Cord Impingement

There is no universally accepted classification system for pathological disc changes. Basically, an abnormal disc may be described as bulging or herniated. Herniations may be classified as protrusions, extrusions, or free fragments. A bulging disc extends beyond the margin of the vertebral end plate but does not affect the integrity of the encircling annulus fibrosus. A disc protrusion is described when disc material extends focally through a defect in the annulus, although the outer fibers of the annulus remain intact. A disc extrusion extends through the entire annulus but may remain anterior to the posterior longitudinal ligament or extend through it. The extruded disc remains connected with its

parent disc material. In contrast, a free (or sequestered) fragment is an extrusion that is completely separated from its main disc, although it may be either anterior or posterior to the posterior longitudinal ligament. A free fragment may migrate up or down from the cervical level of its origin. The size and lateral location of the disc protrusion or extrusion will determine whether a spinal nerve root becomes impinged and which particular level will be affected. Because cervical spinal nerve roots tend to exit horizontally from the cord to their neural foramina, a paramedian or lateral disc herniation will likely entrap the nerve root corresponding to the number of the vertebral body directly below it.

Neural foraminal stenosis occurs on a chronic basis from osteophyte growth directed posteriorly from uncovertebral joints or anteriorly from facet joints. A very laterally placed disc herniation or free fragment may also impinge the nerve root at this site. Especially at upper cervical levels (C4–5, C5–6), there may be dorsal root ganglion impingement, as the DRG may occupy relatively intraspinal locations at those levels [9]. Osteophytes from facet joints may exert more impingement acutely with neck extension.

Concentric cervical canal stenosis may develop on the basis of a number of underlying pathological changes. Chronic spondylosis and the combination of disc herniation, facet, and uncovertebral osteophyte formation may all act in combination to narrow the canal at one or multiple levels. Hypertrophy of the posterior longitudinal ligament and the ligamenta flava will further decrease central canal size. Ossification of the posterior longitudinal ligament is a degenerative condition significantly associated with narrowing of the cervical canal and compressive myelopathy. It tends to occur in some ethnic groups more than others and is a pathological feature in 27 % of cases of cervical myelopathy in the Japanese population. All the above changes will produce premature cervical canal stenosis in those with a congenitally narrowed canal, usually on the basis of shortened pedicles.

A host of other intraspinal disorders can act to produce cervical nerve root and spinal cord impingement. Infections and inflammatory disorders (such as tuberculosis and sarcoidosis), extradural and intradural tumors (malignant, metastatic, or benign such as neurofibromas and schwannomas), dural fistulae, and arteriovenous malformations can produce clinical pictures identical to those seen with spondylotic changes.

Clinical Examination in Cervical Radiculopathy

The initial diagnosis of cervical radiculopathy rests upon the clinical assessment, based on the history and physical examination. The anatomic localization can be inferred in some cases by the neurological examination, but the precise structural cause can only be determined by neuroimaging procedures. In cases that are not straightforward clinically, in cases where significant weakness is present, and in cases where the neuroimaging findings are complex or confounding, electrodiagnostic testing (EDX) can aid in improving the degree of diagnostic certainty.

Patient History

Obtaining a history consistent with cervical radiculopathy requires exploring the major symptoms of arm pain, paresthesia, numbness, and weakness. Pain is present in virtually all patients with acute cervical radiculopathy, but it is seldom of localizing value. The diagnosis of cervical radiculopathy is supported by the presence of radicular pain emanating from the neck or shoulder, with extension into the arm (sometimes in a specific dermatomal distribution). The diagnosis is further supported when the symptoms are exacerbated by Valsalva maneuvers (cough, sneeze, or strain), indicating stretching of the dura at an intraspinal point of compression.

Paresthesia and numbness are present less often than pain and are usually nonspecific and therefore not of great localizing value, but they are symptoms that are seldom present with non-radicular causes of neck and arm pain. The patient may report intensification of paresthesia with Valsalva maneuvers or lateral head positioning.

If the patient describes Lhermitte's symptoms (spinal or radicular tingling, shock-like paresthesia with neck flexion), there is support for dysfunction of the posterior columns of the spinal cord, possibly due to spondylotic cord compression but also potentially due to intraspinal mass lesions or intramedullary processes such as multiple sclerosis. The presence of bowel or bladder urgency or incontinence, or new constipation or urinary retention, resulting from cervical spinal cord compression, may accompany multiple cervical radiculopathies in the setting of severe cervical spondylosis.

The patient may provide important information regarding the underlying cause of the symptoms. Recent or remote trauma should be explored, including whiplash incidents and injuries during contact sports. Prior episodes of spine pain, prior spine surgery, and a family history of spine disease should be sought. A general medical review of systems and past medical history are important to exclude other possible factors, such as the presence of malignant disease, collagen vascular disease, or infection.

Clinical Examination

The initial part of the examination should be a limited general physical examination as dictated by the findings during

Table 44.1 Typical clinical attributes of solitary cervical root lesions

Root	Pain	Numbness	Weakness	Reflex loss
C5	Neck, shoulder	Axillary distribution	Shoulder abduction, external rotation, elbow flexion, forearm supination	Biceps, brachioradialis
C6	Neck, shoulder, lateral upper arm, lateral forearm, thumb and lateral hand	Lateral forearm, thumb and index	Shoulder abduction, external rotation, elbow flexion, forearm supination and pronation	(Biceps, brachioradialis)
C7	Neck, shoulder, middle finger, hand	Index and middle finger, palm	Elbow and wrist (radial aspect) extension, forearm pronation, wrist flexion	Triceps
C8	Shoulder, medial forearm, fourth and fifth digits, medial hand	Medial forearm, fourth and fifth digits, medial hand	Finger extension, wrist (ulnar aspect) extension, distal finger flexion, distal thumb flexion, finger abduction and adduction	Triceps
T1	Medial arm and forearm, axillary chest wall, medial forearm	Medial forearm, fourth and fifth digits	Thumb abduction, distal thumb flexion, finger abduction and adduction	

the historical interview. The general neurological examination should include gait assessment, screening mental status testing, cranial nerves II–XII, motor testing in all four extremities, testing for increased tone in the extremities, sensory testing in all four extremities, coordination testing in all four extremities, deep tendon reflexes in all extremities, plantar stimulation, and inspection and percussion of the spine.

The specific examination for radiculopathy forms the core of a comprehensive general neurological examination. A classification of the typical neurological attributes of solitary cervical root lesions is listed in Table 44.1.

Specific bedside clinical maneuvers for the provocation of symptoms of cervical radiculopathy have come in to use, although their accuracy and safety have not been carefully studied. *Lhermitte's sign* can be elicited by actively flexing the patient's head and observing for the development of tingling paresthesia down the cervical spine or into the symptomatic arm. *Spurling's* test (the neck compression maneuver or foraminal compression test) is performed by extending and rotating the neck to the side of the pain, followed by applying downward pressure on the head [10]. This maneuver may produce limb pain or paresthesia, as neck extension causes posterior disc bulging, while lateral flexion and rotation cause narrowing of the ipsilateral neural foramina [11]. It may be safer to perform this maneuver by asking the patient to actively extend the neck, then laterally flex and rotate toward the side of the pain, followed by application of pressure through the examiner's hands on the vertex of the head [12]. When radiating pain or limb numbness develops, the maneuver should be stopped. This maneuver is rather specific but not sensitive. The *shoulder abduction relief sign* (or shoulder abduction test) is performed by asking the patient to lift the symptomatic arm over the head, resting the hand on the top of the head [13]. This may be a useful therapeutic maneuver as well as a diagnostic one for lower cervical radiculopathy [14].

One study reviewed the various provocative and relief signs and reported that for roots C6–8 the neck compression maneuver had a specificity of 100 % for radicular pain and 92–100 % for neurological and radiological signs, respectively. For the shoulder abduction maneuver, the specificity was 100 % for neurological signs and 80 % for radiological signs. The sensitivity of these tests for radicular symptoms, neurological signs, and radiological signs ranged from about 40 to 60 % [15]. Neither of these maneuvers was useful for C4–5 radiculopathies. A systematic review of the diagnostic accuracy of provocative tests of the neck for diagnosing cervical radiculopathy identified only six studies that met evidence-based methodological criteria for review [16]. After their review, lack of evidence precluded firm conclusions regarding diagnostic value of these tests. However, the review suggested that when consistent with the history and physical findings, a positive Spurling's test, traction/neck distraction, and Valsalva maneuver might be indicative of a cervical radiculopathy, while a negative upper limb tension test might be used to exclude it.

Of all the elements of the clinical examination, the identification of weakness in a specific myotomal distribution has the greatest localizing value for the diagnosis of a solitary cervical (or lumbar) spinal nerve root lesion. Arm weakness provides the most reliable correlation with the structural level of cervical spinal nerve root involvement. The presence of weakness is strong support for a neurological disorder, but the examination seldom fully differentiates radiculopathy from brachial plexopathy, or mononeuropathy in some cases. True neurogenic weakness may be difficult to distinguish clinically from reduced voluntary effort due to pain.

Clinical Localization of Radiculopathy

Clinicians use reference charts to guide them in the correlation of specific distributions of weakness with the likely anatomical level of nerve root involvement. Such charts have been constructed by a number of researchers in the field, and they tend to vary from one another in regard to the

correlation between specific muscles and nerve roots. The lack of agreement from one myotomal chart to another relates to anatomical variations in humans and differences in the nature of the research material used in the collection process. Anatomic charts have been derived by tracing root and peripheral nerve innervations of muscles from cadaver studies. Clinical charts have been derived by correlating the distribution of clinical muscle weakness in patients with specific traumatic lesions. Electromyographic charts have been derived from patterns of muscle denervation in patients with focal nerve root lesions.

The most complete descriptions of the myotomal innervations in man have come from the work of the Dutch anatomist Louis Bolk, beginning in 1894. His work was based on the anatomy of a single 3-year-old boy. Bolk postulated that any anatomic structure contains innervation elements from several adjacent root segments, explaining the anatomical variability seen from one individual to another [17]. Although we recognize errors in some of Bolk's myotomal innervations, his work formed the core of all modern myotomal charts. There are several reasons why one published myotomal chart may vary somewhat from others. First, as noted above, segmental innervation of dermatomes and myotomes is variable from one individual to another, owing to the overlapping nature of segmental innervation from adjacent root segments. Any one chart will necessarily be a composite of the segmental possibilities. Second, there are inherent shortcomings in any single technique of segmental anatomical study. Clinical studies rely on the spectrum of traumatic lesions producing the nerve damage; these may be partial lesions so that the extent and distribution of involvement will vary from one case to another. Anatomical studies rely on the tracing of nerve twigs to muscles, but do not take into account the physiological contribution of innervation. The physiological aspects of the segmental innervation of motor units are best traced by electromyographic myotomal charts, which carry the additional value of precise localization of individual, affected muscles, not possible in clinical studies where motor actions cannot always be defined in terms of the activation of individual muscles (see below).

Electrodiagnosis of Cervical Radiculopathy

For the patient with a solitary cervical spinal nerve root compression in whom the clinical examination is straightforward and neuroimaging studies are entirely consistent, no further workup is required. However, for situations in which the age of the deficits is unclear, the degree and nature of active motor axon loss is in question, or the clinical findings and neuroimaging studies are complex or not consistent with each other, electrodiagnostic testing is useful. It can provide valuable information regarding the physiology of the neurological symptoms (the presence, the severity, and the activity of motor axon loss), as well as the anatomical localization of the lesion. Electrodiagnostic studies will also exclude other disorders that may masquerade as radiculopathy.

Clinical Neurophysiology of Radiculopathy

Cell bodies of the motor nerve fibers reside in the anterior horns of the spinal cord, while those of the sensory nerve fibers reside in the dorsal root ganglia (DRG). DRG are in general located within the neural foramina and are therefore not strictly speaking intraspinal. The preservation of sensory nerve action potentials (SNAPs) is a cornerstone of the electrodiagnostic presentation of radiculopathy. Axon loss lesions occurring within the intraspinal canal will affect both sensory and motor root fibers and will produce both sensory and motor symptoms, but will only produce peripheral wallerian degeneration along the motor fibers, as long as the DRG are distal to the site of nerve root damage. Peripheral sensory axons do not degenerate when they remain connected to their cell bodies.

However, there is a tendency for DRG to reside within the spinal canal at some segmental levels. While this is especially true at the L5 and S1 levels, it is also seen in the cervical region, especially at the C5 and C6 levels [9].

Nerve root fibers are vulnerable to the same types of injury as other peripheral nerves: entrapment, compression, infiltration, necrosis, and transection. Mild damage may result in focal demyelination leading to conduction block or conduction velocity slowing along nerve root fibers. Axon loss at the root level results in wallerian degeneration along the whole course of affected nerve fibers. Both conduction block and axon loss produce symptoms and signs of sensory loss and weakness if a sufficient number of nerve fibers are affected. Conduction velocity slowing alone is insufficient to produce weakness or significant sensory loss, although sensory modalities requiring timed volleys of impulse transmission along their pathways, such as vibration and proprioception, can be altered.

Nerve Conduction Studies

A number of factors reduce the sensitivity of NCS in the diagnosis of radiculopathy. First, most radiculopathies are due to compression from disc protrusion or spondylosis and result in damage to only a fraction of nerve root fibers, producing limited motor and sensory deficits. Second, in the acute setting, radiculopathy manifests itself most commonly by symptoms of pain and alteration of sensory perception. Sensory radiculopathy can only rarely be reliably localized segmentally by electrodiagnostic techniques. This is the case

because symptoms of pain and paresthesia are mediated through C-type sensory fibers that are too small to be studied by routine electrodiagnostic techniques, and because the peripheral processes of sensory root fibers remain connected to their cell bodies in intraspinal lesions, so sensory nerve action potentials (SNAPs) remain normal. Third, the intraspinal location of most lesions makes it impossible to perform direct nerve conduction studies (NCS) on the nerve root proximal to the damaged segment, preventing the diagnosis of conduction block and focal conduction velocity slowing across the damaged segment of the root.

Routine Studies

Sensory NCS performed along peripheral nerve trunks are characteristically normal in radiculopathy. The SNAP distal latency and nerve conduction velocity are never involved in radiculopathy. The SNAP amplitude may be abnormal if DRG are affected in the pathological process. In pathological processes that infiltrate or extend from the intraspinal space into the neural foramen, such as malignancy, infection, and meningiomas, DRG are damaged and wallerian degeneration along sensory axons occurs, resulting in SNAP amplitude loss. When DRG reside in an intraspinal location, as mentioned above, they become vulnerable to compression by disc protrusion and spondylosis.

Motor NCS are relatively insensitive in the diagnosis of motor radiculopathy for several reasons. First, most radiculopathies interrupt only a fraction of the total number of motor root fibers, while loss of close to 50 % of motor axons in a nerve trunk is required to reliably establish a significant reduction in the compound muscle action potential (CMAP) amplitude, when compared to the same response on the uninvolved side [18]. Second, to identify an abnormality of CMAP amplitude in a motor radiculopathy, the muscle belly from which the CMAP is generated must be in the myotome of the injured root. For example, a severe C8 radiculopathy would be expected to produce some change in the ulnar CMAP amplitude, recording from either the abductor digiti minimi or the first dorsal interosseous. In the C5 myotome, the musculocutaneous and axillary nerve trunks can be stimulated to assess CMAPs from the biceps and deltoid muscles, respectively. However, in the C6 and C7 myotomes, there are no major peripheral nerve trunks that carry only C6–7 fibers, and there are no isolated muscle bellies from which to assess the CMAP amplitude.

Late Responses

Late responses are evoked motor potentials that can be used to measure the travel time of propagated nerve action potentials from a distal point of electrical stimulation along a peripheral nerve trunk, to the spinal cord, and then back down the limb to a muscle belly innervated by the same peripheral nerve trunk. Theoretically, they make possible the assessment of conduction through the damaged segment of a nerve root, but there are a number of limitations. First, because the traditional measurement is latency, the sensitivity is low because even severe slowing over a short segment will not usually prolong the total latency enough to be significant. Second, as long as a few nerve fibers conduct normally through a damaged segment, a normal "shortest" latency will be recorded, even in the presence of severe nerve root damage. Finally, late responses such as F waves are of limited value in the diagnosis of radiculopathy because they are not recorded along sensory nerve fibers, and are useless in the assessment of sensory symptoms.

The F wave was first described by Mc Dougal and Magladery in 1950 and was so named because they were originally recorded from foot muscles. The F wave is a motor response often recorded from a muscle belly after stimulation of the peripheral nerve trunk innervating the muscle. It is thought to arise from the "backfiring" of motor neurons as impulses arrive antidromically from a peripheral site of nerve trunk stimulation. The F wave occurs after the CMAP, but as the point of nerve trunk stimulation is moved more proximally, the CMAP latency lengthens and the F wave latency shortens, indicating that the impulse eliciting the F wave travels away from the recording electrodes toward the spinal cord before returning to activate distal muscles. Traditionally, the shortest latency of at least eight consecutive discharges is measured. The absence of an F wave response from stimulation of the median, ulnar, or tibial nerve in the presence of normal evoked CMAPs from the same muscle suggests conduction block or very recent (less than 5–8 days) axon loss somewhere along the nerve trunk proximal to the point of nerve stimulation. This is most often encountered in the setting of acute demyelinating polyneuropathy but could conceivably be a feature of isolated radiculopathy when occurring in a single myotomal distribution. The F amplitude and duration and the range of F wave latencies have not been of clinical value in the diagnosis of focal radiculopathy. A measure of the interval between the shortest and longest F latency in a consecutive series of stimuli is described as chronodispersion and can be abnormally increased in demyelinating polyneuropathies, but does appear to have significant application to focal radiculopathy.

The H reflex is a monosynaptic spinal reflex first described by Hoffmann in 1918. Traditionally, this response is obtained by stimulating the tibial nerve at low voltage in the popliteal fossa to preferentially activate Ia sensory afferents, whose fibers terminate directly on motor neurons in the same spinal cord segment, completing a reflex arc that ends in an H wave recorded over a distally recorded muscle in the tibial nerve distribution, such as the soleus muscle. In clinical practice, only the tibial H reflex is routinely performed. When elicited from the tibial nerve, the H reflex is the electrophysiological equivalent of the Achilles tendon muscle stretch reflex.

The H reflex can be elicited from other nerve trunks. In the presence of corticospinal tract disease, the H reflex can be elicited from many nerve trunks, as a result of loss of the normal central inhibitory influences on motor neuron pools. Under normal circumstances, aside from the tibial H reflex, the H reflex can be elicited reliably only from the median nerve, recording over the flexor carpi radialis. Abnormalities of the median H reflex may be seen in patients with C6–7 radiculopathy; one study identified 11 of 25 patients with absence of the median H reflex and 6 of the remaining 14 with prolonged H reflex latency [19]. The upper limit for the median H reflex has been reported as 20 ms, but nomograms taking into account the effect of arm length allow more precision in diagnosis.

Somatosensory Evoked Potentials

Theoretically, somatosensory evoked potentials (SEPs) should be a valuable tool in the assessment of conduction abnormalities along sensory fibers at the root level. Electrical stimuli are delivered on the skin surface to a mixed sensory and motor nerve trunk, a sensory nerve trunk, or the skin in a specific dermatomal distribution. Responses are recorded over the spine and scalp, and latencies are measured to assess the conduction time along large-diameter sensory fibers across various segments of the peripheral and central conduction pathways primarily subserving proprioception and vibratory sense.

Unfortunately, a number of limitations diminish the value of this technique. First, amplitude measurements are too variable in normal individuals to have clinical significance; thus, the assessment of partial axon loss lesions and partial conduction block is not reliable. Second, focal slowing in the root segment is diluted by normal conduction along the rest of the sensory pathway. Third, nerve trunk stimulation often simultaneously activates nerve fibers belonging to more than one root segment, masking the abnormality in the abnormal root in question [20].

Given the above-mentioned limitations, SEPs obtained from nerve trunk stimulation are of little diagnostic value. In patients with signs of cervical radiculopathy, with or without signs of myelopathy, nerve trunk stimulation may yield abnormal SEPs [21]. However, in these studies the abnormal SEP results contributed little to electrodiagnosis, because the patients in general also demonstrated clear electromyographic features of cervical radiculopathy.

Cutaneous sensory nerves have more specific and isolated root innervations, and thus, SEPs derived from cutaneous nerve stimulation have a potential diagnostic advantage. Scalp-recorded cutaneous SEPs were abnormal in 57 % of 28 cases of cervical and lumbosacral radiculopathy in one report, based on findings of abnormal amplitude and waveform configuration [22]. Overall, SEPs do not have the specificity or sensitivity of other electrodiagnostic techniques, such as the needle electromyography (EMG) examination, to recommend them at this time for the routine diagnosis of radiculopathy.

The Needle EMG Examination

For cervical radiculopathy, a systematic evidence-based literature review concluded that needle EMG examination provided confirmatory evidence of cervical root pathology in 30–72 % of patients presenting with appropriate symptoms or signs. Needle EMG abnormalities were highly correlated with weakness. Good agreement between imaging studies and needle EMG was seen in 65–85 % of cases [23, 24].

General Concepts

Although the needle EMG assesses only the motor component of radiculopathy, it is the most specific and sensitive of the electrodiagnostic tests for the identification of axon loss radiculopathy. In many cases the needle EMG may provide information regarding the root level of involvement, the degree of axon loss present, the degree of ongoing motor axon loss, and the chronicity of the process. Several general comments can be made. In most laboratories, patients with arm pain receive a general needle EMG survey that samples all major root and nerve trunk distributions in the limb in question. If abnormalities are identified, the examination is modified to focus on the cause for the abnormality. If there is a symptom in a specific region of the limb, such as the shoulder girdle, muscles in that region are also examined. Table 44.2 outlines the screening NCS for nonspecific arm symptoms. Table 44.3 outlines the screening needle EMG for nonspecific arm symptoms.

The localization of a nerve root lesion requires the identification of neurogenic abnormalities in a distribution of muscles that shares the same root innervation. The abnormalities may include increased insertional activity in the form of positive waves or sharp spikes, abnormal spontaneous activity in the form of fibrillation potentials, reduced (neurogenic) recruitment of motor unit action potential (MUAP) firing, and features of chronic MUAP reinnervation, such as increased duration, increased amplitude, and polyphasia.

The timing of the needle EMG is important. In acute radiculopathy, fibrillation is the abnormality most likely to confirm the presence of a motor radiculopathy. Fibrillation seldom develops before 2 weeks has elapsed from the onset of symptoms and in some patients may not appear until 4–6 weeks after the onset of symptoms. To utilize the EMG most effectively, the needle EMG should be delayed for at least 3 weeks after the onset of symptoms.

Table 44.2 Screening nerve conduction studies for arm pain

Sensory
Distal amplitude and latency:
Median
Ulnar
Radial
Motor
Distal latency, distal and proximal amplitudes, conduction velocity, and F latency:
Median (recording from thenar eminence)
Ulnar (recording from hypothenar eminence)

Table 44.3 Screening needle EMG survey for arm pain

Muscle	Root level	Nerve trunk
Abductor pollicis brevis	T1 (C8)	Median
First dorsal interosseus	C8 (T1)	Ulnar
Flexor pollicis longus	C8 (T1)	Anterior interosseous (median)
Extensor indicis proprius	C8	Posterior interosseous (radial)
Pronator teres	C6–7	Median
Triceps	C6–7	Radial
Biceps	C5–6	Musculocutaneous
Deltoid	C5–6	Axillary
C7 paraspinal	Overlap	

Root Localization by Needle EMG

The choice of muscles for the needle EMG must be tailored to the clinical question and specific symptoms but must be comprehensive enough to maximize diagnostic certainty. The particular muscles showing neurogenic changes in the myotome in question will vary from case to case because most root lesions are partial and not all muscles in the myotome will be affected equally. During the needle EMG, the more muscles identified as abnormal in the myotome, the more secure the electrodiagnosis. To make a reliable diagnosis of a single-root lesion, at least two muscles in that myotome should be found with neurogenic changes, and they should not share the same peripheral nerve innervation. In myotomes where it is possible, involvement of proximal and distal muscles should be sought to increase the certainty of the diagnosis and exclude peripheral mononeuropathy as the cause for the abnormalities. To complete the needle EMG in an individual with an identified single-root lesion, muscles in the myotomes framing the involved root level should be examined to verify that those myotomes are normal. For example, the biceps and first dorsal interosseous muscles should be normal in a patient with a C7 radiculopathy.

Paraspinal muscle involvement should always be sought, as it adds important support for the diagnosis of an intraspinal lesion and essentially rules out plexopathy and peripheral mononeuropathy as the cause of extremity muscle involvement. However, a number of factors reduce their value. First, paraspinal muscle fibrillation can be seen not only in disorders of the root but also in processes affecting the anterior horn cells and in muscle disorders such as necrotizing myopathy. Second, paraspinal muscle involvement cannot precisely localize the segmental level of root damage because the segmental innervation of paraspinal muscles can overlap by as much as 4–6 segments [23]. Third, clear evidence of paraspinal denervation with cervical (and lumbosacral) radiculopathies is seen in only about 50 % of cases [24]. Likely causes include the overlapping segmental innervation of paraspinal muscles and the tendency for muscles close to the site of the nerve lesion to reinnervate sooner and more completely than muscles at greater distance from the point where nerve regeneration begins. Finally, in paraspinal muscles that are close to a prior laminectomy site, fibrillation potentials may persist indefinitely due to iatrogenic denervation. In routine practice, we do not examine paraspinal muscles in areas of prior surgery.

Anatomically and clinically derived myotomal charts are not entirely applicable to the needle EMG. Muscles are chosen for the needle EMG because of specific attributes of root innervation and accessibility. Some muscles, such as the anconeus, pronator teres, and brachioradialis, are not easily isolated in the clinical examination but are easily isolated by the needle EMG and are important in root localization. Thus, electromyographically derived myotomal charts are useful in the electrodiagnosis of radiculopathy [24]. Figure 44.4 is an electromyographically derived myotomal chart for the cervical root segments.

Defining an Acute Radiculopathy

In an axon loss radiculopathy, determining the age of the lesion requires combining information about the duration of the symptoms with needle EMG findings. When MUAPs are of normal configuration and size, the presence of abnormal insertional or spontaneous activity (fibrillation) in the form of trains of brief sharp spikes or positive waves indicates recent motor axon loss. Abnormal insertional activity alone suggests that the process may be only several weeks old. The presence of spontaneous activity in the form of fibrillation potentials indicates a process at least 3 weeks of age.

While electrodiagnostic testing for radiculopathy is most valuable when significant axon loss has occurred, indirect evidence on the needle EMG may support the presence of a prominent conduction block lesion at the root level as the cause for weakness. When examining a muscle whose CMAP is of normal amplitude, the presence of a reduced recruitment pattern of MUAPs, in the absence of fibrillation potentials and chronic neurogenic MUAP changes, suggests conduction block. If this pattern is seen in multiple muscles of a specific myotome, a diagnosis of radiculopathy can be made. This diagnostic strategy is not reliable if the onset of weakness is less than 4 weeks prior to the electrodiagnostic study, since acute axon loss lesion may not clearly manifest fibrillation potentials for 3 or more weeks after onset of symptoms.

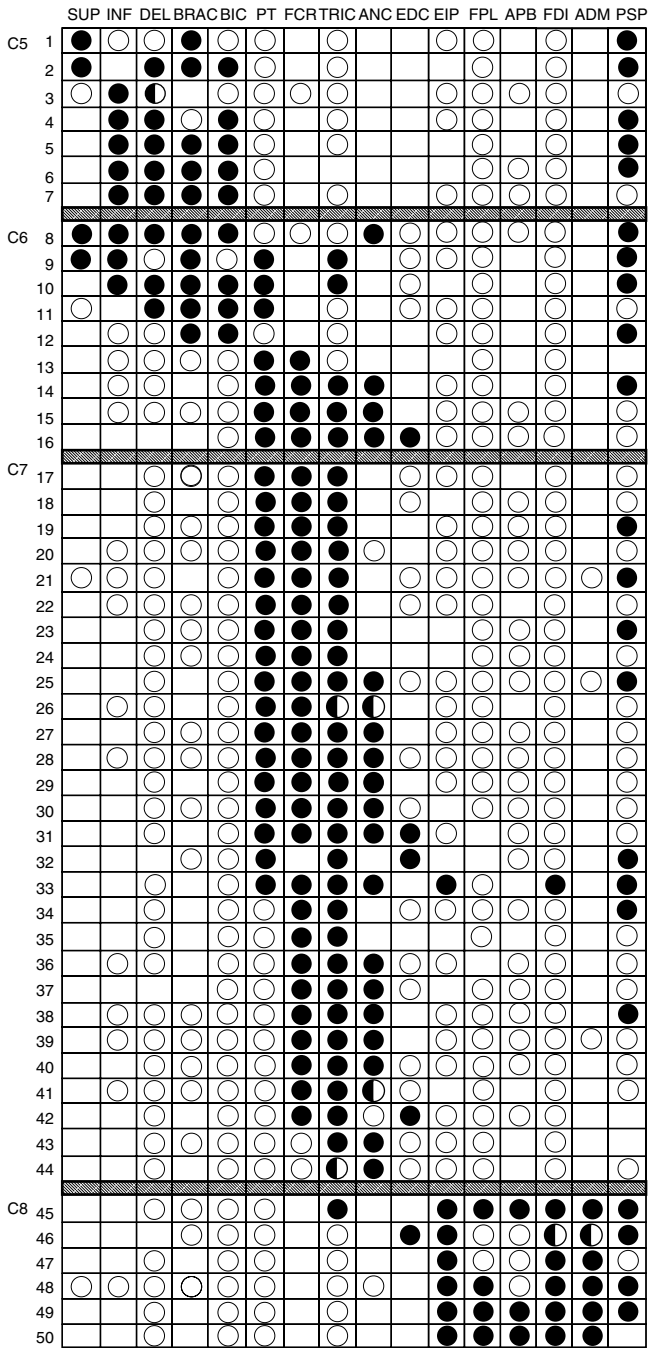

Fig. 44.4 Electromyographically derived myotomal chart for the cervical root segments, based on cases of isolated single-root lesions confirmed surgically. *Closed circle* positive waves or fibrillation potentials, with or without neurogenic recruitment and motor unit changes; *half-closed circle* neurogenic recruitment changes only; *open circle* normal examination. *SUP* supraspinatus, *INF* infraspinatus, *DEL* deltoid, *BRAC* brachioradialis, *BIC* biceps, *PT* pronator teres, *FCR* flexor carpi radialis, *TRIC* triceps, *ANC* anconeus, *EDC* extensor digitorum communis, *EIP* extensor indicis proprius, *FPL* flexor pollicis longus, *APB* abductor pollicis brevis, *FDI* first dorsal interosseus, *ADM* abductor digiti minimi, *PSP* paraspinal muscle (Reprinted from Levin et al. [24] with permission)

Defining a Chronic Radiculopathy

The diagnosis of a chronic/active or a chronic/remote root lesion is based on the observation of neurogenic MUAP changes, in the presence or absence of evidence of fibrillation potentials. In the early stages of reinnervation of denervated muscle fibers, between 6 and 26 weeks after nerve root injury, collateral sprouting from surviving nerve fiber terminals to denervated muscle fibers gives rise to MUAPs which are polyphasic and show moment-to-moment variation in morphology. As more time elapses, reinnervation becomes more complete, moment-to-moment MUAP variation resolves, and MUAPs develop the characteristic features of increased duration and amplitude, the typical electrodiagnostic signature of a chronic lesion. A needle EMG demonstrating these chronic neurogenic MUAP changes without fibrillation indicates the residuals of a remote lesion. These MUAP changes are permanent, reflecting the histopathological changes in the reinnervated muscle, and will remain unchanged unless the motor unit is injured again. After a significant motor axon loss process has occurred, MUAPs never return to their pre-injury morphology.

Chronic lesions can be classified into a chronic/active category if there are both fibrillation potentials and chronic neurogenic MUAP changes. In root distributions where the myotome includes muscles in both distal and proximal regions of a limb (in the arm only the C5–6 segments qualify), the presence of a chronic and ongoing axon loss process can be even more clearly defined when fibrillation potentials are seen in both distal and proximal muscles in the root distribution. In lesions where fibrillation potentials are seen in distal muscles only, the presence of an ongoing axon loss process is less certain. Some inactive but severe axon loss processes never fully reinnervate, especially in muscles farthest from the injury site, leaving some muscle fibers denervated indefinitely. The needle EMG findings at progressive stages of axon loss radiculopathy are summarized in Table 44.4.

Defining the Severity of a Radiculopathy

The severity of an axon loss process can be assessed during the needle EMG by the degree of motor unit loss in the root distribution. This is determined by a subjective measurement of the degree of reduced recruitment of MUAPs. While there is a correlation between the degree of reduced MUAP recruitment in a neurogenic process and the degree of weakness, reduced recruitment is not necessarily due to axon loss unless the CMAP elicited from the same muscle is also reduced in amplitude. Thus, defining the severity of an axon loss radiculopathy requires evaluation of both the CMAPs in the myotome in question (when possible) and the degree of reduced recruitment of MUAP activation. Measuring the number of fibrillation potentials present in a muscle is highly subjective and does not correlate as well with the degree of axon loss.

Table 44.4 Findings in the needle EMG examination at progressive stages of axon loss radiculopathy

	RECRUIT	INSERTION	PSP	FIB	POLY/VAR	NEUR	MTP/CRD
<3 weeks	++	+/+	+				
3–6 weeks	++	++	++	+++			
6–26 weeks	++	+	+/−	++	+++		
Chronic/active	++		+/−	+	++	++	
Chronic/remote	+/++					+++	+

RECRUIT neurogenic recruitment of myotomal motor units, *INSERTION* abnormal insertional activity in myotomal muscles, *PSP* paraspinal fibrillation, *FIB* fibrillation potentials in myotomal muscles, *POLY/VAR* polyphasic motor unit potential changes/motor unit potential variation, *NEUR* neurogenic motor unit potential changes (increased duration and amplitude), *MTP/CRD* myotonic discharges/complex repetitive discharges, +/− equivocal amount, + mild amount, ++ moderate amount, +++ greatest amount

Individual Root Lesions

Individual root lesions can be diagnosed with precision in many cases by a comprehensive needle EMG. By establishing familiarity with the electrical presentation of single-root lesions, it is often possible to identify radicular patterns when confronted with more complex combinations of root lesions in polyradiculopathies.

The most complete clinical study of specific cervical root lesions was carried out by Yoss et al. [25]. According to that study, clinical and radiographic evidence of radiculopathy occurs at the C7, C6, C8, and C5 levels 70 %, 19–25 %, 4–10 %, and 2 % of the time, respectively. The following needle EMG data on individual cervical radiculopathies comes from a study of isolated single-root lesions based on confirmed surgical localization [24] (see Fig. 44.4).

C5 radiculopathy produces a rather stereotyped pattern of muscle involvement, affecting the spinati, biceps, deltoid, and brachioradialis with about equal frequency, but not all of them together in each patient. The pronator teres is never involved in C5 radiculopathy [24]. Because the rhomboid major muscle has prominent C5 innervation, it should be examined in unclear cases. The upper trapezius, with its prominent C4 innervation, is spared in C5 radiculopathy. NCS are not likely to be helpful, although severe lesions may be associated with axillary and musculocutaneous CMAP amplitude loss.

C7 radiculopathy produces a rather stereotyped pattern of muscle involvement, affecting particularly the triceps but also the anconeus, flexor carpi radialis, and pronator teres. The triceps muscle is affected in essentially all cases of C7 radiculopathy [24]. Because the extensor carpi radialis is not reliably affected in most C7 radiculopathies, it is not usually part of the routine needle EMG survey for radiculopathy. An important part of the clinical diagnosis of C7 radiculopathy rests upon the finding of a diminished triceps deep tendon reflex, but several studies have shown that the reflex is abnormal in less than 70 % of patients [24, 25]. There are no reliably performed motor NCS that can be used to generate CMAPs from C7-innervated muscles.

With *C6 radiculopathy* there is no single characteristic pattern of muscle involvement. Rather, two patterns are discernible: the first very similar to the C5 pattern, with additional involvement of triceps and pronator teres in some; and the second similar to the C7 pattern. The pronator teres is abnormal in 80 % of patients with C6 radiculopathy but is also abnormal in 60 % of the cases of C7 radiculopathy [24]. The triceps is abnormal in over half the cases of C6 radiculopathy. Thus, significant electromyographic overlap occurs between C5 and C6 radiculopathy and between C6 and C7 radiculopathy. There are no reliably performed motor NCS that can be used to generate CMAPs from C6-innervated muscles.

C8 radiculopathy produces a stereotyped pattern of muscle involvement, including the ulnar-innervated muscles, extensor indicis proprius, and flexor pollicis longus. Abductor pollicis brevis is involved less often and to a lesser degree than other muscles. Of all the root lesions, C8 radiculopathy is the most clearly identified by needle EMG because of the limited myotomal overlap. NCS are not likely to be helpful, although severe lesions may be associated with ulnar (recording from the abductor digiti minimi or first dorsal interosseous) CMAP amplitude loss.

Although not strictly speaking a cervical radiculopathy, T1 root lesions present as upper extremity disorders. They are the most uncommon isolated root lesion affecting the arm. Although all C8 muscles of the hand are said to have T1 contributions, the abductor pollicis brevis muscle appears to be the only muscle with predominantly T1 innervation [26]. A single case of T1 radiculopathy with neuroimaging and intraoperative confirmation has been reported. The EMG picture showed chronic and active denervation limited to the abductor pollicis brevis [27].

Value of Electromyography in the Diagnosis of Radiculopathy

The lack of an established reference standard for the diagnosis of radiculopathy, other than the observation of nerve compression at surgery for structural radiculopathy, and the subjective nature of electromyographic data collection and analysis make a comparison of sensitivity and specificity of

various diagnostic tests studied in the scientific literature difficult. As a result few electrodiagnostic scientific studies have been able to meet the traditional standards set for class I or II evidence of effectiveness. Those studies that do meet evidence-based guidelines in systematic literature reviews often do not directly answer the question of clinical utility that is important to have in daily clinical care of patients.

For cervical radiculopathy, a systematic evidence-based literature review concluded that needle EMG examination provided confirmatory evidence of cervical root pathology in 30–72 % of patients presenting with appropriate symptoms or signs. Needle EMG abnormalities were highly correlated with weakness. Good agreement between imaging studies and needle EMG was seen in 65–85 % of cases [28]. One study retrospectively analyzed 47 patients with a clinical history compatible with either cervical or lumbosacral radiculopathy who were evaluated with both an EMG and a spine MRI. Among these patients, 55 % had an EMG abnormality and 57 % had an MRI abnormality that correlated with the clinically estimated level of radiculopathy. The two studies agreed in a majority (60 %) of patients, with both normal in 11 and both abnormal in 17; however, only one study was abnormal in a significant minority (40 %), suggesting that the two studies were complementary diagnostic modalities. The agreement was higher in patients with abnormal findings on neurologic examination [29].

Neuroradiology of the Cervical Spine

Neuroimaging of the cervical spine has been revolutionized by the availability of MRI technology. This has markedly reduced the use of invasive techniques such as myelography, except for those patients with implanted defibrillators and pacemakers, those with inconclusive MRI studies due to prior surgery, and those who are above the weight limit of the MRI examination table.

Neuroradiological studies are not required for all patients with neck pain and radiculopathy. In straightforward cases where there are minimal neurological deficits, conservative therapy without extensive diagnostic workup is the standard of care. When symptoms do not resolve over time or when there are significant neurological deficits, there is a greater need to understand the underlying anatomical changes, and neuroimaging should be undertaken.

Plain radiographs are of no use in the visualization of neural structures. Their use now is in the evaluation of the spine in the setting of acute trauma. They may also be used for localization during radiological, anesthetic, and surgical procedures.

Computed tomography (CT) imaging does permit visualization of neural structures and is useful in distinguishing nerve root compression due to disc versus osteophyte. CT is superior to MRI in the assessment of bony changes at the lateral recesses and neural foramina. When CT follows myelography, the resolution of cord and nerve root compression syndromes is excellent.

Disadvantages of CT include the effects of partial volume averaging, the slow acquisition time for multiple thin sections, streak artifacts in areas of dense bone such as the shoulder, and changes in configuration of the spine occurring between successive motion segments [30].

MRI technique is clearly superior in most cases to all other imaging modalities for the spine. In the cervical spine, MRI correctly predicts 88 % of the surgically proven lesions, in comparison with 81 % for post-myelogram CT, 58 % for myelography, and 50 % for CT [31]. Small osteophytes are not consistently identified on MRI scans so that in the setting where a distinction between disc and osteophyte is required, plain radiographs are an ideal additional study for identification of the osteophytes.

Specific MRI protocols differ from one institution to another, but certain basic sequences are needed to maximize the evaluation [32]. T1-weighted two-dimensional spin-echo images provide best contrast between dark CSF and high-signal-intensity bone marrow. Two-dimensional or three-dimensional spin-echo T2 or gradient-echo T2 imaging provides high-signal-intensity CSF to assess for anterior extradural disease, producing a myelogram-like effect. With a history of prior surgery, gadolinium-DTPA administration with T1-weighted sagittal and fat-saturation axial images will help assess for epidural scar, which enhances immediately following contrast injection, regardless of the time since surgery. Gadolinium-enhanced studies are also useful to assess epidural inflammatory disease in patients with possible vertebral osteomyelitis.

When bony metastatic disease is to be evaluated, screening can be carried out with a T1-weighted sagittal study. T1-weighted axial images are required to exclude epidural disease and cord compression. To assess the presence of intradural or leptomeningeal disease, sagittal and axial T1-weighted images before and after gadolinium enhancement are necessary.

Management of Cervical Radiculopathy

In any medical condition, the treatment plan should correspond to the severity of the symptoms and signs. The management approach for cervical radiculopathy covers the gamut from avoidance of heavy lifting to cervical laminectomy and fusion. No outcome studies have been published that compare specific modalities of medical care or that compare medical and surgical treatments in a similar patient population. For cervical radiculopathy, the goals of treatment should be the reduction of pain, the stabilization or amelioration of neurological deficits, and the stabilization or prevention of cervical spinal cord complications.

The initial management of acute neck pain must be directed toward an understanding of the likely pathophysiology. In the presence of a history of recent trauma or serious underlying medical illness, more aggressive evaluation is warranted. The presence of acute and progressive neurological dysfunction is an urgent medical problem. This is especially so when there is clinical evidence of bilateral neurological dysfunction, increasing the likelihood of involvement of the spinal cord. Manifestations include bilateral leg weakness and sensory symptoms, and loss of bowel or bladder control. Such symptoms should trigger an urgent workup that should include MRI studies and possible neurosurgical consultation.

A number of reports have performed systematic reviews of the literature regarding aspects of management, including diagnosis, medical treatment, and surgical interventions. Few studies have reached the level 1 or 2 significance by evidence-based criteria [33, 34].

Acute Nonspecific Neck Pain

There is general agreement that patients with nonspecific acute neck pain or nonlocalizable cervical radiculopathy without neurological signs or significant neurological symptoms require only conservative medical management. Radiographs of the spine are not indicated unless there is a significant history of trauma. Patients should abstain from heavy lifting, but bed rest is not helpful. Recommended medications include nonsteroidal anti-inflammatory drugs such as ibuprofen or aspirin. If there are complaints of muscle spasm, muscle relaxants such as cyclobenzaprine may be used. Narcotic analgesia should, in general, be avoided.

Patients suffering from cervical whiplash injuries constitute the only group that has been systematically studied. The Quebec Task Force recommended early mobilization of the neck, return to usual activities, and avoidance of bed rest and inactivity [35]. Cervical collars are not recommended because they prevent early mobilization of the cervical spine. Based on a review of the literature, another study concluded that manual therapies such as mobilization, exercises, and massage are beneficial for patients with mechanical cervical pain, but did not distinguish these therapies from more forceful manipulation, including thrust procedures [36]. A literature review identified reports that supported early mobilization but none that assessed the value of manipulation [37]. Therefore, it appears that data are not available to support the use of cervical manipulation for acute neck pain.

Patient education is an important part of the therapeutic effort. First, acute neck pain is very common, and the likelihood of spontaneous recovery is in the range of 80–90 %. Most patients are able to return to normal activities within 1–6 months. Second, prolonged inactivity will delay recovery. Third, potential causative activities should be avoided acutely, and perhaps indefinitely, such as heavy lifting, diving from a diving board, and possibly smoking.

There should be a follow-up visit with the patient within a month of the first visit. If significant symptoms persist, the patient's condition has moved into a subacute or chronic phase. If not already initiated, physical therapy evaluation and exercises should begin. In the absence of contributing psychosocial issues, the possibility of underlying structural or systemic causes should now be considered. After 4–7 weeks of an unimproved state, neuroimaging studies of the spine should be considered. Acute or chronic spine pain may be related to serious underlying medical illness. Warning signals that a medical illness may be at cause include prior history of cancer; unexplained weight loss; lack of pain relief with bed rest; failure to improve with conservative therapies; history of intravenous drug use; recent infection of the skin, urinary tract, or heart valve; and presence of risk factors for vertebral compression fractures.

Acute Cervical Radiculopathy with Focal Features

Acute Radiculopathy with Sensory Features Only

Patients with clear radicular pain and symptoms of paresthesia or numbness in a segmental distribution should be treated as though they have a focal intraspinal lesion. Such symptoms are often increased with specific provocative maneuvers during the examination. The prognosis for these patients is as favorable as for the group with nonspecific symptoms, regardless of the treatment plan. Management should consist of the avoidance of provocative activities, use of nonnarcotic analgesics, muscle relaxants if symptoms suggest a component of spasm, and early mobilization. Prolonged inactivity is not beneficial. If tolerated, gentle exercises, massage, and mobilization are beneficial, but spinal manipulation is not. If the suspicion is strong for nerve root impingement by disc protrusion or spondylosis, a high-dose, fast-taper course of corticosteroids can be used. A typical course would be prednisone 60–80 mg daily for 5–7 days, followed by a fast taper to discontinuation over the next 7–14 days. Prophylaxis against gastritis is recommended, and special precautions are needed in diabetics, but otherwise, the short course of treatment is not likely to produce complications.

With the clinical setting outlined, neuroimaging is not indicated unless there are specific historical features that suggest myelopathy or recent trauma. Patients with acute symptoms in the absence of significant neurological deficits are very likely to respond to conservative management, and surgery is not indicated. Treatment with cervical traction and spinal manipulation is not recommended in the presence of spinal cord compression or large disc protrusion and should not be considered unless the intraspinal anatomy has already been defined by neuroimaging.

In the patient with acute cervical radiculopathy due to neural foraminal stenosis from facet or uncovertebral osteophytes, cervical traction may provide temporary relief by modestly increasing the separation between vertebral bodies. This therapy can be self-administered with a pulley-system traction device. The initial counterweight should not exceed 5–7 lb but can be increased as tolerated to 15 or more pounds. 15–20-min episodes of traction should be repeated through the day as needed. Reports indicate that during cervical traction and for some minutes after, some anterior cervical vertebral separation does occur. In one study greater separation appeared with 50 lb than with 30 lb of traction, but traction applied for over 7 s at a time provided no further separation [38]. With 7 s of 30 lb of applied traction alternating with 5 s of rest, maximal separation occurred at 25 min, but the effect was lost within 20 min of the last applied traction. The efficacy of cervical traction has not been proven, but it is a standard therapy, and a number of patients claim benefit. If traction induces increased symptoms or pain, it should be discontinued.

Acute Radiculopathy with Neurological Deficits

Even patients with neurological deficits, such as segmental distributions of weakness, segmental loss of sensation, and reflex changes, are likely to have significant spontaneous recovery. The initial approach to their treatment need not be different from that outlined for the patient with radicular sensory symptoms only. Reliable outcome studies are not available that establish guidelines for medical versus surgical treatment in this patient group. However, the risk is clearly greater in this group for progression of the neurological deficits and residual neurological impairment if spinal nerve root compression persists. In the presence of a significant motor deficit, it is important to understand the underlying structural cause, first of all, in order to identify lesions that are amenable to surgical correction and, second, in order to exclude the additional (and at times subclinical) presence of spinal cord compression. Thus, early MRI studies in this setting are appropriate.

Management should consist of the avoidance of provocative activities, use of nonnarcotic analgesics, and muscle relaxants if symptoms suggest a component of spasm. Prolonged inactivity is not beneficial, and mobilization should be encouraged once symptoms stabilize. Gentle exercises, massage, and mobilization are beneficial, but spinal manipulation is not. If the suspicion is strong for nerve root impingement by disc protrusion or spondylosis, a high-dose, fast-taper course of corticosteroids can be used, as noted above.

Shoulder abduction over the head, with the hand and wrist resting on the vertex, has been used as a supportive sign of cervical radiculopathy but may also be used for temporary relief of sensory symptoms [14].

Chronic Cervical Radiculopathy and Chronic Neck Pain

When symptoms of radiculopathy extend beyond 4 weeks, in the presence of neurological deficits that are fixed or worsening, reassessment of the underlying cause of the symptoms and treatment options is necessary. A number of alternative nonsurgical approaches are also available, although their efficacy has not been proven. Physical therapy evaluation and the use of exercises to promote ideal posture, the use of transcutaneous electrical nerve stimulation (TENS) units, and continued cervical traction all have their advocates, and patients appear to respond to one or more of these maneuvers.

Epidural corticosteroid injections at the cervical levels have been performed for several decades, but not to the extent of epidural injections at the lumbar levels. Epidural injection of a combination of corticosteroid and anesthetic can lead to temporary reduction of pain in some patients. The few studies that have been performed have not been well controlled, and patient accession into the studies was not highly selective. Nevertheless, injections performed at the C5–6 and C6–7 interspaces produced "good or better" pain relief for 1 month or longer in 38 % of patients [39].

One retrospective study of 100 patients attempted to identify a patient profile that predicted response to cervical epidural injection of a combination of corticosteroid and anesthetic [40]. Based on clinical outcomes determined by subjective reports of pain relief and return to activities of daily living, only the presence of radicular pain predicted a better outcome from epidural injection. Other measured predictors, including age, abnormal sensory examination, change in deep tendon reflexes, motor changes on examination, and abnormal electromyographic findings, were not found to be significant. Predictors of a poor outcome included normal radiological examination findings and the presence of a herniated disc. In those whose pain relief amounted to 50 % or more, the response occurred irrespective of the cervical level involved. In patients with symptoms and neurological signs of true radiculopathy, whether or not a structural abnormality was seen radiographically, the probability of at least 50 % improvement was 62 %, while the probability was only 35 % for patients with only radicular pain symptoms and radiological structural changes. The poorest probability was seen in patients with radicular symptoms without structural changes and in patients with nonspecific axial pain symptoms.

Another local injection procedure, selective nerve root block, has been used for both diagnostic and therapeutic purposes at both the lumbosacral and cervical levels. This diagnostic technique has been used when there is lack of agreement between clinical and neuroimaging findings, when there is atypical limb pain, and when there is a history

of failed surgery at the level in question. Their use is contraindicated in the presence of systemic infection, local infection, or bleeding diathesis. For the therapeutic procedure at the cervical level, it is standard practice to use a combination of 0.5 cc of a 1 % xylocaine and a long-acting corticosteroid. The therapeutic injection is preceded by a localization procedure under fluoroscopic guidance, using a nonionic contrast medium to outline the selected nerve root. Contrast injection is also critical to exclude intravascular needle positioning, epidural positioning, and positioning at the sinuvertebral; injection at the latter two positions would no longer assure a selective nerve root block. The sinuvertebral nerve, derived from sympathetic fibers from the ramus communicans and fibers from either the primary anterior or posterior ramus, provides innervation over several segments to adjacent dura, posterior longitudinal ligament, and annulus. A further drawback of this technique is the placebo response rate, reported to be as high as 38 % [41]. Although reports have studied the efficacy of selective nerve root block at the lumbosacral levels, no studies have directly addressed the value of selective nerve root block in the treatment of cervical radiculopathy.

Chronic neck pain resulting from whiplash injury is a difficult therapeutic problem. A small number of patients who have suffered whiplash injuries have pain that persists 6 months or more after onset. In about half of these patients, the pain is thought to originate in the cervical zygapophyseal (facet) joints [42]. This chronic pain disorder does not appear to have specific clinical or radiological hallmarks, but it responds to local anesthetic block to the nerves supplying the painful joint. Although a controlled trial showed that intra-articular injections of corticosteroids offered no particular benefit, percutaneous radiofrequency neurotomy of the medial branch of the cervical dorsal ramus that innervates the joint provided pain relief for up to 263 days, compared to 8 days in the placebo group [43]. Patient selection was based on double-blind controlled trials of local anesthetic to the medial branches of the cervical dorsal rami at the levels of clinical involvement. Return of pain after a successful radiofrequency procedure was thought to represent regeneration of nerve branches to the joint and was treated with repeat neurotomy, with variable results.

A small number of patients fail to respond to all the above-mentioned therapeutic interventions. Some of these patients have chronic spine pain without evidence of structural intraspinal pathology, others have had previously treated structural lesions, and some have had multiple previous surgical interventions, a condition described as the failed spine syndrome. The goal in such patients is to improve the ability to perform activities of daily living and refocus attention away from pain perception.

A number of nonmedical factors play a role in the triggering and perpetuation of pain behavior. These include psychosocial issues such as job dissatisfaction, family stresses, and underlying psychiatric disorders. In other cases patients develop and ingrain a behavior of pain avoidance and fear of pain. Patients with chronic pain are best treated in dedicated centers for the rehabilitation of patients with multifactorial pain syndromes. Pain programs concentrate on the reeducation of the patient to diminish fear of activities of daily living through graded exercise programs, the exploration of psychosocial stressors, and the nonnarcotic treatment of pain.

Surgical Management of Cervical Spinal Disease

The factors that increase the likelihood that surgery will be performed for cervical radiculopathy include an obvious neurological deficit, progression of the deficit over time, unresolved pain, identification of an anatomic lesion that corresponds with the neurological picture, and spinal cord compression on neuroimaging in the presence of associated myelopathic neurological deficits. The general surgical approach to several different clinical scenarios will be presented.

A common surgical scenario is that of a large disc protrusion giving signs and symptoms of a unilateral C6 nerve root compression. When asked how to approach such a patient, four surgeons rendered four different opinions [44]. The opinions included anterior discectomy with fusion, anterior discectomy without fusion, anterior discectomy with anterior plating and screw fixation, and standard partial hemilaminectomy and foraminotomy to remove the disc fragment, without fusion. The last choice is favored because the disc space is not entered and recurrence and complications are rare [44, 45]. This procedure has been further refined with microdiscectomy techniques [46].

In the patient with osteophyte in the uncovertebral region causing nerve root compression, hemilaminectomy and foraminotomy as noted above are usually successful. This approach is also appropriate for the common combination of osteophyte and extruded disc at the C5–6 or C6–7 level.

The surgical treatment of spondylotic spinal cord compression and myelopathy is more involved. In the presence of a normal cervical lordosis, multilevel laminectomy is a satisfactory approach, allowing the spinal cord to migrate posteriorly. In the presence of reversal of the cervical curvature or overt kyphosis, multilevel fusion, internal fixation, and corpectomy are favored to reestablish stability.

The recurrence of symptoms after surgery may be due to a number of issues: inappropriate patient selection, insufficient decompression or disc removal, nerve root trauma, residual free fragment, and postoperative hematoma and infection. Postoperative symptom recurrence requires repeat clinical evaluation and repeat neuroimaging. The

identification of a retained disc fragment or a recurrent disc extrusion will likely lead to reoperation. Recurrent disc extrusions at the same level suggest the need for a fusion at that level. The presence of epidural scar is not in general an indication for reoperation.

A Cochrane systematic review of surgery for cervical radiculopathy or myelopathy identified only two studies out of 52 that met evidence-based medicine criteria for review [47]. Methodological flaws also occurred in these studies such as risk of bias, and neither study provided reliable evidence on the effects of surgery. It was unclear whether the short-term risks of surgery were outweighed by long-term benefits. There was low-quality evidence that surgery may provide pain relief faster than physical therapy or hard collar immobilization, and there was little or no evidence of such over the long term.

Differential Diagnosis of Cervical Radiculopathy

Acute Disorders

A number of other peripheral neuropathic disorders can present clinically or electrodiagnostically as acute cervical radiculopathy. The most likely to cause confusion in my experience is neuralgic amyotrophy. This disorder may best be described as a regional mononeuropathy multiplex. Although usually predominant in a single limb, in over 25 % of cases, there is either clinical or electrodiagnostic evidence of bilateral involvement. Classically the disorder begins with severe pain in the scapula or shoulder, preventing sleep in the recumbent position. Over subsequent days, weakness develops and reaches a maximum over hours to days. The pain usually subsides over several weeks but can persist. The motor disorder often takes the form of some combination of the spinal accessory, suprascapular, long thoracic, axillary, and musculocutaneous nerve trunks. Most cases involve nerve trunks around the shoulder girdle, but the clinical and electrodiagnostic picture can be extremely patchy, selectively affecting median nerve branches to the pronator teres muscle or the anterior interosseous nerve trunk. Rarely cranial nerves are involved. Sensory involvement is rare, perhaps owing to the fact that the disorder has a predilection for nerve trunks around the shoulder girdle, which are purely or mainly motor. Some patients describe numbness over the lateral aspect of the forearm, and this may coincide with loss of the lateral antebrachial cutaneous sensory nerve action potential. The pathophysiology is axon loss, but few comprehensive pathological studies have been performed because the disorder is always self-limited and rarely reaches bulbar or respiratory structures. Significant recovery is the rule, although atrophy and weakness may persist in severely affected muscles. Because the usual combination of nerve trunk involvement affects muscles with C5–6 segmental innervation, differentiating radiculopathy at those levels can be extremely difficult unless the EMG findings are clear cut. Neuroimaging is often required to completely exclude radiculopathy.

Acute brachial plexopathy can also mimic cervical radiculopathy. Traumatic lesions may occur to any of the trunks or cords, and the more selective the damage (such as isolated upper or lower trunk, lateral or medial cord), the more likely the confusion with radiculopathy. Lesions affecting the whole plexus produce weakness in the C5 through T1 distributions, an unlikely pattern in unilateral cervical radiculopathy. Electrodiagnostic studies will almost always exclude cervical radiculopathy because of abnormalities of sensory nerve action potentials, with the exception of some upper trunk lesions where C5 damage is not reflected in any of the dermatomes studied with routine sensory nerve conduction.

Severe trauma to the neck, shoulder girdle, or arm can produce enough traction on cervical nerve roots to cause avulsion from the spinal cord at the root entry zones. The clinical presentation includes profound weakness and anesthesia in the distributions of the avulsed root segments. Electrodiagnostic studies show absent compound motor action potentials in the affected myotomes, but the corresponding sensory responses are normal, as the dorsal root ganglia have been avulsed along with the sensory axons, maintaining ganglion-axon integrity.

Acute musculoskeletal conditions can masquerade as radiculopathy. Rotator cuff tears prevent full shoulder abduction and external rotation, a pattern often confused with C5 or C6 radiculopathy, but the EMG will be normal. Subacromial bursitis and acute intrinsic shoulder joint disease may also pose a diagnostic problem early on.

Chronic Disorders

Several neurogenic disorders can be confused with cervical radiculopathy early in their course. When amyotrophic lateral sclerosis (ALS) or progressive muscular atrophy (the pure lower motor neuron form of ALS) has its onset in a unilateral upper extremity distribution, root disease is often considered first. This is especially true when it begins in the C8–T1 segments. Another disorder, multifocal motor neuropathy with conduction block, is characterized by a primarily upper extremity presentation without clinical or electrodiagnostic sensory abnormalities. Early on in its course, nerve trunk involvement is patchy and may appear to conform to a specific root distribution. Electrodiagnostic testing may show a root or isolated motor nerve trunk pattern of neurogenic recruitment, with or without conduction block on nerve conduction studies and with or without chronic motor axon loss features on the needle EMG examination.

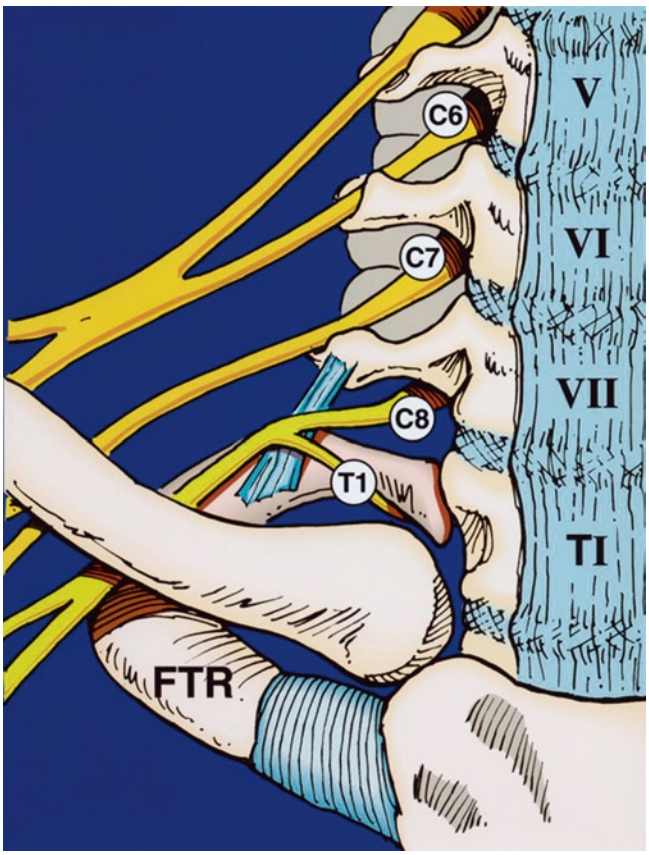

Fig. 44.5 Diagram depicting the likely anatomic relationship between the T1 and C8 nerve roots and the offending ligamentous band in neurogenic thoracic outlet syndrome, showing entrapment of the T1 and C8 nerve trunks. *Roman numerals* indicate vertebral body levels, *circled numbers* indicate root levels, and *FTR* indicates first thoracic rib (Reprinted from Levin et al. [26] with permission)

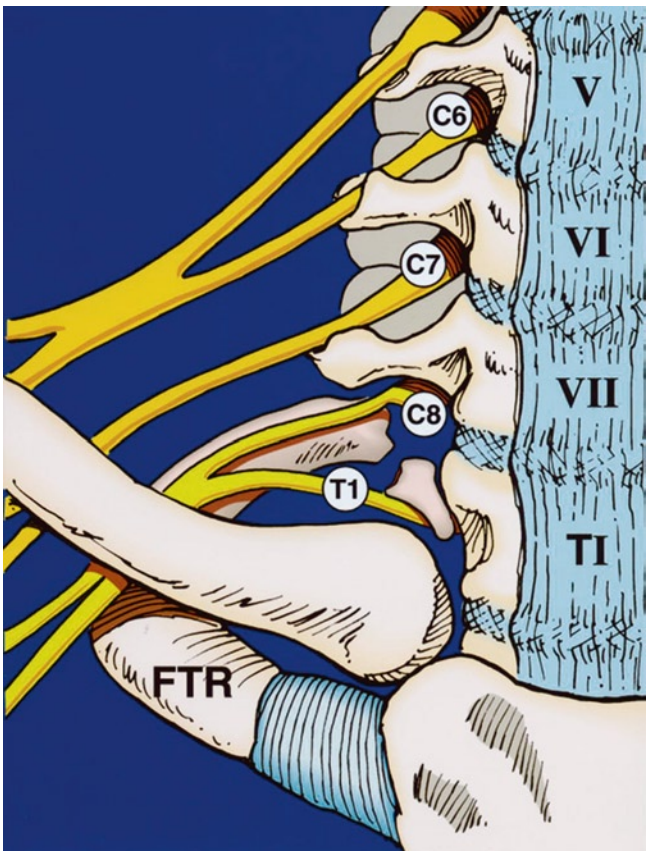

Fig. 44.6 Diagram depicting the anatomic relationship between the C8 nerve root and fracture of the first rib near the costotransverse articulation, in a patient who has undergone median sternotomy. *Abbreviations* as in Fig. 44.5 (Reprinted from Levin et al. [26] with permission)

Uncommonly, individual mononeuropathies may resemble radiculopathy. This is especially true of pure motor ulnar neuropathies in the hand, radial neuropathies, and posterior interosseous, axillary, musculocutaneous, and suprascapular neuropathies.

At times, other intraspinal disorders may produce damage to a single or several spinal nerve roots. Leptomeningeal deposits of malignant cells, epidural abscess, and schwannoma can masquerade as uncomplicated root disease.

Disorders of Anterior Primary Rami

Extraspinal radiculopathy (focal damage to anterior primary rami) constitutes an unusual group of disorders that is difficult to diagnose. Two such disorders have traditionally been categorized as types of brachial plexopathy, but electrodiagnostic evidence suggests that they are more likely to represent damage to extraspinal root distributions affecting the anterior primary rami. First, neurogenic thoracic outlet syndrome, long considered a type of lower trunk brachial plexopathy, produces most severe damage in the abductor pollicis brevis muscle and the medial antebrachial cutaneous SNAP, both sharing principally T1 root innervation [26]. In most cases lower trunk/C8 structures are affected to a much lesser extent. Second, median sternotomy brachial plexopathy, a condition that occurs in the course of coronary artery bypass graft and cardiac valve repair procedures and also considered a type of lower trunk brachial plexopathy, produces most severe damage in the ulnar and C8 root distribution, with little involvement of T1-innervated structures. These two lesions show distributions of involvement that, in their purest forms, may be mutually exclusive: the abductor pollicis brevis and the medial antebrachial cutaneous response with neurogenic thoracic outlet syndrome, and C8 muscles and the ulnar sensory response with median sternotomy brachial plexopathy. However, the nerve fibers innervating all these structures travel together in the lower trunk of the brachial plexus. Therefore, neurogenic thoracic outlet syndrome and median sternotomy brachial plexopathy more likely represent, respectively, extraspinal T1 and C8 root lesions proximal to the formation of the lower trunk, as diagramed in Figs. 44.5 and 44.6.

Table 44.5 Differential diagnosis of polyradiculopathies

	Polyradiculopathy	Polyneuropathy	Myelopathy
Disorders with true root involvement			
Arachnoiditis	+	–	–
Inflammatory polyneuropathy	+	+	–
Diabetes	+	+	–
HNPP	+	+	–
Adrenal insufficiency	+	+	–
Procainamide polyradiculoneuropathy [48]	+	+	–
Spondylosis	+	–	+
Radiation	+	–	+
Vascular malformation (conus medullaris)	+	–	+
Malignant invasion	+	+	+
Sarcoidosis	+	+	+
Lyme disease	+	+	+
Viral infection (HZ, CMV, HSV, EBV)	+	+	+
Mycoplasma infection	+	+	+
Vasculitis	+	+	+
Angiotropic lymphoma	+	+	+
Disorders mimicking root involvement			
Porphyric polyneuropathy	–		–
Tangier disease	–		+
X-linked bulbospinal neuronopathy	–		+
Motor neuron disease	–	–	+
Juvenile monomelic amyotrophy	–	–	+
Spinal cord infarction	–	–	+
Multiple sclerosis	–	–	+
Syringomyelia	–	–	+

HNPP hereditary neuropathy with tendency to pressure palsy, HZ herpes zoster, *CMV* cytomegalovirus, *HSV* herpes simplex virus, *EBV* Epstein-Barr virus

Polyradiculopathies

The term polyradiculopathy indicates damage to multiple root segments simultaneously or in progressive order, occurring in a single limb, or more frequently bilaterally and sometimes diffusely. The causes are diverse and at times unclear. In general this is a process that affects the lumbosacral segments and the cervical segments later on or not at all. In some neurological disorders polyradiculopathy coexists with lesions in distal peripheral nerves, or lesions in the central nervous system, or both. The following discussion will be limited to those disorders that are likely to be associated with significant root involvement at the cervical levels. Table 44.5 lists some causes of cervical polyradiculopathy and disorders that fall into the differential diagnosis.

Compressive Polyradiculopathies

Spondylosis of the spine is often multifocal, and multiple roots may suffer compressive damage concurrently. This is especially true at the lumbosacral level, where spondylosis causes lumbar canal stenosis and multilevel neural foraminal stenosis. At the cervical level, bilateral compressive polyradiculopathy usually occurs due to diffuse spondylosis, perhaps associated with congenital narrowing of the intraspinal canal or hypertrophy of the ligamentum flavum. This condition is often associated with cervical myelopathy. The immediate cause of the myelopathic deficits and motor axon loss in root distributions may not be compressive but rather venous congestion in the spinal cord arising from the compression, causing ischemia and infarction of long tracts and anterior horn cells. This mechanism would explain how a focal lesion in the proximal spinal cord could produce anterior horn cell loss at a distance from the actual site of compression [49].

When the cervical polyradiculopathy is chronic and active, the clinical and EMG pattern may be difficult to distinguish from early to mid-stage progressive motor neuron disease (ALS), especially in patients who have changes in the lower extremities limited to upper motor neuron signs. There are several EMG features that may help distinguish one disorder from the other. Compressive polyradiculopathy is a more chronic process, and there may not be much evidence of fibrillation potentials, while in mid-stage ALS, fibrillation potentials are prominent, as is MUAP configuration instability as a feature of ongoing active reinnervation. Second, the degree of motor unit dropout is usually greater in ALS than in most radiculopathies.

Other Causes of Polyradiculopathy

The polyradiculopathy associated with diabetes can be among the most disabling of all the neuropathic complications of that condition. Although almost always confined to the thoracic, lumbar, and sacral segments, the cervical myotomes may also affected in severe cases [50, 51]. Although usually associated with underlying diabetic polyneuropathy, diabetic polyradiculopathy may be seen in isolation in as many as 25 % of cases [52].

Processes that infiltrate or compress nerve roots lead to polyradiculopathy. Infectious causes include Lyme disease, tuberculosis, syphilis, and fungal infections. While these processes usually begin at the lumbosacral levels, they may also affect cervical levels subsequently or in the initial phase of disease. Malignancy produces polyradiculopathy by compression and invasion. Malignancies with a predilection for bone are especially likely to cause polyradiculopathy, myelopathy, or both, because of their tendency to spread into contiguous regions. Malignant cells may also gain entry into the intraspinal canal by hematogenous spread.

Myelopathy

Intramedullary processes produce motor axon loss in myotomal distributions when anterior horn cells are damaged. There may or may not be sensory symptoms and signs, but as long as the process remains strictly intramedullary, electrodiagnostic studies will show preservation of sensory nerve action potentials. The clinical picture of motor axon loss may mimic ALS, both in terms of the distribution of peripheral motor axon loss features, and because of the concomitant presence of corticospinal tract deficits. Examples include cervical syringomyelia, radiation radiculomyelopathy, severe demyelinating disease, intramedullary glioma and other malignancies, and spinal muscular atrophy. Juvenile amyotrophy of the upper extremity is considered an isolated form of lower motor neuron disease [53], but the same slowly progressive picture can be seen with arteriovenous malformations affecting the cord [54].

Polyradiculoneuropathies

The diagnosis of polyradiculoneuropathy indicates the presence of coexisting features of polyradiculopathy and peripheral polyneuropathy. The clinical presentation includes weakness in both proximal and distal root distributions of the legs (and in some disorders the arms as well), often in a distal to proximal gradient, associated with features of sensory axon loss. Electrodiagnostically the picture is characterized by loss of sensory responses, combined with features of motor axon loss, or demyelinating conduction block in multiple root distributions, or both. The leading causes include acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barre syndrome), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and diabetes. We now recognize both demyelinating and pure axon loss forms of inflammatory polyradiculoneuropathy [55]. Guillain-Barre syndrome may occasionally present in a relatively isolated distribution affecting cervical root distributions.

Uncommonly hereditary disorders produce a picture of polyradiculoneuropathy. Hereditary neuropathy with tendency to pressure palsy (HNPP) has been reported to present in this fashion [56]. Alpha-lipoprotein deficiency (Tangier disease) produces motor and sensory neuronopathy in a progressive segmental pattern that often affects the upper extremities first, and mimics a pattern of polyradiculopathy [57, 58]. Porphyric polyneuropathy is characterized by marked proximal and distal weakness, sometimes asymmetric and affecting the arms more than the legs. Sensory responses are variably affected, but the clinical presentation is predominantly motor.

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Lumbosacral and Thoracic Radiculopathies

45

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Introduction

Radiculopathy, particularly of the lumbosacral region, is one of the most common clinical problems seen by neuromuscular clinicians and among the leading reasons for referral to electrodiagnostic laboratories. While the term sciatica was first introduced by Hippocrates, its connection to intervertebral disc disorders was not widely appreciated until Mixter and Barr's 1934 work describing lumbosacral radiculopathy resulting from disc herniation [1]. It was still later that there was general recognition of thoracic radiculopathy as a distinct clinical entity, following a series of work on the subject in the early 1950s [2].

General Anatomy

Lumbosacral Spine and Spinal Nerves

The lower spine is comprised of 5 lumbar, 5 sacral, and 4 coccygeal vertebrae and their associated intervertebral discs and facet joints, with the facet joints being formed by the articular processes of the pedicles. The intervertebral foramina are formed by notches in the superior and inferior surfaces of adjacent pedicles. The disc is anterior and medial to the foramen, while the facet joint is posterior. The ligamentum flavum is attached to the articular processes of the facet joints and forms part of the posterior aspect of the spinal canal (Fig. 45.1).

The spinal cord terminates at the lower edge of L1, forming the conus medullaris. Arising from the conus is the cauda equina, which gradually separates into the individual lumbosacral nerve roots. Of the 31 pairs of dorsal and ventral roots arising from the spinal cord, there are 5 lumbar, 5 sacral, and 1 coccygeal. Ventral roots arise from motor neurons in the anterior and lateral gray columns of the spinal cord (Fig. 45.2). Dorsal roots extend proximally from sensory neurons in the dorsal root ganglia (DRG), which lie within the neural foramen. The ventral and dorsal roots join one another just distal to the DRG, forming a spinal nerve; upon exiting the foramen, the nerve divides into dorsal and ventral rami. The dorsal rami supply the paraspinal muscles and skin overlying the paraspinous region, while the ventral rami form the lumbosacral plexus, which branches into the individual peripheral nerves that supply the lower limb and sacral region. The cauda equina is contained within the arachnoid membrane, which continues along individual nerve roots to form a portion of the root pouch or nerve root canal, along with a short sleeve of dura mater which covers the nerve root within the foramen (Fig. 45.2).

Inherent disparity in the lengths of the vertebral column and the spinal cord creates a situation in which the spinal segments are relatively higher than the corresponding vertebral spinous processes. This translates into a difference of approximately two segments in the thoracic region and three segments in the lumbosacral region. In contrast to the cervical and thoracic roots, the lumbosacral nerve roots comprising the cauda equina traverse a long intraspinal course before exiting at some distance from their corresponding spinal segment. Also, the thoracic and lumbosacral nerve roots exit below their correspondingly numbered vertebrae

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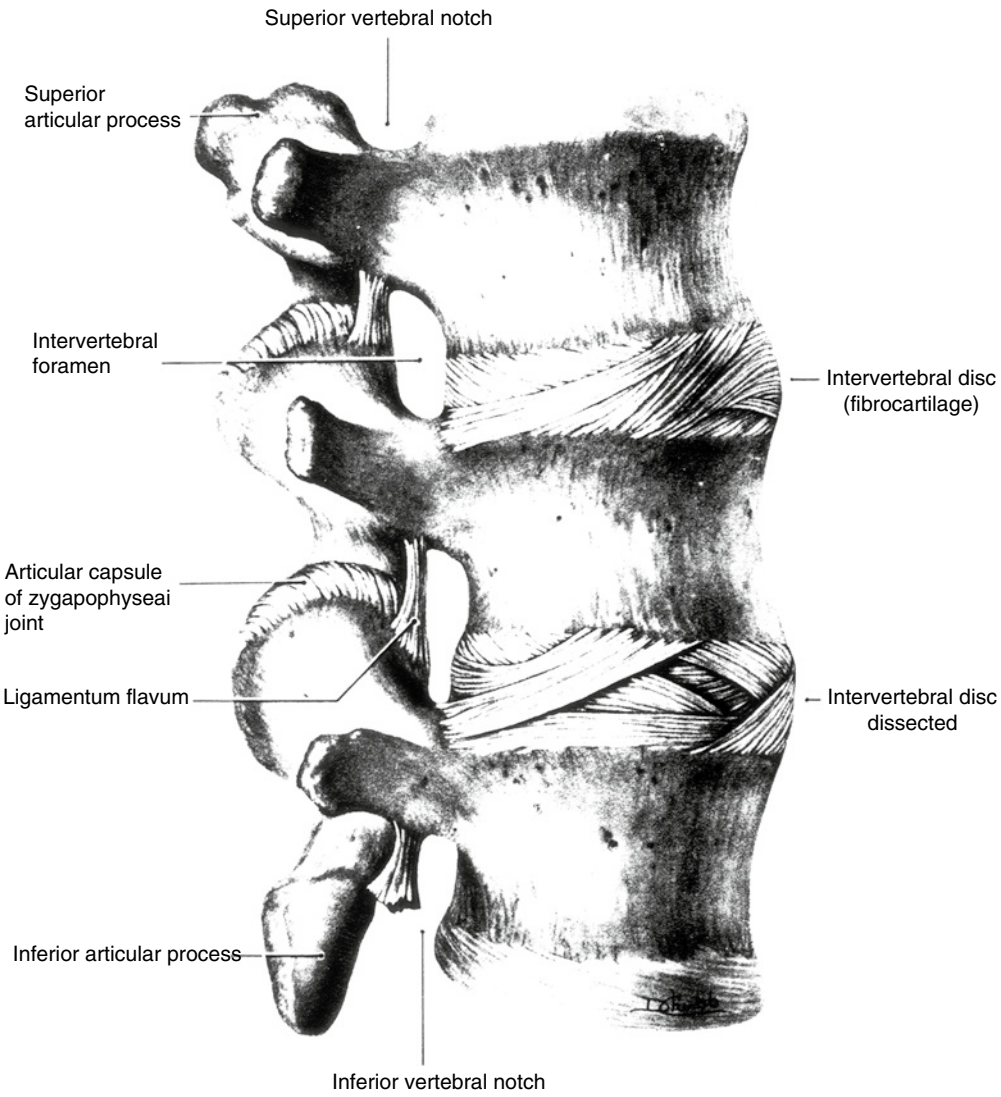

Fig. 45.1 Lateral view of the upper lumbar vertebral column, demonstrating intervertebral foramen formed by the pedicles inferiorly and superiorly, the intervertebral disc anteriorly, and the facet joint with overlying ligamentum flavum posteriorly (Reproduced with permission from Moore [3])

(i.e., L4 nerve root exits between the L4 and L5 vertebrae) (Fig. 45.3).

The muscles innervated by a single spinal segment constitute a myotome; the skin region innervated by a single spinal segment is a dermatome. There is significant variability in individual myotomal and dermatomal representation for a particular muscle or skin region. Each muscle receives innervation from multiple contiguous nerve roots, and each dermatome overlaps extensively with neighboring dermatomes.

Localization of nerve root disorders is often complicated, in part due to the intricate anatomic relationships between the nerve roots and surrounding structures. For example, a disc herniation at a single level may injure different nerve roots, depending on its location. If a disc herniates in a posterolateral direction, which is the usual tendency, it will compress the nerve root that is situated in the lateral recess as it descends to exit one level below that disc. Thus, an L4–5 disc herniation will compress the L5 nerve root in the lateral recess (Fig. 45.4). Less often, a far lateral disc herniation will compress the nerve root exiting through the foramen at that level, i.e., a far lateral L4–5 disc herniation will compress the exiting L4 root (Fig. 45.5). A particularly large disc prolapse may compress the two adjacent nerve roots by both of these mechanisms. A posterior or central disc herniation may compress multiple nerve roots in the central aspect of the cauda equina (Fig. 45.6).

Thoracic Spine and Spinal Nerves

Twelve pairs of thoracic spinal nerves innervate all of the muscles and skin of the trunk except for the lumbar paraspinal muscles and overlying skin. As in the lumbosacral spine, each spinal nerve is formed from a dorsal and ventral root,

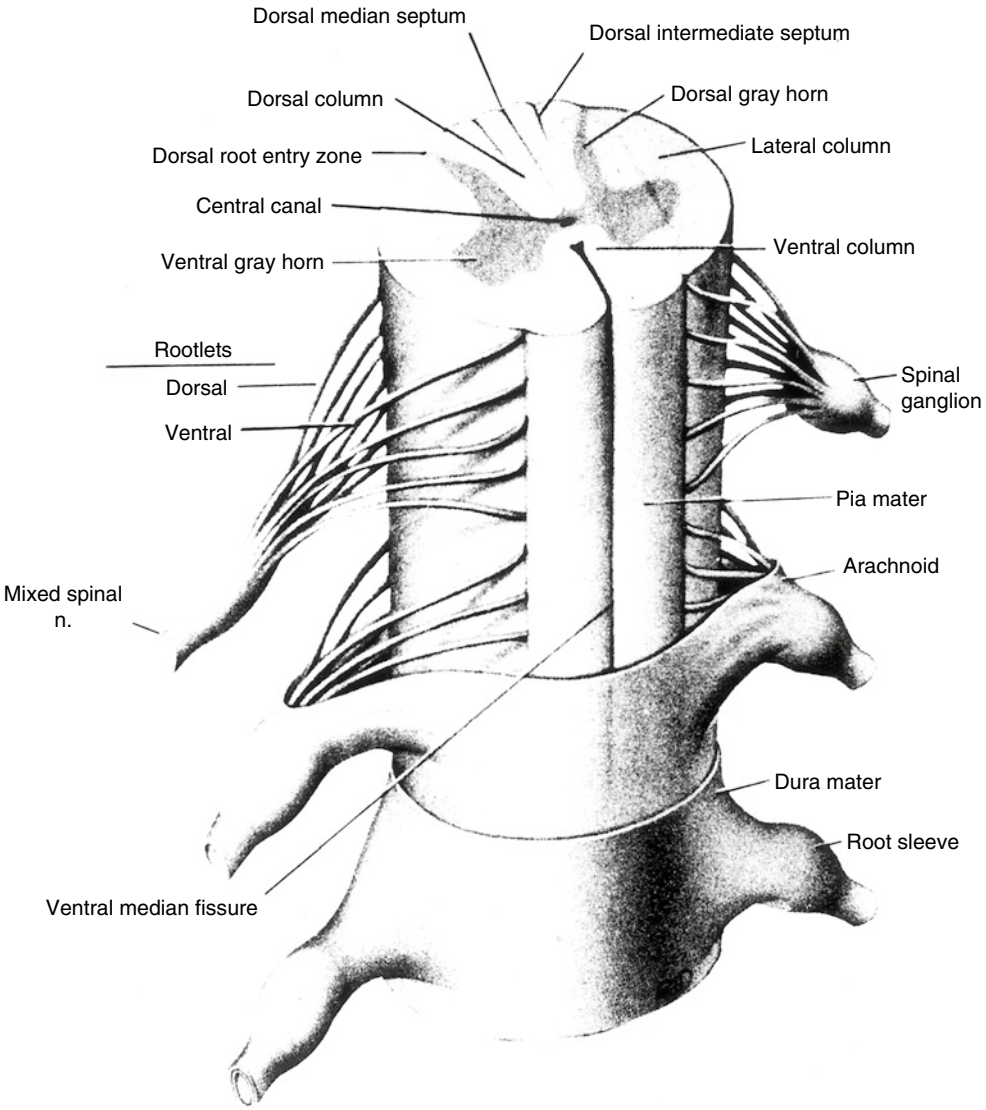

Fig. 45.2 The spinal cord, nerve roots, and meninges. Each nerve root emerges as a series of rootlets; each spinal nerve is formed by the joined dorsal and ventral nerve roots. The spinal or dorsal root ganglion contains the nerve cells whose axons make up the dorsal roots. Individual nerve roots are covered by a root sleeve formed by the dura mater (Reproduced with permission from Moore [3])

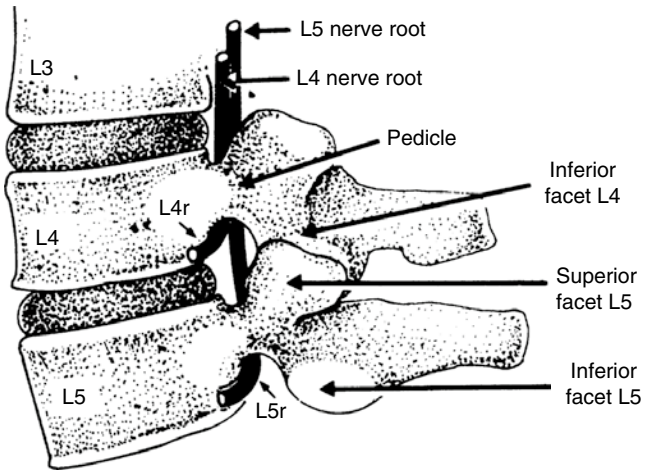

Fig. 45.3 The L4 nerve root exits the intervertebral foramen formed by the inferior facet of L4 and the superior facet of L5, i.e., the L4–5 disc space. The L5 nerve root, situated medially, descends to exit one level below (Reproduced with permission from Stewart [4])

arising from the spinal cord approximately two segments above the corresponding vertebral level. The spinal nerves divide into dorsal and ventral rami after exiting the neural foramina. The dorsal rami proceed posteriorly to innervate the adjacent paraspinal muscles and overlying skin. In the thoracic region, the ventral rami do not form large nerve plexuses but run individualized courses. In general, they may be categorized into three groups: T1, T2–6, and T7–12. The T1 ventral ramus gives off a large branch which joins C8 to form the lower trunk of the brachial plexus and, a smaller branch, the first intercostal nerve. Ventral rami from T2–6 form the intercostal nerves; T7–11 ventral rami form the thoracoabdominal nerves. The intercostal nerves curve around the chest wall between the intercostal muscles, giving off the lateral cutaneous nerves of the thorax about midway around the chest and then terminating as the anterior (medial) cutaneous nerves of the thorax (Fig. 45.7). The thoracoabdominal nerves (T7–12) also run along the intercostal spaces but

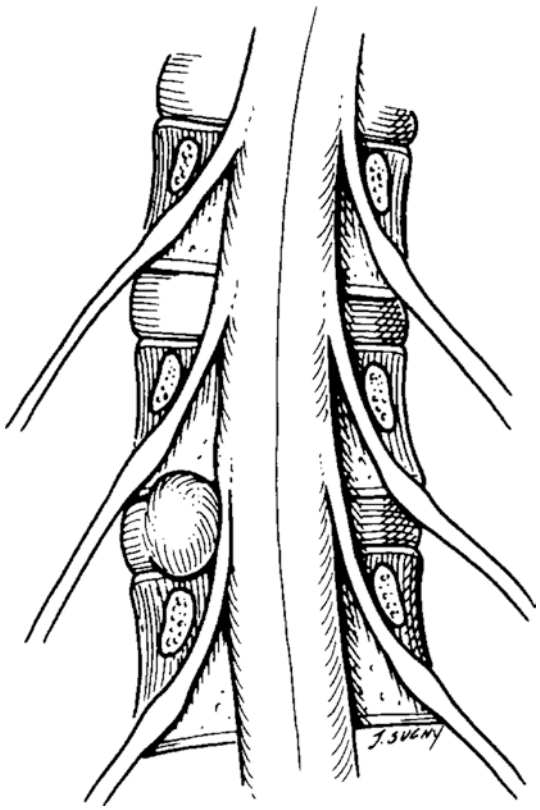

Fig. 45.4 A posterolateral disc herniation compresses the nerve root descending to exit the intervertebral foramen one level below the corresponding vertebrae (i.e., an L4–5 disc herniation compressing the L5 nerve root) (Reproduced with permission from Hardy and Plank [5])

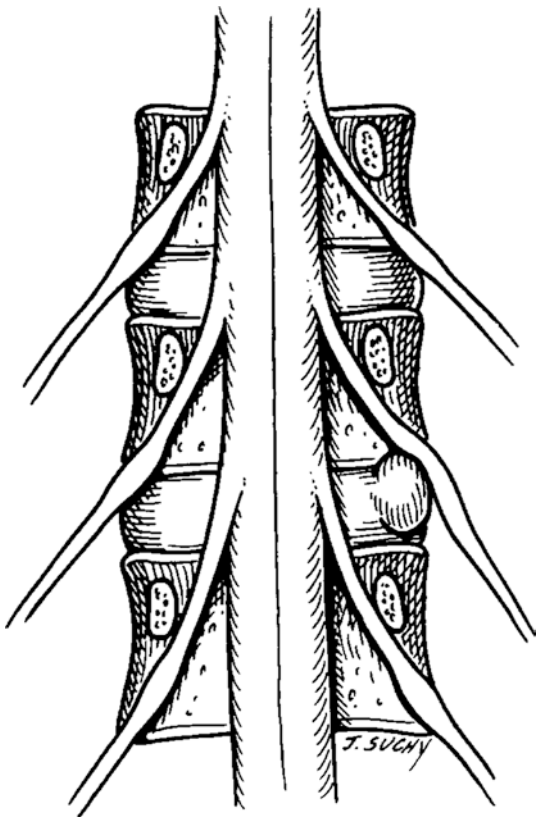

Fig. 45.5 A far lateral disc herniation compresses the nerve root exiting through the foramen at that vertebral level (i.e., an L4–5 disc compressing the L4 nerve root) (Reproduced with permission from Hardy and Plank [5])

pursue a longer course into the abdomen, giving off lateral cutaneous branches before continuing as the nerves supplying the rectus abdominis and other abdominal wall muscles, and anterior (medial) cutaneous branches of the abdomen. The thoracic and upper lumbar spinal nerves also carry preganglionic sympathetic fibers.

Pathophysiology

The pathophysiology of nerve root injury depends upon the underlying cause. Both direct trauma involving nerve roots and indirect trauma involving nearby or contiguous structures, such as the lumbosacral plexus, will result in mechanical disruption, either stretching or compression of the nerve roots. On the other hand, nontraumatic lesions may either be structural, thereby likely to cause compressive injury to the nerve root, or inflammatory/infiltrating lesions, therefore likely to cause injury by either ischemic, metabolic, or other mechanisms which are nonmechanical in nature. Compression

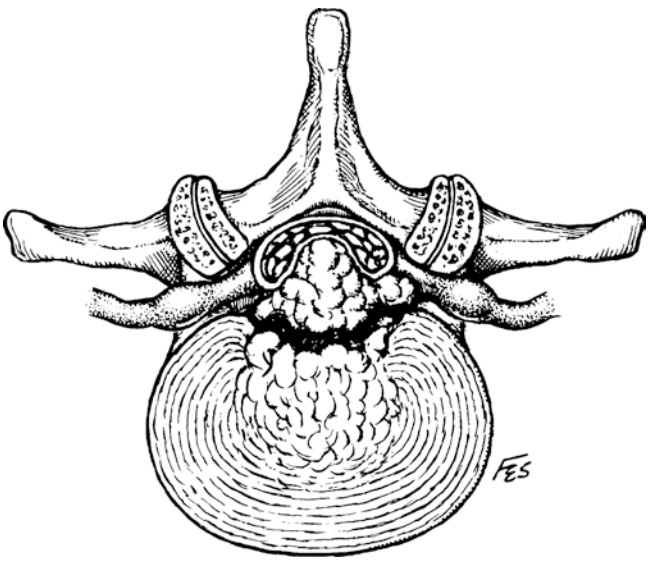

Fig. 45.6 Cross-sectional view demonstrating midline cauda equina compression by large lumbar disc herniation (Reproduced with permission from Fager [6])

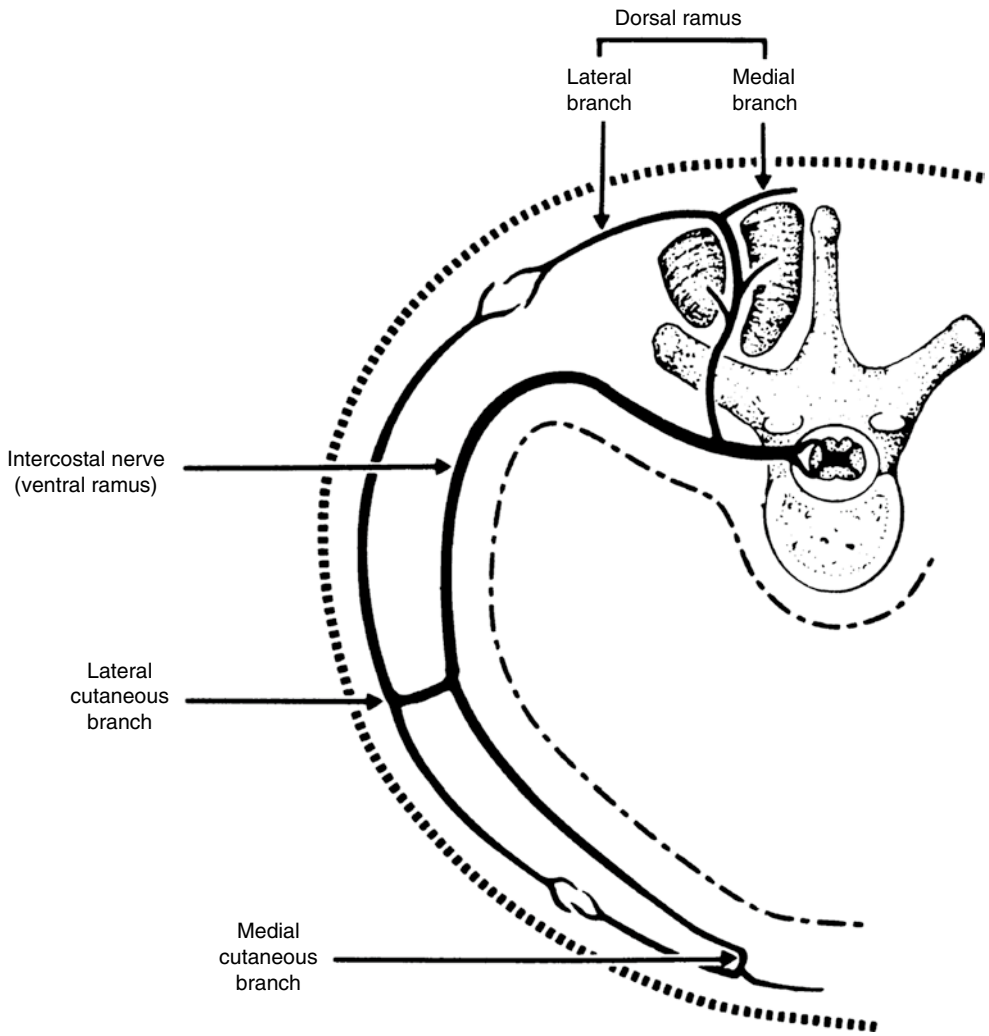

Fig. 45.7 Course and branches of a thoracic spinal nerve. Thicker, *outer stippled line* represents skin; *inner stippled line* is the pleura or peritoneum (Reproduced with permission from Stewart [7])

is the most common mechanism of nerve root injury. Compared to peripheral nerves, nerve roots have a paucity of endoneurial collagen and no epineurium, leaving the axons with considerably less surrounding fat and connective tissue, thus increasing their vulnerability to compression [8]. The absence of perineurium in the nerve roots also results in markedly increased susceptibility to the effects of stretching and compression compared to the rest of the peripheral nerve [8]. Thus, major trauma causing stretch injury to various plexus elements may result in overt avulsion of the nerve roots from the spinal cord. Fortunately, lumbosacral nerve root avulsion is relatively rare, due to the secure arrangement of the nerve roots and plexus elements within the pelvis. In addition to providing tensile strength, the perineurium provides a barrier against attack from infectious and inflammatory agents, and its absence in the nerve roots increases their susceptibility to injury by nonmechanical mechanisms [8].

Ultimately, regardless of the initial mechanism of injury, the pathophysiologic consequence of nerve root insults is either segmental demyelination or axonal loss in the fibers of the nerve roots; in the majority of injuries, there is a combination of both. The clinical and electrodiagnostic (EDX) features of a given lesion will be determined by the predominant physiologic mechanism as well as the type, size, and overall number of nerve fibers involved. One important physiologic consideration is the relationship of nerve root injury to the DRG. Regardless of the underlying etiology, nearly all nerve root injuries occur in a location proximal to the DRG. Thus, the peripheral sensory fibers will be spared, regardless of the severity and nature of the injury to the central processes of the DRG. This has very important implications for the EDX findings in radiculopathy.

Clinically, injury to nerve roots most often affects sensory fibers only, followed by combined motor and sensory

fibers; rarely are motor fibers affected in isolation [5]. Paresthesias, reflex changes, and weakness reflect damage to larger-diameter fibers, while pain reflects involvement of smaller myelinated and unmyelinated fibers. A lesion causing pure focal demyelination with slowed conduction alone would not be expected to result in significant clinical weakness or sensory loss, although reflex changes might occur. Lesions causing axonal loss or demyelinative conduction block affecting a large number of fibers are clinically indistinguishable, as both are associated with fixed sensory or motor deficit and deep tendon reflex (DTR) abnormalities; only the EDX findings would help differentiate these two processes.

Clinical Presentation

Localization of Radiculopathy

Lesion localization is of critical importance and is based primarily on clinical and EDX examination. It is on the basis of these findings that the relevance of any imaging or other laboratory abnormalities is determined. Localization depends upon demonstration of a segmental myotomal and/or dermatomal distribution of abnormalities, which requires knowledge of the neurological deficits produced by lesions at individual segmental levels. In most cases, the primary differential diagnostic considerations include lesions of the plexus, peripheral nerves, and possibly the spinal cord. A useful, though rare, clue on physical examination that a lesion is at the nerve root level is finding sensory loss over the paraspinal region innervated by the dorsal ramus of the involved root. In the lumbosacral and thoracic regions, lesions may involve a single-root level (monoradiculopathy) or multiple, usually contiguous, root levels (polyradiculopathy). Involvement of the cauda equina tends to cause polyradiculopathy and is often associated with lesions of the conus medullaris. Lesions of this region will be considered separately.

In general, radiculopathy is characterized by pain. Although dermatomal radiation of the pain may indicate which nerve root is involved, more reliable is the distribution of any accompanying paresthesias or sensory loss demonstrable on neurologic examination. Notably, an entire dermatome is rarely affected, with a tendency for distal portions to be more involved. Weakness may similarly involve only the more distal muscles in the myotome, thus making differentiation from plexus or peripheral nerve lesions difficult. DTRs are generally reduced but elicitable, unless multiple nerve roots are involved.

Lumbosacral Monoradiculopathy

Table 45.1 outlines the typical neurological examination findings with lumbosacral radiculopathies at each level. Differential diagnostic considerations depend on the particular nerve root involved but include mononeuropathies and lumbosacral plexopathies (Table 45.2).

In the lumbosacral region, the most common causes of radiculopathy are disc herniation and compression of nerve roots by spondylotic bony lesions. These lesions are almost always manifested by symptoms of pain in the lower back and/or leg (i.e., sciatica). Pain radiating into the leg is one of the signs of nerve root irritation; paresthesias radiating into a particular dermatomal region are a more specific localizing sign. Both of these symptoms may be aggravated by Valsalva maneuvers. Other signs of nerve root irritation include positive findings on straight leg and reverse straight raising maneuvers.

The straight leg raise maneuver has a number of different eponymous characterizations, but the basic test maneuver always involves stretching of the sciatic nerve and its associated L5 and S1 nerve roots in an attempt to produce radiating

Table 45.1 Neurologic findings in lumbosacral monoradiculopathies

Root level	Pain	Sensory loss (paresthesias)	Motor abnormalities/weakness	Deep tendon reflex abnormalities
L1	Inguinal region	Inguinal region	None	None
L2	Groin, anterior thigh	Anterolateral thigh	Iliopsoas	None
L3	Anterior thigh to knee	Medial thigh and knee	Quadriceps, iliopsoas, hip adductors	Knee jerk
L4	Anterior thigh to medial foreleg	Medial leg	Tibialis anterior, quadriceps, hip adductors	Knee jerk
L5	Lateral thigh and leg to dorsum foot	Lateral leg, dorsum foot, and great toe	Toe extensors, ankle dorsiflexors, everter and inverters, and hip abductors	None (unless S1 involved)
S1	Posterior thigh, calf, heel	Sole, lateral foot and ankle, lateral two toes	Toe flexors, gastrocnemii, hamstrings, gluteus maximus	Ankle jerk
S2–4	Medial buttocks	Medial buttocks, perineal and perianal region	None unless S1–2 involved	Bulbocavernosus and anal wink (ankle jerk if S1 involved)

Table 45.2 Differential diagnosis of lumbosacral monoradiculopathies

Root level	Nerve lesion	Plexus lesion	Differentiating features
L1	Ilioinguinal neuropathy Genitofemoral neuropathy	Unlikely	Sensory loss outside single nerve territory
L2	Lateral femoral cutaneous neuropathy (meralgia paresthetica); femoral neuropathy	High lumbar plexopathy	Strength normal in meralgia paresthetica; quadriceps more involved with femoral neuropathy
L3	Femoral neuropathy	High lumbar plexopathy; diabetic amyotrophy	Adductor weakness not seen w/femoral neuropathy
L4	Femoral neuropathy; common peroneal neuropathy	Mid-lumbar plexopathy	Tibialis anterior, hip adductors not involved in femoral neuropathy; quadriceps not involved in peroneal neuropathy
L5	Common peroneal neuropathy	Mid-lumbar plexopathy	Ankle inversion and hip abduction not involved in peroneal neuropathy
S1	Sciatic neuropathy; tibial neuropathy	Lower lumbosacral plexopathy	Hamstrings not involved in tibial neuropathy; glutei not involved in sciatic neuropathy

pain. The painful leg is flexed at the hip and extended at the knee with the patient supine. Pain at less than 70° is considered a positive test. Variations include reproduction of pain upon straight leg raising of the unaffected leg or aggravation of pain with forceful dorsiflexion of the involved ankle or firm pressure in the popliteal fossa. Reverse straight leg raise testing evaluates the upper lumbar roots (L2–4) and involves hip extension with the patient prone. Pain in the anterior thigh and/or lower back is considered a positive test. Although useful clinically, these maneuvers are not specific for radicular lesions and may be seen in lumbosacral plexopathies, femoral neuropathies, and diseases of the hip joint. Similarly, sciatic-type pain, usually not extending distal to the knee, may occur in the setting of mechanical lower back injuries. The clinical presentation of monoradiculopathies at individual levels is discussed briefly.

L1 Radiculopathy

L1 radiculopathy is rare as disc herniation at this level is extremely uncommon. Pain and paresthesias are the presenting complaints, with associated sensory loss in the inguinal region. There is no specific myotomal representation and no associated DTR for this segmental level. The differential diagnostic considerations include ilioinguinal and genitofemoral neuropathy.

L2 Radiculopathy

L2 radiculopathy is also rare and disc herniation a very uncommon cause of radiculopathy at this level. L2 radiculopathy presents as paresthesias with or without sensory loss in the anterolateral thigh and weakness of the iliopsoas muscle; DTRs are normal. In the absence of motor involvement, the primary differential diagnosis is lateral femoral cutaneous neuropathy (i.e., meralgia paresthetica); additional considerations include femoral neuropathy or high lumbar plexopathy, especially if motor weakness is present. However, femoral neuropathy is more likely to cause quadriceps weakness and loss of the knee jerk.

L3 Radiculopathy

Disc herniation is more likely to occur at this level than the higher levels but significantly less likely than at the L4–S1 levels. L3 radiculopathy is most often confused with femoral neuropathy, as the quadriceps muscle is predominantly affected in both. Iliopsoas weakness may be present in either. Additional involvement of hip adductor muscles, which are innervated by the L3 nerve root via the obturator nerve, indicates a plexus or root lesion. Paresthesias and/or fixed sensory deficits occur predominantly in the medial thigh and knee. The knee jerk may be reduced or absent. In addition to femoral neuropathy, the differential diagnosis includes upper lumbar plexopathy, including diabetic amyotrophy.

L4 Radiculopathy

Unlike the higher lumbar levels, disc herniation is the most common cause of radiculopathy at this level. As with L3 radiculopathy, there may be significant quadriceps weakness, leading to confusion with femoral neuropathy; however, additional involvement of tibialis anterior (peroneal nerve), as well as hip adductors, helps localize the lesion to the L4 root level. Alternatively, foot drop may be the initial clinical presentation. Sensory abnormalities occur primarily in the medial leg (saphenous nerve territory). The knee jerk is often reduced. Lumbosacral plexopathy, including diabetic amyotrophy, is the primary differential diagnostic consideration.

L5 Radiculopathy

Significant L5 radiculopathy is most likely to present with foot drop with or without "toe drop," secondary to involvement of the tibialis anterior and extensor hallucis longus, respectively. Subtle weakness of these muscles may be elicited by having the patient walk on their heels. Sensory loss is prominent over the lateral lower leg and great toe. There is no easily elicitable DTR for assessment of L5 root integrity; however, concomitant involvement of S1 will cause a reduced ankle jerk. The primary lesion which mimics L5 radiculopa-

thy is common peroneal neuropathy. Although both have weakness of ankle eversion (subserved by peroneal-innervated L5 muscles), additional weakness of ankle inversion (subserved by tibial-innervated L5 muscles) excludes a common peroneal nerve lesion and localizes the lesion more proximally. Determination of ankle inversion strength is critical to the clinical examination and should be documented in all cases of foot drop. Sciatic neuropathy and lower lumbosacral plexopathy are differential diagnostic considerations once the lesion has been localized proximal to the peroneal nerve. Weakness of the gluteus medius (hip abduction) places the lesion proximal to the sciatic nerve but does not differentiate L5 radiculopathy from lumbosacral plexopathy.

S1 Radiculopathy

Isolated S1 radiculopathy results in weakness of gastrocnemius and soleus muscles, as well as hamstrings and glutei. Subtle weakness of these muscles may be difficult to determine on examination. Difficulty of toe-walking or rising on the toes of one foot is useful for demonstrating gastrocnemius/soleus weakness. Gluteus maximus is best tested by having the patient extend the leg at the hip while prone. Involvement of gluteal muscles is an important indicator of a lesion proximal to the sciatic nerve. Sensory loss involves the sole and lateral aspect of the foot and lateral three toes. The ankle jerk is asymmetrically reduced or absent in unilateral S1 radiculopathy; in patients with bilateral S1 lesions or polyneuropathy, ankle jerks may be reduced or absent bilaterally. The differential diagnostic considerations include tibial and sciatic neuropathies as well as lumbosacral plexopathy.

Lower Sacral Radiculopathy: S2–S4

Radiculopathy involving lower sacral nerve roots is uncommon; typically, S2–5 are involved together, given their close anatomical relationship. Often, these roots are involved with central disc herniations causing pressure on the midline region of the cauda equina. The presenting symptoms are pain and sensory loss involving the perineal region and medial buttocks ("saddle region"), along with urinary retention and fecal incontinence. Physical examination demonstrates sensory loss in a variable distribution within the S1–4 dermatomes, reduced or absent anal sphincter tone, and absence of the anal wink and bulbocavernosus reflexes. Gluteal muscle weakness is associated with S1–2 involvement. Ankle jerks may be reduced or absent bilaterally or unilaterally if S1 root is involved.

Lumbosacral Polyradiculopathy and Cauda Equina Syndromes

Multiple, contiguous, and ipsilateral radiculopathies may result from disorders affecting several individual nerve roots (i.e., multilevel neural foraminal stenosis, multiple disc herniations) either in the vertebral canal or the nerve root foramina or from lesions of the cauda equina. Cauda equina lesions should be considered when more than two contiguous nerve roots are involved. Multiple, bilateral lumbar and/or sacral radiculopathies are most suggestive of lesions of the cauda equina.

The clinical presentation of lesions involving the cauda equina is variable and depends upon the nature and location of the particular lesion, as well as the time course over which it develops. Generally, two important syndromes are recognized: midline cauda equina/conus medullaris syndrome secondary to compression and intermittent neurogenic claudication due to central spinal stenosis.

Midline cauda equina syndrome usually results from compression of the nerve roots lying within the central aspect of the cauda equina. They may develop either acutely or gradually. Acute compression is most commonly due to large, central disc herniations, usually involving the L4–5 disc. Because the sacral nerve roots lie medially in the cauda equina, they are most often involved, leading to a clinical picture of sacral polyradiculopathy. However, in more extensive lesions, lumbar nerve roots may be involved as well. The syndrome is typically one of acute pain and paresthesias in sacral dermatomes, accompanied by objective sensory loss in these dermatomes ("saddle anesthesia") as well as bladder and bowel dysfunction. Depending on the extent of the lesion, leg weakness may develop either early or later in the course; ultimately, this can result in paraplegia if multiple nerve roots are involved. Often, the syndrome is progressive and early recognition is crucial, as bladder dysfunction and leg weakness are often permanent once they are fully developed.

The term *intermittent neurogenic claudication* (or cauda equina claudication) is used to describe a syndrome of lower back and leg pain brought on by walking and relieved with rest. Occasionally, the pain is brought on merely by standing but is exacerbated by walking. This syndrome is a common presentation of lumbar spinal stenosis. Lower back and leg pain and paresthesias develop over increasingly shorter distances; once pain symptoms develop, further exercise only increases the pain and may be accompanied by sensory loss or weakness. Eventually, the patient is forced to stop and rest, with relief of symptoms after several minutes. Sitting down or raising one leg results in more rapid relief. Also, bending at the waist may offer some relief. Pain is usually bilateral but may be unilateral.

The neurologic examination of patients with intermittent neurogenic claudication is frequently normal. Occasionally, neurological signs, including reflex, sensory, and motor abnormalities, are demonstrable only after a period of walking [5]. Alternatively, the neurologic examination may show evidence of a patchy polyradiculopathy involving the lower extremities.

Thoracic Radiculopathy

The typical clinical presentation of lesions involving thoracic nerve roots involves pain and/or paresthesias radiating from the posterior thorax, in the approximate dermatomal distribution of the involved root level. However, the pain may involve only a portion of a given dermatome and may not have a clear radicular quality, leading to confusion with pain of abdominal or cardiac origin. Sensory deficits may be demonstrated in all or only a portion of the involved dermatome, depending on the location, nature, and extent of the lesion. Muscle weakness is often subtle but may sometimes be demonstrated by having the patient cough or attempt a sit-up, which will produce bulging of a weak intercostal or abdominal muscle, which may be observed or palpated.

Etiology

The vast majority of lesions causing lumbosacral radiculopathy are compressive in nature and due to either disc herniation or spondylosis. However, as listed in Table 45.3, the differential diagnosis of lesions producing lumbosacral radiculopathy is broad and includes a variety of neoplastic, infectious, and inflammatory disorders.

Unlike the lumbosacral region, acute disc herniations and spondylotic lesions in the thoracic spine cause radiculopathy only infrequently and are much more likely to cause spinal cord compression which dominates the clinical picture. Thus, compressive thoracic radiculopathy is relatively rare compared to lumbosacral radiculopathy and is more likely to be caused by a non-compressive lesion. Table 45.4 lists the differential diagnosis of lesions producing thoracic radiculopathy.

Table 45.3 Causes of lumbosacral radiculopathy

Monoradiculopathy	Polyradiculopathy or cauda equina syndrome
Degenerative spine disease	Degenerative spine disease
Disc herniation	Disc herniation—usually large, central
Spondylosis/lumbar spinal stenosis	Spondylosis/lumbar spinal stenosis
Neoplastic disease	Neoplastic disease
Primary spinal tumors	Leptomeningeal metastases
Epidural and vertebral metastases	Carcinomatous meningitis
Infectious disease	Infectious disease
Spinal epidural abscess	Polyradiculopathy in HIV/AIDS
Herpes zoster	CMV, HSV, syphilis
Lyme radiculoneuropathy (early, late)	Herpes zoster Lyme radiculoneuropathy (early, late)
Diabetic radiculopathy	Diabetic polyradiculopathy (amyotrophy)
Complication of epidural/spinal anesthesia	Complication of epidural/spinal anesthesia
Spinal epidural hematoma	Spinal arachnoiditis
Spinal cysts	Tethered cord syndrome
Traumatic nerve root injury	Hypertrophic nerve roots in CIDP, HMSN I

Degenerative Spine Disease

Lumbosacral Disc Herniation

In patients under age 40–50 years old, disc herniation is the most common cause of lumbosacral radiculopathy. The most common levels of disc herniation are L4–5 and L5–S1; consequently, L5 and S1 radiculopathy are most frequent, L4 is less common, and herniation at the higher lumbar levels is distinctly unusual. Herniation of the nucleus pulposus (HNP) may leave some of the fibers of the annulus fibrosis intact (prolapsed or bulged disc) or may rupture through the annulus fibrosis (extruded or herniated disc) and be contained by the posterior longitudinal ligament (PLL); occasionally, the disc ruptures through both the annulus and the PLL and floats freely within the spinal canal (sequestered disc). Sequestered disc fragments may migrate in the epidural space; rarely, herniated discs may penetrate the dura.

The pathogenesis of radiculopathy from acute HNP appears related to both mechanical and ischemic-metabolic injury to the nerve root, due to the combined effects of compression and local inflammation [9, 10]. Mechanical injury is related to physical stretching or compression of the nerve root by the herniated disc, with associated disruption of axons and/or myelin. Ischemic-metabolic injury is the result of several interrelated factors. Compression of the nerve root impairs intraneural blood flow, leading to ischemia, in addition to altering vascular permeability. Altered vascular permeability results in endoneurial edema, which further jeopardizes the microcirculation [9]. Partial arachnoid block may also contribute to metabolic injury through interference with local cerebrospinal fluid (CSF) flow, a potentially important nutritional support system for the nerve roots [11]. Finally, ischemic-metabolic injury may be compounded by acute inflammatory substances released by the extruded disc contents, which further alters vascular permeability and intraneural blood flow [10].

Table 45.4 Causes of thoracic radiculopathy

Herpes zoster
Lyme
Diabetic thoracoabdominal radiculopathy
Spinal tumors—primary and metastatic
Disc herniation
Spondylosis
Traumatic nerve root injury
Spinal epidural abscess
Spinal epidural hematoma

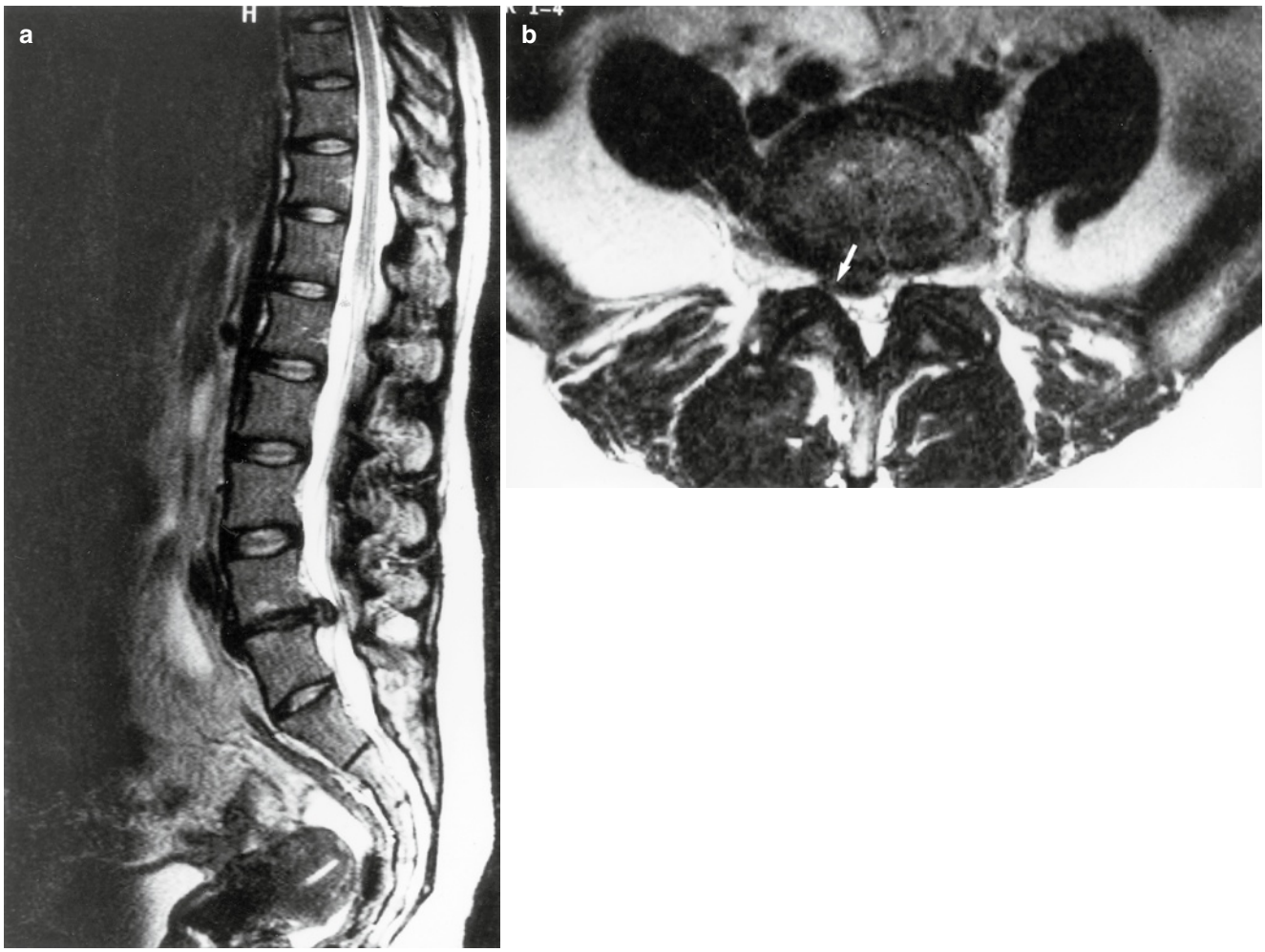

Fig. 45.8 Lumbosacral disc herniation causing nerve root compression. (**a**) Sagittal, T2-weighted MR image of the lumbosacral spine showing a large herniated disc at the L4–5 level. (**b**) Axial, T2-weighted MR image of the same patient at the L4/5 disc level showing the right, paracentral disc herniation (*white arrow*) obliterating the lateral recess and compressing the descending L5 nerve root on the right

The level and severity of nerve root injury is determined by the direction and vertebral level of the disc herniation, as well as its size and the location of any free fragments. Figure 45.8 shows a large paracentral disc herniation compressing the descending L5 nerve root. Because disc herniation at a given vertebral level may produce radiculopathy at more than one root level, the clinical syndrome cannot reliably determine the level of the disc lesion.

Pain in the low back, with or without sciatica, is a hallmark of acute HNP. Pain is characteristically of abrupt onset and severe but may be minor, usually precipitated by bending over or lifting. Patients may complain of sciatica without low back pain. Aggravation of pain with movement, particularly forward or lateral bending, or with Valsalva maneuver, is typical; pain is relieved with recumbency. Patients maintain a rigid upright posture, generally stooped forward, with associated paraspinal muscle spasm. In addition to pain, patients frequently report paresthesias in the involved dermatome. They may note fasciculations and/or weakness in muscles of the involved myotome. The physical examination is aimed towards determining the presence of radiculopathy as well as identifying its anatomic level and severity. Straight leg raising maneuvers (Lasegue test) are nearly always positive with a sensitivity of 91 % but specificity of only 26 % in pooled analysis. In contrast, crossed straight leg raising test has a sensitivity of 29 % but specificity of 88 % for a herniated disc [12, 13]. The reverse straight leg raise (also called the femoral tension sign) has a high sensitivity (84–95 %) for an upper to mid-lumbar radiculopathy, but unknown specificity [14]. Motor, sensory, and reflex changes depend on the level of radiculopathy (see section "Lumbosacral Monoradiculopathy"). Acute HNP may cause monoradiculopathy or polyradiculopathy at two contiguous levels; alternatively, a large, central disc herniation may produce bilateral, usually asymmetrical, lumbosacral radiculopathies or an acute cauda equina syndrome. Urinary retention or fecal incontinence suggests cauda equina compression and should prompt urgent evaluation and decompression, as

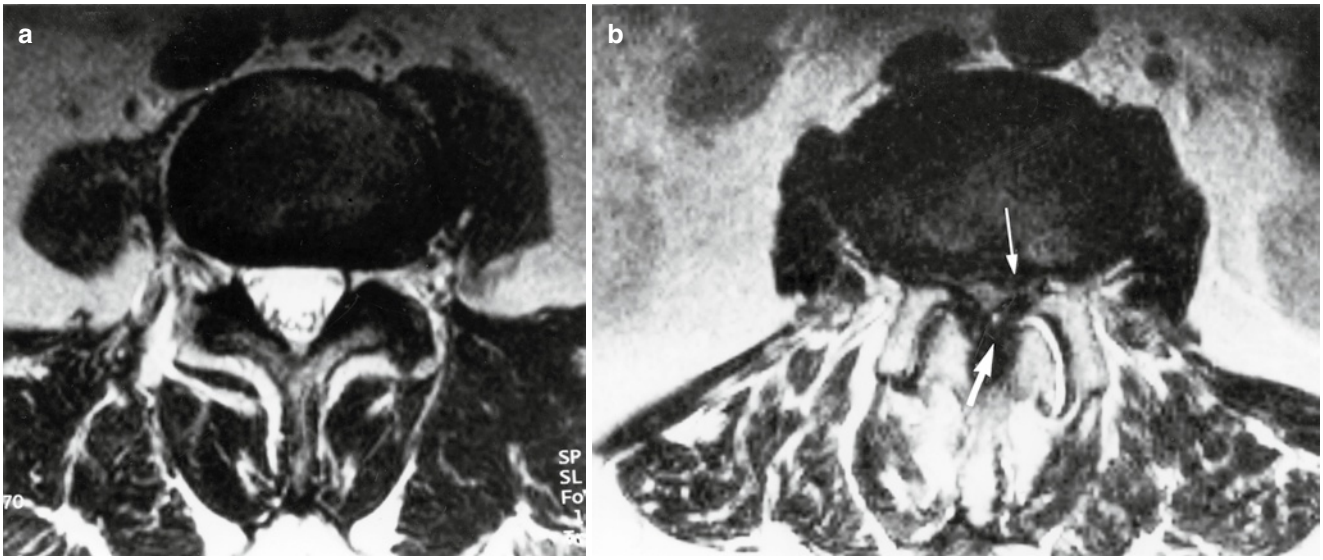

Fig. 45.9 Lumbar spinal stenosis. Axial, T2-weighted MR images at the L3/4 level. (**a**) Normally, the nerve roots of the cauda equina can be distinctly seen in the thecal sac, surrounded by CSF, which appears bright. (**b**) Spinal stenosis, due to hypertrophy of the ligamentum flavum posteriorly (*large arrow*) and to disc bulge anteriorly (*small arrow*). These structures have compressed the thecal sac into the characteristic trefoil configuration, crowding the cauda equina so that the individual nerve roots can no longer be distinguished

delayed decompression is associated with poor recovery of sphincter function [15].

Lumbosacral Spondylosis and Spinal Stenosis

Compression of nerve roots secondary to degenerative changes in the lumbosacral spine is the most common cause of radiculopathy in patients over the age of 40–50 years. Degenerative changes in the spine involve the facet joints as well as the intervertebral discs and intraspinal soft tissues. Hypertrophic changes of the facet joints lead to partial subluxation with narrowing of the lateral recess and/or nerve root foramen. Associated loss of disc height further narrows the foramen vertically. The enlarged facet joints encroach on the posterolateral aspect of the spinal canal, creating a trefoil appearance in cross section (Fig. 45.9). Hypertrophic changes in the soft tissues, notably the ligamentum flavum, further reduce the diameter of the spinal canal. Degeneration of the facets is also associated with spondylolisthesis or forward movement of one vertebra over another. Spondylolisthesis, which most commonly affects L5 on S1, contributes to narrowing of the foramina and abnormal stress on the discs.

Developmental anomalies, such as congenital spinal stenosis or fused vertebrae, may be contributing factors; these conditions are most likely to become symptomatic after superimposed degenerative changes occur. Lumbar spinal stenosis most commonly affects L4–5, followed by L3–4, L5–S1, and L1–2 in descending order [16].

As in acute radiculopathy, the pathogenesis of chronic radiculopathy is likely related to both ischemic and mechanical factors. For instance, in neurogenic claudication secondary to spinal stenosis, lumbar extension reduces the cross-sectional area of the central canal as well as the neural foramina, increasing pressure on the venules surrounding the nerve roots, with subsequent engorgement and ischemic nerve impairment. This may explain the alleviation of symptoms by forward flexion of the spine [17].

In spondylotic disorders, compressive radiculopathy may occur as a result of bony nerve root entrapment in the spinal canal, either in the lateral recess or the intervertebral foramen, or as a result of central spinal stenosis. In the former situation, lumbosacral nerve roots may be affected at single or multiple levels, either unilaterally or bilaterally, producing either lumbosacral monoradiculopathy or polyradiculopathy. Central spinal stenosis typically produces either cauda equina compression or intermittent neurogenic claudication. The most common symptom with lumbar spinal stenosis is neurogenic claudication—discomfort classically brought on by walking and improved with sitting; typically, the pain radiates from the spine into buttocks, thigh, or lower leg, but leg pain may predominate [17]. Radicular symptoms, i.e., pain radiating from lower back into buttocks, thigh, or lower leg, are a fairly sensitive indicator of lumbar spinal stenosis (sensitivity 88 %), though of low specificity (34 %). A more specific and sensitive symptom is one of back pain while standing which is relieved by sitting (specificity 93 %, sensitivity 46 %) [17, 18]. Radicular and claudicant syndromes may coexist, although one typically dominates the clinical picture. Additionally, disc herniation may complicate any of these syndromes [19].

Although degenerative spondyloarthropathies are most common, there are a number of chronic disorders associated with inflammatory spondyloarthritis. These include rheumatoid arthritis, psoriasis, ankylosing spondylitis, ulcerative colitis, Crohn's disease, Whipple's disease, and Behcet's disease. The clinical syndromes associated with nerve root compression for these disorders are similar to those seen in degenerative disease of the spine.

Thoracic Disc Herniation and Spondylosis

Symptomatic intervertebral thoracic disc herniations are distinctly uncommon. With improved imaging techniques, greater numbers of thoracic disc herniations are being diagnosed than previously recognized, and many are identified incidentally [20]. Most occur in the lower thoracic region, from T8–T11 [21]. When symptomatic, the usual clinical picture is that of midline back pain and myelopathy due to spinal cord compression from a centrally herniated disc. Radicular pain is reported in less than half of patients, and pure radicular signs are even less commonly reported. In nearly all symptomatic patients, a radiculomyelopathy is seen, with variable motor, sensory, and bowel/bladder deficits [21]. The diagnosis is often delayed, in part due to lack of a characteristic clinical syndrome. The symptoms are chronic (greater than 6 months) in most patients.

Degenerative spondyloarthropathy of the thoracic spine is common in the elderly and rarely causes myelopathy. Symptomatic radiculopathy from thoracic spondylosis is almost never seen.

Neoplastic Disease

Primary Tumors

Radiculopathy may result from a tumor located anywhere within the spinal canal; most often, extramedullary lesions are responsible. The primary spinal tumors are mostly intradural, while metastatic lesions are mostly extradural [22, 23]. In general, primary spinal tumors tend to occur singly, while spinal metastases are frequently multiple. Infrequently, extraspinal tumors may involve segmental spinal nerves, simulating radiculopathy. While the mechanism of injury due to spinal tumors is likely multifactorial, the primary pathophysiologic process is one of direct mechanical compression [23, 24].

Among primary spinal tumors, the anatomic site of tumor is most frequent in spinal cord (approximately 70 %), followed by spinal meninges (approximately 25 %) and cauda equina (approximately 5 %); the most common tumor types are meningioma, ependymoma, and schwannoma [25]. Intradural tumors are rare; the majority are extramedullary, with meningiomas and nerve sheath tumors seen with highest frequency. Neurofibromatosis I (NFI or von Recklinghausen's disease) is identified in 35–45 % of patients with spinal nerve sheath tumors; multiple tumors are a hallmark of NF1 [26]. Intramedullary tumors are uncommon, mostly comprised of low-grade astrocytomas and ependymomas [26].

In the thoracic spine, meningiomas are seen most frequently. However, the intrinsic tumors that most often involve the lumbosacral nerve roots are myxopapillary ependymomas and neurofibromas arising from the cauda equina. Less common cauda equina tumors include schwannomas, meningiomas, lipomas, and dermoid tumors; hemangioblastomas, paragangliomas, ganglioneuromas, osteomas, and lymphomas/plasmacytomas are rare [27]. Clinically, primary spinal tumors are frequently confused with disc herniation or spondylosis, with similar symptoms including pain, weakness, paresthesias, incoordination or balance difficulty, and urinary incontinence [25]. Back pain, with or without sciatica, is the earliest and most common presenting symptom; onset may be sudden or gradual. The pain related to tumor, unlike disc disease, usually becomes unremitting and increasingly severe over time. Notably, the pain tends to be worse when lying down and is often most troublesome at night, causing sleep disturbance [27]. The nature of the pain is the most helpful clinical feature in differentiating tumor from other causes of radiculopathy [27]. Motor and sensory symptoms typically follow the onset of pain by weeks or even years. Sphincter and sexual dysfunction from radiculopathy indicate involvement of the cauda equina. Rarely, these lesions present with intermittent neurogenic claudication or spinal subarachnoid hemorrhage; ependymomas have the highest propensity for bleeding [28]. The physical examination demonstrates varying abnormalities consistent with individual or multiple radiculopathies, dependent upon the tumor location. With cauda equina lesions, straight leg raise testing may be positive. There may be tenderness to gentle percussion over the involved vertebrae.

Epidural and Vertebral Metastases

Metastatic tumor is the most common type of neoplasm involving the spinal canal. An estimated 5–10 % of patients with cancer will have spinal metastasis, and epidural spinal cord compression is the initial manifestation of malignancy in 20 % of these [29]. While epidural, intraspinal, or leptomeningeal metastases may involve nerve roots, epidural metastases do so most commonly. The vertebrae are the most frequent site of skeletal metastasis, in part due to facilitation of hematogenous spread via Batson's venous plexus [30]. Epidural metastases nearly always result from the direct extension of metastatic vertebral tumor. Less commonly, extension of paravertebral tumor through the intervertebral foramina occurs. Rarely, tumors metastasize directly to the epidural space [31]. Most often, vertebral neoplasms cause radiculopathy by direct compression of nerve roots within

the foramen or compression of the conus medullaris/cauda equina. Less commonly, vertebral tumors may compress the entire cauda equina secondary to pathologic fracture or compress individual spinal nerves via extension into the paravertebral area [23, 30]. Metastatic lesions generally remain confined to the extradural space, with the dura providing a relatively effective barrier against extension into the subdural or subarachnoid space.

The tumors most frequently responsible for vertebral metastases in adults are breast, lung, and prostate cancer; other tumors seen with relatively high frequency are melanoma, renal cancer, sarcoma, and multiple myeloma. Lymphoma has a predilection for metastasis to the paravertebral lymph nodes [23, 32]. Tumors of the pelvic region, including colon and prostate cancers, preferentially metastasize to the lumbosacral region of the spine [32]. Overall, the thoracic spine is the most frequent site of metastasis (70–80 %), followed by the lumbosacral (20 %) and cervical spine (10 %) [30, 33]. Hence, myelopathy secondary to spinal cord compression is the most typical clinical finding, but radicular symptoms and signs are often associated. Weakness is present at diagnosis in over two thirds of cases [29]. Physical examination findings are dependent upon the level and extent of involvement of the tumor, and prognosis is closely correlated with degree of neurological dysfunction at diagnosis.

As with primary tumors of the spine, pain is the most frequent initial symptom, with motor and sensory symptoms developing later, over a variable time course. Back pain is present in approximately 90 % of cases of spinal metastases, reported an average of 7 weeks before onset of neurologic deficits. Symptoms reported in the thoracic region, where disc herniation and spinal stenosis are uncommon, heighten suspicion for malignancy [29]. Local pain near the site of the lesion is nearly universal; radicular pain is more variable. Percussion tenderness at the site of the lesion is characteristic.

Radicular pain from lesions in the thoracic region is usually bilateral and may be described as a squeezing sensation around trunk or abdomen but may be unilateral or bilateral with lumbosacral lesions. When present, radicular pain is usually localizing within one or two vertebral segments [32]. As with primary tumors, the pain is characteristically worse with recumbency and Valsalva [32]. Herpes zoster has been reported to affect patients at the level of spinal cord involvement, presumably secondary to activation of virus by tumor involvement in the DRG [32]. Rarely, patients present with painless leg weakness with variable sensory or sphincter involvement. Although most patients with metastatic spinal lesions have known malignancy, in a small percentage, spinal metastasis is the presenting syndrome. MRI is highly sensitive and specific (>90 %) for detecting lesions causing metastatic epidural spinal cord compression [29]. Median survival after diagnosis is 3–6 months, with primary tumor type and ambulatory status being the most significant prognostic indicators [29]. Thus, the importance of maintaining a high index of suspicion for spinal metastases in patients with known malignancy cannot be overemphasized.

Leptomeningeal Metastases and Meningeal Carcinomatosis

Cancer cells from primary systemic or central nervous system tumors may seed the meninges via CSF pathways, creating multifocal deposits of nodular tumor or diffuse leptomeningeal involvement (meningeal carcinomatosis). Generally, malignant cells gain entry to the subarachnoid space through hematogenous dissemination but may also spread from adjacent bone via the dural sinuses or epidural plexus. Less often, direct extension occurs from a brain metastasis, or systemic tumor spreads along nerve or perineural lymphatics into the subarachnoid space [34]. Previously considered rare, leptomeningeal metastases are reported with increasing frequency, likely due to improved survival of patients with systemic cancer as well as earlier recognition of the clinical syndrome. While any systemic cancer can seed the meninges, certain malignancies have a propensity to do so. Carcinoma of the breast and lung (particularly small-cell type), acute leukemia, lymphoma, and melanoma have the highest incidence of meningeal carcinomatosis [30, 31]. Of the primary CNS tumors, medulloblastomas have the highest incidence of leptomeningeal metastasis.

In general, meningeal carcinomatosis is a late manifestation of systemic cancer, associated with relapse of disease elsewhere in over 70 % of cases but occurring during a disease-free interval in 20 % of cases and as the first manifestation of cancer in 5–10 % [35]. Typically, cranial and spinal leptomeninges are involved; extension into the brain parenchyma is less common [30]. The nerve roots of the cauda equina are the most heavily involved, likely due to the influence of gravity on tumor dissemination in the CSF [36].

The clinical manifestations of meningeal carcinomatosis reflect diffuse involvement of the central nervous system (CNS), specifically involving three areas: cranial nerves, spinal nerve roots, and brain. Patients have diverse complaints including headache, memory or concentration difficulty, and gait disturbance in addition to specific symptoms referable to cranial or spinal nerve involvement, the latter most often involving the cauda equina. Typically, radicular symptoms include pain, weakness, or paresthesias; bowel/bladder dysfunction is uncommon. Physical examination findings include cranial neuropathies, frequently multiple, as well as evidence of patchy lumbosacral polyradiculopathy, dependent upon tumor distribution and extent. Signs of meningeal irritation may also be present [30].

CSF examination reveals an elevated protein, low glucose, and normal or mildly increased cell count. The diagnosis is established by demonstration of malignant cells on CSF cytologic examination. Large volumes and repeated lumbar punctures may be required [30]. CSF cytology is diagnostic in approximately 50 % of cases on the first lumbar puncture, 70–80 % after the second, and 70–85 % after three CSF examinations; however, CSF cytology may be persistently negative in 10–15 % of patients [37, 38]. CSF flow cytometry is particularly useful in evaluating hematologic malignancies [35]; numerous biochemical markers, including carcinoembryonic antigen, lactate dehydrogenase, alkaline phosphatase, b-human chorionic gonadotropin, creatine kinase, monoclonal immunoglobulins, b2-microglobulin, and vascular endothelial growth factor, have been studied but noted to have poor sensitivity and specificity [34].

MRI may reveal contrast enhancement of the basal meninges or ependyma; diffuse or nodular enhancement of the cauda equina is also characteristic. A study of 61 patients with meningeal carcinomatosis comparing the diagnostic utility of MRI and CSF cytologic examinations found a sensitivity of 75 % for CSF versus 76 % for Gad MRI, while the diagnostic specificity of CSF cytology was 100 % compared to Gad MRI 77 % [39].

Infectious Disease

In general, infectious diseases cause radiculopathy either by their presence in the epidural space, creating a compressive syndrome at one or more levels, or by diffuse involvement of the leptomeninges, causing polyradiculopathy. The latter situation is most often associated clinically with cauda equina syndrome, due to meningeal inflammation in the caudal sac. Herpes zoster is the most frequently encountered infectious radiculopathy and causes symptoms by destructive inflammation, rather than active infection, years after the primary infection.

Herpes Zoster

Acute herpes zoster (HZ), or shingles, is the clinical syndrome associated with reactivation of varicella-zoster virus which infects the dorsal root ganglia during the primary attack of chickenpox. HZ is a common disorder, with a dramatically increased frequency in adults over age 50 years old and in the immunocompromised. HZ most often involves the thoracic region, causing a radicular and cutaneous syndrome involving one or two dermatome segments [40]. Burning, aching, itching, or electric shock-like pain in the distribution of the involved dermatome is the overwhelming complaint and usually precedes the vesicular eruption by several days [41]. Pre-herpetic neuralgia has been reported to precede the rash by up to several months; rarely, cutaneous lesions never develop (zoster sine herpete) [42]. In the majority of patients, pain improves gradually as the vesicles crust over. In approximately 10–15 %, pain persists beyond 3 months following resolution of the rash, a condition known as postherpetic neuralgia (PHN) [41, 42]. Patients over the age of 50 years have a significantly higher prevalence of PHN.

In most cases, HZ affects only the dorsal roots, with cutaneous and sensory manifestations. In a small percentage of cases, the ventral rami and/or anterior horn cells are involved, causing weakness in a myotomal distribution, a condition known as segmental zoster paresis (SZP) [40]. Typically, weakness involves one or two contiguous myotomes, correlating with the root level of the cutaneous involvement; however, rare cases are described in which the motor and sensory levels are dissociated [40, 43a]. Motor weakness is nearly always preceded by skin lesions, by an average of 2–3 weeks. The diagnosis may be difficult in those cases where weakness precedes the cutaneous eruption. Reported SZP most often involves lumbosacral and cervical nerve roots; however, the subtle findings associated with thoracic involvement (i.e., abdominal muscle weakness) may result in significant underreporting. Good functional recovery is expected in the majority of patients.

Spinal Epidural Abscess

Acute and chronic bacterial infections are most likely to cause radiculopathy through development of spinal epidural abscesses (SEA) or granulomas, which are rare, but appear to be increasing in incidence. The thoracic and lumbosacral regions are most frequently affected in acute and subacute SEA, with chronic lesions more often reported in the thoracic region [44, 45]. Increasing frequency of lumbosacral lesions is likely related to complications of epidural anesthesia and paraspinal injections. Fourteen to 22 % of cases of epidural abscess occur in relation to spinal surgery or percutaneous spinal procedures, though these are rare complications, with a reported incidence of 1 in 2,000 epidural catheterizations. An indwelling catheter increases risk of developing abscess substantially. PMID 20060254 *Staphylococcus aureus* is the commonest organism but gram-negative rods, anaerobes, mycobacterium, and fungus are being reported with increasing incidence [46]. Until recently, tuberculosis of the spine was the commonest cause of SEA; it usually causes a subacute or chronic syndrome. Tuberculous spondylitis (Pott's disease) is still relatively common in countries where tuberculosis is prevalent and may cause spinal cord or cauda equina compression.

The clinical syndrome associated with SEA is dependent in part on the location and extent of infection, with some common presenting features. Severe back pain is nearly universal (85–90 % of patients); associated neurological deficits (70–80 %) and fever (35–70 %) are less frequent at time of presentation. Radicular pain and signs of spinal cord or cauda

equina compression develop if the disorder remains untreated. Erythrocyte sedimentation rate or C-reactive protein is elevated in over 90 % of patients, while peripheral white blood cell count is elevated in only 50–60 %. The causative organism is identified in blood cultures in 50–70 % of cases and tissue cultures in 90 % [47]. A high index of suspicion should be maintained in patients at risk. Risk factors for development of SEA include diabetes mellitus, history of intravenous drug abuse, spinal surgery, spinal or paraspinal injection, epidural catheter placement, and immunocompromised status [45]. T1-weighted MRI scanning with contrast is currently the diagnostic procedure of choice for SEA.

Polyradiculopathy in Human Immunodeficiency Virus (HIV) and AIDS (Acquired Immunodeficiency Syndrome)

Acute lumbosacral polyradiculopathy is a rare and devastating disorder that occurs in patients with AIDS. Early recognition of the syndrome is important as many cases improve with appropriate treatment. The clinical presentation is distinctive, consisting of a rapidly progressive cauda equina syndrome. The majority of cases are secondary to cytomegalovirus (CMV) infection of the nerve roots and, rarely, compression from infectious or other masses in the conus medullaris [48]. Other etiologic considerations include lymphomatous infiltration of nerve roots, syphilitic polyradiculopathy, herpes simplex virus (HSV), HIV-related polyradiculopathy, and cryptococcal and mycobacterial infections [48, 49]. Patients present with rapidly ascending leg weakness and paresthesias, often accompanied by sphincter dysfunction and perineal/perianal numbness, leading to flaccid paraplegia with urinary retention and obstipation over several weeks [48]. Severe low back pain is frequent. Findings include lower extremity areflexia, asymmetric motor, and sensory loss with frequent involvement of lower sacral dermatomes [50]. Significant CSF pleocytosis with polymorphonuclear (PMN) predominance and elevated protein, and low glucose is characteristic; EDX studies demonstrate evidence of lumbosacral polyradiculopathy with acute denervation [50]. Cytomegalovirus culture of CSF is positive in only 50 % of cases, but detection of CMV by polymerase chain reaction analysis of CSF has a sensitivity of 92 % and specificity of 94 % in CMV-associated polyradiculopathy [51]. In patients with AIDS, CSF anti-CMV antibody production is a nonspecific finding [50]. In less than half of patients, MRI may demonstrate gadolinium enhancement of the leptomeninges [50].

Acute anogenital infection with HSV 2 may produce a superficially similar clinical syndrome due to involvement of the sacral motor neurons or nerve roots. The main differentiating characteristic is the early and almost exclusive involvement of sacral dermatomes. Physical examination may reveal the primary herpetic lesions. CSF pleocytosis, predominantly lymphocytic, is common. EDX reveals active denervation in the involved myotomes. Depending on the dermatomes involved, sensory responses may be abnormal due to dorsal root ganglionitis.

Lyme Polyradiculoneuropathy

Lyme neuroborreliosis (LNB) is the neurologic disease associated with infection with *Borrelia burgdorferi*, a spirochete closely related to *Treponema pallidum*, the causative organism in syphilis. Neurologic symptoms complicate Lyme infection in approximately 5–10 % of patients [52]. Radicular signs and symptoms associated with LNB are most frequently encountered within the first few months of the infection, often as part of a triad including cranial neuropathy, particularly facial palsies, and lymphocytic meningitis (Bannwarth syndrome) [53]. The classic rash of erythema migrans may be seen acutely. In the early meningeal syndrome, protracted radicular pain is followed by motor and/or sensory symptoms and signs in a distribution that is typically multifocal and asymmetrical but may involve single nerve roots. While cranial neuropathy, specifically facial palsy, is the predominant clinical presentation in the United States, radicular syndromes occur twice as often as cranial neuropathies in European patients. Radicular syndromes may be underrecognized in the USA due to patients without accompanying meningeal symptoms or rash [54]. When a classic skin rash is reported, it typically precedes meningeal symptoms by weeks or months. CSF usually demonstrates a lymphocytic pleocytosis and elevated protein; intrathecal production of specific antibody can usually be demonstrated and PCR is often positive [53]. The acute infection is typically self-limited, although antibiotic treatment likely speeds recovery. Improvement occurs over the course of months, and symptoms may fluctuate but ultimately resolve [54].

In contrast to acute radiculoneuritis, a rare syndrome of chronic radiculoneuropathy related to Lyme disease usually presents months to years after initial untreated infection, is clinically mild, and is unassociated with meningitis or cranial neuritis. Patients typically present with one of two symptom complexes—either intermittent symptoms of mild, distal paresthesias or complaints of radicular pain, often involving multiple body segments. Of these two, the radicular pain syndrome is least common in the USA but is more prevalent among older European patients [52, 55]. Regardless of the presenting symptoms, the physical examination findings are generally subtle and mostly sensory, with minimal motor or reflex changes. The EDX findings in both groups are similar and suggest a polyradiculoneuropathy with predominantly axonal features and radicular patterns on needle EMG examination; the findings may also suggest a mononeuropathy multiplex [54, 55]. CSF protein may be elevated but pleocytosis is distinctly uncommon.

Diabetic Radiculopathy

Radiculopathy associated with diabetes typically presents as a subacute, painful, asymmetric, predominantly motor syndrome, involving multiple nerve roots, lumbosacral plexus, or proximal nerves, usually in the high lumbar or thoracic region. The lumbar disorder, often called *diabetic amyotrophy or diabetic radiculoplexus neuropathy*, is fairly well recognized (see Chap. 31). However, diabetic thoracoabdominal neuropathy is less common and probably less well recognized, leading to inappropriate GI and cardiac evaluation in some cases. These disorders are most commonly seen in patients over 60 with fairly well-controlled type II diabetes. Associated weight loss (10 lb or more) is frequent. The chief presenting complaint is nearly always pain, which has a radicular and/or neuropathic quality and is usually worse at night; allodynia may be severe. Involvement of multiple nerve roots is most common, frequently involving noncontiguous myotomes and spreading from one limb to another. Weakness is prominent and occurs early in the course. Paresthesias and sensory loss are often inconspicuous.

Physical examination findings include weakness involving myotomes corresponding to the dermatomal distribution of pain, usually lower thoracic and high lumbar (L1–3); often, weakness is more widespread than the distribution of pain indicates. In thoracoabdominal neuropathy, weakness of iliopsoas or quadriceps muscles is a common finding [56]. Thoracoabdominal weakness may be difficult to demonstrate. Sensory loss or hyperesthesia is a variable finding; when present, it usually involves the symptomatic dermatome. Reflexes are diminished in affected dermatomes. However, in many cases, there is only stocking sensory loss and reflex changes secondary to underlying polyneuropathy. Sphincter involvement is noticeably absent.

Electrodiagnostic studies demonstrate evidence of polyradiculopathy with moderate to marked active denervation at multiple, bilateral paraspinal levels as well as involved limbs or abdominal muscles [56]. Often the findings are more extensive than predicted clinically. Evidence for underlying, distal axonal polyneuropathy is seen in most patients. CSF protein is elevated without associated pleocytosis. The underlying pathological process is probably altered immunity and microvasculitis of nerve rather than metabolic derangement [57].

Complications of Epidural and Spinal Anesthesia

Neurologic deficits complicating epidural and spinal anesthesia are rare; the true incidence is difficult to determine due to probable underreporting [58, 59]. In a prospective study of over 100,000 French patients following spinal and epidural anesthesia, neurologic complications occurred in only 34 of them, and recovery was complete within 3 months in 19 patients. Needle trauma and local anesthetic neurotoxicity were the most common neurologic complications [60]. Spinal cord compression, cauda equina syndrome, and isolated lumbosacral monoradiculopathies have been described [58, 59]. Mechanisms of injury include epidural hematoma, toxic effects of anesthetic agents, direct injury to nerve roots from needle or catheter, inadvertent subarachnoid injection of medication during epidural anesthesia, and epidural abscess [59]. Very rarely, adhesive arachnoiditis has been described as a complication of spinal anesthesia; review of most of these cases suggests contamination of anesthetic medication with detergents or other chemical irritants [58]. Hemorrhagic complication rates are estimated to be less than 1:150,000 epidural and less than 1:220,000 spinal anesthetics. Infectious complications such as arachnoiditis, meningitis, and abscess following spinal or epidural anesthesia are rare; three cases of meningitis were reported in one combined series of more than 65,000 spinal anesthetics [60].

Factors which appear to increase the risk of neurologic complications of these types of anesthesia include the presence of lumbar spinal stenosis, the inadvertent subarachnoid injection of high volumes and dosages of medication intended for epidural administration, the combination of general and epidural anesthesia, and increased age [59]. Continuous delivery spinal anesthetics have a higher incidence of complications compared with single-dose techniques [60]. The majority of patients with radicular syndromes have good functional recovery; however, severe, permanent neurologic sequelae may persist in a small number [58, 59]. A meta-analysis of 32 studies from 1995 to 2005 found permanent neurological injury after spinal and epidural anesthesia ranged from 0 to 4.2:10,000 and 0 to 7.6:10,000, respectively [61].

Spinal Arachnoiditis

Adhesive arachnoiditis is the end result of an inflammatory response that leads to fibrosis of the arachnoid membrane, compromise of meningeal blood vessels, and atrophy of nerve roots. The lumbosacral region is most often affected, but any spinal region may be involved [62]. Causes include surgical trauma, infections, and intrathecal irritants such as contrast agents, steroids, or anesthetics. Generally, there is insidious development of low back pain and/or leg pain, anywhere from days to years after the initial insult, which becomes fairly constant over time. Pain is exacerbated by activity and unrelieved with rest. Neurologic deficits are dependent on the extent of involvement; typically, multiple nerve roots are involved but the severity is highly variable. Physical examination reveals evidence of polyradiculopathy with variable sensory, motor, and reflex deficits. CSF protein

may be normal or elevated, particularly in the setting of spinal subarachnoid block [62].

Tethered Cord Syndrome

Tethered cord syndrome (TCS) presenting in adulthood is uncommon. The most common causative lesions are tight thickened filum terminale, intradural fibrous adhesions, dermal sinus tracts, diastematomyelic septae, intradural lipomas, (lipo)myelomeningoceles, bone spicula, fibrous adhesions, and adhesive arachnoiditis. The physiologic changes are due to stretching of the filum terminale and spinal nerves causing reduced regional blood flow, disruption of oxidative metabolism, neuronal membrane changes, and progressive fibrosis [63]. While the pathologic lesions are the same as those seen with children, the clinical syndrome is distinct [64]. In adults, pain is the most common presenting feature, often localized to the anal, perineal, or gluteal region or diffuse over one or both extremities; typical radicular pain is uncommon. The neurologic picture is one of a variable cauda equina and conus medullaris syndrome, with frequent motor, sensory, and bladder dysfunction. Physical examination findings correspond to the level and extent of involvement; Babinski and other long track signs may be present, as well. Unlike children, the majority of adults have no cutaneous lesions suggestive of spinal dysraphism (subcutaneous lipomas, hair tufts, sacral dimple), although these should be sought. Progressive scoliosis and pes cavus, also common in children, are rare. Patients may develop symptoms after an acute precipitating event producing significant stretch of the conus or following the development of acquired spinal stenosis. MRI is diagnostic, with evidence of a thickened filum, often with associated lipoma, and low conus medullaris. Surgical resection is usually effective for relief of pain and good functional improvement of motor and sensory deficits; however, bladder dysfunction is often refractory [63, 64].

Unusual Compressive Lesions

The following lesions are described as rare causes of compressive radiculopathy. Surgical excision and/or spinal decompression lead to improvement of symptoms in many cases. However, given their rarity, surgical treatment should be considered only if disabling or progressive manifestations are clearly attributable to these lesions.

1. Cysts. Spinal cysts that may cause nerve root compression include synovial cysts (arising from facet joints), cysts of the ligamentum flavum, and perineural cysts, also called Tarlov's cysts [28]. Tarlov's cysts are focal outpouchings of the dural root sleeves, usually occurring in the sacral region. Generally, when symptomatic, cysts are associated with spinal dysraphism or cord compression. Unlike Tarlov's cysts, the other types are found most often in the lumbar region and may present with lumbosacral radiculopathy or cauda equina compression [28].
2. Vascular Lesions. These include epidural and subdural spinal hematomas, spinal arteriovenous malformations, vertebral hemangiomas, spinal epidural cavernous hemangiomas, aortic aneurysms, and ligamentum flavum hematomas. Epidural hematomas may occur spontaneously or after lumbar puncture, epidural anesthesia, epidural injections, or spinal surgery. One third of cases are associated with anticoagulant therapy [65]. Patients with inferior vena cava obstruction may develop epidural venous plexus enlargements presenting with back pain and radiculopathy [66].
3. Demyelinating Polyneuropathy. Hereditary motor and sensory neuropathy type I (HMSN I) and chronic inflammatory demyelinating polyneuropathy (CIDP) may be associated with symptomatic radiculopathy secondary to compression of abnormal, hypertrophic nerve roots [67, 68]. In the lumbosacral region, the symptoms are primarily a result of cauda equina dysfunction with pain, bladder disturbance, and intermittent neurogenic claudication described [67, 68]. In CIDP patients, immunosuppressive therapy leads to improvement in symptoms in most cases.
4. Spinal Epidural Lipomatosis (SEL). The deposition of excessive amounts of normal adipose tissue in the spinal canal may cause compression of the spinal cord or nerve roots. SEL is associated with exogenous steroid use and, less commonly, with obesity and Cushing syndrome [69].
5. Sarcoidosis. Rarely presenting as a polyradiculopathy and often associated with central nervous system sarcoidosis, the lesions typically involving thoracolumbar or lumbosacral roots. Symptoms may progress rapidly, mimicking Guillain-Barre syndrome. Imaging, chest radiographs, and/or CSF are typically diagnostic [70].

Evaluation and Diagnosis

Evaluation of a patient with a suspected lumbosacral or thoracic radiculopathy begins with the question of whether any diagnostic testing is needed at all. The most important aspect of the initial evaluation is a careful history and neurologic examination, with specific attention to risk factors for etiologies other than degenerative disorders. In patients with typical sciatica, in whom the cause is likely to be disc herniation or spondylosis, a course of conservative therapy with close follow-up is usually appropriate, with further evaluation only if patients do not improve as expected after 6–8 weeks. Patients need more urgent evaluation if there has been spinal trauma, if tumor or infection is suspected, if cauda equina

Table 45.5 Clues that a radiculopathy needs urgent evaluation

Suspect cancer or infection if	Suspect spinal fracture if	Suspect cauda equina syndrome if
History of cancer	History of significant trauma	Acute urinary retention or overflow incontinence
Unexplained weight loss	Prolonged use of steroids	Fecal incontinence or reduced anal sphincter tone
Chronic immunosuppression	Age over 70	Saddle anesthesia
Urinary or other infection		Widespread, bilateral lower extremity weakness
History of intravenous drug use		
Age over 50		
Fever		
Pain not improved with rest		

Table 45.6 Sensitivity of diagnostic tests in lumbosacral radiculopathy

Test	Reported sensitivity range (%)	Comment	Selected references
Needle EMG	41–82	Sensitivities appear higher with more severe or predominantly motor radiculopathy	[71–75]
Late responses	26–50		[71, 74, 75]
SEPs	10–70	Most reported sensitivities <50 %, except for cutaneous SEPs in L5 root lesions	[71, 76]
Neuroimaging	57–86		[71–73, 75, 77]

syndrome is present, or if there is a severe or progressive neurologic deficit or a pattern of deficits inconsistent with a monoradiculopathy. Table 45.5 lists some red flags which suggest the need for immediate evaluation. Because of the relatively reduced likelihood of degenerative spine disease in the upper lumbar and thoracic regions, early evaluation of upper lumbar and thoracic radiculopathies is reasonable.

The most common diagnostic tests are electrodiagnostic (EDX) studies and neuroimaging studies. Table 45.6 shows the relative sensitivities of these two other tests. In patients at risk for more unusual causes of radiculopathy, additional studies such as blood work (e.g., complete blood count, erythrocyte sedimentation rate, blood glucose, Lyme titer, and HIV antibody), lumbar puncture, or tissue biopsy may be needed. A careful history aimed at identifying the presence of diabetes, immunocompromise, cancer, or risk factors for infections such as Lyme or HIV will help identify the patients in whom a more extensive work-up is indicated.

Electrodiagnostic (EDX) Studies

EDX studies are best utilized as an extension of the clinical examination. They help confirm the diagnosis of radiculopathy, provide information about its severity and chronicity, and exclude an alternative cause for the patient's symptoms, such as a mononeuropathy or plexopathy. Routine EDX studies include motor and sensory nerve conduction studies, late responses, and needle electromyography (EMG). Less commonly used studies are somatosensory evoked potentials (SEPs) and motor evoked potentials (MEPs). Though historically performed for evaluation of radiculopathy, the sensitivity and specificity of SEPs are too low for them to be worthwhile in equivocal cases where other tests are normal [71, 78] (Table 45.6). MEPs are essentially a research tool and will not be discussed further.

Conventional Nerve Conduction Studies

Routine motor nerve conduction studies (NCS) are usually normal in lumbosacral radiculopathies [79]. If focal demyelination is the primary pathology, they are normal because the routine stimulation sites are distal to the root lesion. If axon loss is the primary pathology, the studies remain normal unless the axon loss is severe in the distribution of the recorded muscle. Even then, the reduction in the compound muscle action potential (CMAP) amplitude is usually mild because of the contribution to the recorded CMAP from neighboring intact roots. Routine peroneal and tibial motor NCS provide information about the L5 and S1 nerve roots, respectively. Uncommon motor NCS can be done to assess other thoracolumbar roots, such as a femoral motor NCS and the saphenous sensory NCS, to assess the L2, L3, and L4 nerve roots; however, this is not always necessary as the diagnosis may often be clearly established with needle EMG.

Sensory nerve conduction studies are the single most useful EDX parameter for differentiating radiculopathies from mononeuropathies and plexopathies. The sensory nerve action potential (SNAP) amplitude is almost always normal in compressive radiculopathies, whether the lesion is axonal or demyelinating, because the lesion lies proximal to the dorsal root ganglion. SNAP amplitudes may be abnormal with the rare compressive lesion which extends into the neural foramen [80] or with inflammatory radiculopathies which also involve the dorsal root ganglion (e.g., herpes zoster). The SNAP may be less helpful in distinguishing a radiculopathy from a distal peripheral nerve lesion in individuals over age 60 or in patients with polyneuropathy in whom SNAP amplitudes may be reduced or absent in the lower extremities. Saphenous sensory potentials are difficult to obtain, even in normal individuals, complicating the distinction of a lumbar plexopathy or femoral neuropathy from an L4 radiculopathy. Comparison of SNAP amplitudes from the contralateral, asymptomatic limb is often helpful.

Late Responses

F responses provide an assessment of proximal motor pathways. Unfortunately, the sensitivity of F responses in radiculopathy appears low. This may be because F responses are mediated by more than one nerve root (i.e., L5/S1). It may also be due to fact that most radiculopathies are partial, leaving some motor axons intact to result in a normal minimum F latency; for this reason, a prolonged minimum-maximum latency range may be more a more sensitive measure [79]. F responses also have a low specificity, as axon loss or demyelination anywhere along the entire length of the motor fiber being studied may prolong the F latency.

The H reflex assesses both sensory and motor pathways. However, it provides information about the S1 nerve root only. It has an advantage over EMG in diagnosing acute radiculopathies (3 days to 3 weeks) since it becomes abnormal within days of an injury. However, once a reflex is lost, it may not return with resolution of the clinical syndrome, which makes it difficult to differentiate an acute from a chronic S1 radiculopathy. H reflexes are also limited in specificity because they can be abnormal with pathology anywhere along the course of the tibial and sciatic nerves. They can also be bilaterally prolonged or absent with a generalized polyneuropathy.

Needle Electromyography

Needle EMG is the most reliable of all electrodiagnostic methods for detecting radiculopathy. The EMG diagnosis of lumbosacral radiculopathy is based on finding evidence of ongoing denervation and/or chronic reinnervation in at least two muscles innervated by the same root, but by different peripheral nerves. In order to make the diagnosis of a monoradiculopathy, muscles innervated by adjacent roots should be normal.

The presence of denervation in the paraspinal muscles is an important localizing finding, as this provides evidence that the lesion is at the root level, proximal to the takeoff of the dorsal ramus. Because thoracic myotomes contain few muscles, and examination of intercostal and abdominal muscles carries the risk of perforating a viscus, the EMG diagnosis of thoracic radiculopathy usually rests entirely on demonstrating ongoing denervation in the thoracic paraspinal muscles.

The absence of paraspinal denervation does not rule out a radiculopathy, however. Paraspinal muscles may be spared in an incomplete root lesion or may be reinnervated in chronic lesions. Because the paraspinal muscles are innervated by multiple roots, denervation may also be missed with limited sampling. In the largest study describing paraspinal examination in patients with surgically proven radiculopathy, paraspinal denervation was present in only approximately 50 % of cases [81]. Similarly, the presence of paraspinal denervation is not specific for radiculopathy. Paraspinal denervation can be seen in other conditions, such as motor neuron disease, inflammatory myopathy, diabetic neuropathy, acid maltase deficiency, and after lumbar laminectomy. Mild paraspinal denervation, consisting of a few runs of positive sharp waves, or even occasional fibrillations in people over age 40, may be seen in the lumbosacral paraspinal muscles of normal, asymptomatic individuals, likely reflecting asymptomatic root injury as part of age-related degeneration of the spine [82].

The myotomal distribution of EMG abnormalities indicates which nerve root is injured. Because most muscles are innervated by more than one root, however, it is sometimes impossible to determine electrophysiologically which of two contiguous roots is involved. This is especially true of the L2, L3, and L4 roots because they overlap extensively in their muscular innervation. It is also impossible to determine the level of spinal pathology by needle EMG, because a single root may be compressed by a disc or osteophyte at more than one level, depending on its size and location.

Lesions of the cauda equina are most often associated with EMG findings of polyradiculopathy, with involvement of bilateral nerve roots at multiple levels. Sacral radiculopathies from any cause are often bilateral, and the S2, S3, and S4 roots are usually involved together. EMG of the anal sphincter can provide supportive evidence for involvement of this group of nerve roots. Involvement of multiple roots is also commonly seen in lumbar spinal stenosis, with half of patients demonstrating chronic, bilateral lumbosacral radiculopathies at multiple levels and most of the remaining having bilateral single-root lesions or an isolated radiculopathy [78]. In patients with chronic reinnervation and ongoing denervation in multiple lumbosacral myotomes bilaterally, it may be necessary to examine cervical, thoracic, and/or cranial muscles to exclude a more widespread degeneration of motor neurons.

The EMG diagnosis of radiculopathy is subject to several limitations. First, the findings on EMG are the result of loss of motor axons, and thus, EMG cannot detect sensory root injury. Second, the needle EMG is generally normal in lesions producing primarily demyelination at the root level; although severe demyelinating conduction block may lead to reduced recruitment of motor unit action potentials (MUAPs), this is rarely severe or widespread enough at the root level to allow detection by needle EMG. Third, detectable abnormalities may be minimal unless the injury is extensive, even with lesions causing axon loss, due to the broad myotomal overlap in innervation of individual muscles. Finally, the needle EMG findings also depend on the timing of the EMG in relation to the root injury. Because fibrillations may not develop in the paraspinal muscles for 7–10 days, and in the limb muscles for 3–6 weeks, an EMG done early in the course may show only reduced recruitment of MUAPs, or be entirely normal. Reinnervation proceeds in a proximal to distal

fashion, with chronic changes appearing in proximal muscles by about 2–3 months and in distal muscles by about 3–6 months. With injury to especially long nerve roots, such as L5 and S1, reinnervation may be prolonged or incomplete, and fibrillation potentials may be found in distal muscles of these myotomes 12–18 months after a static lesion. Findings of chronic reinnervation with long-duration, high-amplitude, and polyphasic MUAPs are often most prominent in, or even limited to, distal muscles of an involved myotome. Notably, needle EMG studies may be negative if performed early, before evidence of denervation has developed or in subacute lesions, after denervation has resolved and reinnervation is incomplete.

Neuroimaging

In general, imaging studies are used in the evaluation of radiculopathy when the clinical picture suggests an etiology requiring urgent intervention, such as trauma, tumor, or infection, or when patients with suspected degenerative spine disease is associated with unremitting pain and/or severe clinical deficits are potential candidates for surgery or epidural steroid injection [83]. Imaging studies such as plain radiographs or bone scans, which are used in the evaluation of patients with back pain, are rarely useful in the assessment of patients with radiculopathy, as the identification of spondylosis, spondylolisthesis, tumor, or infection can be made as easily with tests that provide better anatomic detail of the nerve roots themselves. Standard methods for imaging the thoracic and lumbosacral spine include myelography, computed tomography (CT), CT-myelography, and magnetic resonance imaging (MRI).

Recent studies using surgical findings as a gold standard suggest that MRI and CT-myelography have roughly equivalent sensitivities and specificities in the diagnosis of lumbar disc herniation as a cause for suspected nerve root compromise, although MRI may be a bit more sensitive [84]. All three methods are superior to plain myelography [77, 84]. One exception may be those radiculopathies due to discrete degenerative abnormalities in the lateral recess, where plain myelography appears to be an important supplemental study and may have superiority to both MRI and CT-myelography [85]. MRI and CT-myelography appear to provide similar diagnostic accuracy in the diagnosis of spinal stenosis, with both superior to plain myelography [86, 87].

In general, MRI is the preferred initial study for patients with lumbosacral radiculopathy [88, 89]. This is based on the evidence that MRI is comparable to CT in diagnosing herniated discs and most other degenerative spine abnormalities but provides superior ability to diagnose other inflammatory, malignant, or vascular etiologies [88, 90]. CT may be most appropriate when fractures or other bone abnormalities are suspected and is acceptable as an initial study when the diagnosis of disc or spinal stenosis is fairly certain clinically. CT-myelography is probably best reserved for the occasional preoperative patient in whom a specific technical question remains unanswered [91]. MRI performed with an intravenous contrast agent such as gadolinium-DTPA is the most sensitive study for diagnosing paravertebral soft tissue abnormalities, intradural pathology (e.g., tumor, metastasis, cyst, infection, or arachnoiditis), and intrinsic cord lesions. It is the most useful study for differentiating recurrent disc herniation from postoperative fibrosis [89].

Table 45.7 Prevalence of asymptomatic intervertebral disc herniations on imaging studies

Imaging modality	Prevalence (%)	Mean age (years)	References
Myelography	24	51	[92]
CT	20	40	[93]
MRI	28	42	[87, 94]

The significance of any spine abnormality seen on neuroimaging must be interpreted in the context of the patient's clinical syndrome, given the high prevalence of abnormalities seen on imaging studies of the lumbosacral spine in asymptomatic individuals, especially with advancing age [87]. Table 45.7 summarizes the prevalence of asymptomatic disc herniations with various imaging modalities. Less significant disc abnormalities, such as degeneration or bulging, have been seen on MRI in 93 % of subjects over age 60 [95]. Asymptomatic disc herniations and bulges are common in the thoracic spine as well, with a prevalence of 37 and 53 %, respectively [96]. These findings emphasize the need for interpreting imaging abnormalities in light of their potential clinical relevance.

Diagnostic Utility of EMG Versus Neuroimaging

EMG and imaging studies are complementary in the diagnosis of lumbosacral radiculopathy. These two types of studies differ in that EMG provides information about nerve root function, whereas imaging studies provide information about the anatomy of the nerve roots and surrounding structures. Neither study is completely sensitive. As Table 45.6 illustrates, comparative studies in patients with clinical radiculopathy suggest that the sensitivity of EMG is comparable to that of myelography, CT, and MRI, with sensitivities for both studies for the most part varying from 50 to 85 %, depending on the patient population studied [72, 73, 78]. EMG appears to have a very low false-positive rate [73, 78] compared with the high incidence of false-positive abnormalities seen with imaging modalities. The relative sensitivity of the two studies in thoracic radiculopathy is unknown.

As a general rule, EDX studies should be performed when confirmation of the clinical diagnosis of radiculopathy is needed. This includes patients whose history or examination are limited, whose presentation could also be consistent with a mononeuropathy or plexopathy, or in whom the clinical significance of an imaging abnormality is unclear. Imaging studies should be performed when the etiology of a radiculopathy is in question or when surgical intervention or steroid injections are being contemplated. There is no compelling evidence that routine imaging within the first 6 weeks affects treatment decisions or improves outcomes over clinical assessments alone [97].

Approach to Thoracic Radiculopathies

The diagnosis of thoracic radiculopathy is usually suspected on clinical grounds. The diagnosis can be confirmed by needle EMG. As reviewed above, the EDX of thoracic radiculopathy is usually made based on the presence of denervation in the form of fibrillation potentials in the paraspinal muscles. As degenerative spine disease is less common in the thoracic than in the lower lumbar spine, imaging studies are appropriately obtained early in the course, to exclude an unusual compressive lesion. Serum glucose testing is indicated if a compressive lesion is not found, to exclude diabetes, a common cause of thoracic radiculopathies.

Management and Prognosis

Degenerative Spine Disease

Lumbosacral Disc Herniation

Management options for lumbosacral disc herniations include surgical and nonsurgical ("conservative") treatments. Long-term outcome, based on pain, working capacity, and neurologic deficits, appears no different for patients treated conservatively than for those treated surgically, although the short-term outcome may be better following surgery [98–100]. Furthermore, the natural history of most patients is for improvement within the first 6 weeks with noninvasive management. Thus, the common practice of a 4- to 6-week trial of conservative therapy is reasonable for most patients. Nonetheless, there are certain patients in whom early, if not urgent, surgical treatment is necessary. These include patients with marked or progressive leg weakness and acute cauda equina syndromes, because of the risk of permanent sphincter dysfunction or leg weakness if left untreated. A relative indication for early surgery is intolerable pain which cannot be controlled with medications. In patients who are still symptomatic after a 6-week trial of conservative therapy and whose symptoms and signs are not intolerable or functionally limiting, consideration of surgical intervention is appropriate [101].

Conservative therapy includes a number of different modalities. Early mobilization is often recommended for patients with lumbar radiculopathy; an aerobic exercise program that minimizes stress on the back, and conditioning exercises that strengthen trunk muscles, may be helpful. However, specific recommendations are lacking on type, duration, and benefit of early activity, physical therapy, or spinal manipulation; evidence-based reviews remain inconclusive [100, 102].

Medications are generally required for symptomatic relief of the acute episode. Acetaminophen and nonsteroidal anti-inflammatory agents are comparable in pain relief. Muscle relaxants may be used in selected patients with pronounced paraspinal muscle spasm but may be limited by adverse effects, primarily sedation. For severe pain, opioid analgesics or tramadol is often necessary but should be used on a time-limited basis due to risk of dependency. Medications typically prescribed for neuropathic pain, including anticonvulsants such as gabapentin and pregabalin, selective serotonin reuptake inhibitors, and tricyclic antidepressants, are probably of some benefit in treating the pain of radiculopathy, though results are mixed and high-quality evidence for their role in management is lacking [14, 103, 104]. Systemic corticosteroids are generally not recommended for pain relief [105, 106].

Injections of steroids and anesthetic agents may be used in selected patients with focal irritative symptoms referable to a single segmental level in whom oral analgesics are ineffective. The procedure involves the injection of a concentrated drug dose of medication into the epidural space, close to where the nerve root enters the intervertebral foramen, with the objective of reducing swelling, inflammation, and pain. Epidural injections provide short-term pain relief but do not improve the long-term outcome (beyond 3 months) as far as impairment of function or pain relief, nor do they alter the need for eventual surgery [107, 108].

Other conservative therapies include trigger point injections, biofeedback, lumbar corsets, transcutaneous nerve stimulation, and acupuncture. However, there is little available evidence regarding the efficacy of these methods of treatment for low back pain with radiculopathy [109]. In 60–90 % of patients treated conservatively for radiculopathy due to lumbar disc herniations, symptoms resolve satisfactorily without surgical intervention within approximately 6–12 weeks, though there may be continued improvement following this period [13, 110, 111]. However, there may be recurrent painful episodes throughout the patient's lifetime [14].

Several surgical approaches are available, all aimed at reducing pressure on the nerve root. These approaches include conventional laminectomy, microdiscectomy, percutaneous discectomy, or arthroscopic disc excision. Alternatively, elimination of nerve root irritation may be

achieved by preventing movement between adjacent spinal segments through spinal fusion [111]. In the appropriate patient population, the success of surgery using modern techniques for relief of radiculopathy due to lumbosacral disc herniation is favorable (85–95 %); however, there are no evidence-based recommendations to guide decision-making in individual cases [109, 112]. The largest randomized study to date examining surgical versus nonoperative treatment, prospectively examined 501 patients with radiculopathy of at least 6 weeks duration and lumbar disc herniation confirmed by imaging. While the "as-treated" analysis showed favorable effects of surgery, significant flaws in the study design considerably limit the generalization of results [113]. Other studies have also suggested hastened recovery from radiculopathy following surgical treatment but without change in long-term outcomes compared to conservative treatment [101, 114–116].

Lumbar Spinal Stenosis

In patients with lumbar spinal stenosis resulting in neurogenic claudication or foraminal nerve root entrapment, it is reasonable to begin with a trial of conservative therapy in patients without significant compromise of activities of daily living or in patients with significant medical comorbidity for whom surgery poses high risks. The regimen of conservative therapy is similar to that used for management of disc herniations and includes physical therapy aimed at strengthening the abdominal musculature and improving spinal mechanics, analgesic and anti-inflammatory medications, as well as epidural injections of steroids or anesthetic agents for pain relief [17]. Patients may respond to conservative measures but symptoms often recur as the disease is generally slowly progressive [16].

The decision to undergo surgical intervention for relief of neurogenic claudication or radiculopathy is based upon the severity of functional limitation and neurologic deficits. There are multiple surgical options, all involving decompression of nerve roots, including laminectomy, facetectomy, foraminotomy, and laminotomy. If extensive decompression is performed or if the lumbar stenosis is accompanied by degenerative scoliosis, kyphosis, or spondylolisthesis, arthrodesis may be needed for spinal stabilization [5]. Decompressive surgery provides modest but consistent improvement in functional ability compared to nonoperative measures, with good results and return to premorbid activity levels reported in 60–85 % of pooled cases [16]. Patients with claudicant symptoms are most likely to benefit; those with chronic neurologic deficits such as muscle atrophy are less likely to achieve full recovery, and those with paraspinal low back pain, which may be due to underlying degenerative arthritis rather than entrapment radiculopathy, often fail to improve [16]. Less favorable outcomes may be associated with congenital stenosis, tight canal stenosis, and multilevel decompression [117]. Furthermore, advantages in pain reduction and functional status for surgical versus conservatively treated patients narrow over the course of follow-up, and symptoms may recur, necessitating further operations, typically with diminishing results [17, 118, 119]. Among nearly 100 patients with lumbar spinal stenosis completing 8- to 10-year follow-up in the Maine Lumbar Spine Study, low back pain relief, predominant symptom improvement, and satisfaction with the current state were similar in patients initially treated surgically or nonsurgically, though leg pain relief and greater back-related functional status continued to favor those initially receiving surgical treatment [119]. Given the limitations of current evidence, a shared decision-making approach between physicians and patients is recommended when discussing treatment options for lumbar spinal stenosis.

Thoracic Disc Herniation

Surgical decompression is usually indicated for thoracic disc herniation causing symptomatic spinal cord compression. Most patients with thoracic disc herniation causing radiculopathy without myelopathy are managed conservatively. The approach is similar to the conservative management of lumbosacral disc herniation and includes analgesic and anti-inflammatory medications, physical therapy, and epidural steroid injections. Although most patients respond to conservative therapy, surgical decompression may be necessary if radicular complaints persist. In one series, 27 % of patients with thoracic disc herniation demonstrated by MRI required surgery after a trial of medical management [20].

Thoracic Spondylosis

Thoracic spondylosis is relatively rare. The only clear indication for surgery in thoracic spondylosis is the presence of canal narrowing sufficient to cause myelopathy. The indications for surgical decompression in thoracic radiculopathy due to spondylosis have not been studied sufficiently, but surgery is likely appropriate for patients with incapacitating pain not responding to conservative management or for patients with T1 radiculopathies and resultant hand weakness.

Neoplastic Disease

Primary Tumors

The initial treatment of primary spinal tumors is almost always surgical [22]. Total resection is generally possible as these are discrete masses. With incomplete resection, residual tumor foci may result in recurrence. Radiation therapy has an established role in the treatment of incompletely excised tumors, recurrent tumors, and tumors with malignant histology and is more often performed in patients with

lymphoma/plasmacytoma, astrocytoma, and occasionally with ependymoma [25, 120].

Epidural and Vertebral Metastases

Treatment for metastatic vertebral body disease is selected based upon extent of neurologic compromise and vertebral body destruction [121]. Additional considerations include the anticipated survival time and general health of the patient. Therapy objectives are usually palliative. Patients with pain and radiculopathy without significant bony involvement should undergo radiotherapy as their primary therapeutic modality, particularly when the tumor is highly radiosensitive (e.g., lymphoma or myeloma). Metastatic lesions from lung, kidney, breast, colon, and prostate tumors also respond to radiotherapy, chemotherapy, or both [22, 121]. In patients with vertebral collapse resulting in spinal instability, spinal cord compression, or intractable pain, spinal decompression and stabilization may be necessary.

Whenever there is resultant neurologic dysfunction due to spinal metastases, high-dose corticosteroids should be given intravenously as soon as possible. Prognosis is closely correlated with degree of existing neurological dysfunction, so early diagnosis is crucial. The primary therapy now offered to patients with metastatic epidural disease is radiotherapy. Surgical decompression should be considered when the diagnosis is in doubt or in patients with progressive neurologic deterioration despite radiation and steroids, with radioresistant tumors, with symptomatic spinal instability, or with intractable pain [31]. There is some evidence that early surgical intervention may be superior to radiation therapy in selected cases [29]. The most radiosensitive tumors are breast, prostate, small-cell lung cancer, lymphoma, and multiple myeloma. Renal cell carcinoma and melanoma are extremely radioresistant [122].

Chemotherapy may play a role in patients who are poor surgical candidates due to widespread metastatic disease and for those who have previously undergone radiotherapy [33]. Surgical morbidity ranges from 10 to 15 %. In appropriately selected patients, approximately 80 % have improved neurologic function and pain relief, although the overall prognosis remains poor. In one study, two thirds of patients were able to ambulate following surgery compared to one third preoperatively [123].

Leptomeningeal Metastases and Meningeal Carcinomatosis

The goal of therapy is to improve neurologic status and prolong survival time. Because tumor cells disseminate widely throughout the subarachnoid space, therapy must reach the entire neuraxis. Treatment consists of intrathecal chemotherapy in combination with radiation to the affected areas; methotrexate is the drug of first choice in almost all patients. Radiation therapy can rapidly relieve pain, stabilize neurologic function, and improve CSF flow, making subsequent intrathecal chemotherapy more effective [34]. Without therapy, median survival time is 4–6 weeks, with death usually a result of progressive neurologic dysfunction. Treatment increases median survival to 3–6 months [124].

Infectious Disease

Herpes Zoster and Postherpetic Neuralgia

Treatment with oral acyclovir, famciclovir, or valacyclovir, if started within 72 h of the onset of zoster eruption, is effective in accelerating cutaneous healing of lesions and reducing acute neuritis [125]. Although there is evidence to suggest that early treatment with these antiviral agents reduces the risk of PHN, this has not been confirmed in large epidemiologic studies [125, 126]. The addition of corticosteroids appears to accelerate healing of acute lesions but does not reduce the incidence of PHN; they should be considered as adjunctive early therapy in high-risk (e.g., older) patients with severe pain in whom there is no contraindication [125, 127]. There is evidence suggesting that low-dose amitriptyline, started when herpes zoster (HZ) is first diagnosed, results in a 50 % reduction in the incidence of PHN; however, this is not a common clinical practice [41, 128].

Once PHN is established, tricyclic antidepressants, gabapentin, pregabalin, opioids, and lidocaine patches are effective in reducing pain (Level A, class I, II evidence) [41, 129, 130]. Though opiates are efficacious, they are not recommended as first-line treatment due to concerns of misuse and dependency. Topical capsaicin is also efficacious but adverse effects are a major limitation in most patients [129, 130]. Combination therapy with medications such as nortriptyline and gabapentin may be more successful than monotherapy [130]. The majority of patients with PHN have spontaneous resolution of symptoms over months or years; however, a small number are incapacitated by chronic pain.

Varicella zoster vaccine is a live vaccine FDA approved for use in immunocompetent adults over age 60, regardless of a prior episode of HZ. Because it contains live virus, the vaccine is contraindicated in immunocompromised patients. In a large randomized, double-blind, placebo-controlled trial, the vaccine reduced the incidence and burden of illness of HZ by over 50 %, as well as reducing the incidence of PHN by over 60 % [131]. Vaccination is recommended in nonimmune children and adults, as well as all immunocompetent adults ≥60 years of age; low-dose acyclovir is recommended for prophylaxis in patients receiving immunosuppressive regimens [132].

Spinal Epidural Abscess

Treatment of spinal epidural abscess (SEA) must be initiated urgently, following the collection of blood cultures, with

empirical antimicrobial therapy covering both gram-positive cocci including MRSA as well as gram-negative bacilli in patients at risk [133]. The mainstay of treatment for pyogenic SEA is surgical decompression of the thecal sac and abscess drainage [47, 133]. After surgical drainage, parenteral antibiotics are recommended for at least 2–4 weeks followed by 4 weeks of oral therapy, although precise recommendations on duration of treatment vary [46, 133, 134]. Medical management alone may be appropriate in selected patients in whom the organism has already been isolated and the location of the abscess poses little risk to the spinal cord or cauda equina, in whom there is no neurologic deficit, or in whom the risks of surgery are unacceptable due to comorbid illness. These patients require 8–12 weeks of intravenous (IV) antibiotics followed by 2–3 months of oral agents. Close monitoring is necessary and urgent surgical decompression is performed if neurologic compromise develops [46, 47].

In contrast to bacterial SEA, the mainstay of treatment for spinal tuberculosis is antituberculous chemotherapy, although surgical debridement may be required in some cases. The development of neurologic compromise constitutes an important indication for surgery. Drug regimens for spinal tuberculosis are identical in composition to those used for pulmonary tuberculosis but are administered for 12 months.

Polyradiculopathy in HIV and AIDS

The natural history of untreated CMV polyradiculopathy is one of rapid progression of ascending paralysis, with death usually occurring within 8 weeks of symptom onset [50]. When CMV polyradiculopathy is suspected, an empiric course of ganciclovir should be initiated while awaiting microbiologic confirmation, based on CMV PCR. Alternative therapy with foscarnet or cidofovir, either alone or in combination with ganciclovir, should be instituted in patients already receiving ganciclovir for systemic CMV infection or CMV retinitis or in patients who worsen despite treatment, as this may indicate ganciclovir resistance [50, 135]. The overall prognosis, based on retrospective studies of patients prior to the development of protease inhibitors, is fairly poor, even with treatment [50]. A minority of patients make significant functional recovery, and their survival time, with treatment, is only 3–5 months [50].

Lyme Radiculoneuropathy

Evidence-based guidelines for the management of Lyme borreliosis have been published by numerous North American and European expert groups in recent years and are largely in agreement on recommendation [52, 136]. The choice of treatment regimen for Lyme neuroborreliosis is based upon the clinical presentation. Intravenous ceftriaxone (2 g daily) is recommended for patients with acute neuroborreliosis associated with central nervous system involvement, i.e., encephalitis or myelitis, or patients with late neuroborreliosis and vasculitis. Oral doxycycline (100 mg twice daily) has been found in a number of studies to be as effective as intravenous ceftriaxone (2 g twice daily) in patients with acute neuroborreliosis confined to the meninges, cranial nerves, nerve roots, or peripheral nerves and is the currently recommended treatment [52, 136, 137]. Recommended treatment duration is 14 days as longer courses of treatment have not shown superior outcomes [52, 136]. Only a limited number of class III and IV studies have addressed the treatment of the rare syndrome of late neuroborreliosis presenting as chronic, mild neuroradiculopathy. Based on the available evidence, current recommendations are to treat as for acute neuroborreliosis syndromes involving the peripheral nervous system (including radiculopathy, diffuse neuropathy, mononeuropathy multiplex, cranial neuropathy with normal CSF), i.e., with oral doxycycline [136]; however, in late neuroborreliosis, a 3-week regimen is recommended [52, 136, 138].

Since it takes time for damaged nerves to recover, improvement typically occurs over a few months, often with some fluctuation, but patients ultimately return to baseline. Antibodies remain detectable in the serum for some time after successful treatment so are a poor indicator of treatment response [54, 136].

Persistent symptoms following accepted courses of antibiotic treatment, including fatigue, arthralgias, myalgias, headache, paresthesias, poor sleep, irritability, and concentration difficulties, are referred to as post-Lyme disease syndrome (PLS). There is compelling class I evidence that PLS is not due to active Borrelia infection and is not responsive to further antibiotic therapy, particularly with respect to overall health-related quality of life and cognitive and depressive symptoms. As prolonged courses of antibiotics do not improve the outcome of PLS and are potentially associated with adverse events, they are not recommended (Level A recommendation) [136].

Diabetic Radiculopathy

Management of these painful syndromes is symptomatic with the use of analgesics, tricyclic antidepressants, or anticonvulsants, including carbamazepine, phenytoin, and gabapentin. Transcutaneous nerve stimulation has also been used with variable success [139]. This painful condition is generally self-limited and in most cases the pain resolves in 6–24 months [56, 139]; however, patients may be left with some motor deficit. Methylprednisolone and IVIG have shown some therapeutic potential, mostly insofar as pain relief, but larger, controlled studies are needed, particularly given the toxicity of these agents in diabetic patients [140]. Polyradiculopathy recurs in approximately 20 % of patients [56, 139].

Spinal Arachnoiditis

Unfortunately, few effective treatment options are available for spinal arachnoiditis; even symptomatic pain relief is elusive in most cases. Recognition and avoidance of iatrogenic causes of arachnoiditis is an important aspect of management. Symptomatic treatment of neuropathic pain with tricyclic antidepressants and anticonvulsants, such as gabapentin, is appropriate. Excision of extradural scar and performance of a foraminotomy may provide pain relief in some cases. Intradural lysis is not advised, however, as there is no way to prevent reformation of scar [141]. Implantation of a spinal cord stimulator (SCS) may be another consideration; however, this involves several surgical procedures and long-term pain control achieved with SCS is often incomplete [142]. Neuroablative procedures, such as dorsal rhizotomy and dorsal root ganglionectomy, do not provide benefit and are not recommended [143].

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Brachial Plexopathies

46

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Introduction

The brachial plexus, which innervates the upper extremity and most of the shoulder, is the most complex structure in the peripheral nervous system (PNS). Its susceptibility to trauma, especially closed-traction injury, is directly related to its large size, superficial location, and position between two highly mobile structures (i.e., the neck and upper extremity) [1, 2]. In addition, it is vulnerable to indirect injury from disorders involving structures adjacent to it (e.g., lymph nodes, major blood vessels, lung tissue) [3] (Fig. 46.1). These susceptibilities explain why the incidence of brachial plexopathies is many times higher than the combined incidence of cervical, lumbar, and sacral plexopathies. Accurate diagnosis and management requires that the examining physician integrate anatomic, pathophysiologic, and neuromuscular knowledge with the clinical features, thereby permitting localization and initial characterization of the lesion, which, in turn, dictates the appropriate management of the patient and permits accurate prognostication.

Anatomy

The brachial plexus is a triangular-shaped structure that extends in an inferolateral direction from the spinal cord (its base) to the axilla (its apex). It has an average extraforaminal length of 15.3 cm [4], is composed of connective and neural tissue in a 2:1 ratio [4–6], and consists of several elements: 5 roots (classically, C5 through T1), 3 trunks (upper, middle, and lower), 6 divisions (3 anterior and 3 posterior), 3 cords (lateral, posterior, and medial), and several terminal nerves (Fig. 46.2). The brachial plexus contains over 100,000 individual nerve fibers [2]. Of these, 25 % enter via C6, 25 % via C7, and 25 % via C8; the C5 and T1 roots are the conduits for the other 25 % [4]. The percentage of sensory and motor fibers composing each root varies: the C5 and C6 roots contain the highest percentage of motor fibers (the C7 and T1 roots contain the lowest percentage), and the C7 root contains the highest percentage of sensory fibers, followed in descending order by C6, C8, T1, and C5 [6, 7].

Roots

After exiting the spinal cord, the dorsal and ventral rootlets fuse to form the dorsal and ventral roots, respectively, which then traverse the intraspinal canal to enter the intervertebral foramen. Just distal to the dorsal root ganglion (DRG), the dorsal and ventral roots fuse, to form a spinal nerve (it also is termed a *mixed* spinal nerve because it contains sensory and motor nerve fibers). After exiting the intervertebral foramen, the spinal nerve gives off a posteriorly directed branch (the posterior primary ramus) and then continues peripherally as the anterior primary ramus (APR) (Fig. 46.3). The APR emerges from between the anterior and middle scalene muscles. Nerves arising from the APR include the nerves to the scalene and longus colli muscles (C5–C8); the long thoracic nerve, which innervates the serratus anterior (C5–C7 APR); a portion of the phrenic nerve, which innervates the diaphragm (C5 APR); and a portion of the dorsal scapular nerve, which innervates the levator scapulae and the rhomboideus major and minor muscles (C5 APR) [8]. In addition, preganglionic sympathetic fibers exit from the APR, via white rami communicantes, to reach the sympathetic ganglia. The sympathetic ganglia then send postganglionic fibers, via gray rami communicantes, to the C5–T1 spinal nerves. The preganglionic sympathetic autonomic fibers that

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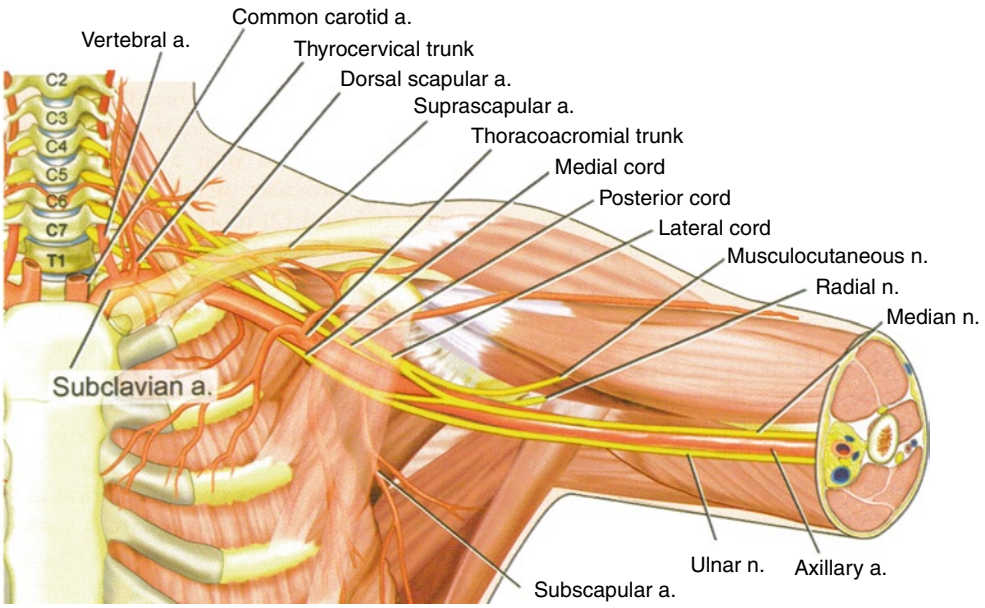

Fig. 46.1 The relationship between the brachial plexus and its neighboring structures

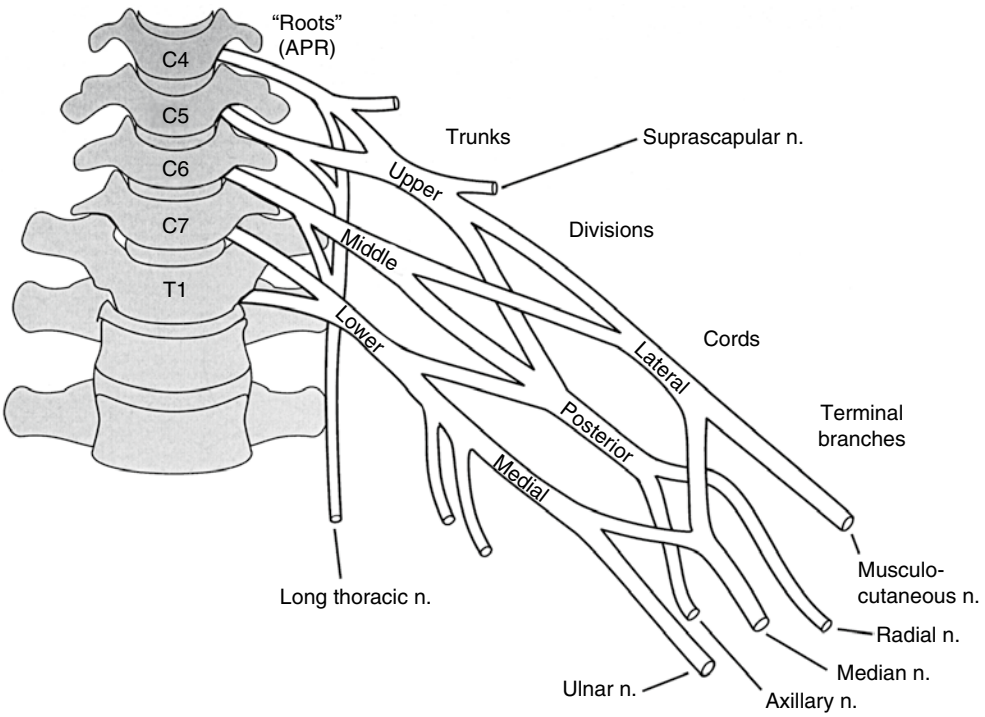

Fig. 46.2 The brachial plexus

supply the head and neck travel with the C8 and T1 spinal nerves to reach the inferior cervical ganglion. Thus, brachial plexus lesions associated with Horner syndrome must be located at or proximal to the spinal nerve level. In its classic formation, the brachial plexus consists of motor and sensory fibers derived from the C5 through T1 anterior horn cells (AHCs) and DRG, respectively [8, 9]. Vertical variations in its composition are not uncommon, such as expansions related to contributions from C4 or T2 or vertical shifts one level upward or downward. Whenever the C4 contribution is large and the T1 contribution is small, the brachial plexus is said to be *prefixed* (C4 through C8), whereas it is considered *postfixed* whenever the C5 contribution is small and the T2 contribution is large (C6 through T2) [10]. It is important to realize that these one-segment shifts do not affect the arrangement of the plexus – it still consists of 5 roots, 3 trunks, 6 divisions, 3 cords, and 5 terminal nerves – and, for this reason, the clinical examination still accurately localizes the lesion. Infrequently, the C7 root may contribute fibers to the ulnar nerve [4]. A final point concerns the

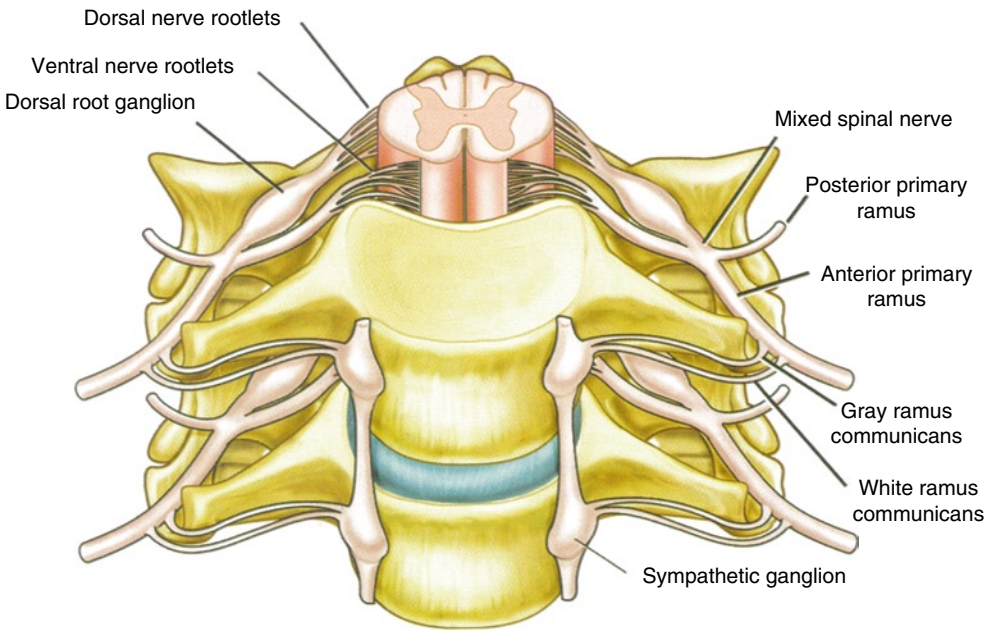

Fig. 46.3 The proximal elements of the brachial plexus

definition of the term *root*. Although anatomists consider the root of the brachial plexus to be the APR, most physicians and surgeons dealing extensively with brachial plexus define the root as the APR, posterior primary ramus, spinal nerve, and all of the dorsal and ventral roots and rootlets contributing to them (i.e., the PNS elements proximal to the trunk) [2]. With the latter definition, the roots have intraspinal canal and intraforaminal and extraforaminal segments, and avulsion injuries are brachial plexopathies. Because of its clinical utility, the more expansive definition of root is used in this chapter.

Trunks

The trunks are named for their relationship to each other – upper, middle, and lower. They are formed from the APR at the lateral borders of the scalene muscles and traverse the anteroinferior region of the posterior cervical triangle of the neck (behind the clavicle and sternocleidomastoid muscle) relatively superficially. Classically, the C5 and C6 APR join to form the upper trunk, the C7 APR continues as the middle trunk, and the C8 and T1 APR coalesce to form the lower trunk. The trunk elements are infrequently anomalous – the upper trunk is of classical formation more than 90 % of the time, the middle trunk is a direct continuation of the C7 APR 100 % of the time, and the lower trunk is of classical formation more than 95 % of the time [11]. The lower trunk is adjacent to the apex of the lung and lies very near the subclavian artery. Two branches derive from the trunk level of the brachial plexus – the nerve to the subclavius muscle and the suprascapular nerve [8].

Divisions

With the body situated in the anatomic position, the divisions lie between the midportion of the clavicle and the first thoracic rib (i.e., they are retroclavicular). In general, the divisions do not give off any nerve branches [8]. Each trunk element divides into two processes, one directed anteriorly and the other posteriorly, thereby generating three anterior divisions and three posterior divisions. The anterior divisions primarily supply flexor muscles, whereas the posterior divisions primarily supply extensor muscles. Although the anterior and posterior divisions of the upper trunk are similar in caliber, the posterior division of the middle trunk is much larger than its anterior division (because the C7 motor fibers innervate more extensor muscles than flexor muscles), whereas the anterior division of the lower trunk is much larger than its posterior division (because the C8 and T1 motor fibers innervate more flexor muscles than extensor muscles) [6]. Following division formation, the segmental nature of the root and trunk elements is lost and, for this reason, the clinical deficits associated with infraclavicular lesions are in the distribution of one or more peripheral nerves or nerve branches.

Cords

The cords, which form at or just beyond the clavicle, are named for their relationship to the second segment of the axillary artery to which they typically are bound (see Fig. 46.1). They are the longest elements of the brachial plexus and lie in the proximal portion of the axilla, near the

axillary lymph node chain [8, 12–15]. The anterior divisions of the upper and middle trunks join to form the lateral cord, the posterior divisions of all three cords unite to form the posterior cord, and the anterior division of the lower trunk continues as the medial cord. The lateral cord, which contains C6 and C7 sensory and C5–C7 motor fibers, gives off the lateral pectoral and musculocutaneous nerves before terminating as the lateral head of the median nerve. The posterior cord, which contains C5–C7 sensory and C5–C8 motor fibers, gives off the subscapular and thoracodorsal nerves before terminating as the axillary and radial nerves. The posterior cord delivers the C5 sensory fibers via the upper and lower lateral brachial cutaneous nerves (branches of the axillary and radial nerves, respectively). The medial cord, which contains C8 and T1 sensory and motor fibers, gives off the medial pectoral, medial brachial cutaneous, medial antebrachial cutaneous (MABC), and ulnar nerves before terminating as the medial head of the median nerve. Cord formation anomalies may produce unexpected findings. For example, when the C7 root or lateral cord contributes motor fibers to the ulnar nerve, lesions of the C7 root or lateral cord can be associated with abnormalities in ulnar nerve-innervated muscles [4, 14, 16, 17]. Although the posterior cord occasionally contains T1 fibers, when present, they account for less than 5 % of its fibers [4, 18]. Nerves usually do not arise from the cord elements of the brachial plexus.

Terminal Nerves

The terminal nerves are situated in the distal portion of the axilla and are the most distal components of the brachial plexus. They number from three (median, ulnar, radial) to five (when musculocutaneous and axillary are included), depending on the author. Since all five of these structures are cord-derived and enter the upper extremity, we consider them to be five terminal nerves. Except for the median nerve, which is derived from two cords (lateral and medial), the terminal nerves originate from a single cord: the musculocutaneous nerve from the lateral cord, the radial and axillary nerves from the posterior cord, and the ulnar nerve from the medial cord. The terminal nerves continue distally as the peripheral nerves of the upper extremity and bear the same name (e.g., the radial terminal nerve of the brachial plexus becomes the radial nerve proper of the upper extremity). There is no anatomical change to demarcate their point of transition, and thus, this point has been defined in different ways by different authors. Narakas defined the transition point as 3 cm distal to the cord [19], but this is challenging to identify clinically. Wilbourn defined the transition point as occurring where the nerves exit the axilla, which is more clinically appreciable [15]. The other cord-derived nerves – the lateral pectoral nerve from the lateral cord, the thoracodorsal nerve from the posterior cord, and the medial pectoral, medial brachial cutaneous, and medial antebrachial cutaneous nerves from the medial cord – like the previously listed APR- and trunk-derived nerves, are not considered as terminal nerves.

Classification

Brachial plexus lesions can be classified in a number of ways. Because of its vast size, most brachial plexus lesions are focal in nature. Consequently, like other lesions of the nervous system, brachial plexus lesions are best classified anatomically. Based on its relationship to the clavicle, the brachial plexus is divided into *supraclavicular* (roots and trunks), *retroclavicular* (divisions), and *infraclavicular* (cords and terminal nerves) plexuses. This subdivision has significant clinical relevance because supraclavicular and infraclavicular plexopathies differ in their incidence, severity, and prognosis. Supraclavicular lesions have a higher incidence, tend to be more severe, and, when severe, have an overall worse prognosis than infraclavicular ones [2, 20, 21]. Their greater severity reflects the greater force associated with their production and the higher incidence of closed-traction injuries (e.g., obstetric paralysis and vehicular accidents), which often produce lengthy and more severe lesions (e.g., nerve root avulsion). Consequently, overall, supraclavicular plexopathies tend to have a worse prognosis [2, 20–23]. The lesion types observed in these two regions also differ. Lesions commonly involving the supraclavicular plexus include closed-traction injury (e.g., obstetric paralysis, vehicular accidents, and burner syndrome), malpositioning (e.g., classic postoperative paralysis), rucksack palsy, neoplastic processes (especially lung or breast cancer), and true neurogenic thoracic outlet syndrome, whereas infraclavicular plexopathies are more frequently related to trauma (gunshot and stab wounds, humerus fractures and dislocations), radiation, medial brachial fascial compartment syndrome, crutch use, and iatrogenicity (e.g., following shoulder operations, shoulder arthroscopy, axillary arteriograms, axillary regional anesthetic blocks, and postmedian sternotomy) [3].

The supraclavicular plexus is further divided into three regions: the upper plexus (upper trunk and C5 and C6 roots), the middle plexus (the middle trunk and C7 root), and the lower plexus (the lower trunk and C8 and T1 roots) (Fig. 46.4). This division also has clinical utility in regard to incidence, severity, and prognosis. Upper plexus lesions have the highest incidence, tend to occur in isolation, and usually are traumatic in etiology (especially closed traction); however, most large series of brachial plexus lesions are compiled by surgeons and, thus, have an etiologic bias [15, 24]. Middle plexus lesions, which rarely occur in isolation, usually are traumatic in etiology and related to traction injury [25, 26].

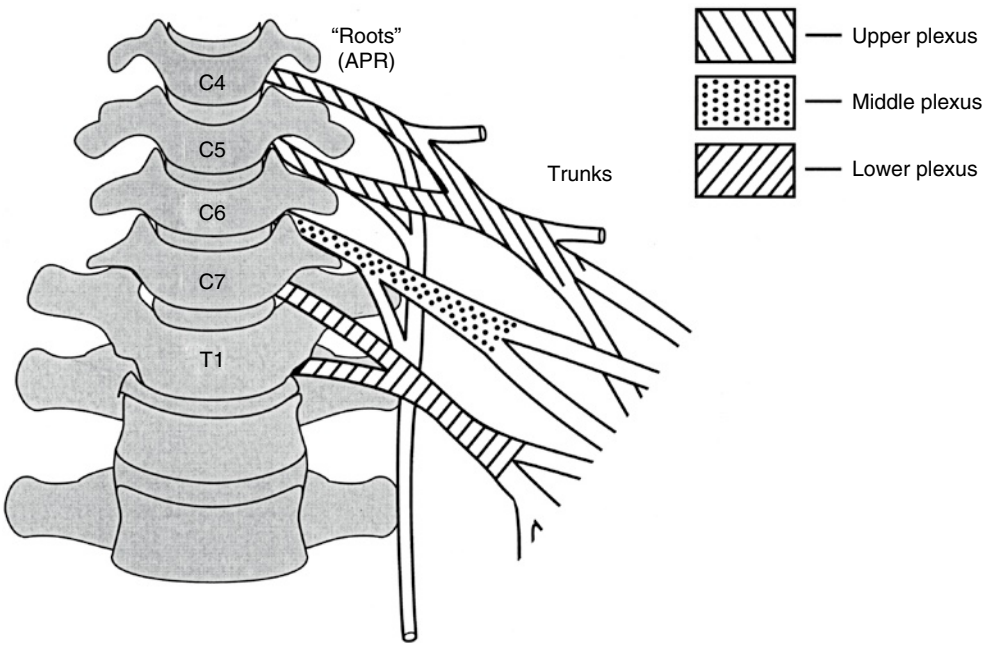

Fig. 46.4 The upper, middle, and lower plexuses

Lower plexus injuries have the lowest incidence. In general, upper plexus lesions are less severe than lesions of the lower plexus because they (1) more frequently are demyelinating conduction block (remyelination is more complete than axon regeneration), (2) usually are located more proximate to the muscles that they innervate (more amenable to reinnervation via axon regrowth), and (3) more frequently are extraforaminal (more amenable to surgical intervention) [2]. For these reasons, upper plexus lesions tend to have a better prognosis. Consequently, a remote process that originally involved all three supraclavicular regions equally may subsequently appear as an isolated lower plexus lesion. Retroclavicular plexopathies rarely occur in isolation. For example, when clavicular fractures damage the underlying divisions, they usually cause concomitant traction injury to the supraclavicular plexus. Unlike the supraclavicular plexus, the infraclavicular plexus is not further divided anatomically because lesions affecting it do not show significant regional differences in incidence, severity, prognosis, or lesion type [3].

Because most clinicians assessing brachial plexus disorders first attempt to localize the lesion, this classification system has clinical utility. Moreover, because many brachial plexus disorders are site specific, this approach also helps establish a differential diagnosis, especially when considered in relation to the lesion itself. For example, forearm flexion weakness following a stab wound to the supraclavicular fossa is most likely associated with a supraclavicular process, whereas following pacemaker placement, an infraclavicular plexopathy is more likely. Finally, this classification system facilitates communication among physicians, especially in the acute setting, when there are examination limitations (e.g., pain, mental status changes, or nonneural injuries with a higher priority for assessment) or prior to diagnostic testing. This is particularly true for the subdivisions of the supraclavicular plexus. For example, it is much easier to discuss a patient with a lesion involving the upper plexus than to commit to one of its internal elements (i.e., upper trunk, C5 root, C6 root).

Pathology and Pathophysiology

Although the nerve fibers composing the brachial plexus may be injured in a countless number of ways, their pathologic and pathophysiologic responses are limited. Regardless of cause, axon disruption causes the nerve segment distal to the disruption site to degenerate. This pathologic process is termed Wallerian degeneration, after Augustus Waller, who first described it [27]. It is also referred to as axon degeneration or axon loss. Seddon utilized Greek terms to pathologically classify nerve trauma into three levels of severity: *neurapraxia* (nonaction of nerve) was applied to lesions restricted to the myelin coating of the nerve (termed demyelination), *axonotmesis* (a "cutting of the axon") to lesions restricted to the axon, and *neurotmesis* (a "cutting of the nerve") when the nerve was either completely severed or so severely disorganized by scar tissue that regeneration was not feasible (e.g., following laceration or ischemic injuries, respectively) [28]. Sunderland later introduced a system that included the degree of connective tissue injury [29]. In his system, *grades I and II* are equivalent to neurapraxia and axonotmesis, respectively, and represent grades of neural involvement, whereas *grades III–V* are equivalent to neurotmesis and represent degrees of connective tissue disruption. A *grade III* lesion

involves the myelin, axon, and endoneurium; a *grade IV* lesion also involves the perineurium; and a *grade V* lesion also involves the epineurium (see Chap. 39). Pathophysiologically, with axon loss, *conduction failure* occurs because the distal nerve fiber segments can no longer conduct impulses. With demyelination, action potentials either traverse the disruption site at a slower rate (demyelinating conduction slowing) or, with more significant degrees of demyelination, are unable to traverse it (demyelinating conduction block). Each of these pathophysiologies has unique EDX manifestations. In order to perform an EDX assessment of the brachial plexus (discussed later in this chapter), these manifestations must be understood. These classification systems also have clinical merit. With neurapraxia, the prognosis for complete recovery is excellent, as it often is with axonotmesis, especially when the Schwann cell tubes are spared. With increasing connective tissue layer involvement, the prognosis for recovery progressively worsens. In general, it is good when disruption is restricted to the endoneurium, extremely poor with perineurial involvement, and nil with epineurial involvement. Unfortunately, the degree of connective tissue involvement cannot be determined clinically or by EDX testing, and in addition, PNS lesions (especially those caused by trauma) often produce a combination of these grades.

Electrodiagnostic Manifestations

Axon Loss

Most brachial plexus lesions are axon loss in nature and result in conduction failure. Thus, the affected sensory and motor nerve fibers do not contribute to the sensory nerve action potential (SNAP) and compound muscle action potential (CMAP), respectively. The recorded amplitude and negative area under the curve (AUC), which reflect the total number of conducting fibers, are decreased. In contrast, the latencies and conduction velocities (CVs) reflect the conduction rate along only the fastest conducting fibers (i.e., those with the largest diameters and the thickest myelin sheaths) and, thus, only reflect a small percentage of the stimulated nerve fibers. Consequently, these values do not become abnormal until all or most of the fastest fibers are affected. Therefore, even with severe axon loss lesions demonstrating low CMAP amplitudes, whenever some of the fastest fibers remain unaffected, latency and CV values remain normal. In summary, *the amplitude and negative AUC values are by far the most sensitive nerve conduction study (NCS) parameters for identifying axon loss lesions, whereas the latency and CV values are fairly insensitive until the lesion is quite severe*. On needle electromyography (EMG) examination, axon disruption causes motor unit action potential (MUAP) dropout and fibrillation potentials. MUAP dropout, which is present from the time of motor axon disruption, is proportional to the number of disrupted motor axons. Because it typically is only apparent when the motor response is 50 % or less than that recorded from the contralateral asymptomatic side, it is usually not apparent on needle EMG unless the lesion involves at least 50 % of the motor axons (i.e., is moderate to severe in severity). Because most extremity muscles have an innervation ratio of several hundred or more, a large number of fibrillation potentials are produced per disrupted motor axon. These potentials typically appear around day 21, are preceded approximately 7 days earlier by insertional positive waves, and can be quite prominent, even when the lesion is only minimal in degree. As successful reinnervation occurs – via progressive distal advancement of the proximal motor fiber stumps from the disruption site to the denervated muscle fibers (*proximodistal regeneration*) or via *collateral sprouting* from the unaffected intramuscular motor fibers – the affected motor response normalizes, and the MUAPs show chronic neurogenic changes (e.g., prolonged durations and increased amplitudes).

Unlike the focal nature of myelin disruption, which persists until remyelination occurs, axon disruption becomes nonfocal because it triggers Wallerian degeneration, which affects the entire distal stump. Once this process of degeneration is complete (see The Timing of the EDX Studies), the entire distal stump is incapable of generating or conducting nerve fiber action potentials. For these reasons, regardless of stimulation site (proximal to, at, or distal to the lesion), the recorded response only reflects the unaffected fibers, and consequently, all of the responses have the same size and appearance (i.e., they are uniform).

Demyelination

Like axon loss lesions, demyelinating lesions may be focal, multifocal, or generalized. Of these, only focal and multifocal (e.g., multifocal motor neuropathy, radiation injury) are pertinent to this chapter. Unlike axon loss lesions, myelin disruption does not induce distant nerve fiber changes (i.e., it remains focal). Thus, the nerve fiber segments proximal and distal to the site of myelin disruption conduct normally and, for this reason, focal demyelination can only be observed on NCS when the stimulating and recording electrodes bracket the lesion (i.e., stimulation current must traverse it). Consequently, *focal demyelinating lesions are localizable by NCS*. Because physiological dispersion causes the sensory responses to decay when recorded over long nerve fiber segments – a reflection of their small size (microvolts), their shorter duration (1–2 ms), and their broader range of CVs (about 25 m/s difference between the fastest and slowest fibers) – focal demyelinating lesions typically are sought

during performance of the motor NCS by moving the stimulating electrodes more and more proximally until the morphology of the recorded waveform changes. The most proximal site utilized by surface stimulation in a patient with suspected brachial plexopathy is the supraclavicular fossa, which can detect focal lesions at or distal to the mid-trunk level. Lesions located proximal to the mid-trunk level are not detectable by surface stimulation. With mild degrees of myelin disruption, the propagating motor nerve fiber action potentials are slowed (demyelinating conduction slowing), whereas with more severe degrees of myelin disruption, they are blocked (demyelinating conduction block). When the motor nerve fibers are slowed to the same degree (uniform slowing, synchronous slowing), their relative rates of conduction across the lesion remain the same. Consequently, the morphology of the recorded waveform appears normal. The only abnormality is that its arrival time is delayed, and thus, either the distal latency is prolonged or the calculated proximal nerve CV is reduced, depending on whether the lesion is located distal to the most distal stimulation site or between the two stimulation sites, respectively. Uniform demyelinating conduction slowing is commonly observed among patients with early carpal tunnel syndrome. When the lesion slows action potential conduction along the affected motor nerve fibers to differing degrees (nonuniform slowing, nonsynchronous slowing), the morphology of the recorded waveform changes – the duration of the negative phase increases, resulting in negative and positive phase cancelation among the dispersed action potentials. Consequently, the negative AUC and amplitude values decrease. Nonuniform conduction slowing may be accompanied by paresthesias but not fixed sensory loss or weakness. The calculated motor CV may be normal (when some of the fastest conducting fibers are spared) or reduced (when all of the fastest conducting fibers are involved). Nonuniform demyelinating conduction slowing is commonly observed among patients with ulnar neuropathies at the elbow. Demyelinating conduction slowing of either form has no effect on the needle EMG and, because it produces neither weakness nor sensory loss, is rarely observed among patients with brachial plexus lesions.

With demyelinating conduction block, the NCS response is normal with stimulation below the lesion, but with stimulation above the lesion, it is either unelicitable (complete lesion) or reduced in size (partial lesion). When the lesion lies proximal to the standard stimulation sites, its presence can be inferred when a clinically weak muscle generates discordance on the motor NCS (normal or nearly normal motor response) and the needle EMG (markedly decrease recruitment of rapidly firing MUAPs). Most significant demyelinating conduction block lesions disrupt at least a few axons and are therefore often accompanied by at least some fibrillation potentials. When demyelinating conduction block is noted among patients with brachial plexus lesions, it typically accounts for a minority of the nonconducting motor fibers, with the majority of the affected fibers being due to axon disruption. Unlike demyelinating conduction slowing, demyelinating conduction block lesions are symptomatic (static sensory deficits or weakness) because the action potentials cannot traverse the lesion site. Most of the brachial plexus lesions that are predominantly demyelinating conduction block are associated with acute trauma, recover via remyelination, and are referred to as *neurapraxia* or as *neurapractic* lesions. Although most demyelinating conduction block lesions of the brachial plexus have a good prognosis, there are at least two that do not – those due to radiation and those attributable to multifocal motor neuropathy. The demyelinating conduction block associated with the early and middle stages of radiation-induced plexopathy tends to persist, to progressively involve more nerve fibers, and to convert to axon loss. With multifocal motor neuropathy and its variants, slow progression and conversion to axon loss also occur.

The Timing of the EDX Studies

The transected distal segments of the affected nerve fibers initially retain their ability to conduct, and therefore, the recorded sensory and motor responses initially appear normal with stimulation below the lesion despite the clinical presence of sensorimotor deficits. With stimulation above the lesion, however, the action potentials cannot traverse the lesion site, and the recorded response is reduced in size (partial axon loss lesion) or absent (complete axon loss lesion). For this reason, prior to Wallerian degeneration, the recorded responses have an appearance identical to that observed with demyelinating conduction block – the response recorded with stimulation proximal to the lesion site is diminished in size in comparison to the one recorded with stimulation distal to the lesion site (partial demyelinating conduction block) or is absent (complete demyelinating conduction block). This phenomenon has been referred to by many terms but will be referred to as *transient axonal conduction block* in this chapter. The time period over which this phenomenon is observable differs due to the different techniques utilized in their recording. On motor NCS, stimulation below the lesion prior to Wallerian degeneration results in a normal CMAP. As the affected motor nerve fibers lose their ability to generate and transmit action potentials, the recorded CMAP decreases in size. In general, this decline begins on day 3 or 4 and maximizes around day 6 or 7 when all of the disrupted motor nerve fibers have lost their ability to generate and conduct action potentials. At this point, the recorded motor response reflects only the unaffected (normal) fibers and indirectly reflects the affected (degenerated) ones. With incomplete lesions, the percentage of affected nerve fibers can be estimated by comparing the

recorded negative AUC/amplitude values of the distal motor response to those recorded from the contralateral side (in the setting of a unilateral lesion) or to the normal control values of the laboratory (when the contralateral side cannot be utilized for this purpose). The recorded SNAP shows the same several-day decrement, but it begins later (around day 6 or 7) and reaches its nadir later (around day 10 or 11). Because neuromuscular junction (NMJ) transmission is lost before the distal nerve segments stop transmitting action potentials, the conduction failure is apparent on motor NCS prior to its appearance on sensory NCS because the CMAP reflects the intervening NMJs. Thus, the time elapsed between the onset of the symptoms and the performance of the EDX study must always be considered to avoid misleading conclusions (e.g., the underlying pathophysiology) and mislocalization. For example, if the study were done around day 6, the low motor-normal sensory response pattern would mislocalize the lesion proximally (i.e., intraspinal canal) or distally (i.e., distal to the takeoff site of the sensory branch). On needle EMG, axon disruption produces fibrillation potentials and dropout of MUAPs. Because of the high innervation ratio of most extremity muscles, hundreds of fibrillation potentials are generated per disrupted motor axon. Thus, they can be quite prominent even when the lesion is only minimal in degree. Although this attribute makes the needle EMG the most sensitive portion of the EDX study for identifying motor axon loss, fibrillation potentials do not appear in the early setting (they generally appear around day 21), and they may quickly disappear as reinnervation via collateral sprouting occurs. Although MUAP dropout occurs at the time of lesion onset, it is an insensitive parameter and typically is not apparent unless the lesion is at least moderate in severity (i.e., about half of the motor axons innervating the muscle under study are disrupted).

EDX Severity Assessment

When lesions affect brachial plexus elements that contain both sensory and motor fibers, the least severe lesion manifests as isolated fibrillation potentials (the sensory and motor responses and MUAP recruitment are normal). With more severe lesions, the appropriate sensory responses decrease in size. As the severity increases further, the sensory responses become quite low or absent, at which point, there are motor response decrement and MUAP dropout, although the latter may not yet be appreciable. With even more severe lesions, the CMAP amplitudes decrease further and the MUAP loss becomes more pronounced and obviously neurogenic (decreased number firing with rapid firing rate). Accordingly, the motor responses are extremely helpful in severity assessment and pathophysiology determination. Specifically, the amplitude and negative AUC values can be used to estimate the percentage of affected motor axons and the underlying pathophysiology. To illustrate this point with a hypothetical and mentally friendly set of motor amplitude response values, suppose a patient with a 5-week history of foot drop has bilateral peroneal motor responses (recording tibialis anterior, the primary dorsiflexor of the foot) performed. On the symptomatic side, the value of the motor response amplitude with stimulation below the fibular head is 4 mV; it is 2 mV with stimulation above the fibular head. On the contralateral, asymptomatic side, the response is 8 mV with stimulation below the fibular head. Comparison of the distal motor response amplitude values of the two sides indicates an axon loss process that involves approximately 50 % of the motor fibers of the common peroneal nerve (4 mV versus 8 mV). The distal and proximal response values on the symptomatic side indicate that there is a demyelinating conduction block that affects 50 % of the conducting fibers (4 mV versus 2 mV). Thus, regarding the motor fibers of the common peroneal nerve, 50 % are affected by axon loss, 25 % are affected by demyelinating conduction block, and 25 % are unaffected. By comparing the distal response values of the two sides, the erroneous conclusion – that the common peroneal neuropathy represents a 50 % demyelinating conduction block (4 mV versus 2 mV) – is avoided. It is important to be aware that following reinnervation via collateral sprouting, although the CMAP improves as the muscle fibers are reinnervated, the of degenerated motor fibers is unchanged. Thus, in the more chronic setting, comparison of the distal motor responses between the symptomatic and asymptomatic sides underestimates the severity of the lesion.

Assessment of Brachial Plexopathy

Clinical Assessment

Brachial plexus assessment begins with a detailed history. Documentation of the onset date, the symptoms at onset and subsequently (e.g., severe shoulder pain followed by wasting and weakness 7–10 days later), and the circumstances surrounding the onset (e.g., following backpack usage, median sternotomy, an axillary or scalene block anesthesia, or trauma) are imperative. With trauma, the position of the neck, shoulder, and upper extremity at impact should be ascertained, as it dictates the nerve fibers at greatest risk of injury. Concomitant injuries should be also noted since they may also be contributory (e.g., fractures of the scapula, clavicle, or humerus; glenohumeral dislocation; scapulothoracic dissociation) [30].

With traumatic brachial plexopathies, the general examination must include a visual inspection of the skin and bones for signs of trauma and of the affected shoulder and upper extremity muscles for evidence of atrophy. In addition, the neck, axilla, and the supraclavicular, infraclavicular, and

scapular regions are palpated for evidence of a mass, bony abnormalities, tenderness, and Tinel sign. The neurological examination is important for preliminary lesion localization. The status of the cervical spinal cord, cervical plexus, and the spinal accessory and phrenic nerves is determined. Dysautonomic features (e.g., sudomotor or vasomotor abnormalities) in the head, neck, shoulder, and upper extremity are sought. The presence of Horner syndrome and/or involvement of the dorsal scapular, long thoracic, or phrenic nerve indicates a proximal localization and portends a worse prognosis. The triad of severe pain, an anesthetic limb, and Horner syndrome is strongly associated with avulsion injury (discussed below) [3]. Since the overwhelming majority of these lesions are axon loss in nature, sensory loss and weakness are expected. With supraclavicular plexopathies, the sensorimotor deficits are segmental in distribution and resemble those observed with involvement of one or more root elements, whereas with infraclavicular plexopathies, they are nonsegmental in their distribution and resemble those observed with involvement of one or more terminal nerves. With *upper plexus* involvement, sensory disturbances involve the C5 and C6 dermatomes (the lateral aspects of the arm, forearm, and hand (especially the thumb)). This includes the cutaneous distributions of the superior and inferior lateral brachial cutaneous nerves, lateral antebrachial cutaneous nerve, and the median nerve territory of the thumb. The cutaneous territories of the superficial radial, median to index finger, and median to middle finger are less frequently involved (60, 20, and 10 %, respectively). Upper plexus weakness involves muscles of the C5 and C6 myotomes such as those involved in external humeral rotation, shoulder abduction, forearm flexion and supination, and, to a lesser degree, forearm pronation and extension, as well as muscles innervated by the dorsal scapular and long thoracic nerves. The biceps and brachioradialis muscle stretch reflexes may be reduced or absent. With *middle plexus involvement*, the sensory loss has a C7 distribution, as does the weakness, including forearm extension and pronation, radial wrist extension and flexion, and, to a lesser extent, finger extension. The triceps muscle stretch reflex may be reduced or absent. With *lower plexus involvement*, the sensory loss involves the medial aspects of the arm, forearm, and hand, and the weakness has a C8 and T1 distribution, affecting the C8-radial (e.g., EIP, EPB) and the C8 and T1 median and ulnar nerve-innervated muscles. The finger flexor reflex may be reduced or absent. In addition, Horner syndrome may be noted.

Radiologic Assessment

The circumstances surrounding the lesion, including the suspected etiology, lesion site, urgency, and study availability, dictate the radiologic procedures employed. Plain films of the cervical spine, clavicle, scapula, chest, and humerus are of value in the assessment of concomitant injuries (e.g., elevated hemidiaphragm with phrenic nerve injury, mediastinal widening with vascular trauma, pneumothorax or hemothorax with lung breach) and, with open injuries, foreign body identification [11]. Certain radiologic features are associated with brachial plexus injuries. For example, avulsion injuries are associated with fractures (of the transverse process, the proximal portion of the first rib, or neighboring bones) and with lateral tilt of the cervical spine; inadequately treated midshaft clavicular fractures resulting to nonunion or excessive callus formation may disrupt plexus fibers (e.g., divisions); infraclavicular plexus lesions are associated with humeral fracture or glenohumeral dislocation; neoplastic and radiation damage are associated with bone or lung abnormalities; and true neurogenic thoracic outlet syndrome is associated with rudimentary ribs and elongated C7 transverse processes [31]. Computerized tomography, despite its drawbacks (e.g., monoplanar imaging, poor tissue differentiation, beam-hardening artifacts), is useful for identifying bony abnormalities and blood [32]. CT myelography can be used to image spinal cord edema or atrophy (the width of the dye column in the cervical gutter is narrowed or widened, respectively) and can identify intraspinal canal masses. When nerve root avulsion is suspected, very-thin-slice (2-mm) CT myelography can be used to image the axially oriented preganglionic nerve root elements [33]. A contrast-filled meningeal diverticulum may be observed when the meninges are pulled through the intervertebral foramen. Other features associated with root avulsion include deformed dural pouches, poor root sleeve filling, and cord edema or atrophy [20, 33–35]. Extraforaminal injuries and meningeal tearing without root damage lead to false-positive conclusions, whereas healing and scarring of the dural pouch produce false-negative conclusions [3]. Overall, the reliability of CT myelography is greatest for avulsions involving the C8 and T1 nerve roots [36].

Because of its multiplanar imaging and tissue differentiating abilities, its lack of radiation and degradation by bone, and its noninvasiveness, magnetic resonance (MR) imaging is the radiologic procedure of choice for imaging the more distal components of the brachial plexus. Although it is also useful for proximal brachial plexus element assessment, it is less sensitive than CT myelography for root avulsion [37], and when multiple slices and planes are required, acquisition time can be considerable. Magnetic resonance myelography is a newer, relatively quick technique in which T2-weighted images of the cerebrospinal fluid (CSF) are reconstructed in three dimensions to generate myelogram-like images of the intraspinal canal and intervertebral foramina [31, 38, 39]. Magnetic resonance neurography is a technique that images peripheral nerves using either diffusion neurography (tissue differentiation reflects diffusion differences rather than T1 or T2 differences) or T2-based neurography (intraneural fascicles are imaged using T2 weighting following fat and blood

suppression and voxel shortening) [40]. With diffusion neurography, because the water molecules within a nerve diffuse longitudinally, a perpendicular magnetic field gradient is applied to make them spin at exactly the same rate and in phase with one another, thereby causing the neural tissue to appear brighter than the surrounding tissue. Unfortunately, this technique is very sensitive to patient motion, and in addition, it can be difficult to image the brachial plexus elements because they are not truly perpendicular to the sagittal plane of the applied magnetic field gradient [40, 41]. These techniques, which are best applied following lesion localization by clinical or EDX assessment, may be helpful in identifying nerve discontinuities and ball neuromas (e.g., upper trunk disruption), nerve deflections (e.g., true neurogenic thoracic outlet syndrome), and primary nerve tumors (e.g., schwannomas) [3, 40].

Vascular Assessment

Angiographic studies may be of diagnostic utility in the assessment of brachial plexus injuries because these lesions may follow trauma to the subclavian or axillary vessels (via hematoma, aneurysm, or pseudoaneurysm formation). This is especially when the plexopathy follows a penetrating injury or when the general examination identifies an absent carotid or radial pulse or when a bruit, thrill, or expanding mass is noted near the injury site [20, 31]. In general, when brachial plexus injury is associated with concomitant vascular injury, the prognosis for recovery is less favorable because, in general, the distractive force associated with neural and vascular disruption is greater than that associated with isolated neural disruption [20].

Electrodiagnostic Assessment and Prognostication

Although an extension of the clinical examination, the EDX examination of brachial plexus lesions is valuable for determining lesion localization and severity, both of which contribute to patient management and treatment. Rather frequently, patients diagnosed with brachial plexopathies in the EDX laboratory are referred with a different diagnostic consideration, and the brachial plexopathy becomes apparent during the EDX assessment. If only the diagnostic considerations put forth by the referring physicians were sought, many brachial plexopathies would go unrecognized. To avoid this pitfall, an organized approach is required. All three components of the EDX examination – sensory NCS, motor NCS, and needle EMG – are performed because each yields information not provided by the others. Thus, omission of one component renders the study incomplete and potentially misleading. Due to its large size, a complete assessment of the entire brachial plexus would require the performance of a large number of NCS and an extensive needle EMG, as well as contralateral studies; this is impractical and would be unnecessarily time-consuming and unjustifiably costly. For this reason and, more importantly, because most brachial plexus lesions are focal, a regional approach is useful in its assessment. We prefer to begin with the sensory NCS, which are the most useful studies for brachial plexus lesion localization and the only studies that assess its sensory nerve fibers. As previously discussed, the sensory response amplitudes are the most important measurement in the assessment of an axon loss process. In addition to differentiating pre- and postganglionic lesions, the pattern of sensory response abnormalities has regional localizing value. Although the motor NCS are quite insensitive to motor axon loss (and hence less useful for localizing) and are normalized by reinnervation, they are extremely useful for determining the pathophysiology and severity of the lesion. We perform the needle EMG last to further localize the lesion (especially its proximal extent), to determine its rate of progression (dictated by the relationship between the acute and chronic motor axon loss), and to confirm the information gleaned from the sensory and motor NCS. In addition, it can determine lesion continuity when there is no muscle movement clinically. The conclusions from all three components of the EDX study should be concordant with each other; otherwise an error or misinterpretation has occurred. Similarly, the final EDX impression should be in concordance with the clinical impression; otherwise one of these two impressions is inaccurate (typically the clinical impression).

Because each brachial plexus element is composed of nerve fibers derived from different spinal cord segments, elemental lesions of the brachial plexus have unique (and occasionally pathognomonic) EDX findings, the recognition of which permits localization. The muscles innervated by a given spinal cord segment or nerve root are referred to as a *myotome* to reflect the segmental nature of the spinal cord. As these motor fibers progress distally, this segmental nature is lost and the suffix *-tome* is inappropriate. We prefer to use the term *muscle domain* to refer to the muscles innervated by a given PNS element. Through anatomic reasoning, the muscle domain of any brachial plexus element is easily derived from the standard myotomal charts [42–48]. The muscle domains of the brachial plexus elements are provided in Table 46.1. The CMAP and SNAP domains of each brachial plexus element, which are determined by the motor and sensory fibers contained within that element and whether they are assessable by NCS, are also calculable [3, 26, 48]. The CMAP domains of the brachial plexus elements are provided in Table 46.2. Because the sensory fibers assessed by the different sensory NCS do not derive from the same DRG, the brachial plexus elements assessed by each sensory NCS vary with the particular sensory NCS. The SNAP domains of the brachial plexus elements are provided in Table 46.3. Based

Table 46.1 The muscle domains of the brachial plexus

Upper plexus	Middle plexus	Lower plexus
Supraspinatus	Pronator teres	Abductor pollicis brevis
Infraspinatus	Flexor carpi radialis	Flexor pollicis longus
Biceps	Triceps	Pronator quadratus
Deltoid	Anconeus	Extensor indicis proprius
Teres minor	Extensor carpi radialis	Extensor pollicis brevis
Triceps	Extensor digitorum communis	Extensor carpi ulnaris
Pronator teres	Serratus anterior	First dorsal interosseous
Flexor carpi radialis		Abductor digiti minimi
Brachioradialis		Adductor pollicis
Extensor carpi radialis		Flexor digitorum profundus – 4, 5
Brachialis		Flexor carpi ulnaris
Levator scapulae		
Rhomboids		
Serratus anterior		
Lateral cord	**Posterior cord**	**Medial cord**
Biceps	Latissimus dorsi	Abductor pollicis brevis
Brachialis	Deltoid	Opponens pollicis
Pronator teres	Teres minor	Flexor pollicis longus
Flexor carpi radialis	Triceps	First dorsal interosseous
	Anconeus	Adductor pollicis
	Brachioradialis	Abductor digiti minimi
	Extensor carpi radialis	Flexor carpi ulnaris
	Extensor digitorum communis	Flexor digitorum profundus – 3, 4
	Extensor pollicis brevis	
	Extensor carpi ulnaris	
	Extensor indicis proprius	

Only those muscles easily assessed by needle EMG are shown

Table 46.2 The CMAP domains of the brachial plexus

Upper plexus	**Lateral cord**
Musculocutaneous recording biceps	Musculocutaneous recording biceps
Axillary recording deltoid	
Middle plexus	**Posterior cord**
Radial recording anconeus	Axillary recording deltoid
	Radial recording extensor digitorum communis
	Radial recording extensor indicis proprius
	Radial recording anconeus
Lower plexus	**Medial cord**
Ulnar recording abductor digiti minimi	Ulnar recording abductor digiti minimi
Ulnar recording first dorsal interosseous	Ulnar recording first dorsal interosseous
Median recording abductor pollicis brevis	Median recording abductor pollicis brevis
Radial recording extensor indicis proprius	

Table 46.3 The SNAP domains of the brachial plexus

Upper plexus	**Lateral cord**
LABC (100 %)	LABC (100 %)
Median sensory NCS recording thumb (100 %)	Median sensory NCS recording thumb (100 %)
Superficial radial (60 %)	Median recording index finger (100 %)
Median recording index finger (20 %)	Median recording middle finger (80 %)
Median recording middle finger (10 %)	
Middle plexus	**Posterior cord**
Median recording index finger (80 %)	Superficial radial (100 %)
Median recording middle finger (70 %)	
Superficial radial (40 %)	
Lower plexus	**Medial cord**
Ulnar recording little finger (100 %)	Ulnar recording little finger (100 %)
MABC (100 %)	MABC (100 %)
Median recording middle finger (20 %)	Median recording middle finger (20 %)

The percentages shown in parentheses represent the frequency with which the sensory nerve fibers subserving the listed sensory NCS traverse the different trunk and cord elements

on these SNAP domains, the brachial plexus elements assessed by each sensory NCS, and hence, the pathways traversed through the brachial plexus can be depicted.

Sensory Fiber Pathways

In 1995, a study of focal supraclavicular brachial plexus lesions and their effect on the standard upper extremity sensory NCS defined the DRG from which the sensory fibers for each sensory NCS are derived [26]. This information defined the brachial plexus pathways that these sensory fibers travel when traversing the brachial plexus and, consequently, the brachial plexus elements assessed by each of the sensory NCS (Table 46.4):

- The sensory fibers composing the LABC nerve derive from the C6 DRG [26], and therefore, the PNS elements assessed by the LABC sensory NCS include the LABC nerve, musculocutaneous nerve, lateral cord,

upper trunk, and the C6 APR, spinal nerve, and DRG (Fig. 46.5).

- The median sensory fibers innervating the thumb derive from the C6 DRG [26]. Consequently, the median sensory NCS, recording thumb (Med-thumb), assesses the median nerve, lateral cord, upper trunk, and the C6 APR, spinal nerve, and DRG (Fig. 46.6).
- The median sensory fibers innervating the index finger derive from the C6 and C7 DRG approximately 20 and 80 % of the time, respectively [26]. Thus, the median sensory NCS, recording index finger (Med-index), assesses the median nerve and lateral cord 100 % of the time; the upper trunk and the C6 APR, spinal nerve, and DRG 20 % of the time; and the middle trunk and the C7 APR, spinal nerve, and DRG 80 % of the time (insert Fig. 46.7).
- The median sensory fibers innervating the middle finger derive from the C6, C7, and C8 DRG approximately 10, 70, and 20 %, respectively [26]. Thus, the median sensory NCS, recording middle finger (Med-middle), assesses the median nerve 100 % of the time; the lateral cord and the C6 APR, spinal nerve, and DRG 10 % of the time; the lateral cord and the C7 APR, spinal nerve, and DRG 70 % of the time; and the medial cord and the C8 APR, spinal nerve, and DRG 20 % of the time (Fig. 46.8). Of the sensory NCS performed in the assessment of brachial plexus lesions, because of this wide distribution, this is the least sensitive and specific sensory NCS.
- The sensory fibers composing the superficial radial nerve derive from the C6 and C7 DRG approximately 60 and 40 % of the time, respectively [26]. Thus, the PNS elements assessed by this sensory NCS include the superficial radial nerve, radial nerve, and posterior cord

Table 46.4 The brachial plexus elements assessed by various sensory NCS

LABC: LABC nerve, lateral cord, C6 fibers of upper plexus
Med-thumb: median nerve, lateral cord, C6 fibers of upper plexus
Med-index: median nerve, lateral cord, C6 fibers of upper plexus (20 %), C7 elements of middle plexus (80 %)
Med-middle finger: median nerve, lateral cord, C6 fibers of upper plexus (10 %), C7 elements of upper plexus (70 %), C8 elements of upper plexus (20 %)
Superficial radial: superficial radial nerve, radial nerve, posterior cord, C6 elements of upper plexus (60 %), C7 fibers of middle plexus (40 %)
Ulnar-little finger: ulnar nerve, medial cord, C8 fibers of lower plexus
MABC: MABC nerve, medial cord, T1 fibers of lower plexus

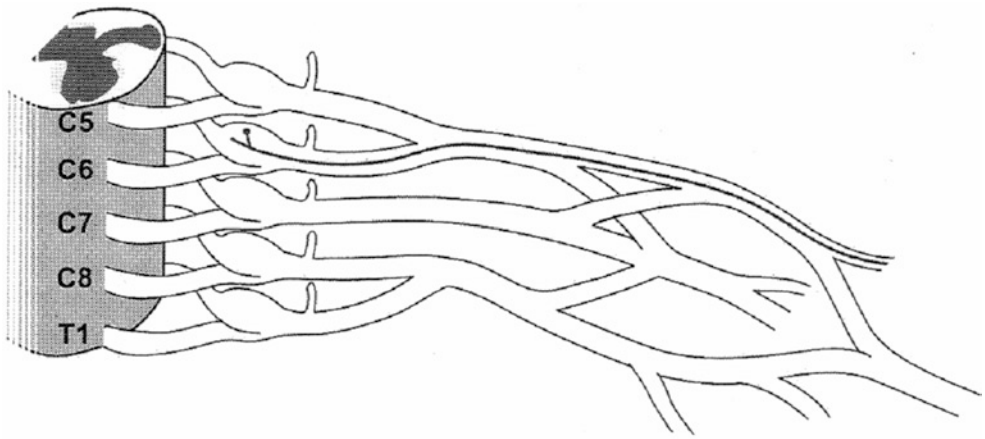

Fig. 46.5 The proposed brachial plexus pathway for the sensory nerve fibers assessed by the LABC SNAP

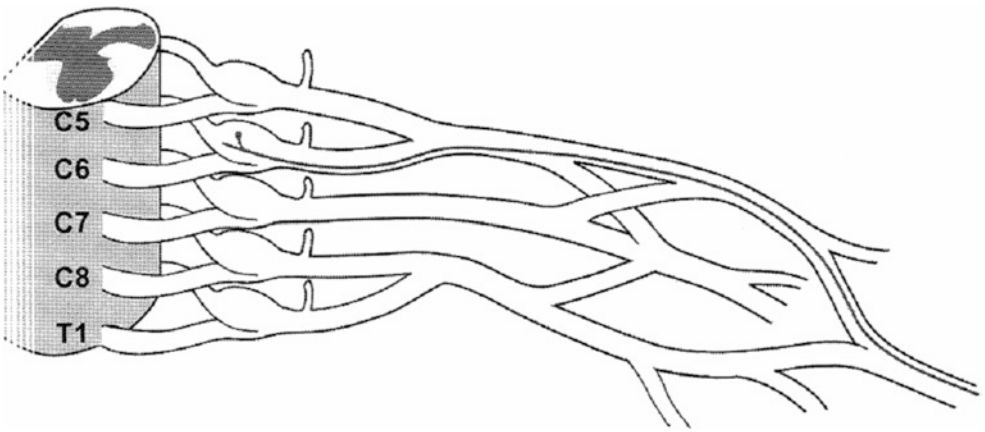

Fig. 46.6 The proposed brachial plexus pathway for the sensory nerve fibers assessed by the median SNAP recording from the thumb

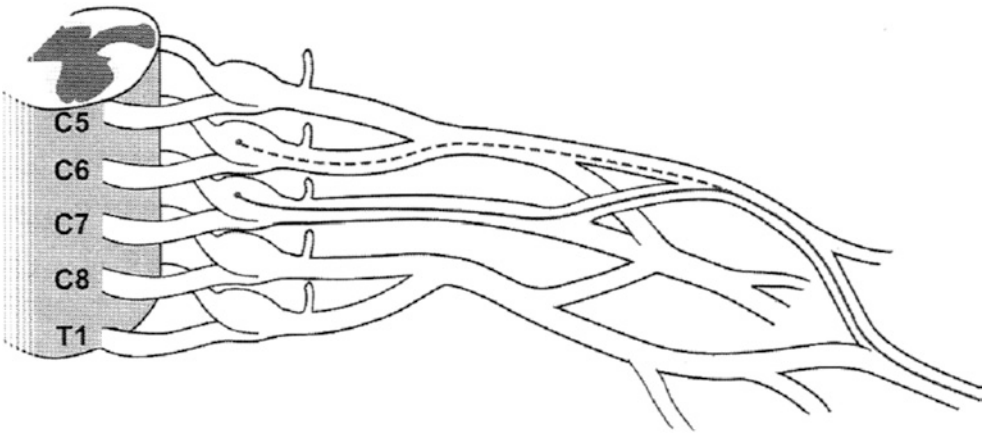

Fig. 46.7 The proposed brachial plexus pathway for the sensory nerve fibers assessed by the median SNAP recording from the index finger

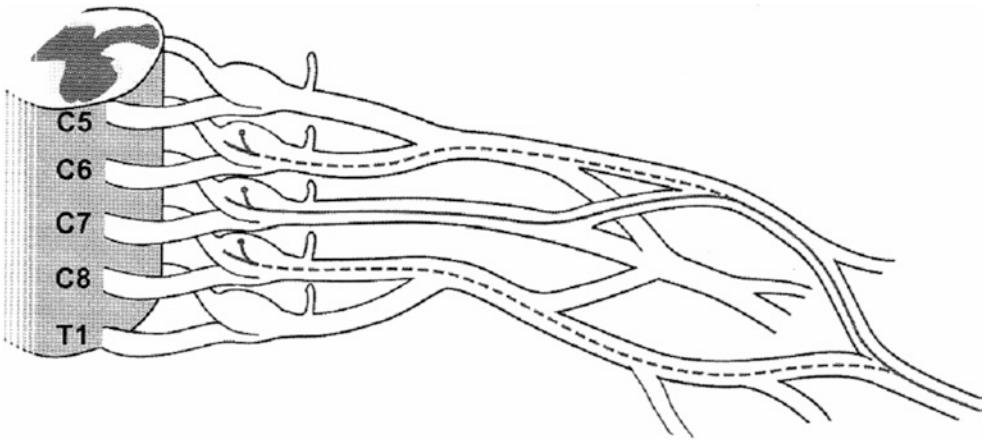

Fig. 46.8 The proposed brachial plexus pathway for the sensory nerve fibers assessed by the median SNAP recording from the middle finger

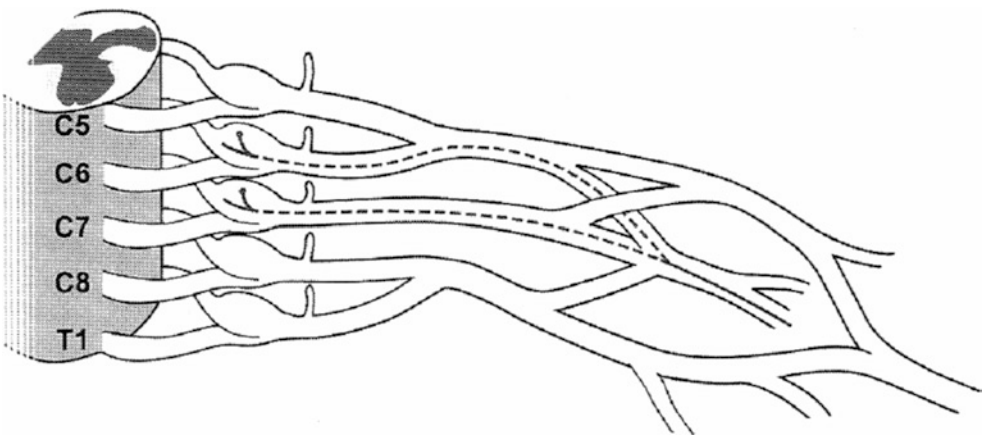

Fig. 46.9 The proposed brachial plexus pathway for the sensory nerve fibers assessed by the superficial radial SNAP

100 % of the time; the upper trunk and the C6 APR, spinal nerve, and DRG 60 % of the time; and the middle trunk and the C7 APR, spinal nerve, and DRG 40 % of the time (Fig. 46.9).

- The sensory fibers composing the ulnar nerve derive from the C8 DRG [26, 49, 50], and consequently, the PNS elements assessed by the ulnar sensory NCS, recording little finger (Ulnar-D5) include the ulnar nerve, medial cord, lower trunk, and the C8 APR, spinal nerve, and DRG (Fig. 46.10).
- The sensory fibers composing the medial antebrachial cutaneous (MABC) nerve derive from the T1 DRG [4, 12, 26, 49–51], and hence, the PNS elements assessed by the MABC sensory NCS include the MABC nerve, medial cord, lower trunk, and the T1 APR, spinal nerve, and DRG (Fig. 46.11).

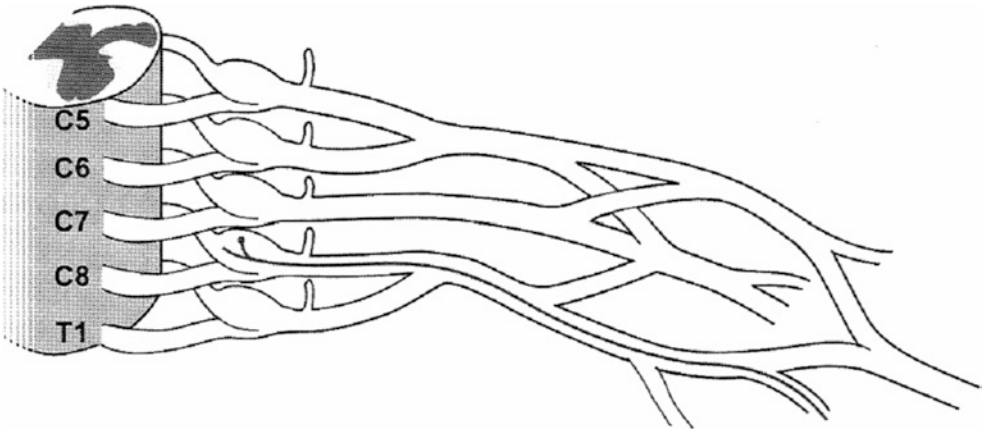

Fig. 46.10 The proposed brachial plexus pathway for the sensory nerve fibers assessed by the ulnar SNAP recording from the little finger

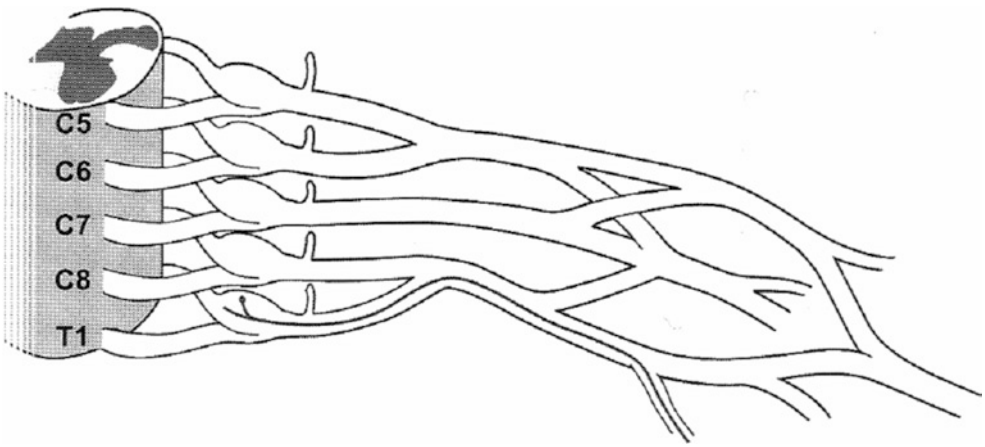

Fig. 46.11 The proposed brachial plexus pathway for the sensory nerve fibers assessed by the MABC SNAP

NCS Assessment of Brachial Plexus Regions

Upper Plexus

The upper plexus contains motor and sensory nerve fibers from C5 and C6. Table 46.5 lists the EDX studies useful in its assessment (Table 46.5). On sensory NCS, the LABC and Med-thumb sensory NCS assess its C6 fibers and, when abnormal, tend to affected to equal degrees [26]. At least one of these studies may need to be performed contralaterally to avoid missing a relative abnormality (i.e., side-to-side differences exceeding 50 %). The superficial radial and Med-index sensory NCS also assess the C6 fibers of the upper plexus but less frequently (60 and 20 %, respectively) [26]. There are no reliable sensory NCS to assess its C5 sensory fibers. On motor NCS, the musculocutaneous study, recording biceps (MC-biceps), and the axillary study, recording deltoid (AX-deltoid), assess all of the upper plexus elements (i.e., upper trunk and C5 and C6 roots). These studies are performed contralaterally whenever the sensory NCS localize the lesion to the upper plexus or whenever the motor response amplitudes are abnormal or near the lower limit of normal. On needle EMG, shoulder girdle and upper extremity muscles belonging to the C5 and C6 myotomes are helpful (see Table 46.1).

Middle Plexus

The middle plexus contains motor and sensory nerve fibers derived from C7. Table 46.5 lists the EDX studies useful in its assessment. On sensory NCS, the Med-index, Med-middle, and radial NCS are useful 80, 70, and 40 % of the time [26]. Again, contralateral studies help identify relative abnormalities. On motor NCS, the radial study, recording extensor digitorum communis (Radial-EDC), which assesses the upper, middle, and lower plexus, is performed bilaterally. Although there is no motor NCS that solely assesses the middle plexus, this motor NCS limitation usually is not a problem because isolated middle plexus lesions are rare [11, 22, 26]. Needle EMG of selected muscles is more specific in the EDX assessment of this element (see Table 46.1).

Lower Plexus

The lower plexus contains motor and sensory nerve fibers from C8 and T1. Table 46.5 lists the EDX studies useful in its assessment. On sensory NCS, the ulnar, recording little finger (Ulnar-little), and MABC studies are available for its assessment. For localization within the lower plexus, both usually are required. Both typically are affected by lower trunk lesions, whereas their involvement is more discordant with lower plexopathies located proximal to the lower trunk

Table 46.5 The electrodiagnostic assessment of the supraclavicular plexus

Upper plexus	
Sensory NCS	*Needle EMG*[a]
LABC	Spinati muscles
Median (thumb)	Deltoid
Superficial radial	Biceps
Median (index finger)	Brachioradialis
	Pronator teres
	Extensor carpi radialis
	Triceps (lateral head)
Motor NCS	
Axillary (deltoid)	
Musculocutaneous (biceps)	
Radial (extensor digitorum communis)	
Middle plexus	
Sensory NCS	*Needle EMG*[a]
Median (index finger)	Triceps (lateral head)
Median (middle finger)	Anconeus
Superficial radial	Pronator teres
	Flexor carpi radialis
Motor NCS	
Radial recording from the anconeus	
Lower plexus	
Sensory NCS	*Needle electrode examination*[a]
Ulnar (little finger)	Abductor pollicis brevis
Ulnar (ring finger)	Flexor pollicis longus
MABC	First dorsal interosseous
	Adductor pollicis
	Adductor digiti minimi
	Flexor carpi ulnaris
	Flexor digitorum profundus (digits 4, 5)
	Extensor indicis proprius
	Extensor pollicis brevis
Motor NCS	
Ulnar (abductor digiti minimi)	
Radial (extensor indicis proprius)	
Median (abductor pollicis brevis)	

[a]The full muscle domain of each supraclavicular plexus region is not shown; only those muscles considered most helpful by the author are included. Other helpful upper plexus muscles include the serratus anterior, rhomboids, teres minor, brachialis, flexor carpi radialis, and, to a lesser degree, the pectoralis major and levator scapulae muscles. Other helpful middle plexus muscles include the extensor digitorum communis, extensor carpi ulnaris, and extensor carpi radialis. Other helpful lower plexus muscles include the extensor carpi ulnaris, extensor digitorum communis, pronator quadratus, and pectoralis minor

(i.e., those restricted to or predominantly involving the C8 or T1 root). On motor NCS, the ulnar, recording abductor digiti minimi (Ulnar-ADM); the ulnar, recording first dorsal interosseous (Ulnar-FDI); and the median, recording abductor pollicis brevis (Median-APB), assess the lower plexus. The radial nerve study, recording extensor indicis proprius (Radial-EIP), is useful for assessing the C8 fibers of the lower plexus. These four motor NCS assess the pre-trunk fibers of the lower plexus differentially – the Radial-EIP study assesses the C8 root, the Ulnar-ADM and Ulnar-FDI studies assess the C8 root to a greater extent than the T1 root, and the Median-APB study assesses the T1 root to a greater extent than the C8 root [26, 49, 50]. On needle EMG, C8,T1-median, C8,T1-ulnar, and C8-radial muscles are useful.

Lateral Cord

The lateral cord contains motor (C5–C7) and sensory (C6–C7) fibers. Its EDX assessment is provided (Table 46.6). On sensory NCS, it is assessed by the LABC, Med-thumb, Med-index, and Med-middle sensory NCS. Most lateral cord lesions affect the LABC, Med-thumb, and Med-index responses to similar degrees, and 80 % of these lesions also affect the Med-middle sensory response, typically to a lesser degree. This pattern helps to differentiate lateral cord lesions from upper trunk lesions, which only affect all four of these studies 2 % of the time and tend to affect the LABC and Med-thumb uniformly and to a greater extent than the Med-index and Med-middle responses [26]. On motor NCS, the MC-biceps response may be affected, but the AX-deltoid is spared. Any needle EMG abnormalities are restricted to musculocutaneous and C6,7-median nerve-innervated muscles. Unlike with upper plexus lesions, the C5,6-axillary, C5,6-radial, suprascapular, long thoracic, and dorsal scapular nerve-innervated muscles are spared.

Posterior Cord

The posterior cord contains motor (C5–C8) and sensory (C5–C7) fibers. Its EDX assessment is provided (see Table 46.6). On sensory NCS, the superficial radial NCS assesses it. On motor NCS, the AX-deltoid and the radial motor responses (recording EIP and EDC, respectively) are useful in its assessment. On needle EMG, axillary, radial, and thoracodorsal nerve-innervated muscles are helpful. Unlike lesions of the middle plexus, posterior cord lesions do not affect the Med-index or Med-middle sensory responses or C6,7-median nerve-innervated muscles.

Medial Cord

The medial cord contains motor (C8–T1) and sensory (C8–T1) fibers. Its EDX assessment is provided (see Table 46.6). On sensory NCS, it is assessed by the Ulnar-little and MABC NCS. The dorsal ulnar cutaneous (DUC) sensory NCS also assesses this element but usually is not required. On motor NCS, the Ulnar-ADM and Median-APB motor NCS are helpful. On needle EMG, C8,T1-median and ulnar nerve-innervated muscles may be affected, but C8-radial nerve-innervated muscles (EIP, extensor pollicis brevis (EPB)) are spared.

Table 46.6 The EDX assessment of the infraclavicular plexus

Lateral cord
Sensory NCS:
LABC (100 %)
Median sensory NCS recording thumb (100 %)
Median recording index finger (100 %)
Median recording middle finger (80 %)
Motor NCS:
Musculocutaneous recording biceps
Needle electrode examination:
Biceps, brachialis, flexor carpi radialis, pronator teres
Posterior cord
Sensory NCS:
Superficial radial (100 %)
Motor NCS:
Axillary recording deltoid
Radial recording extensor digitorum communis
Radial recording extensor indicis proprius
Radial recording anconeus
Needle electrode examination:
Latissimus dorsi, deltoid, teres minor, triceps, anconeus, brachioradialis, extensor carpi radialis, extensor digitorum communis, extensor indicis proprius, extensor carpi ulnaris, extensor pollicis brevis
Medial cord
Sensory NCS:
Ulnar recording little finger (100 %)
Dorsal ulnar cutaneous (100 %)
Median recording middle finger (20 %)
MABC (100 %)
Motor NCS:
Ulnar recording abductor digiti minimi
Median recording abductor pollicis brevis
Ulnar recording first dorsal interosseous
Needle electrode examination:
Abductor pollicis brevis, opponens pollicis, flexor pollicis longus, flexor digitorum profundus (median part), adductor pollicis, abductor digiti minimi, flexor carpi ulnaris, first dorsal interosseous

The percentages shown in parentheses represent the frequency with which the sensory nerve fibers subserving the listed sensory NCS traverse the various cord elements

Terminal Nerves

Reliable NCS are available to assess the five terminal nerves of the brachial plexus, and most of the muscles innervated by these nerves are easily assessed by needle EMG. It is not possible by clinical or EDX means to differentiate a terminal nerve lesion of the brachial plexus (distal axilla) from a proximal peripheral nerve lesion.

A Practical Approach

As stated above, because most brachial plexus disorders are regional, a complete EDX assessment of the brachial plexus typically is not required. In general, we begin with the sensory NCS and perform a *general* survey – superficial radial, Med-index, and Ulnar-little sensory NCS – on all patients referred for EDX assessment of the upper extremity. Subsequent studies are dictated by the general survey findings (and the clinical diagnoses under consideration). If the superficial radial or Med-index response is abnormal, we add the LABC and Med-thumb NCS, whereas if the Ulnar-little response is abnormal, we add the MABC NCS. After the screening and added sensory NCS are performed, the lesion usually can be localized. From a clinical perspective and because our general survey does not assess the upper plexus well, we usually add the LABC and Med-thumb studies whenever a patient is referred with sensory or motor dysfunction in a C5 or C6 distribution. Likewise, we often add the MABC whenever a patient is referred with sensory or motor dysfunction in a C8 or T1 distribution.

The motor NCS are then performed to assess the underlying pathophysiology and severity, as well as to confirm the localization indicated by the sensory NCS. The motor NCS survey includes Ulnar-ADM and Median-APB studies. It is expanded based on the sensory and motor NCS findings. The needle EMG follows the NCS and is useful for further characterizing the lesion, including its chronicity and rate of progression, as well as defining its proximal extent and confirming the impression of the NCS. With intraspinal canal lesions, the preganglionic sensory and motor root fibers may be affected. Because the NCS assess the nerve fibers under study from the nerve segments located below the more distal surface recording electrodes to their cell bodies of origin, the motor NCS and needle EMG assess the intraspinal canal portions of the motor fibers, whereas the sensory NCS do not. (An exception to this statement occurs when the DRG are located within the intraspinal canal [52].) Thus, whenever there is motor response involvement with sensory response sparing at the same PNS level, there are three possibilities: (1) the lesion is preganglionic, (2) the lesion lies distal to the sensory branch takeoff site (e.g., disorders involving individual motor branches (e.g., distal neuralgic amyotrophy), terminal motor branches (e.g., early Guillain-Barre syndrome), NMJs (e.g., Lambert-Eaton syndrome, myasthenia gravis), and muscle fibers (myopathies)), and (3) when a mixed lesion is studied after motor fiber degeneration has occurred but before sensory fiber degeneration is apparent (e.g., 6–10 days post-injury).

Prognostication

Like that of all PNS lesions, the prognosis of brachial plexopathies primarily reflects the underlying pathophysiology: demyelinating conduction block or axon loss. With demyelinating conduction block, the prognosis is excellent because remyelination typically occurs within 6 weeks. With axon loss, the prognosis usually is dictated by its potential for reinnervation, which reflects three factors: (1) the grade of the injury, (2) the distance between the site of injury and the

denervated muscle fibers, and (3) the completeness of the lesion. The grade of the injury reflects the disruption incurred by the connective tissue elements of the nerve (endoneurium, perineurium, epineurium). When these structures are spared, there is no impediment to proximodistal reinnervation, and since these lesions tend to be milder, there also is no impediment to reinnervation via collateral sprouting. Conversely, with significant connective tissue involvement, proximodistal reinnervation cannot occur because the nerve fibers of the proximal stump cannot advance distally. In order for successful reinnervation via proximodistal reinnervation to occur, the distance between the lesion and the denervated muscle fibers cannot exceed 20–24 in. because axon advancement occurs at a rate of approximately 1 in. per month and muscle fibers only remain in the denervated state for 20–24 months before degenerating. Thus, distances exceeding this range are not amenable to reinnervation via proximodistal reinnervation but, rather, must be reinnervated via collateral sprouting. In order for successful reinnervation to occur via collateral sprouting, the lesion must be incomplete because with complete lesions there are no unaffected intramuscular motor fibers available from which sprouting can occur.

In summary, the best prognosis for motor recovery following axon disruption occurs when (1) the connective tissue structures are spared, (2) the distance between the lesion and the denervated muscle fibers is short, and (3) the lesion is incomplete. These statements also pertain to the sensory fibers except that there is no distance requirement because the sensory end organs do not degenerate. Repeat clinical and EDX assessments are necessary to determine if the lesion is progressing, static, or improving. Clinically, the motor assessment is more reliable in this regard because the sensory examination can improve without concomitant motor improvement (1) when the adjacent sensory nerve fibers extend into the anesthetic area, thereby diminishing its size, and (2) when sensory nerve fiber regeneration occurs without motor nerve fiber regeneration (rare) [15]. In addition, an advancing Tinel sign may reflect advancing sensory nerve fibers without accompanying motor fiber advancement and should not be used to define motor nerve fiber advancement.

Selected Site-Specific Disorders of the Brachial Plexus

Supraclavicular Plexopathies with Regional Predilection

Upper Plexus

The upper plexus is the most commonly affected region of the brachial plexus. Most of these lesions represent closed-traction injury [2, 31]. Specific brachial plexus disorders that have a predilection for the upper plexus include burner syndrome, rucksack paralysis, and classic postoperative paralysis.

Burner Syndrome (Stinger Syndrome)

An upper plexus traction injury may follow the application of sudden force to the shoulder or head when that force causes the shoulder and head to deviate away from each other. When these injuries, which are more common among males involved in contact sports, are associated with transient (minutes to hours) pain or paresthesias, the term *burner* or *stinger* is applied. Among sports-related injuries, these injuries are the most common ones encountered, accounting for 38 % of 190 injuries in one report [53]. Most sports medicine personnel recognize this syndrome and only refer the patient for evaluation when the symptoms persist or when a more severe process is suspected. Typically, the pain is sharp, burning, and of sudden onset and resolves within a few minutes. The pain and paresthesias extend distally into the upper extremity, often to the thumb. Clinically, mild sensorimotor and reflex dysfunction may be noted in an upper plexus distribution. When EDX assessment identifies abnormalities, they typically indicate an axon loss process of mild severity (i.e., a small number of fibrillation potentials present in an upper plexus distribution without NCS abnormalities). Although this constellation of EDX abnormalities could also be observed with a C6 radiculopathy that spares the paraspinal muscles, most sports medicine physicians localize the lesion to the upper plexus, thereby avoiding the debate as to whether the lesion is preganglionic (i.e., a radiculopathy) or postganglionic [31, 54, 55]. As would be expected from these EDX abnormalities, permanent neurologic injury is rare, and most sports medicine physicians allow the patient to return to the sport once the weakness has completely resolved [15]. One long-term follow-up study reported that these patients often later demonstrate pathologic fatigue following vigorous use of the previously affected limb [56].

Rucksack Paralysis

Rucksack paralysis, which is also referred to as *pack palsy* or *cadet palsy*, represents a rare upper plexus lesion that is related to wearing a rucksack or similar device (e.g., backpack, child carrier). It most likely results from nerve fiber compression related to direct pressure from the pack straps where they pass over the shoulders. Patients with rucksack paralysis typically present with painless, unilateral weakness in an upper plexus distribution that followed or started during rucksack usage. A history of transient weakness following rucksack usage may be elicited [2]. Sensory symptoms (e.g., paresthesias) in the same distribution are common. Risk factors include the weight of the load transported, the duration worn, and the device characteristics

(e.g., presence of a metal frame or waist belt) [14]. Individuals with previous local injury or an underlying abnormality (e.g., cervical rib, vertebral anomaly) may be more susceptible [57]. In approximately two-thirds of patients, the lesions are predominantly demyelinating conduction block [2]. For this reason, the sensory NCS are normal, and the abnormalities are noted on motor NCS and needle EMG, which define its severity and localization. With discontinuance of the precipitating activity, rapid recovery is expected and, therefore, treatment is conservative. In the one-third of patients with predominantly or solely axon loss, the outcome varies from no recovery to full recovery [2]. Recurrences are prevented through patient education such as the application of a waist belt to shift the majority of the weight from the shoulder straps to the hips, widening and padding the straps, and frequent rest periods with backpack removal [58].

Classic Postoperative Paralysis

Classic postoperative paralysis, which was first described by Budinger in 1894, is a traction or pressure injury that presents in the immediate postoperative setting [59]. This disorder is related to multiple variables, including patient positioning, loss of muscle tone (from anesthesia), and unconsciousness (blocks weight-shifting ability). Factors believed to predispose to this disorder include the Trendelenburg position, upper extremity abduction exceeding 90°, contralateral deviation and rotation of the head, and use of an arm board restraint in an abducted, extended, and externally rotated position [60]. Patients present with unilateral, painless weakness, with or without associated paresthesias, and the diagnosis is made based on the history and examination features. It typically is restricted to the upper plexus or, when it involves the entire supraclavicular plexus, disproportionately affects the upper plexus. When involved, the middle and lower plexuses recover quicker, ultimately leaving an isolated upper plexopathy [2, 55]. The underlying pathophysiology is the demyelinating conduction block; axon loss infrequently predominates. On EDX testing, when studied prior to remyelination, the sensory NCS are normal, the motor NCS show demyelinating conduction block lesions located between the two stimulation sites (i.e., the axilla and supraclavicular fossa) along the involved upper plexus nerve fibers (e.g., musculocutaneous, recording biceps; radial, recording brachioradialis). The axillary response, recording deltoid, may be reduced or absent, but because this motor NCS can only be recorded with supraclavicular stimulation (i.e., single-site stimulation), the pathophysiology cannot be determined. The lack of muscle atrophy and the unimpressive number of fibrillation potentials are consistent with a predominantly demyelinating process. Treatment is conservative and patients typically recover rapidly and fully [3].

Middle Plexus

The middle plexus is rarely affected in isolation. In one review of 417 brachial plexus lesions, 53 focal supraclavicular plexopathies were noted; of these, only one (surgically verified fibrosis restricted to the middle plexus) was an isolated middle plexus lesion [26]. Thus, most lesions involving the middle plexus are associated with upper plexus or lower plexus involvement, the majority of which are due to closed traction.

Lower Plexus

Among supraclavicular plexopathies, the incidence of lower plexus involvement is less than that of upper plexus involvement [55]. Although the percentage of lower plexus lesions related to closed traction is lower than that observed among upper or middle plexopathies, traction-induced avulsion injuries are more common at the lower plexus level [31]. This susceptibility reflects the lack of connective tissue tethering of the C8 and T1 spinal nerves to the transverse processes of their respective vertebral bodies following their exit from the intervertebral foramina. Because traction injuries tend to disrupt the stretched nerve fibers at their tether points, these fibers are disrupted at their connection to the spinal cord. Several disorders have a predilection for this region of the brachial plexus, including true neurogenic thoracic outlet syndrome, postmedian sternotomy brachial plexopathy, and Pancoast syndrome.

True Neurogenic Thoracic Outlet Syndrome

The thoracic outlet (actually the thoracic inlet) is defined as the body region extending from the supraclavicular fossa to the axilla and includes the area between the clavicle and the first rib (Fig. 46.1). Both neural (the brachial plexus) and vascular (the subclavian and axillary arteries and veins) elements traverse it. The term *thoracic outlet syndrome* (TOS) refers to a heterogeneous group of disorders, all of which have in common compression of one or more of these neurovascular elements at some point within the thoracic outlet. This group is divided into vascular TOS (arterial and venous), neurogenic TOS (true and nonspecific), and neurovascular TOS (traumatic) [61]. Pertinent to this discussion is *true neurogenic TOS*, also referred to as *classic TOS* and the *cervical rib and band syndrome.* This entity has a lower plexus predilection and is a rare disorder with an incidence of approximately one per million persons [51]. It more commonly affects young to middle-aged individuals, especially women, a gender predisposition that may partially be accounted for by the higher incidence of cervical ribs among females [62]. Overall, however, the presence of a cervical rib does not increase the risk for true neurologic TOS significantly. Based on the reported incidences of cervical ribs and true neurogenic TOS, for every 20,000–80,000 individuals with a cervical rib, only one will have true neurogenic TOS [62].

The pathogenesis of true neurogenic TOS was first reported in 1903 by Thomas and Cushing, who described angulation and stretching of the inferior elements of the supraclavicular brachial plexus by a taut fibrous band extending from the first thoracic rib to a bony anomaly at the C7 level, either a small (rudimentary) cervical rib or an elongated transverse process [63]. The site at which the band affects the brachial plexus usually is along the distal portions of the C8 and T1 APR or, less commonly, at the proximal aspect of the lower trunk [64]. In addition, a single case with clinical manifestations similar to those observed in true neurogenic TOS – but without radiologic evidence of either a cervical rib or an elongated transverse process – was reported in a competitive swimmer in whom the lower trunk was compressed by a fibrous band located within a hypertrophied scalene muscle (this even rarer disorder is referred to as scalenus anticus syndrome) [65]. Anatomically, when the lower plexus fibers are angulated and stretched from below, the T1 fibers, which lie inferior to the C8 fibers, are angulated and stretched more profoundly and, consequently, sustain greater injury [51, 64]. This difference in the severity of involvement of the T1 and C8 APR has profound effects on both the clinical and the electrodiagnostic examinations [26, 62]. With rare exception, the motor abnormalities are more pronounced than the sensory ones, and for this reason, most patients present with a chief complaint of hand muscle atrophy, weakness, or progressive loss of dexterity [51]. On motor examination, upper extremity weakness and wasting in a lower trunk distribution are apparent. Because the thenar eminence muscles are innervated primarily by motor nerve fibers derived from the T1 spinal cord segment, they are more affected than the ulnar nerve-innervated hypothenar muscles, which, in turn, show more involvement than the medial forearm muscles. The sensory examination shows abnormalities in the C8 and T1 distributions (typically patchy) that are either more pronounced in the T1 distribution or equally pronounced in these two distributions. In retrospect, most patients acknowledge a long history of intermittent, mild, upper extremity aching pain and paresthesias along the medial aspects of the arm and forearm and, to a lesser degree, the hand. On EDX examination, this same pattern of T1 involvement exceeding C8 is more easily demonstrated and is essentially pathognomonic [3, 26]. The MABC SNAP (often unelicitable) and median CMAP, recording thenar eminence (usually very low in amplitude), are affected to a greater extent than are the ulnar sensory and motor studies because the former two studies primarily assess the T1 fibers of the lower plexus, whereas the latter two studies primarily assess its C8 fibers [26, 49, 50]. On needle EMG, features of a slowly progressive axon loss process are observed. As expected, the latter have a lower plexus distribution and are most prominent in the more heavily T1-innervated thenar eminence muscles. The chronic changes (e.g., increased duration, neurogenic MUAP firing pattern) involve all of the median and ulnar nerve-innervated hand muscles as well as the flexor pollicis longus, ulnar forearm muscles, and, depending on the degree of C8 APR involvement, the C8-radial nerve-innervated muscles (e.g., EIP, EPB). Because of the slowly progressive nature of this disorder, maximal reinnervation via collateral sprouting has already occurred, and consequently, fibrillation potentials are sparse in number and may be restricted to the thenar eminence muscles. Since the fibrous band compressing the brachial plexus is radiolucent, it cannot be reliably visualized by plain films or CT imaging. MRI may identify brachial plexus distortions, but it does not reliably identify the responsible band [66–68]. Although the bony anomalies associated with this condition are reliably identified by plain films of the neck, special views are occasionally required [68]. When the bilateral cervical ribs are identified, the smaller rib is usually on the symptomatic side [69].

Because maximal reinnervation has already occurred, patients are not treated conservatively. Rather, true neurogenic TOS is electively treated by surgical sectioning of the fibrous band. Because the band affects the supraclavicular portion of the brachial plexus elements, a supraclavicular approach is better than a transaxillary one, which is not only too distal but also provides inadequate anatomic visualization. The distal portion of the bony anomaly may also be removed, but the normal first thoracic rib should be left in place, as should the ipsilateral scalene muscles [31, 62, 64]. Following division of the band, the affected nerve fibers are no longer angulated and stretched, and typically, the aching pain and intermittent paresthesias and dysesthesias resolve and the hand weakness and loss of dexterity stop progressing. Because of the limitations of reinnervation (collateral sprouting has already been maximized and reinnervation via proximal-distal advancement is impossible due to the distance between the lesion and the denervated hand muscle fibers), motor improvement of hand function is unexpected. The more proximally located forearm muscles may show some improvement if the disrupted motor nerve fibers can traverse the lesion site, which depends mostly on the degree of connective tissue formation impeding their advancement.

Postmedian Sternotomy Plexopathy

This condition follows operations that require median sternotomy [70], the most frequent of which is coronary artery bypass surgery [71]. The clinical and EDX manifestations of this lower plexopathy indicate that it involves the C8 APR in isolation or disproportionately [3]. Etiologic proposals implicate a lower plexus traction injury that is related to the first thoracic rib. Either chest wall retraction pushes the clavicle into the retroclavicular space, thereby rotating the first thoracic rib into the C8 APR, or chest wall retraction fractures the first rib (the more likely possibility), which, in turn, damages the lower plexus fibers [70, 72, 73]. Because the C8

APR contains sensory fibers destined solely for the ulnar nerve, patients with C8 APR lesions present with paresthesias in an ulnar nerve distribution and, for this reason, mimic a postoperative ulnar neuropathy at the elbow. When the true nature of this disorder goes unrecognized, it may be misattributed to operative malpositioning and inappropriately blamed on the anesthesiologist. In addition, the patient may undergo unnecessary operative intervention of the ulnar nerve at the elbow segment. Because the motor fibers contained within the C8 APR supply the radial and median nerves, in addition to the ulnar nerve, mislocalization usually is avoidable by thorough clinical assessment of the C8-radial (e.g., extensor indicis proprius, extensor pollicis brevis) and C8-median (e.g., flexor pollicis longus) muscles. An incomplete EDX study may also mislocalize the lesion to the ulnar nerve because, on sensory NCS, an absent or low-amplitude Ulnar-little response is essentially always observed. However, low-amplitude Ulnar-D5 responses are also observed with medial cord, lower plexus, and C8 APR lesions. Thus, the MABC sensory NCS should also be performed. It is spared with ulnar and C8 APR lesions. In the setting of medial cord or lower trunk lesions producing a low-amplitude or absent Ulnar-little response, it usually is affected [26, 49, 50]. On motor NCS, isolated ulnar CMAP response abnormalities are commonly needle EMG, which is the most important portion of the EDX assessment for lesion localization, typically demonstrates involvement of C8-radial nerve-innervated muscles (e.g., extensor indicis proprius, extensor pollicis brevis), thereby excluding an ulnar neuropathy and localizing the lesion to, at, or proximal to the lower trunk. Because the median nerve-innervated thenar eminence muscles are more heavily innervated by T1-derived motor fibers, the C8-median nerve-innervated muscles (e.g., flexor pollicis longus) often are spared or affected to a lesser degree than the affected ulnar nerve-innervated muscles. When the needle EMG study is performed early, in addition to fibrillation potentials, discordance between the CMAP size (e.g., normal to near normal) and the MUAP recruitment pattern (neurogenic) indicates a demyelinating conduction block pathophysiology [47, 55]. Even with predominantly axon loss lesions, because the lesion tends to be incomplete, reinnervation via collateral sprouting readily occurs. Consequently, these lesions do not benefit from surgical interventions (e.g., first rib removal) and typically are treated conservatively (unless significant axon loss involves the dominant limb or causalgic pain develops) [3, 31, 55].

Pancoast Syndrome

The direct extension of cancer from the lung apex to the lower plexus and the clinical features associated with such an extension were reported by Pancoast in 1924 [74, 75]. Apical lung cancer, which constitutes 3 % of all lung cancer, frequently involves the lower plexus because only the pleural lining of the lung separates it from the lower plexus. Although Pancoast syndrome most frequently accompanies bronchogenic carcinoma, accounting for its higher incidence among middle-aged to elderly males with heavy smoking histories, it may occur with any disorder of the thoracic inlet, including other tumors (both benign and malignant), tumor recurrences, and infectious and inflammatory disorders [76]. Unlike most lung cancers, apical lung cancers are slow growing, predominantly extrapulmonary, locally aggressive, and radiosensitive and infrequently metastasize. Typically, the initial and most pronounced clinical feature is severe, unrelenting shoulder pain that is characterized as burning or boring and that is worse at night, typically interfering with sleep. It tends to extend into the axilla and along the medial aspect of the arm to the elbow level (T2); less frequently, it also involves the medial aspects of the forearm (T1) and hand (C8). This shoulder pain may reflect pleural, lower plexus, rib, or spinal column involvement. When the superior mediastinum or posterior primary rami become involved, medial scapular pain may also appear [77]. The pain quickly becomes dysesthetic [78]. As expected, the associated weakness and sensory loss are in a lower plexus distribution. Involvement of the T1 root or the inferior cervical sympathetic ganglion leads to Horner syndrome (miosis, facial anhidrosis, and ptosis). Other reported clinical features include supraclavicular fullness, venous distension, upper extremity edema, and bone destruction of the upper thoracic ribs and, less often, the adjacent vertebral bodies [75, 79]. Diagnosis usually is by tissue procurement following imaging studies that often were ordered following EDX studies that localized the lesion to the lower plexus. Many patients with this syndrome will demonstrate fibrillation potentials in the paraspinal muscles (lesion is at or proximal to the posterior primary ramus takeoff site) and abnormal sensory responses (lesion is ganglionic or postganglionic), indicating a two-level lesion. Therapy is directed toward the underlying cause. Narcotics and radiation therapy may be required when the pain is severe [76, 80]. It is important to be familiar with this syndrome because it often is the first manifestation of an underlying neoplasm and early recognition and treatment are associated with a higher cure rate [81].

Other Supraclavicular Plexopathies

Root Avulsions

Root avulsions, which follow high-energy traction (stretch) injury, represent one of the most devastating types of brachial plexus injury because the disrupted nerve fibers are unable to spontaneously regenerate and are not amenable to surgical repair. For these two reasons, they result in irreversible loss of function. Root element susceptibility to this type of injury reflects lack of a connective tissue covering and a

spinal cord anchorage point. Of the five roots comprising the brachial plexus, the upper two are more susceptible to traction-induced extraforaminal rupture, whereas the lower two are more susceptible to traction-induced avulsion. This reflects differences in their sites of proximal anchorage, their angles of exit from the intervertebral foramina, and their lengths. Anatomically, connective tissue securely anchors the C5 and C6 spinal nerves as they pass through a groove in the transverse process located between the intertransversalis muscles; it variably anchors the C7 spinal nerve and typically does not anchor the C8 and T1 spinal nerves. For this reason, traction injuries, which tend to disrupt nerve fibers at their anchorage sites, have a tendency to disrupt the C5 and C6 nerve roots at their transverse process attachment sites (i.e., extraforaminal disruption) and to disrupt the C8 and T1 nerve roots at the spinal cord (i.e., avulsion). Additionally, the oblique angle of the upper cervical roots also favors extraforaminal disruption over avulsion, whereas the short length of the T1 nerve root favors avulsion [22]. Overall, because they are of lesser caliber, have thinner dural sacs, and are more dispersed along the spinal cord, the ventral roots are more easily avulsed than the dorsal ones [82]. Another important variable is the position of the upper extremity at the moment that the traction force occurred. When the upper extremity is alongside the torso, the C5 and C6 roots are most susceptible, whereas the C8 and T1 roots are most susceptible when it is located above the shoulder; the greatest susceptibility for the C7 root occurs when it is parallel to the ground. Thus, it is important to document the position of the head, neck, and arm at the time of the traction injury, if possible. However, in the setting of strong traction forces, all of the roots may be avulsed regardless of limb position, although limb position still contributes to the order of the avulsions. Approximately 15 % of these lesions involve both preganglionic and postganglionic components (i.e., they are two-level processes), especially when the upper two cervical roots are involved [22]. The suprascapular, musculocutaneous, and axillary nerves may also be disrupted at their anchorage sites (the suprascapular or spinoglenoid notch, the coracobrachialis muscle, and the quadrangular space, respectively). In addition to sensory loss or weakness in the distribution of the disrupted nerve root, severe pain (often involving the hand) is common, the incidence of which increases with the number of involved nerve roots [15]. It typically is described as a relatively constant burning or crushing discomfort with superimposed, episodic, much more pronounced, shock-like pain of short duration. Avulsion pain tends to be lessened by warming and worsened by cooling [2, 20, 21, 57, 83]. Other clinical features associated with avulsion injuries include bony injuries (especially transverse process fractures), long tract signs (associated with more severe trauma), severe burning pain, shooting pain in the anesthetic area, the presence of Horner syndrome, scapular winging, and asymmetrical chest wall excursion (the long thoracic and phrenic nerves are formed at the APR level and indicate a more proximal lesion) [3, 57]. Following avulsion of the spinal root from the spinal cord, spontaneous proximodistal axon regeneration cannot occur. Although some surgeons attempt to reinsert the avulsed root fibers back into the spinal cord, the utility of this approach has not been confirmed [21, 84]. Salvage procedures have been performed utilizing neurotization, a technique in which the avulsed brachial plexus element is reattached proximally, but not to its original source. Instead, it is reattached to the proximal stumps of different plexus elements that remain in continuity with the spinal cord or to extraplexal nerves following their intentional transection (e.g., ipsilateral spinal accessory, phrenic, or intercostal nerves). In this manner, a specific function can be restored, typically forearm flexion. A more recent procedure to restore shoulder or forearm flexion function is contralateral C7 nerve root transfer; however, significant donor site morbidity has been described using this method [85]. Although good outcomes have been reported with bypass coaptation of the C3 and C4 APR (distal to their contribution to the phrenic nerve) to the upper and lower trunk of the brachial plexus, this technique requires further assessment before being routinely employed [86]. The Oberlin procedure involves transfer of a nerve fascicle to the flexor carpi ulnaris muscle from the ulnar nerve to the musculocutaneous nerve with reports of elbow flexion strength obtained in nearly 90 % and should be considered in patients who have suffered nerve root avulsion in the upper plexus distribution [87]. Several reconstructive orthopedic procedures are also available (e.g., tendon transfers, shoulder orthodeses). The feasibility of these approaches varies inversely with the number of brachial plexus roots avulsed. Another major issue is the alleviation of the associated root avulsion pain, which is notoriously difficult to accomplish. Analgesic agents, including neuropathic pain medications, seldom provide substantial or sustained relief. Transcutaneous nerve stimulation, sympathectomy, stellate ganglionectomy, amputation of the flail limb, and anterolateral high cordotomy are ineffective. Epidural-placed spinal cord stimulation is being explored as a potential treatment for this pain as well. When C8 and T1 root avulsions coexist with C5–C7 plexus fiber ruptures, repair of the ruptures may diminish the pain. The DREZ operation, which consists of coagulation of the dorsal root entry zones of the avulsed roots, is the most helpful surgical procedure of all but has enough associated risk that some surgeons are reluctant to perform it [15, 84].

Obstetric Brachial Plexopathy

Obstetric brachial plexopathy, which is the most common cause of arm paralysis in the neonatal period, is another supraclavicular plexopathy that follows traction injury. Shoulder dystocia, which is the most common risk factor for obstetric

brachial plexopathy, is defined as anterior shoulder impaction behind the maternal symphysis pubis that requires obstetric maneuvers to affect vaginal delivery. When lateral traction on the head is used to free the shoulder, obstetric brachial plexopathy may result [88, 89]. Its incidence, which appears to be declining, ranges from 0.4 to 4.0 per 1,000 full-term live births [14, 89, 90]. In addition to shoulder dystocia, other reported risk factors include infantile macrosomia (birth weight greater than 4 kg), short mothers, maternal obesity, multiparity, ethnic background, uncommon fetal presentations (e.g., breech, face), second-stage labor exceeding 1 h, low or midforceps delivery, vacuum extraction, passive head rotation with the shoulders fixed, and delivery of a previous infant with this disorder [3]. Of these, shoulder dystocia and infantile macrosomia are the two major risk factors, and consequently, fetal growth restriction and prematurity are protective [3, 91]. In about 50 % of cases, there is no recognizable risk factor [92]. With breech deliveries, there is an increased risk of bilateral involvement and of avulsion injury (usually the C5 and C6 roots, less commonly the C5–C7 roots) [93]. Importantly, because obstetric brachial plexopathy also follows delivery by cesarean section, this disorder cannot simply be attributed to poorly performed deliveries [3, 94]. An *in utero* onset is further supported by the presence of fibrillation potentials and MUAPs with chronic neurogenic changes on EDX studies performed shortly after delivery. Other disorders must also be considered, including congenital root absence, congenital constriction band syndrome, brachial plexus neoplasms, humeral osteomyelitis, neonatal hemangiomatosis, exostoses of the first thoracic rib, congenital varicella, cerebellar disorders, and cervical osteomyelitis with paracervical abscess with unilateral presentations; amyoplasia congenita and cervical spinal atrophy are considerations with bilateral presentations [15].

Five patterns of nerve fiber involvement have been reported: (1) C5–C6, (2) C5–C7, (3) C5–T1 with some finger flexion sparing, (4) C5–T1 with flail arm and Horner syndrome, and (5) C8–T1 [89]. The C5–C6 pattern (*classic Erb's palsy*) is the most common form, comprising about 50 % of these injuries, and generally has the best prognosis. The C5–C7 pattern (*Erb's-plus palsy*, 25–35 %) results in the waiter's tip position (adduction and internal rotation of the arm, extension and pronation of the forearm, and wrist and finger flexion) and has an intermediate prognosis. The C8–T1 pattern (*Klumpke palsy*) is almost never seen [95]. Concomitant postganglionic lesions are more common with C5–C7 fiber involvement (extraforaminal connective tissue anchoring), whereas avulsion is more common with C8–T1 fiber involvement (spinal cord anchoring) [33].

Obstetric plexopathies are diagnosed by the clinical features. The inability of the infant to cooperate with the EDX study limits its utility in determining the extent, pathophysiology, and severity of the underlying lesion. Among the available neuroimaging studies, MRI is considered the modality of choice, especially when modifications specific to the needs of the infant are available (e.g., phased-array surface coils custom built for infants). Despite their initial description in 1764, the management of these lesions is somewhat controversial [96]. Although, there is a tendency for this type of traction injury to be less severe than that observed among adults, the outcome reflects a number of factors, including the degree of connective tissue disruption, the distance between the lesion site and the denervated muscles, the completeness of the lesion, whether the lesion involves both preganglionic and postganglionic elements (i.e., a two-level process), and the presence of avulsion injury. Because of the higher incidence of avulsion injury and the distance between the lesion site and the denervated muscles, the outcome tends to be the worst for those with C8–T1 fiber involvement [3]. Although many reports suggest that spontaneous recovery occurs in over 90 % of patients with obstetric brachial plexopathy, two Swedish studies of patients not undergoing surgical intervention reported significant impairment in later life among 20–25 %, an outcome that has been corroborated by more recent reports [89, 97–101]. Although remyelination may contribute to early recovery in those individuals with a demyelinating component, spontaneous recovery does not follow avulsion injury. Thus, the primary focus is in determining if operative intervention is required and, if so, at what point it should be performed. Because there are no clinical or EDX assessments capable of distinguishing patients destined to have spontaneous recovery from those who will become significantly impaired, most patients undergo an initial period of watchful waiting with interventions to prevent contractures, pressure ulcers, and further traction injury [102]. If antigravity forearm flexion strength has not returned by 6 weeks of age, surgical referral is indicated because some of these neonates will require microsurgical intervention for avulsion and rupture injuries and these are best performed by 3 and 6 months, respectively [90]. Even with less severe injuries, most groups agree that the observation period should not extend beyond 3–6 months, although some groups operate as late as 9 months [33, 90]. Physical rehabilitation – to maintain range of motion, prevent glenohumeral joint deformity as the child grows, and maximize function – is always indicated and is started within the first 7–10 days of life and continued until the injury has recovered [91].

Infraclavicular Plexopathies with Regional Predilections

The regional proclivity of infraclavicular plexopathies is much lower than that of supraclavicular lesions. At the cord level, axillary lymph node irradiation tends to involve the

infraclavicular plexus, especially the lateral cord, whereas the medial cord is more susceptible to injury in the setting of midshaft clavicular fractures [3]. At the terminal nerve level, medial brachial fascial compartment syndrome has a predilection for the median terminal nerve, crutch palsies more frequently involve the radial terminal nerve, procedures in the vicinity of the coracoid process more frequently affect the musculocutaneous terminal nerve (e.g., operative procedures to correct anterior shoulder dislocations), and proximal humerus fractures and glenohumeral dislocations more frequently affect the axillary terminal nerve [3].

Medial Brachial Fascial Compartment Syndrome

The medial brachial fascial compartment syndrome was first described in 1966 by Staal et al. [103]. This compartment, which extends from the clavicle to the elbow, is formed by the medial intermuscular septum following its division into two fascial extensions, both of which extend to the brachial fascia surrounding the arm. It contains the axillary blood vessels and the five terminal nerves of the brachial plexus. The latter exit this compartment in the following order: musculocutaneous, axillary, radial, ulnar, and median. Intracompartmental vascular disruptions (e.g., penetrating injuries from gunshot or stab wounds, cannula insertion during percutaneous axillary arteriography, axillary artery penetration during local anesthetic injection, spontaneous bleeding in the setting of a blood dyscrasia or anticoagulation) produce mass effect (e.g., hematomas, aneurysms, and pseudoaneurysms) and increase the intracompartmental pressure, thereby impeding the nerve fiber microcirculation without causing overt signs of large-vessel occlusion distally. Of the five nerves contained within this compartment, the median nerve characteristically is the first to be affected, the most severely affected, and the most frequently affected in isolation. The ulnar or radial nerve rarely is affected in isolation [104, 105]. Concomitant involvement of the median and ulnar nerves represents the most common two-nerve combination [105]. The radial, axillary, and musculocutaneous are the least frequently affected nerves. It may be that the nerves nearest the lesion (e.g., the hematoma) are exposed to the greatest pressure and manifest the most impaired microcirculation [106]. For example, with axillary arteriogram-related medial brachial fascial compartment syndrome, because the median and ulnar nerves lie near the axillary artery at its point of cannulation, the local formation of a hematoma may account for the higher incidence of involvement of these two nerves. Another possibility is that because they are the last two nerves to exit the compartment, longer lengths of nerve are affected. Clinically, pain and paresthesias develop in the distribution of the affected nerves, followed by weakness in the same or a more widespread distribution. Without prompt recognition and surgical decompression, the likelihood of recovery is poor. In one study, complete recovery was 8.3 times more likely when surgical intervention occurred within 4 h of symptom onset [107]. Thus, it is imperative to recognize this disorder early. In the setting of obvious trauma, recognition usually is straightforward. However, in the setting of iatrogenic injury, symptom-free intervals of up to 2 weeks have been described, making misdiagnosis or delayed diagnosis much more common [2, 55, 104, 105]. EDX testing has no role in the early diagnosis of these patients.

Selected Site-Nonspecific Disorders of the Brachial Plexus

Neuralgic Amyotrophy (Parsonage-Turner Syndrome)

Among the many titles applied to this disorder, *neuralgic amyotrophy* best conveys its two most important clinical features: severe pain and muscle wasting. Neuralgic amyotrophy is a multifocal, inflammatory disorder of the PNS that most commonly involves the forequarter region of the body and that is believed to be immune-mediated. It affects individuals of any age but is uncommon during the first decade of life and is somewhat more common among males. In one series of 281 patients, the average age was 41.4 years, approximately 70 % of patients were male, and 80 % presented unilaterally (the dominant limb was involved 60 % of the time) [108]. Neuralgic amyotrophy has a predilection for purely or predominantly motor nerves. For this reason, the long thoracic, suprascapular, axillary, and musculocutaneous nerves are most susceptible proximally, whereas, more distally, the anterior and posterior interosseous nerves and motor nerve branches innervating individual muscles (e.g., the motor branch to the pronator teres) are most susceptible [108, 109]. Less commonly, extraplexal motor nerves are involved, including the spinal accessory, phrenic, and recurrent laryngeal nerves, as well as other forequarter nerves composed predominantly of motor nerve fibers. The major upper extremity nerves – radial, median, and ulnar – are involved less frequently due to their mixed (sensory and motor) composition. Pure sensory nerves are rarely involved. Among the latter, the LABC nerve has the highest incidence of involvement [108, 109]. When the LABC nerve is significantly involved (very low amplitude or absent response) without clinical or EDX evidence of motor fiber involvement (normal brachialis and biceps on needle EMG), it is likely involved distal to its takeoff from the musculocutaneous nerve. In our series of 703 individual lesions, only 18 involved a pure sensory nerve: 15 LABC, 1 MABC, 1 superficial radial, and 1 median digital branch [108]. It is most often unilateral in distribution; when bilateral, it may involve the two sides sequentially (more common) or simultaneously and may be symmetric or asymmetric. Although

most affected individuals only have a single bout, patients are infrequently encountered who have had multiple bouts. When it recurs in a previously affected limb, it may involve the same or different nerves [2, 15]. The pathophysiology of these lesions usually is axon loss but, on occasion, patients are encountered who recover so quickly (e.g., several days) that the underlying pathophysiology must have been predominantly demyelinating conduction block. Clinically, most patients present with excruciating, sudden-onset, shoulder pain that commonly has a nocturnal onset and either awakens the patient or is present immediately upon awakening (*neuralgic*). The shoulder pain usually reaches its maximum intensity quickly and most commonly is located laterally. Pain may also be noted over the involved nerve – lateral shoulder pain with axillary nerve involvement, posterior scapular region pain with suprascapular nerve involvement, superolateral thoracic pain with long thoracic nerve involvement, antecubital fossa pain with anterior interosseous nerve involvement, and lateral arm or forearm pain with musculocutaneous nerve involvement. The pain typically resolves within a few weeks or is replaced by dull aching pain. Paresthesias may also be present, but numbness is less common. As the pain abates and the patient is able to move the affected limb, weakness and obvious atrophy become apparent (*amyotrophy*). Approximately 75 % of affected individuals report an antecedent event (trigger), such as a recent flu-like illness, medical illness, invasive medical or dental procedure, unaccustomed exertion, recent trauma, vaccination, and childbirth [110]. In one study of 268 bouts of neuralgic amyotrophy, a trigger preceded 196 (73 %): operative or medical procedure (57), recent illness (48), excessive or unaccustomed activity (34), closed trauma (19), childbirth (13), dental procedure (11), vaccination (10), and open trauma (4) [110]. There typically is a delay between the trigger occurrence and the onset of pain. The time interval ranges from a few hours to 30 days, but most commonly does not exceed 7 days. In one study of 268 bouts of neuralgic amyotrophy, the time interval between the identified trigger and the onset of pain ranged from 1 to 28 days but within over two-thirds of patients occurs within 1 week [110]. There also typically is a delay between the onset of the shoulder pain and the recognition of the atrophic weakness. This time interval likely reflects lack of awareness related to limitations imposed by the pain (most patients splint the upper extremity against the chest). About 50 % of patients have only a single nerve involved (i.e., a *mononeuropathy*) and 50 % have involvement of two or more nerves [108]. When patients present with involvement of only a single nerve, neuralgic amyotrophy may not be considered and the diagnosis missed. When patients present with involvement more than one of the proximal nerves listed above, the lesion may be mislocalized to the upper plexus. Imaging studies frequently are utilized to exclude other possibilities (e.g., rotator cuff test, acromioclavicular joint separation), especially initially when the pain limits accurate examination or in the setting of a mononeuropathy. EDX studies reliably establish the distribution of the muscle involvement, often identifying abnormalities not clinically apparent, including contralateral ones. When more than one nerve is involved, EDX assessments typically identify the lesion as a multiple mononeuropathy rather than a focal brachial plexopathy. In one series of 703 lesions, only four were localized to the brachial plexus [108]. Accurate diagnosis helps protect the patient from unnecessary surgical procedures (e.g., cervical spinal column surgery, rotator cuff repair, nerve release). For example, when a patient with neuralgic amyotrophy presents with severe posterior shoulder pain related to a suprascapular mononeuropathy and the consulting physician, unfamiliar with this presentation of neuralgic amyotrophy, diagnoses the patient with suprascapular nerve entrapment, the patient may undergo an unnecessary release procedure. This scenario may account for the reason that the suprascapular nerve is the most commonly affected nerve overall but is second to the long thoracic nerve when only mononeuropathies are tabulated [108]. In addition, recognition and accurate diagnosis prevent unjustified medical malpractice claims. Unfortunately, a large majority of these claims are filed against physicians who may be unaware of this entity (e.g., anesthesiologists, surgeons).

Treatment consists of analgesics (including narcotics), often with a short course of corticosteroids, for the initial severe pain while awaiting more chronic neuropathic pain medications (e.g., tricyclic and antiepileptic agents) to take effect. Like other PNS lesions associated with significant muscle weakness, strengthening and stretching exercises are indicated. Tsairis et al. reported recovery rates of 36 % by 1 year, 75 % by 2 years, and 89 % by 3 years [111]. However, because of the multifocal nature of this disorder, we have found it more reliable to prognosticate the lesions individually using completeness of the lesion and the distance between the lesion and the denervated muscle fibers as guidelines. Unlike sporadic neuralgic amyotrophy, the hereditary form has a younger onset age, typically recurs, and is associated with dysmorphic features (e.g., hypotelorism, syndactyly, high-arched palate) and septin 9 gene mutations [3, 112–118].

Neoplastic Brachial Plexopathies

Although cancer is a leading cause of death in the USA, neoplastic plexopathies are uncommon, occurring in only 1 % of cancer patients [76]. Of the four primary PNS plexuses, they most commonly involve the brachial plexus and account for 15 % of all brachial plexus lesions [80]. In 1969, Harkin and

Reed pathologically detailed and classified peripheral nerve tumors, and in 2000, the World Health Organization classified peripheral nerve tumors into four groups: (1) neurofibromas, (2) schwannomas, (3) perineuriomas, and (4) malignant neural sheath tumors (NSTs); the latter are also referred to as neurogenic sarcomas [119, 120]. Neurofibromas are further divided into discrete and plexiform (involvement of multiple nerve fascicles) types. Another approach divides these tumors into four groups based on their cell of origin and malignancy status: (1) benign NSTs, (2) malignant NSTs, (3) benign non-NSTs, and (4) malignant non-NSTs (i.e., all malignant tumors of extraplexal origin that invade the plexus by either direct extension or metastasis). Perhaps the simplest approach, and the one used in this chapter, divides these tumors based on whether they originate from the plexus itself (primary) or from outside of it (secondary invasion via metastasis or direct extension) and on their malignancy status (benign versus malignant), resulting in four categories: primary and secondary neoplastic plexopathies that are then further divided into benign and malignant categories. Because the clinical management of patients with sporadic neurofibromas differs from those with neurofibromatosis type 1 (NF1), these two types must be considered separately. Neoplastic processes may also affect plexus fibers indirectly, such as by compression, infection (e.g., related to immunosuppression), or ischemia (e.g., leukemic infiltration) [80]. Accurate diagnosis is important because when neoplastic plexopathies are misattributed to orthopedic or other neuromuscular disorders, diagnostic delays result that adversely affect outcome and quality of life. Because of the wide diversity of neoplastic plexopathies, treatment plans must be individualized based on etiology, location, tumor aggressivity, sensitivity to radiation therapy and chemotherapy, degree of involvement of adjacent structures, and general health and wishes of the patient, as well as the treatment goals (e.g., cure, restoration of function, symptom relief, palliation, cosmetic improvement). In general, most nonmetastatic lesions are treated surgically. With benign lesions, intralesional incisions (visible tumor remains) or marginal excisions (includes surrounding capsule or reactive zone) are usually applied, whereas malignant lesions usually require wide resection with a cuff of normal tissue or radical resection (removal of entire anatomical compartment). Chemotherapy and radiation therapy serve adjunctive roles.

Primary Neoplastic Brachial Plexopathies

Most primary neoplastic plexopathies derive from the nerve sheath (nerve sheath tumors, NSTs), with benign lesions outnumbering malignant ones [121–123]. Most benign NSTs are solitary paraneural schwannomas or intraneural neurofibromas that involve the proximal aspects of the upper or middle plexus. Solitary schwannomas are slow-growing, encapsulated tumors that have a peak incidence in the fourth and fifth decades and that more commonly involve the upper plexus. Although schwannomas are more frequent among women, when they involve the brachial plexus, their sex distribution is more uniform [20, 121, 123, 124]. When they grow through the neural foramen and expand at both ends, they are dumbbell-shaped [119]. Rarely, schwannomas are multiple, undergo malignant transformation, or occur in NF1 patients [125]. Among non-NF1 patients, neurofibromas usually are sporadic, solitary, nonencapsulated tumors that originate from the neural sheath, are more common on the right, are more common among females, have a low risk of malignant degeneration, and involve the supraclavicular plexus nearly twice as often as the infraclavicular one (most frequently the upper and middle plexuses) [20, 121–123]. The incidence of neurofibromas is higher among the NF1 population because defective neurofibromin (a protein product with a role in tumor suppression) predisposes to neurofibroma formation [126, 127]. Among NF1 patients, neurofibromas more frequently are multiple and plexiform, do not have a regional plexus predilection, have a higher risk of malignant degeneration (5–10 %), and more frequently recur following excision [31, 33]. Only 10 % of patients presenting with solitary neurofibromas have NF1 [128]. Benign non-NSTs include desmoids tumors, lipomas, hamartomas, ganglioneuromas, myoblastomas, lymphangiomas, myositis ossificans, osteochondromas, and vascular tumors (e.g., venous angiomas, hemangiopericytomas, glomus tumors, hemangioblastomas) [76]. Most patients with benign NSTs present with painless palpable masses that overlie the course of a nerve, often with associated paresthesias, that occur spontaneously or are precipitated by movement or percussion (i.e., Tinel sign). Their mobility tends to be greater laterally than longitudinally. Associated sensorimotor deficits are more common with neurofibromas (intraneural) than with schwannomas (paraneural). Unlike non-NF1 patients, the neurofibromas associated with NF1 are larger, are more frequently multiple, do not show a gender bias, are noted roughly two decades earlier, involve the brachial plexus more diffusely, have a much higher rate of malignant degeneration (15 %), and are more frequently plexiform [20, 122, 123]. Plexiform neurofibromas, which may produce overlying soft tissue hypertrophy or skin hyperpigmentation, are virtually pathognomonic for NF1, are seen in up to 44 % of NF1 patients, and are locally invasive because they lack a capsule and thus are able to grow along tissue planes [80]. NF1 patients may also demonstrate café au lait spots, axillary or inguinal freckling, or Lisch nodules (iris hamartomas) on general examination. Bony dysplasia and optic gliomas are other features associated with NF1. The evaluation of patients with plexus region masses is discussed below. The treatment of benign NSTs usually is conservative when there is no associated neurological dysfunction, pain, disfigurement, or suspicion of malignancy. Surgical excision generally is

employed in the presence of one of these features. Schwannomas typically are excised without neurologic deficit or recurrence because they are well encapsulated and do not arise from the fascicle. With neurofibromas, intraoperative EDX studies are useful to identify the nonfunctioning fascicles so that they can be excised with the parent fascicle (always nonfunctioning) and tumor. Although neurologic deficits are uncommon following excision, the risk is greater for NF1 patients than for non-NF1 patients [121, 122]. The likelihood of incomplete resection and postoperative deficits is increased with plexiform fibromas because of their poor delineation, increased vascularity, and infiltrative nature [122, 129, 130]. Nerve grafting may be required when nerve function cannot be preserved. When symptoms of sarcomatous transformation (new deficits, localized swelling, intractable pain) develop in patients with long-standing or plexiform neurofibromas, immediate MRI is required to look for evidence of malignant transformation (e.g., inhomogeneous intratumoral enhancement) [127]. Palliative treatment is indicated for regionalized neurofibromatosis (a condition in which hundreds of smaller neurofibromas are present above and below the parent tumor and, occasionally, along other nerves of the limb) [129]. With benign non-NSTs growing extrinsic to their parent fascicles without epineurial adherence (e.g., intraneural lipomas), epineurotomy and excision usually can be performed without further neurologic deficit [131]. Malignant NSTs, which account for 10 % of sarcomas, are rare (incidence of 0.001 %, approaches 5 % among NF1 patients), do not demonstrate a gender bias, and originate from Schwann cells (especially at the myelination transition zone where oligodendrocytes and Schwann cells abut) or from pluripotent neural crest cells [132–134]. Most arise de novo or through the malignant transformation of a plexiform neurofibroma, less commonly from an intraneural neurofibroma, and rarely from a schwannoma [119, 135, 136]. They spread via direct extension or blood-borne metastasis [76]. Because half of these tumors occur among NF1 patients, NF1 is the greatest risk factor for their development. Overall, NF1 patients have a 2–10 % cumulative lifetime risk. Moreover, NF1 patients tend to present one to two decades earlier and have a 10–15-year life expectancy reduction [135, 137, 138]. The second greatest risk factor for malignant NST occurrence is previous radiation therapy (about 11 % of cases), which demonstrates a latency period of 4–41 years (average, 15 years) [139, 140]. Malignant NSTs are much more aggressive, and patients usually present with painful, rapidly growing masses and progressive neurologic deficits. Early and aggressive treatment with wide tumor margins or amputation yields improved disease-free survival [141]. Resectability is primarily a function of location and ranges from around 20 % (for paraspinal tumors) to about 95 % (for extremity tumors). Neural sacrifice usually is unavoidable, and unfortunately, nerve grafting usually cannot be performed due to the length of nerve resected and the adverse effects of radiation therapy on graft tissue [142]. Tumor diameter below 5 cm, gross total tumor resection, and younger age are favorable prognosticators [134]. More proximally located tumors are more likely to infiltrate the spinal cord or brainstem.

Secondary Neoplastic Brachial Plexopathies

Secondary plexopathies, which far outnumber primary ones, are due to plexus invasion from an extraplexal source, such as a metastatic lesion, an adjacent primary cancer (e.g., apical lung cancer), or contiguous lymph node metastases (e.g., breast or cervical cancer). Neoplastic plexopathies also follow invasion from hematogenous (e.g., hematologic malignancies), CSF (e.g., melanoma, breast and lung cancer, hematologic malignancies), or lymphatic dissemination. Much rarer causes include intraneural metastases (reported with carcinoid and hematologic malignancies), direct perineural spread, or via a paraneoplastic phenomenon [76, 143]. The actual incidence of metastatic plexopathies is likely an underestimate because (1) neoplastic plexus involvement may go unrecognized and (2) plexus assessments may not be performed when the results would not affect clinical management, when the patient is too ill, or when the patient refuses further evaluation. Breast and lung cancer, lymphoma, and melanoma account for most metastatic plexopathies [144]. Other sources include sarcoma, thyroid, testicular, bladder, gastrointestinal, and head and neck cancer [121, 145, 146]. Of these, breast carcinoma is the most common and typically invades the plexus from adjacent lymph node metastases [121, 129]. For this reason, most metastatic plexopathies involve middle-aged to elderly females. Unlike primary neoplastic plexopathies, there is no regional predisposition with metastatic involvement [144]. Exceptions to this statement include head and neck cancer, especially squamous and basal cell carcinoma, which tends to infiltrate the upper plexus from above; breast cancer, which favors the infraclavicular plexus when it metastasizes to the lateral group of axillary lymph nodes; and apical lung cancer, which tends to infiltrate the lower plexus [80]. Apical lung cancer, through direct invasion, is the most common nonmetastatic malignancy to involve the brachial plexus [147]. Other common sources include esophageal, gastrointestinal, thyroid, testicular, bladder, pancreatic, sarcoma, rhabdomyosarcoma, and head and neck cancer [121, 123, 145]. In addition to metastatic plexopathy, other considerations include radiation plexopathy (in those who received radiation therapy), neoplastic advancement (e.g., neoplastic meningitis, epidural extension), iatrogenic trauma (e.g., from surgical intervention or anesthetic administration), orthopedic conditions (e.g., rotator cuff tear), and conditions related to treatment (e.g., subclavian artery occlusion, effects of chemotherapy) [76]. Among patients with metastatic

plexopathies, pain usually overshadows the other clinical features. Typically, it is progressively severe and unrelenting, involves the shoulder and axillary regions, interferes with sleep, and radiates along the medial aspects of the ipsilateral upper extremity. Neurologic deficits are frequent, involve the sensory and motor distributions of the plexus elements affected, and progress as the cancer spreads through the plexus [145]. With the possible exceptions of head and neck cancer, lymphoma, and neurotropic skin cancer, most patients with metastatic plexopathies have widely metastatic disease. Typically, they are already known to harbor a malignancy and have already been treated for that malignancy, although in one series, 35 % of patients with metastatic plexopathies presented without a history of known malignancy [148]. Because most metastatic plexopathies are incurable (due to their advanced stage and resistance to chemotherapy and radiation therapy), treatment is palliative. Subtotal resection may be useful for pain relief [129, 149]. External neurolysis and removal of as much tumor as possible may be performed in the setting of metastatic breast carcinoma because it may not invade the nerve beyond the epineurium, whereas with lymphoma and melanoma, tumor removal from epineurial attachments followed by local radiation therapy may be beneficial [129].

Evaluation of Neoplastic Plexopathies

Accurate diagnosis requires coupling of the pertinent clinical features (e.g., personal or family history of NF1 or cancer; constitutional symptoms; NF1 stigmata; pain or tenderness; characteristics of the mass (size, location, and mobility; presence of other masses in the neck, supraclavicular fossa, shoulder, or axilla); neurologic dysfunction; Tinel sign; previous cancer treatments) with ancillary studies. On clinical examination, features of Horner syndrome are sought because of its association with epidural metastasis (risk of spinal cord compression). Sympathetic involvement may also cause the upper extremity to become warm and dry. Imaging studies are the most helpful ancillary studies for assessing these patients. Plain films of the chest, cervical spine, clavicle, scapula, and humerus help in the identification of lung lesions (e.g., superior sulcus tumors), neoplastic bony changes (e.g., intervertebral foraminal enlargement, vertebral erosion), radiation changes, and spinal column instability. Isotope bone scans identify bone metastases. The multiplanar imaging ability, lack of bony degradation, excellent soft tissue contrast, noninvasiveness, and lack of radiation exposure make MRI the imaging modality of choice for defining the location and margins of the lesion, the relationship to adjacent structures, and the presence of lymphadenopathy, all of which are helpful in staging, planning surgical and radiation therapy, and monitoring treatment response. Features of mass effect (e.g., anterior displacement of the anterior scalene muscles) may also identify a supraclavicular mass lesion not otherwise observable. MRI can determine the proximity of the lesion to the epidural space and spinal cord and may directly (enhancement) or indirectly (obliteration of apical lung fat) identify the mass [150, 151]. MRI may not identify malignant cells infiltrating and tracking along the connective tissue sheaths of plexus elements. NSTs, neoplastic invasion, and some metastatic lesions require gadolinium for visualization. On MRI, NSTs appear as fusiform or spherical enlargements that are isointense to muscle on T1 and hyperintense on T2. Schwannomas brightly enhance and often demonstrate exiting, entering, or displaced fascicles, whereas neurofibromas rarely show displaced fascicles [152]. Frequently, the capsule and the nerve of origin are visible. NF1 is suggested by multiple neurofibromas or the multifocal nature of a plexiform tumor. These studies do not differentiate neurofibromas from schwannomas or benign lesions from malignant ones because benign and malignant lesions both display heterogeneous signal and bone erosion and because irregular infiltrative borders are also observed with benign plexiform neurofibromas [80, 151]. MRI is also useful for screening presymptomatic NF1 patients. Other useful imaging techniques include fluorodeoxyglucose positron emission tomography (to identify malignant changes within the plexus, to differentiate benign and malignant plexiform neurofibromas), magnetic resonance neurography (to differentiate intraneural and paraneural masses), and angiography (to define tumor vascularity and neighboring vessels for preoperative planning) [135, 146, 153, 154]. CSF assessment is necessary when neoplastic meningitis is a consideration. Although often downplayed as an extension of the neurological examination, EDX testing provides information critical to patient management and, in addition, has several advantages over clinical assessment, including (1) evaluation of muscles not easily assessed clinically (e.g., brachialis); (2) identification of subclinical muscle involvement; (3) better definition of the extent of the lesion (EDX studies frequently identify involvement beyond the distribution identified clinically or radiographically); (4) determination of severity, chronicity, and rate of progression; and (5) the ability to redirect the evaluation toward non-neurologic entities (e.g., orthopedic disorders) when, for example, the EDX study of a patient with "weakness" is normal. In addition, it also identifies the EDX features of radiation fibrosis syndrome (although this does not exclude tumor recurrence) and, through serial studies, can assess tumor progression and treatment response. Unfortunately, EDX studies often are normal until persistent sensorimotor deficits are present [122]. Overall, the most accurate histologic information follows tissue procurement from the tumor or involved lymph nodes. When benign plexus tumors are mistaken for nonneural lesions and improperly biopsied or excised, severe, permanent, and unnecessary neurologic deficits and pain may result. Not only is patient outcome and quality of life

adversely affected, but subsequent excisions are impeded. Thus, consultation with a neurosurgeon experienced in the evaluation and treatment of such lesions is mandatory [121–123, 145]. When a malignant NST is suspected, definitive diagnosis is made by biopsy and, if confirmed, is followed by a metastatic evaluation, including chest films, bone scan, chest and abdominal CT scans, and MRI of the surrounding structures [129]. When a malignant plexopathy is suspected and the MRI is normal, additional studies to look for extraplexal involvement (e.g., bone, liver, and brain imaging) may be necessary, as may surgical exploration; if these results are negative, repeat studies and reexploration 3–6 months later may be necessary [144].

Radiation-Induced Brachial Plexopathy

Although the PNS is relatively radioresistant, radiation therapy may have toxic effects on its nerve fibers and vasa nervorum, resulting in extensive demyelination (with later conversion to axon loss), blood vessel destruction, and marked tissue fibrosis, a condition termed *radiation fibrosis syndrome* [76, 155]. When this syndrome involves the brachial plexus, the term *radiation plexopathy* is applied, the earliest cases of which were reported in 1964 [156]. Unless midline radiation is given, brachial plexus involvement typically is unilateral and may follow radiation therapy to the neck, upper thorax, or axilla. Because it most commonly follows axillary lymph node irradiation for breast cancer, it usually involves middle-aged to elderly females [15]. Following awareness that the incidence of radiation damage increased with higher total dose, larger fraction size, shorter application time, use of the three-field technique, and concomitant chemotherapy, technical modifications and dosing adjustments (lower doses administered over longer periods) were introduced and the incidence declined [157–162]. Symptoms of radiation plexopathy usually appear within 12–20 months of course completion, but onset times range from a few weeks to over 30 years [163, 164]. Radiation plexopathy most commonly affects females with breast cancer who received axillary lymph node chain radiation therapy months to decades earlier [165]. Most patients present with painless paresthesias in the median nerve-innervated regions of one or more of the lateral three digits (i.e., lateral cord distribution). Pathophysiologically, these symptoms reflect demyelinating conduction block. Over time, the paresthesias become more intense and their distribution expands [2, 55]. Unlike most demyelinating conduction block lesions, which typically recover over several weeks to months (remyelination), these lesions persist and, typically, over a several-year period or greater, convert to axon loss. As this conversion takes place, numbness, sensory ataxia, weakness, and muscle atrophy appear. With continued progression, the extremity may become atrophic, insensate, edematous, and essentially useless [166, 167]. Extremity edema may also be noted. Pain may develop, but its incidence is unclear. It has been reported to occur infrequently by some and in up to two-thirds of patients by others [144, 166]. Initially, the distribution of the paresthesias may result in an erroneous clinical diagnosis of carpal tunnel syndrome or a C6 or C7 radiculopathy and an unnecessary surgical procedure. Tumor recurrence is another consideration, especially in the setting of pain (discussed below). MRI is the imaging study of choice and typically demonstrates diffuse thickening and enhancement [168]. EDX studies may initially be normal, but once the symptomatic digits show continuous paresthesias or numbness, low-amplitude sensory responses with normal latencies typically are recorded. The low-amplitude sensory responses exclude cervical radiculopathy, and the normal latencies exclude carpal tunnel syndrome, thereby sparing the patient from unnecessary surgical procedures. With more advanced lesions, the sensory responses are unelicitable, the motor responses are low in amplitude, and focal demyelinating conduction blocks are apparent with supraclavicular fossa stimulation. The needle EMG shows fibrillation potentials, a neurogenic MUAP firing pattern, chronic neurogenic MUAP changes, and widespread fasciculation potentials as well as myokymic potentials [3, 15, 144, 166, 167, 169, 170]. When these features are encountered on EDX examination, one can reliably diagnose radiation-induced plexopathy. However, radiation plexopathy does not exclude tumor recurrence because both may be present simultaneously. There is no effective treatment for radiation plexopathy and treatment is therefore symptomatic. Physical therapy is used to prevent contractures, capsulitis, muscle atrophy, and lymphedema formation. Pain is treated in a similar manner to neoplastic plexopathy. External neurolysis can break up perineural adhesions and scar tissue and may lessen severe, unresponsive pain but may result in greater clinical deficits [121]. Surgical procedures to restore plexus circulation and impede fibrosis (e.g., neurolysis with omental transfer) have not been shown to be of long-term benefit, and the role of anticoagulation remains unclear [167, 171]. Thus, with inexorable progression and lack of treatment options, the prognosis for this condition is poor, with most patients ultimately developing a functionally useless extremity [80]. Even with incomplete lesions, the associated sensory ataxia often renders the limb functionally useless [31]. Rarely, radiation therapy produces transient sensory symptoms, typically paresthesias, that resolve over a 6–12-month period [160, 164]. Other radiation-induced neurologic complications include ischemic brachial plexus injury from subclavian artery thrombosis, dropped head syndrome and atrophy of neck muscles from cervical AHC damage, and the induction of NSTs (mostly malignant ones).

Radiation Versus Neoplastic Plexopathies

When patients with neoplastic plexopathies and a history of radiation therapy develop recurrent or new upper extremity symptoms, it can be challenging to differentiate tumor recurrence from radiation plexopathy. Features predictive of tumor recurrence include severe shoulder pain, rapid progression, lower plexus involvement, metastatic disease in other body regions, and paraspinal muscle fibrillation potentials. Features predictive of radiation plexopathy include painless paresthesias (often in a lateral cord distribution), slow progression, and certain EDX features (i.e., demyelinating conduction block, fasciculations, grouped repetitive discharges, and myokymic discharges) [80, 144, 148, 163, 166]. The presence of Horner syndrome and the time elapsed since radiation therapy are not helpful differentiating features [121]. The presence of nodular enhancement or a mass on MRI strongly suggests tumor recurrence, whereas homogenous enhancement or signal abnormalities involving the ipsilateral scalene muscles or other neighboring structures without nodularity support radiation plexopathy [80]. Surgical exploration with biopsy may be necessary but can be nondiagnostic. A negative biopsy does not exclude tumor recurrence [144]. The identification of radiation plexopathy never excludes tumor recurrence because these two conditions may exist simultaneously.

Traumatic Brachial Plexopathies

Most traumatic brachial plexopathies follow closed traction and reflect the susceptibility of the brachial plexus to stretch injury. The brachial plexus fibers elongate with movements of the neck, shoulder, and arm. Because these fibers are anchored both proximally (i.e., the spinal cord and transverse processes) and distally (e.g., within the axilla), excessive elongation produces traction injury. Most closed-traction injuries to the brachial plexus involve the supraclavicular plexus and are related to motor vehicle accidents (especially those involving motorcycles), sports, and particular occupations (e.g., industrial accidents) and, consequently, are more frequent among young adult males [2, 3, 11, 20, 21, 23]. Some of these entities have already been discussed (e.g., avulsion injuries, classic postoperative paralysis, obstetric brachial plexopathy, postmedian sternotomy plexopathy) because they are region specific or involve particular brachial plexus elements (e.g., roots). Among supraclavicular plexopathies related to closed traction, most involve the upper plexus and follow forceful separation of the head and shoulder. When more severe, the middle and lower plexuses, in that order, are involved. Traction injuries to the lower plexus are less common, usually follow forceful separation of the upper extremity from the torso, more commonly are associated with bone and blood vessel injuries, and frequently also involve the middle plexus [172]. Again, severe lower plexus traction injury is followed by middle plexus and then upper plexus involvement. Traction lesions restricted to the middle plexus are rare; they usually are accompanied by upper or lower plexus involvement [26]. Theoretically, application of traction to the upper extremity while it is abducted and parallel to the ground favors middle plexus involvement. Open traction injuries, which usually follow gunshot or chainsaw accidents, are much less common than closed-traction injuries [15, 20]. The majority of penetrating injuries affect the infraclavicular plexus. Most low-velocity insults (knife blade, low-velocity round) produce direct plexus damage resulting in conduction failure from axon loss, whereas high-velocity rounds, in addition to directly disrupting the plexus fibers, can indirectly damage them as well – the pressure waves and cavitation created by passage of the bullet produce contusive and traction forces proportional to the cube of its velocity [20, 173, 174]. The pathophysiology associated with high-energy injuries ranges from demyelinating conduction block to axon loss related to plexus fiber disruption. Among 90 civilian patients with gunshot wounds to the brachial plexus, only 6 % showed disruption [172], whereas among military personnel, 24 % had complete loss of continuity [175]. Although indirect forces usually are not disruptive, they can be quite lengthy [20]. When blood vessel disruption occurs, the plexus fibers may be injured secondarily through hematoma or pseudoaneurysm formation. The cords and the median nerve are adherent to the axillary artery and are particularly susceptible. In this setting, the plexus injury may present in a delayed manner, characteristically with painful paresthesias and subsequent weakness in the distribution of the affected fibers. With traumatic neurovascular injuries, the cord elements are most often involved, whereas with iatrogenic insults, the terminal nerves are more frequently involved. The rate of the progression depends on the rapidity of expansion of the responsible hematoma or pseudoaneurysm, and the likelihood of recovery depends almost entirely on the amount of time required to make the diagnosis. When only ischemic conduction block has occurred, all of the symptoms are reversible. Later, after axon disruption has occurred, the potential for recovery is essentially zero. Transection injuries may be either sharp (knife blade, glass) or blunt (animal bites, chainsaw, metal fragments, fan or motor blades). It is important to document the site of injury, the injurious object, and the onset of symptoms in relation to the initial trauma. Symptoms recognized immediately after the injury most likely represent direct plexus damage, whereas those developing subsequently may reflect an expanding hematoma or neuralgic amyotrophy. Because most compression injuries occur between the clavicle and first thoracic rib, the distal trunk, division, and proximal cord elements are most frequently affected. While the plexus fibers are compressed, contralateral head movements

produce traction forces on the supraclavicular elements, whereas downward or lateral upper extremity movement produces traction forces on the cords. Fractures and dislocations (more commonly anterior) of the humeral head or neck may produce infraclavicular plexus damage. These lesions most commonly involve the axillary terminal nerve, less frequently the suprascapular nerve (often in combination with the axillary nerve), and least frequently the musculocutaneous nerve [15]. They are more common among elderly males, almost always are unilateral, and are more frequently right-sided due to the tendency of a falling individual to use the dominant limb to break the fall [2, 176, 177]. With severe lesions, most of the cords or terminal nerves may be involved. The clinical features reflect the particular infraclavicular elements disrupted, and the likelihood for recovery reflects the underlying pathophysiology. Because imaging studies are more helpful in the assessment of intraspinal canal lesions, they typically are uninformative in the setting of closed-traction injury. CT and MRI studies are useful when traumatic plexopathies are associated with hematoma formation, although when the hematomas are induced by iatrogenic injury, they may be too small for visualization and may require axillary arteriography for recognition [104]. Plain films identify humeral fractures and dislocations. Supplemental imaging studies for the latter include ultrasound, CT arthrography, and MRI. In the acute setting, EDX studies are not indicated because the EDX abnormalities associated with axon loss require time to manifest (discussed above). If there is a concern about lesion continuity, the needle EMG may be used acutely to establish continuity. Later, however, EDX studies are used to fully characterize the lesion. These determinations can be challenging, however, in the setting of a concomitant extraplexal lesion (e.g., midshaft humeral fracture-induced radial neuropathy) or a two-level intraplexal process that involves both preganglionic and postganglionic fibers. The treatment of traumatic brachial plexopathies – surgical or conservative – reflects a number of features, including the injury type, location, severity, and chronicity and, consequently, must be individualized. With injured plexus elements, the goal of surgical intervention is to permit proximodistal axonal regeneration to occur. This can be accomplished through a number of techniques. To successfully restore motor function, surgical intervention is best performed within the first 3 months (or at most, the first 6 months) by surgeons with expertise in peripheral nerve disorders.

Most closed-traction injuries produce lesions in continuity and initially are treated conservatively (physical therapy with serial clinical and EDX assessments) because, at this point, it is not possible to determine the likelihood of recovery or the type of surgical intervention required [33]. Initially, the presence of demyelinating conduction block causes the severity of the lesion to be overestimated. At day 7, motor NCS can usually differentiate the percentage of nonconducting fibers due to demyelinating conduction block from the percentage related to axon loss. If no signs of recovery appear after 2–3 months (4–5 months for more pronounced injuries), surgical exploration is considered [33]. Shorter observation periods (3 weeks to 3 months) may be considered with high-energy injuries or those associated with total or near-total paralysis [178]. The ability of the damaged segment to transmit action potentials can be determined through intraoperative nerve conduction studies. In general, when the damaged segment transmits nerve action potentials, only external neurolysis is required [20]. When the damaged segment does not transmit action potentials (because connective tissue proliferation impedes axonal advancement), it is removed and the ends are reattached, either directly (less commonly) or via a cable graft (more commonly). Injuries related to high-velocity rounds are initially (2–4 months) managed conservatively because affected brachial plexus elements are infrequently disrupted. When evidence of recovery is not observed, surgical intervention usually is required (typically resection with graft placement) [20]. In the setting of a transection, the ends of the transected element can be reattached or the damaged portions of each end can be removed and a cable graft placed. Sharp transections usually are repaired within 72 h by primary end-to-end neurorrhaphy because they are easier to assess prior to scarring and easier to repair prior to retraction [20, 33, 178]. Early intervention is also indicated with worsening pain or neurologic dysfunction, hematoma formation, concomitant bone or vascular injuries, and compartment syndrome [33]. With blunt transections, repair is delayed until the full proximal and distal extents of the neuroma can be appreciated [20, 33]. Unless a severe lesion in continuity or a rupture is suspected, most infraclavicular plexus lesions following humerus fracture or glenohumeral dislocation (mostly axillary neuropathies) are initially treated conservatively [31].

Iatrogenic Brachial Plexopathies

Iatrogenic injuries represent 7–10 % of brachial plexopathies, most of which reflect blunt injuries in continuity [3]. Most follow operations or other medical procedures and reflect a number of factors, including patient positioning and the particular procedure performed. In addition to direct injuries (e.g., suture or hardware misplacement, injection injury, transection), indirect injuries (pseudoaneurysm or hematoma formation) also occur. With the latter, the presentation may be delayed, such as when previously placed hardware subsequently detaches and damages an adjacent blood vessel [60, 179, 180]. Treatment is individualized and reflects the type of injury and its location, severity, and chronicity. Injuries related to malpositioning

typically are treated conservatively, as are plexopathies following procedures requiring median sternotomy. With misplaced sutures or hardware, removal and repair are employed. With blunt transections, treatment usually is delayed until enough time has elapsed for neuroma formation to have occurred (e.g., several weeks). With sharp transections, acute end-to-end repair usually is performed within the first 72 h [20].

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Lumbosacral Plexopathies

47

Seward B. Rutkove and Tracy W. Sax

Introduction

The accurate evaluation, diagnosis, and treatment of a lumbosacral (LS) plexopathy often presents a challenge to the clinician. In addition to being relatively uncommon, LS plexopathies can have very varied presentations, due to the fact that any nerve fibers derived from the L1 through S4 levels may be involved. Moreover, it is common to mistake an LS plexopathy for an LS radiculopathy, especially given the high prevalence of structural lumbar spine disease. One final difficulty is that in patients with nonstructural plexopathies, such as idiopathic LS plexitis or diabetic amyotrophy, the diagnosis may be one of exclusion. This can make both patient and physician uneasy, especially if more aggressive treatment options, such as immunosuppression, are under consideration.

Despite these issues, a careful history and examination in conjunction with electrodiagnostic, radiologic, and serologic testing can usually lead to a correct diagnosis and causation (Table 47.1). In addition to avoiding unnecessary LS spine surgery, the patient can receive appropriate therapy directed toward the relief of pain and restoration of function.

Anatomy

The LS plexus consists of two distinct regions: the lumbar plexus and the sacral plexus. The lumbar plexus (Fig. 47.1) is formed from the anterior rami of lumbar roots 1–4 and lies within the posterior portion of the psoas muscle. The anterior rami of roots L2–4 divide into anterior and posterior divisions. The anterior division forms the obturator (L2–4), the genitofemoral (L1, 2), iliohypogastric, and ilioinguinal (L1) nerves. The posterior division of L2–4 forms the femoral and the lateral femoral cutaneous nerves.

The lumbar plexus communicates with the sacral plexus via the anterior division of L4. The sacral plexus is formed from the anterior rami of spinal nerves L4–S3. The anterior division forms the tibial portion of the sciatic nerve, and the posterior division contributes to the peroneal portion of the sciatic nerve. The superior (L4–S1) and inferior gluteal (L5–S2) arise from the posterior division of the sacral plexus. The posterior cutaneous nerve of the thigh arises from the anterior divisions of S1–3.

Clinical Presentation of Lumbosacral Plexopathy

Lumbar plexus disorders cause symptoms in the territories of the iliohypogastric, genitofemoral, ilioinguinal, femoral, and obturator nerves. This results in weakness of hip flexion, knee extension, and thigh adduction with sensory loss in the

Table 47.1 Causes of lumbosacral plexopathy

Compressive disorders
Hemorrhage
Neoplasm
Pregnancy
Traumatic
Postoperative
Aneurysms/large vessel occlusive disease
Gluteal compartment syndrome
Noncompressive disorders
Diabetic amyotrophy
Radiation plexopathy
Idiopathic lumbosacral plexitis
Vasculitic
Infectious/parainfectious
Heroin related

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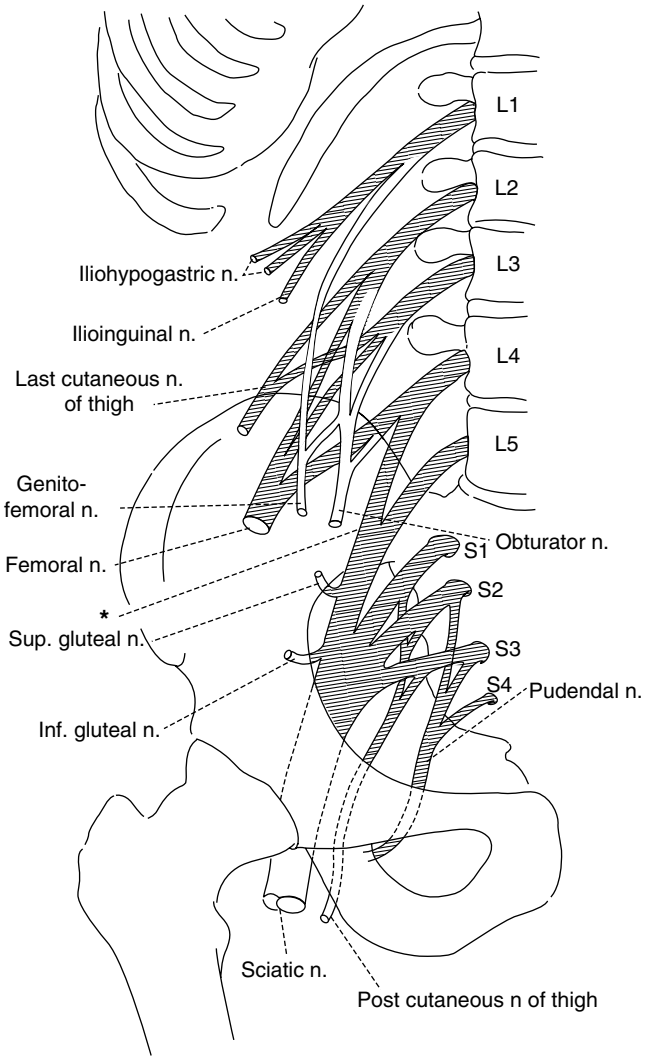

Fig. 47.1 The lumbosacral plexus is divided anatomically into an upper, lumbar plexus and a lower sacral plexus. The iliohypogastric, ilioinguinal, lateral cutaneous nerve of the thigh, genitofemoral, femoral, and obturator are the major nerves derived from the lumbar plexus. The sciatic, superior gluteal, inferior gluteal, posterior cutaneous nerve of the thigh, and pudendal nerves are derived from the lower lumbosacral plexus. The lumbosacral trunk (*) is formed primarily by the L5 root with a contributing branch from the L4 root. It travels a relatively long distance in close contact with the ala of the sacrum adjacent to the sacroiliac joint (Adapted from Hollinshead [1])

lower abdomen, inguinal region, and over the entire medial, lateral, and anterior surface of the thigh and the medial lower leg. The patellar reflex is decreased or absent.

A lesion of the sacral plexus produces dysfunction within the territories of the gluteal, sciatic, tibial, and peroneal nerves, producing weakness in the hip extensors, hip abductors, knee flexors, and foot plantar flexor and dorsiflexors. Diminished sensation may be found over the posterior aspect of the thigh, anterolateral and posterior aspect of the leg below the knee, and almost the entire foot. The ankle jerk may be diminished or absent. A combination of weakness in the glutei and sciatic nerve-innervated muscles helps localize the lesion to the sacral plexus.

Pain in LS plexopathy is very common and, given its intensity, may be one of its most disabling features. Depending on the nature of the plexopathy, pain is often localized to the region of the hip, buttock, and proximal thigh, with prominent radiation down the leg. On examination, certain movements may elicit pain. For example, in sacral plexopathies, the straight leg test may enhance pain, whereas in lumbar plexopathies, hyperextension of the leg at the hip (femoral stretch, reversed straight leg test) may have the same effect. Unlike radicular lesions, however, coughing or straining will usually not produce much change in symptoms. Back pain, although sometimes present, is usually relatively minor.

Electrodiagnostic Studies

As with the clinical presentation of LS plexopathy, the electrodiagnostic findings can be quite variable and complex. Multiple nerve conduction studies, often with comparisons to the opposite limb, and extensive needle electromyography (EMG) are often necessary to accurately characterize an LS plexopathy [2].

Peroneal and tibial motor conduction studies reveal often low compound muscle action potential (CMAP) amplitudes when involvement of the lower lumbar and sacral nerve fibers is present. Femoral motor conduction studies will reveal reduced CMAP amplitude if a lumbar plexus lesion is present.

Sensory conduction studies are usually very helpful in identifying LS plexopathy. Concurrent reductions in the amplitude of superficial peroneal, sural, and saphenous responses demonstrate that the process is at or distal to the dorsal root ganglion. Unfortunately, some of the sensory nerves that would be very helpful to evaluate are, for technical reasons, not possible to study, such as the iliohypogastric and ilioinguinal nerves. The lateral femoral cutaneous sensory response may be difficult to obtain in healthy subjects.

It is important to distinguish LS trunk lesions from peroneal nerve compression or an L5 radiculopathy, because all may present with foot drop. Many patients with peroneal neuropathy across the fibular head have conduction block. In addition, detecting weakness or denervation, or both, in ankle inversion (tibialis posterior), toe flexion (flexor digitorum longus), or hip abduction (gluteus medius or tensor fascia lata) eliminates a peroneal neuropathy. It is more difficult to separate an LS trunk lesion from L5 radiculopathy, because the weakness involves the L5 myotomes exclusively in both conditions. However, in L5 radiculopathy, the superficial peroneal sensory response is normal and paraspinal fibrillation potentials may be present.

Proximal stimulation studies, at the level of the spinal root, are rarely needed but can be helpful to identify mild injury across the plexus by demonstrating slowing of conduction velocity. Some normal latency values have been established for evaluating both the lumbar and sacral plexi, recording from vastus medialis and gastrocnemius [2].

On needle EMG, multiple muscles need to be sampled, including, importantly, those derived from the inferior and superior gluteal nerves (in the case of a low-lumbar/sacral plexopathy) to distinguish this disorder from a sciatic neuropathy. In lumbar plexopathy, evaluation of iliopsoas, hip adductors, and quadriceps is important to distinguish LS plexopathy from a femoral or obturator mononeuropathy. Because the dorsal rami are not part of the plexi, LS plexopathies should spare the paraspinal muscles. Certain disorders, such as diabetic amyotrophy, also may involve the roots, complicating the electrodiagnostic picture.

General Recommendations

Evaluation

Although electrodiagnostic testing may help confirm a diagnosis of LS plexopathy, abnormalities may take a number of days to several weeks to become fully established. Hence, in a patient with an acute onset of possible LS plexopathy, imaging studies are important to obtain early in order to exclude a potentially treatable structural disorder such as tumor. In fact, an imaging study is usually a necessity in any patient with an LS plexopathy of uncertain cause. Although computerized tomography (CT) and magnetic resonance imaging (MRI) both give excellent visualization of the pelvis and can effectively exclude a mass lesion, MRI provides better visualization of the plexus itself and is useful in assessing for inflammation or neoplastic infiltration of the plexus [3, 4].

As part of the initial work-up, serologic tests have relatively limited value although a serum erythrocyte sedimentation rate (ESR), glucose, hemoglobin A1C, Epstein-Barr virus (EBV) titers, and Lyme titers may be useful in assessing for some of the more common inflammatory and infectious causes of LS plexopathy.

Treatment

Regardless of cause, pain is often a prominent complaint in patients with LS plexopathy. Treatment with some of the common neuropathic pain medications including tricyclic antidepressants, gabapentin, or pregabalin may be helpful. However, the addition of opioid medications may also be necessary, as pain may be excruciating in many of these disorders, including diabetic amyotrophy, idiopathic LS plexitis, and in infiltrative neoplastic disease. Once the pain is under improved control, efforts toward treating the underlying illness can be pursued (see below). Physical therapy, assistive devices, and orthoses are important adjunctive treatments, helping to maintain mobility during recovery.

Compressive Disorders

Hemorrhage

Hemorrhage within the retroperitoneum is a well recognized, though sometimes overlooked, cause for LS plexopathy. In most instances, hemorrhage is associated with therapeutic anticoagulation or an underlying clotting disorder, although trauma is another common cause. Several various iatrogenic causes have also been described including secondary to failed lumbosacral plexus anesthetic block and due to femoral vein dialysis [5, 6]. In a review of 26 cases of LS plexopathy due to anticoagulation, two distinct clinical syndromes have been described [7]. If the hemorrhage was located within the iliacus muscle, an essentially pure femoral neuropathy resulted. If the hemorrhage was within the psoas muscle, more widespread injury occurred, causing a complete lumbar plexopathy. The volume of hemorrhage within the psoas can be considerably larger, possibly due to the distensibility of the psoas sheath compared to the iliacus fascia [8].

Initially, patients complain of severe pain in the lower abdomen and groin, followed by motor deficits and sensory loss. In some patients, a palpable mass may be found within the groin. A characteristic posture may be observed in which the patient attempts to decrease the pain by flexing and externally rotating the hip. In a poorly responsive ICU patient, an abrupt reduction in the hematocrit may be the only sign of retroperitoneal hemorrhage. Imaging of the pelvis and abdomen usually reveals the abnormality. Later, EMG may be useful in identifying the extent and severity of the injury.

Conservative treatment, with correction of any hemostatic abnormality, is usually the preferred management approach. Most patients will demonstrate a partial recovery, with only a third to one-half of patients experiencing a full recovery [8]. Surgical decompression has met with only varied success and is generally not recommended. One report, however, suggests that percutaneous drainage might be an effective alternative [9].

Neoplastic Plexopathy

LS plexopathy may occur by direct invasion of the plexus or from external compression by the tumor [10]. Neoplastic plexopathy is relatively uncommon, occurring in less than 1 % of patients with a known neoplasm. The most common

tumors associated with LS plexopathy include colorectal, pelvic, genitourinary, breast, and lymphoma, with direct extension in 73 % of patients and by metastasis from extra-abdominal sites in 27 %. In 15 % of cases, LS plexopathy represents the initial presentation of the neoplasm [11].

On presentation, patients generally complain of severe pain followed by sensory loss and weakness. Unilateral lower extremity edema may also be present. The lumbar plexus alone is affected in about one third of patients, the sacral plexus alone (L5–S3) is involved in about one-half, with the rest demonstrating abnormalities in both areas. Although unilateral plexopathy occurs in most patients, bilateral plexopathy may occur in up to 25 %.

CT and MRI are invaluable in making the diagnosis of neoplastic LS plexopathy. CT, however, is less sensitive, producing equivocal results in some patients in which MRI is suggestive of neoplasm [3]. Positron emission tomography (PET) scanning in conjunction with CT can also be performed and can help identify localized malignant neoplasm [12] but is not routinely performed. In addition to localizing the problem to the plexus initially, electrodiagnostic studies can also be helpful in evaluating a patient with a history of pelvic neoplasm who subsequently develops new weakness and sensory loss in the leg. In this situation, the presence of myokymic discharges supports the diagnosis of radiation-induced plexitis over tumor recurrence (see "Radiation Plexopathy" below).

Radiotherapy and chemotherapy, possibly in combination with surgery, may result in improved strength or stabilization of neurologic deficits. Supportive therapy is also clearly important, to help reduce concomitant lymphedema, superimposed compressive neuropathies, and ulcerations [10]. The majority of patients, however, eventually succumb to the underlying neoplasm, with a median survival of less than 2 years.

Pregnancy and Labor

Direct pressure from the fetus on the LS plexus can develop during pregnancy by 32–34 weeks gestation [13]. Women most susceptible are primigravida mothers of short stature (usually less than 5 ft tall) carrying large infants. The earliest symptoms in most patients, however, do not begin until the onset of active labor, at which point pain, usually in a sciatic distribution, radiates down the leg [14]. Some patients may complain of paresthesias over the lateral aspect of the calf and dorsum of the foot as labor progresses. However, it is usually only when the new mother attempts to walk after delivery that weakness in the leg is generally first appreciated. A foot drop usually is the main problem, occurring on the same side as the infant's brow during labor. Occasionally, bilateral weakness may occur. Injury most results from direct pressure of the fetal head against the plexus as it descends into the pelvis during the second stage of labor [15]. Specifically, the LS trunk, the large bundle made up of L5–S1 fibers which directly overlies the pelvic brim, is predominantly involved. In many cases, labor is arrested and delivery needs to be completed by Caesarean section.

Electrodiagnostic studies typically reveal predominant involvement of L5 fibers with some compression of S1 fibers. This results in reduced superficial peroneal sensory response amplitude and rarely reduced sural amplitude as well. On motor studies, a normal or slightly reduced deep peroneal motor response amplitude recording extensor digitorum brevis and tibialis anterior with prolonged or absent peroneal F responses may be present. The tibial motor study is normal. Tibial H reflex may be prolonged or absent if the S1 fibers are involved. Needle examination discloses denervation predominantly involving the L5 myotomal muscles. Prognosis is very good with complete recovery in most cases within 3 months, consistent with a demyelinating process [15].

Traumatic and Postoperative Plexopathy

Unlike the brachial plexus, traumatic injury to the LS plexus is relatively uncommon, with most cases due to falls or motor vehicle accidents, with fractures involving the pelvic ring or sacrum [16], with the incidence and severity of plexopathy increasing with the number of fractures present and fracture instability [17]. In addition to direct crush injury from bone and bone fragments, hemorrhage and avulsion of the nerve roots may also occur [18]. Although isolated involvement of the sacral plexus occurs commonly, most patients develop simultaneous injury to both lumbar and sacral nerve fibers. Weakness predominantly affects muscles derived from the common peroneal and gluteal nerves with more mild problems in the distribution of tibial and femoral nerves. Prominent sensory loss throughout the leg, most commonly in sciatic and posterior femoral cutaneous nerve distributions, occurs. Electrodiagnostic studies provide helpful prognostic information in addition to localizing the lesion; normal or only mildly reduced motor response amplitudes in affected muscles generally imply a good prognosis, due to primarily demyelinating physiology. Conservative treatment is recommended, unless ongoing compression of nerve fibers can be identified and corrected surgically.

Postoperative lesions of the LS plexus can occur after hip replacement, treatment of a fracture of the femur and acetabulum [16], radical pelvic surgery [13], and aortic vascular surgery [19]. However, even the simple placement of a pacemaker via the femoral vein has been described to cause LS plexopathy [20]. Isolated lesions affect either the lumbar or sacral plexus alone, although simultaneous involvement is again more common. Distinguishing a mononeuropathy from an LS plexus injury can also be difficult as patients with

high sciatic lesions (e.g., secondary to hip replacement) or femoral nerve lesions (e.g., secondary to abdominal or pelvic surgery) may present similarly. Postoperative LS plexus lesions are best treated conservatively, with mild ones improving significantly over time.

Aneurysms and Large Vessel Disease

Expansion of iliac or hypogastric artery aneurysms may cause direct compression on the LS plexus with radiation of pain in the distribution of the sciatic nerve [21, 22]. Likewise, slow leakage of an abdominal aortic aneurysm may lead to a very large retroperitoneal hematoma, producing an LS plexopathy [23]. Unexplained back and leg pain in conjunction with a pulsatile mass on palpation of the abdomen or during rectal exam should alert the clinician to the possibility of aneurysm. CT scans of the abdomen and pelvis usually confirm its presence. Early recognition of an aneurysm is crucial, as the likelihood of survival after aneurysmal rupture is much lower than if treated beforehand. Imminent occlusion of the abdominal aorta due to severe atherosclerotic disease may also affect the LS plexus, likely on an ischemic basis [24].

Abscess

Bacterial abscesses arising from the psoas or paraspinal regions resulting in plexopathy are rare. Psoas abscess was common when tuberculosis was more prevalent [25]. Perirectal abscess may cause bilateral sacral plexopathy and should be considered in immunocompromised patients or in those with a prior history of rectal surgery [26]. Patients present with fever and, depending on the location of the abscess, abdominal, groin, or back pain that radiates down the leg. Associated sensory loss and weakness in the leg may also be present. As with any mass, imaging of the pelvis is extremely important in making a rapid, accurate diagnosis. Electrodiagnostic studies may be useful later when assessing the severity and extent of the lesion. Surgical drainage of the abscess and appropriate antimicrobial therapy are usually effective.

Gluteal Compartment Syndrome

Gluteal compartment syndrome has been described as causing a lumbosacral plexopathy or lumbosacral plexus-like syndrome. This rare syndrome is usually caused by trauma, such as a fall or from prolonged positioning due to drug overdose [27] or as a rare postsurgical complication [28]. Early recognition of the syndrome with aggressive surgical debridement and fasciotomy is critical to ensuring prevention of long-term neurological injury.

Table 47.2 Synonyms for diabetic amyotrophy

Diabetic amyotrophy
Diabetic anterior neuropathy
Diabetic anterior neuronopathy
Diabetic asymmetric proximal motor neuropathy
Diabetic femoral neuropathy
Diabetic femoral-sciatic neuropathy
Diabetic ischemic mononeuropathy multiplex
Diabetic lumbar plexopathy
Diabetic lumbosacral plexus neuropathy
Diabetic myelopathy
Diabetic myopathy
Diabetic plexus neuropathy
Diabetic polyradiculopathy
Diabetic proximal amyotrophy
Diabetic proximal motor neuropathy
Diabetic radiculoplexus neuropathy
Diabetic symmetric proximal motor neuropathy
Diabetic lumbar polyradiculopathy
Garland's syndrome
Bruns-Garland syndrome
Proximal diabetic neuropathy
Subacute proximal diabetic neuropathy

Noncompressive Disorders

Diabetic Amyotrophy

Diabetic amyotrophy is a poorly understood disorder that affects the LS plexus that is discussed in detail in Chap. 31. It is probably most easily considered a radiculoplexus neuropathy in that involvement of nerve roots, plexus, and individual nerves probably occurs simultaneously [29]. A number of other names have been used to describe this disorder, each with its own bias toward mechanism and site of injury (Table 47.2). For the purposes of this discussion, we will employ the term diabetic amyotrophy, as it is commonly used and understood.

Diabetic amyotrophy is a relatively infrequent complication of diabetes with a prevalence of about 0.8 % among patients with both types I and II diabetes mellitus [30]. In some cases, diabetic amyotrophy may herald the onset of diabetes mellitus. In the classic form of diabetic amyotrophy, patients present with subacute onset of weakness and atrophy of the pelvic and femoral muscles with considerable pain in the hip and thigh. Although unilateral onset is common, some patients present with bilateral symptoms, while others first develop symptoms affecting one lower extremity and weeks or months later develop a similar syndrome affecting the opposite side. Rarely, the proximal upper extremities may also be affected. In most patients, definite sensory loss involving the proximal leg is usually not described; however,

distal sensory loss due to a preexisting symmetric polyneuropathy is usually present. An associated weight loss of 10–30 lb often occurs as well.

On examination, weakness is usually found predominantly in iliopsoas, quadriceps, hip abductors, hip adductors, quadriceps, and hamstrings. Mild distal weakness may be identified in foot dorsiflexors and plantar flexors. The patellar reflex is unobtainable. Distal sensory loss and reduced or absent ankle jerks are usually present bilaterally, likely due to the underlying polyneuropathy.

Electrodiagnostic studies are often complex, although a consistent picture generally emerges [31]. First, signs of a predominantly distal symmetric axonal polyneuropathy are often present. Specifically, bilateral peroneal and tibial motor responses are often mildly reduced in amplitude and conduction velocity with corresponding prolongation in F responses. Likewise bilateral distal sensory responses, such as the sural, are usually reduced in amplitude or simply unobtainable [2]. Femoral motor conduction studies reveal a reduction in motor response amplitude on the affected side relative to the unaffected side. Although it might be helpful to obtain a saphenous sensory response in this situation, these responses are usually also unobtainable bilaterally. Needle EMG shows fibrillation potentials and positive sharp waves with decreased recruitment of motor unit action potentials in the weak proximal muscles as well as in the lumbar paraspinal muscles, supporting involvement of the nerve roots.

In evaluating patients with this syndrome, imaging of the pelvis with MRI or CT is reasonable in order to exclude a structural lesion. Imaging of the LS spine may also be obtained, which, unfortunately, may lead to an incorrect diagnosis of structural spine disease. One case, however, has been reported of showing evidence of enhancement on MRI T1 imaging of the LS nerve roots [32]. Although spinal fluid studies may show elevated protein (50–147 mg/dl) [33], lumbar puncture is usually not necessary in a patient with a typical presentation of this disorder. The ESR may also be mildly elevated. In those patients in whom diabetic amyotrophy coincides with the onset diabetes mellitus, a fasting glucose, hemoglobin A1C, and in some patients, glucose tolerance testing may help validate the diagnosis.

The pathophysiology of this disorder remains uncertain. An inflammatory component with a microvasculitis and secondary ischemia is likely [29], given the presence of inflammatory cells on sural nerve and intermediate cutaneous nerve of the thigh biopsies [34, 35]. In its most common form, patients with diabetic amyotrophy experience a gradual but definite recovery in strength on the affected side over a period of 6 months. Eventually strength may normalize, although some quadriceps atrophy and mild weakness may persist. The proximal pain, which can be quite severe initially, usually decreases and resolves entirely often after 2–4 months. In a minority of patients, improvement in strength is more limited.

Given the disorder's relatively good prognosis in most patients, good glycemic control and relief of pain are usually the two initial priorities. Although there is no clear proof that improved glycemic control will hasten recovery, most physicians encourage tight control. Standard pain therapies, including tricyclic antidepressants, gabapentin, and, if necessary, narcotics, are most effective. Directed treatment for this disorder, however, has remained controversial. Some authors have advocated the use of immune-modulating treatments, such as intravenous immune globulin (IVIG), pulsed methylprednisolone, cyclophosphamide, and azathioprine [33–37]. Even a single localized spinal steroid injection has been utilized [32]. However, the evidence argues against any specific treatment. Indeed, in a consensus statement, there was an agreement that there was no convincing evidence to support the use of IVIG in this disorder [38]. Similarly, a Cochrane review supported the absence of any evidence for an effective treatment of this condition [39]. However, this clearly remains a disorder that requires further study and investigation.

Radiation Plexopathy

LS radiation plexopathy usually presents with slowly progressive weakness and sensory loss often years after exposure to radiation in the treatment of cancer. Lymphoma, testicular, ovarian, uterine, and cervical cancers are most commonly associated with radiation plexopathy. With the exception of lymphoma, this group is different from cancers that invade the plexus directly, which usually include prostate, sarcoma, and colon/rectal [11]. Although the median onset of symptoms occurs approximately 5 years after treatment, the effects of radiation can be highly variable with some individuals developing symptoms two to three decades later. There is also no clear relationship between the duration of the latent period and the amount of radiation used, although plexopathy occurs rarely in people receiving less than 4,000 rad. Weakness usually affects distal L5–S1 muscles predominantly; symptoms may be unilateral, but are often bilateral and symmetric. Associated sensory loss is common. Pain is usually more minor, although in some individuals, pain is the initial and most prominent symptom. Approximately 50 % of all patients with the disorder complain of significant pain, which usually has an aching, burning, or lancinating character.

Examination discloses weakness with associated atrophy, reduced or unobtainable patellar and ankle reflexes, and abnormal sensation in the affected extremity. On electrodiagnostic testing, nerve conduction studies demonstrate reduced motor and sensory amplitudes and mild slowing of

conduction velocity, consistent with a predominantly axonal lesion. In addition to demonstrating prominent chronic reinnervation of motor unit action potentials and mild ongoing denervation, the needle EMG of the affected muscles reveals myokymic discharges in 60 % of subjects. Although not sensitive, their presence is highly suggestive of radiation-induced injury, as they are not commonly found in neoplastic disease. Myokymic discharges may not be prominent, occurring in only one or two locations in the entire extremity. Additional testing is often obtained including MRI to exclude the recurrence of neoplasm. Lumbar puncture may reveal an elevated spinal fluid protein but is otherwise generally unhelpful in confirming a diagnosis of radiation plexopathy. Differentiating tumor recurrence from radiation plexopathy is usually reasonably straightforward. In addition to distinct findings on MRI and EMG, tumor recurrence proceeds at a rapid rate (over weeks to months) with pain as a predominant symptom, whereas radiation plexopathy has a slow, often insidious onset (over months to years) with only mild pain.

The course of the disorder is variable, with some patients developing mild weakness, while others have a slowly progressive course leading to prominent weakness, sensory loss, and pain in the affected extremity. Most patients note no further progression in their neurologic dysfunction 1–5 years after diagnosis. Although a diagnosis of radiation plexopathy is preferable to that of recurrent neoplasm, in some individuals the disorder can render the affected limb(s) almost useless.

There is no evidence-based treatment for radiation plexopathy. The use of anticoagulants has been suggested on the basis of maintaining blood flow in vessels with radiation-induced endothelial damage. In one study, warfarin was utilized, keeping prothrombin time more than 1.5 the control values for a period of 3–6 months [40]. Both patients with LS plexopathy experienced mildly improved leg function and reduced pain. Although surgical neurolysis with omental transfer has been utilized with some success in radiation injuries affecting the brachial plexus [41], such treatments have not been described for the LS plexus. Tendon transfers may restore limited function in some individuals. In addition to treatment of any underlying pain, physical therapy and appropriate bracing often become the most important therapeutic modalities.

Idiopathic Lumbosacral Plexitis

In 1981, Sander and Sharp [42] and later Evans and co-workers [43] described a syndrome of acute idiopathic LS plexitis analogous to brachial neuritis (neuralgic amyotrophy, Parsonage-Turner syndrome). In 1984, Bradley and colleagues described a syndrome that had a similar onset, but was more prolonged with persistent or recurrent bouts of pain [44]. They also noted that the patients had an elevated ESR and perivasculitis on sural nerve biopsy. Several of their patients improved with prednisone. Most clinicians, however, now consider these two entities as a single disease with variable course [45]. Some patients appear to have a monophasic illness that requires only treatment of pain, whereas others have a recurrent, sometimes debilitating course. This disorder also has a variable age of onset, affecting children as well as adults. Cases from age 2.5 to 81 years have been reported with a peak incidence occurring before age 20 and then again between 40 and 60 years [46].

Patients generally present with the acute onset of severe pain that starts in the buttock, groin, or thigh and radiates distally down the leg, often in a sciatic or femoral nerve distribution. Like brachial neuritis, mild antecedent trauma or a viral illness often precedes this disorder. An association with EBV has also been suggested. The pain is usually described as burning, jabbing, or sharp and may be so severe as to dominate the entire clinical picture [47]. Weakness usually ensues several days to weeks after the onset of pain and may affect predominantly fibers of either the lumbar or sacral plexus. Sensory symptoms are less prominent and include paresthesias in the affected territory with or without objective sensory loss on exam. In a subset of patients, symptoms may also eventually affect the opposite extremity, although usually to a lesser degree.

On nerve conduction studies, the sural, superficial peroneal, and/or saphenous sensory responses may be normal or only mildly reduced. Motor conduction studies are also usually normal. EMG reveals denervation in assorted limb muscles with normal paraspinal muscles. Notably, the disorder can be quite patchy (again similar to brachial neuritis) or predominantly affecting only one nerve, such as the peroneal. Although laboratory investigations may reveal an elevated ESR, additional serologic testing is negative, including tests for diabetes mellitus (e.g., fasting blood glucose, hemoglobin A1C, and glucose tolerance test). Although imaging is often unremarkable, MRIs of the plexus may reveal inflammation [4]. In one study, biopsy of the sural nerve revealed perivascular collections of inflammatory cells in some patients, although this is not always present [44]. In the end, the diagnosis of idiopathic LS plexitis is simply one of the exclusions: the clinical and electrophysiologic characteristics appear most consistent with plexopathy, and yet no cause can be identified.

The course of the disorder is variable. Children are more likely to have a monophasic illness as compared to adults who are more likely to have a prolonged, recurrent course. Initially pain management is the primary concern. In addition to tricyclics and gabapentin, narcotics may be necessary. In patients with recurrent or persistent disease, a number of immune-modulating treatments have been attempted to reduce pain and improve weakness; these treatments have been met with varying success. In Bradley's initial report, the authors used prednisone at a dose of 60 mg/day alone or in

combination with cyclophosphamide [44]. More recently, the use of IVIG at a dose of 400 mg/kg/day for 5 days has been advocated with or without the concomitant use of prednisone [48]. We initially treat patients with high-dose steroids (either prednisone 60 mg oral daily for 6 weeks or 1,000 mg methylprednisolone IV daily for 5 days). If no improvement occurs, we utilize a 5-day course of IVIG, reserving cytotoxic therapy only as a last resort.

Vasculitis

Rarely, LS plexopathy may occur as an initial sign or as a consequence of an already diagnosed necrotizing vasculitis [48]. Patients present with severe pain, weakness, and fixed sensory loss affecting one or more regions of a leg. Electrodiagnostic studies demonstrate an axon-loss physiology with prominent denervation in affected limb muscles. If a diagnosis of vasculitis has not already been previously established, a variety of laboratory studies including ESR, antinuclear antibody, rheumatoid factor, complement levels, antineutrophil cytoplasmic antibodies, and eosinophil count may be helpful as well as potentially biopsy. Since the plexus itself cannot be readily biopsied, biopsy of the sural nerve may be performed, which would reveal transmural inflammation and vessel wall necrosis, in addition to axonal loss [49]. Aggressive immunosuppression, including the use of cyclophosphamide and prednisone, alone or in combination, may be necessary to control the inflammation, allowing neuronal recovery.

Infectious/Parainfectious Disorders

In addition to abscesses, infections directly or indirectly, through autoimmune mechanisms, may produce LS plexopathy. As noted above, an association between EBV infection and LS plexitis may occur in some individuals. In one study, five patients developed severe gluteal/thigh pain followed by weakness in the leg shortly after clinical and serologic EBV infection [50]. Weakness and sensory loss were predominant with diminished knee and ankle jerks on the affected side. Laboratory studies were normal with the exception of EBV antibody titers. Cerebrospinal fluid studies showed increased lymphocytes (8–9 mm^{-3}) and elevated protein of 57–78 mg/dl. Two of the patients in the study were given prednisone 60 mg/day for 10 weeks although spontaneous resolution within 6 months occurred in those not treated.

Lyme infection may also cause plexopathy. In one report, a patient experienced severe buttock pain followed by weakness 2 weeks later [51]. ESR was elevated and electrophysiologic studies showed abnormalities consistent with plexopathy. Serum and cerebrospinal fluid were positive for antibody against *B. burgdorferi*. The patient was treated with IV penicillin 24 million units daily for 14 days with significant improvement in symptoms.

West Nile and herpes zoster viruses have also been described to cause brachial plexopathy-like syndromes [52, 53], but no such disorder has been reported impacting the lumbosacral plexus.

Heroin

The primary toxin linked to LS and brachial plexopathy is heroin [54–56]. Onset of symptoms may occur several to 36 h following the last injection of heroin. Patients usually complain of intense pain with only mild weakness and sensory loss. Resolution of the pain occurs over a several week period with a more protracted course for recovery of motor function. The mechanism of injury is unknown, although a direct toxic effect of the molecule or adulterants has been suggested [56].

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Part VI

Neuromuscular Disorders: Neuromuscular Junction Disorders

Myasthenia Gravis

48

Henry J. Kaminski

Introduction

In 1895, Friedrich Jolly used the Greek terms for muscle and weakness forming "myasthenia" and the Latin "gravis" for "severe" to describe patients with fatiguing strength that often leads to death [1]. Although Jolly named the disorder, earlier accounts by Wilks, Erb, and Goldflam clearly describe patients with manifestations consistent with myasthenia gravis (MG), and for years the disorder was known as the Erb-Goldflam symptom complex [2]. Earlier descriptions of individuals possibly with MG exist. Some consider the account by Thomas Willis in *De Anima Brutorum* as the first identification of patients with MG [2]. In particular, he reports a woman who "for some time can speak freely and readily enough, but after she has spoke long, or hastily, or eagerly, she is not able to speak a word, but becomes as mute as a Fish, nor can she recover the use of her voice under an hour or two." Willis's account clearly emphasizes the cardinal feature of fatigable weakness, which involves the limbs and bulbar muscles. He further warned physicians not to mistake these patients for hysterics, a warning, which often goes unheeded today.

Effective treatment for MG began in the 1930s. Walker, as a house officer, appreciated the similarity of MG to curare poisoning, and she treated a patient with MG with physostigmine, the treatment for curare poisoning, leading to prompt improvement in the patient's ptosis [3]. At the turn of the last century, reports began to appear which associated the presence of thymic tumors and MG [4]. Blalock removed a thymic cyst from a 19-year-old woman who had suffered for years with worsening relapsing and remitting weakness [5]. After the surgery, the patient improved significantly. Later, Blalock reported the observations from six patients with MG; all improved postoperatively [6]. With these reports thymectomy became an established treatment although its efficacy is poorly supported by evidence-based review [7] and is the subject of an ongoing randomized clinical trial [8].

A mainstay of treatment, corticosteroids, which became available in the 1950s, was not quickly accepted as therapy. Initial results of adrenocorticotropic hormone (ACTH) were not impressive, and widespread use of prednisone waited until the 1970s (for review, see Rowland [9]). Established clearly through the work of Patrick and Lindstrom [10], the autoimmune basis of MG has led to the application of various immunotherapies to treatment.

Etiology and Pathogenesis

Physiologic Defect

MG is characterized by a reduction of the endplate potential necessary for action potential generation secondary to the reduction of skeletal muscle acetylcholine receptors (AChR) [11]. The reduction of AChR is caused by antibodies directed at the receptor directly or through compromise of signaling that clusters AChR at the junction. Antibodies to the muscle-specific kinase (MuSK) [12] were discovered among patients with MG in 2000 and in 2011 to LRP-4 [13, 14]. MuSK and LRP-4 are involved in the concentration of AChR to the neuromuscular junction. With repetitive stimulation or repeated activity, the amount of acetylcholine released is insufficient to activate the remaining AChR of the damaged neuromuscular junctions to achieve an endplate potential above the threshold for action potential generation.

The safety factor for neuromuscular transmission is defined as the difference between the membrane potential and the threshold potential for initiating an action potential. Quantal release, AChR conduction and density, postsynaptic architecture and sodium channel density, and acetylcholinesterase (ChE) activity all contribute to the endplate

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potential and influence the safety factor [15]. AChR are normally activated only once in response to acetylcholine (ACh) released by a nerve terminal action potential. Inactivation of ChE prolongs the duration of action of ACh and slows the decay of the endplate current. Postsynaptic folds form a high-resistance pathway that focuses endplate current flow on voltage-gated sodium channels concentrated in the depths of the folds. Both these factors reduce the action potential threshold at the endplate and serve to increase the safety factor. Human junctions are smaller and have more extensive folding than other mammals, suggesting an evolutionary pressure towards postsynaptic modifications to enhance safety factor. The destruction of the postsynaptic membrane also disrupts the architecture of the secondary synaptic folds and reduces sodium channel density, which contributes to the compromise of the safety factor. Decreased temperature or inhibition of ChE produces an increase in endplate potential, which may be adequate to achieve threshold. In the diagnosis of MG, this property is exploited for the ice pack and edrophonium tests (see below).

Immunopathogenesis

MG is one of the few disorders that fulfills strict criteria for an autoimmune disease [16]. (1) The antigen can be administered to an animal and induce a disorder analogous to MG. (2) Passively transferred antibodies to animals produce the clinical manifestations and electrophysiological abnormalities observed in MG patients. (3) Immunoglobulin is bound to the neuromuscular junction of the myasthenic, and AChR isolated from myasthenic muscle has antibody bound. (4) AChR antibody can be detected in up to 90 % of MG patients. Some seronegative patients may synthesize AChR antibody, which is not detected by the assays commonly used, or antibody to muscle antigens other than the AChR. (5) Treatments that reduce the serum concentration of AChR antibody improve myasthenic weakness.

AChR antibodies produce the neuromuscular transmission defect in MG by three mechanisms (Fig. 48.1) [17, 18]. The most important is complement-mediated destruction of the neuromuscular junction. Complement is associated with degraded membranous material, and the abundance of complement correlates with the degree of junctional fold destruction. Antibody also cross-links AChR and increases their degradation rate, and the ability of AChR antibody to increase degradation correlates with clinical manifestations to some degree. Monoclonal antibodies that bind to the ACh-binding site produce experimentally acquired MG in animals within hours of injection by a direct blockade of ACh-induced opening of the ion channel. Antibodies directly modify AChR channel function although such antibodies appear to be only a small fraction of the total serum AChR antibodies in a given MG patient. Therefore, modification of AChR channel function is not a major mechanism in compromising neuromuscular transmission, but dramatic exceptions do exist. MG patients have small amounts of anti-AChR antibodies that recognize the cholinergic binding site. Such antibodies cause acute, severe weakness in animals, which suggests that antibodies may cause a functional block of the AChR and produce profound weakness at low concentrations.

AChR antibodies are polyclonal IgG subclasses which bind to many different sites on the AChR [18]. Investigators using monoclonal antibodies towards the AChR have defined immunogenic regions on the α-subunit of the AChR. The majority of myasthenic antibodies bind to the so-called main immunogenic region (MIR), which is located on the extracellular loop of α-subunit of the AChR. The reasons for the domination of the MIR over AChR antibody distribution are not known. In other autoimmune disorders, a few epitopes dominate the immune response to a protein antigen, and the MIR may be a particular focus of the antibody response in MG. Cross-reactivity of the MIR with epitopes on microbial or autologous antigens could facilitate the antibody response to the MIR by molecular mimicry. Although AChR antibodies characterize MG, the correlation between their serum concentration in individual patients and clinical severity is poor. Some AChR antibodies bind without causing damage, serving only as a marker of the disease, and explaining why some patients in remission continue to have high levels of serum antibodies [19].

Autoantibody production in MG is a T-cell-dependent process, and a breakdown in tolerance towards self-antigens appears to be the primary abnormality in MG. The thymus plays a key role in tolerance induction to self-antigens and in responsiveness of lymphocytes to foreign antigens. The immature T cells pass through the thymic cortex, and those which recognize self-major histocompatibility complex (MHC) antigens pass through the medulla. During this stage in thymic cortex, T cells, which would react towards self-antigens, are removed; however, the mechanisms by which this occurs are not known. Sequestration of antigens from the immune system may also be important in preventing autoimmune attack. Once in the medulla, the T cells differentiate into helper and suppressor cells and eventually are released to the periphery.

The development of a T-cell-dependent autoimmune disease is caused by a loss of self-tolerance [20]. How a loss of tolerance develops in MG is not understood, but several pieces of data indicate that thymic abnormalities are important [21]. First, pathological changes of the thymus occur in 90 % of myasthenics, lymphoid follicular hyperplasia occurs in 80 %, and neoplasia in the remainder. Some patients have a normal or atrophic gland. Compston et al. [22] found that differences in thymic histology correlated with certain

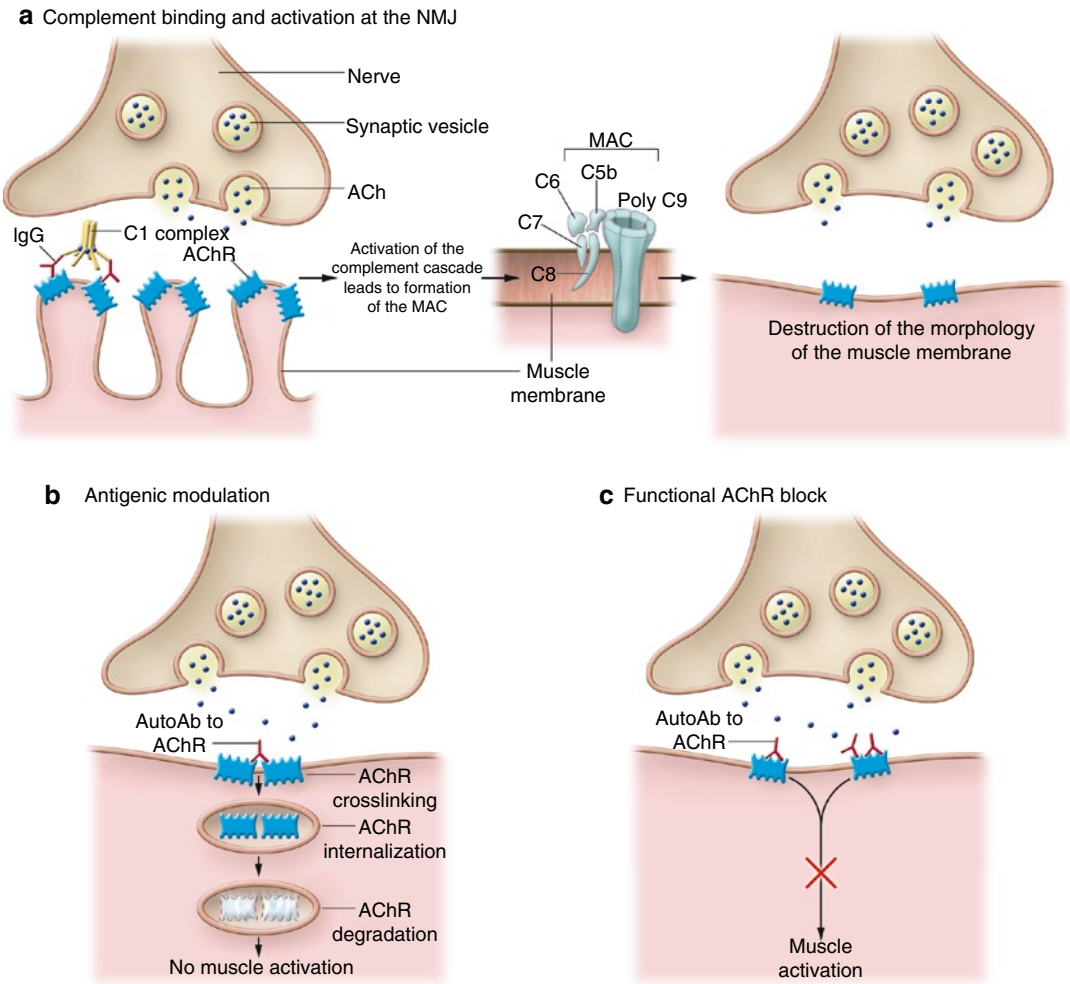

Fig. 48.1 Mechanisms of AChR antibodies that compromise neuromuscular transmission. (**a**) Antibody binds to the AChR, activates the complement cascade, and leads to formation of membrane attack complex (MAC) and localized destruction of the postsynaptic NMJ membrane. This ultimately leads to a simplified morphology of the postsynaptic membrane, which lacks the normal deep folds and has a relatively flat surface. (**b**) Antibodies may cross-link AChR molecules on the postsynaptic membrane, causing endocytosis of the cross-linked AChR molecules and their degradation (antigenic modulation). This ultimately leads to a reduced number of AChR molecules on the postsynaptic membrane. (**c**) Antibodies may bind to the ACh-binding sites of the AChR causing functional block of the AChR by interfering with binding of ACh and failure of neuromuscular transmission (From Conti-Fine et al. [16], with permission)

clinical features. Patients with thymoma had no sex or HLA associations, high titers of AChR antibody, high titers of striated muscle antibodies, and a low frequency of associated autoimmune diseases. Second, thymectomy may improve the clinical course of MG [7]. Third, AChR antibody-producing cells may be isolated from thymus, bone marrow, and peripheral blood, but a greater proportion of antibody is spontaneously produced by thymic cells [23]. These observations may explain the therapeutic benefits of thymectomy and that thymectomy does not lead to complete resolution of the disorder. Finally, the thymus contains proteins which are antigenically similar, or identical, to the AChR. Myoid cells, which express muscle proteins and form muscle fibers in tissue culture, are present in normal and hyperplastic thymus of MG patients. Cultured myoid and thymus cells of MG patients express transcripts of AChR subunits, and some AChR antibodies and α-bungarotoxin will bind to myoid cells. Epithelial cells from thymomas bind AChR antibodies and express transcripts of the α-subunit, but functional AChR are not expressed. The expression of antigenically similar proteins to the AChR in the thymus would provide a source of antigen for autosensitization of T cells towards the skeletal muscle AChR [23].

With increasing disease duration, $CD4^+$ sensitization spreads to larger parts of the AChR. The epitope repertoire of anti-AChR $CD4^+$ cells in MG patients is complex and characteristic of an individual patient. The $CD4^+$ cells recognize epitopes formed by a number of sequence regions on each AChR subunit. A few sequence regions are recognized in most or all MG patients and by large numbers of $CD4^+$ cells.

They form $CD4^+$ epitopes that are both universal and immunodominant. These universal epitopes sensitize pathogenic $CD4^+$ cells and drive the synthesis of AChR antibodies. Thus far, studies of the T-cell receptors of the AChR $CD4^+$ cells in MG patients do not allow the distinction between an initial pathogenic mechanism that entails molecular mimicry and the intervention of a superantigen. Superantigens, found on viruses or bacteria, stimulate particularly powerful proliferative responses, which could stimulate anergic T cells directed towards self-antigens like the AChR [24].

Patients with MG demonstrate a broad and variable spectrum of muscle group involvement. The basis for this differential involvement must be due to a combination of inherent differences in physiological properties of the muscles, a given muscle's ability to adapt to disease-induced damage, and the specific nature of the antibody-mediated damage. With the exceptions of extraocular muscle (EOM), however, the reasons for the differential involvement of a given muscle group are poorly defined (for review, see Ref. [25]).

Clinical Presentation

The manifestations of MG are remarkably varied, and for any patient with weakness and fatigue, MG is a diagnostic consideration [26, 27]. Of course, intermittent symptoms, in particular, those that appear with repetitive activity, are strong indicators of a neuromuscular transmission disorder. However, nearly all patients with diseases of the nervous system complain of excessive tiredness, and a clear deterioration in muscle strength should be determined.

Nearly half of the patients present with EOM weakness, manifested roughly equally between ptosis and diplopia. Most importantly, almost all patients at some point during the course of their illness develop ocular manifestations. Hence, the diagnosis of MG may need to be questioned, if ocular manifestations do not develop. Within 6 months of presentation, slightly more than half of the patients develop generalized disease, and three-quarters of the patients will have bulbar or extremity weakness within the first year. After 3 years of onset, only 6 % of ocular myasthenics develop generalized disease, but rarely a patient with ocular myasthenia develops generalized disease decades after initial presentation. In up to 15 % of MG patients, clinical involvement is restricted to the EOM. On examination, ptosis usually develops within 2 min of constant upgaze. Patients often have different degrees of ptosis of each lid and may have marked unilateral lid weakness and hyper-retraction of the contralateral lid. With elevation of the ptotic lid, the other lid will droop, a sign specific for MG [28, 29].

About 20 % of patients with MG present with prominent manifestations of dysarthria and dysphagia. Because of palatal muscle weakness, speech becomes nasal, and regurgitation of liquids through the nose occurs. Jaw muscles may be prominently affected with a "jaw drop" leading patients to hold their jaw closed. Facial muscle weakness produces a smooth face and the smile becomes straight. The pattern of prominent weakness of cranial-innervated muscles leads some classifications of MG to place such "bulbar" patients into a set category, and such a grouping was supported by the Myasthenia Gravis Foundation of America (Table 48.1) [30, 31]. The justification is that these patients may differ somehow in their underlying disease pathogenesis and, perhaps, response to therapy.

Table 48.1 Myasthenia Gravis Foundation of America clinical classification

Class I	Any ocular muscle weakness
	May have weakness of eye closure
	All other muscle strength is normal
Class II	Mild weakness affecting other than ocular muscles
	May also have ocular muscle weakness of any severity
IIa	Predominantly affecting limb, axial muscles, or both
	May also have lesser involvement of oropharyngeal muscles
IIb	Predominantly affecting oropharyngeal, respiratory muscles, or both
	May also have lesser involvement of limb, axial muscles, or both
Class III	Moderate weakness affecting other than ocular muscles
	May also have ocular muscle weakness of any severity
IIIa	Predominantly affecting limb, axial muscles, or both
	May also have lesser involvement of oropharyngeal muscles
IIIb	Predominantly affecting oropharyngeal, respiratory muscles, or both
	May also have lesser involvement of limb, axial muscles, or both
Class IV	Severe weakness affecting other than ocular muscles
	May also have ocular muscle weakness of any severity
IVa	Predominantly affecting limb, axial muscles, or both
	May also have lesser involvement of oropharyngeal muscles
IVb	Predominantly affecting oropharyngeal, respiratory muscles, or both
	May also have lesser involvement of limb, axial muscles, or both
Class V	Defined by intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb

The breadth of clinical presentations is remarkably varied, and the clinician must be vigilant to this fact. Despite the hallmarks of fatigue and ocular muscle involvement, such manifestations may at times be overwhelmed by severe weakness where fatigue is not readily appreciated, or severe involvement of non-ocular muscle groups. A few examples emphasize this point. Respiratory muscle weakness or upper airway obstruction may occur as an isolated manifestation [32, 33]. Such patients commonly take rapid shallow breaths,

and their condition may be confused with psychogenic hyperventilation. This presentation is particularly dangerous because of the risk of acute respiratory arrest. Rarely, MG may be manifested postoperatively among patients who are unexpectedly difficult to wean from the ventilator. Acute onset of isolated limb weakness or dysarthria may lead to confusion with stroke, especially among the elderly [34, 35]. Weakness of neck extensors or distal limb muscles may occur in isolation [27, 36].

One of the reasons that the diagnosis of MG is often not appreciated by non-neurologists is its relative rarity. The prevalence rate of MG is estimated at about 400 per million with incidence estimates of less than 6 per million [37, 38], but marked variation in rates exists likely related to demographic characteristics and perhaps environmental factors. The incidence and prevalence of MG appears to be higher among African-Americans than Caucasians [39]. The peak incidence of MG in Japanese and Chinese populations occurs before age 20, and ocular myasthenia appears to be more common than in Caucasians [40, 41]. The common characterization of MG as a disease of young women and old men continues to be true. Similar to nearly all autoimmune disorders, women between the ages of 20 and 45 have a peak incidence and prevalence. The overall frequency of MG then rises with age with some studies showing that men and women have equal frequencies of the disease.

Differential Diagnosis

The differential diagnosis of ocular MG is relatively limited (Table 48.2) [29, 42]. Ocular myasthenia may mimic cranial neuropathies or intrinsic brainstem dysfunction, but several features aid in distinguishing these disorders. Since MG never involves the pupil, isolated ptosis is easily differentiated from Horner's syndrome and third cranial nerve dysfunction. Unilateral ptosis may be a sign of a third cranial nerve abnormality, but painless ptosis developing over several days is most consistent with MG. Alternating or recurrent ptosis is usually caused by MG. Isolated abduction weakness caused by MG may mimic sixth nerve palsy but can be differentiated by fatigability or involvement of other muscles. MG may produce isolated medial rectus weakness causing a "pseudo-internuclear ophthalmoplegia." Patients with a true internuclear ophthalmoplegia usually have spared convergence and have other signs of brainstem disease. Graves' ophthalmopathy produces a limitation of ocular movement but can be differentiated from MG by the absence of ptosis and presence of proptosis. Forced ductions confirm the restrictive nature of EOM, and radiologic imaging demonstrates enlargement of EOM. However, one must bear in mind that MG and Graves may coexist. Chronic progressive external ophthalmoplegia, a mitochondrial disorder, leads to progressive symmetric ophthalmoparesis with ptosis that may be confused with ocular myasthenia, but the lack of fluctuating weakness, evidence of systemic disease, and slow saccades in the mitochondrial disorder should differentiate the disorders clinically.

Table 48.2 Clinical presentations and diagnostic considerations in myasthenia gravis

Site of predominant weakness	Other diagnostic considerations
Ocular	Brainstem and motor cranial nerve pathology including Horner's syndrome, oculopharyngeal muscular dystrophy, Kearns-Sayre syndrome, Graves' disease, congenital myasthenia
Bulbar	Brainstem and multiple cranial nerve pathology, motor neuron disease, obstructive lesion of the nasal and oropharynx
Lateralized limb weakness	Stroke, peripheral nerve or root lesion
Distal extremity	
Arm	Distal myopathies
Leg	Peroneal neuropathy or L5 radiculopathy
Isolated respiratory	Acid maltase deficiency, myotonic dystrophy, polymyositis, motor neuron disease, Lambert-Eaton myasthenic syndrome,
Isolated neck	Motor neuron disease, inflammatory myopathy, paraspinous myopathy

Confusion of generalized MG with other neuromuscular disorders must be guarded against (Table 48.2) [42]. Polymyositis, inclusion body myositis, and late-onset muscular dystrophies can be distinguished from MG by the presence of elevated serum creatine kinase, abnormal needle electromyography, and characteristic muscle pathology. Endocrine disorders, such as hyper- and hypothyroidism, glucocorticoid excess, and adrenal insufficiency, produce generalized extremity weakness but usually are differentiated by associated clinical findings and characteristic laboratory abnormalities. Autoimmune thyroid diseases may coexist with MG and complicate the diagnosis of both conditions. Motor neuron disease and MG may mimic each other; however, electromyography should distinguish the disorders. The bulbar form of amyotrophic lateral sclerosis may mimic bulbar MG, but the pyramidal findings associated with motor neuron disease (including brisk jaw jerk and gag reflexes) distinguish the disorders. LEMS and MG may be difficult to differentiate clinically [43], and rarely, LEMS presents with pure ocular manifestations or oculobulbar weakness, more typical of MG [44, 45]. Autonomic manifestations, especially dry mouth, as well as proximal muscle ache point to LEMS. Typical electrodiagnostic findings and detection of serum antibodies against neuronal calcium channels should identify LEMS.

Congenital myasthenic syndromes may be confused with MG, in particular in patients without detectable AChR antibodies. However, these patients usually have a much longer history, often dating to birth, with gradual deterioration in function. Unfortunately, patients with congenital myasthenia may have been treated with immunosuppressive therapies, and a lack of response may also suggest this diagnosis. Certain specific electrodiagnostic findings, such as identification of repetitive compound muscle action potentials to a single stimulation, may suggest the slow channel syndrome or acetylcholinesterase deficiency. A lack of a family history does not eliminate this diagnosis as many of the congenital myasthenic syndromes are autosomal recessive or spontaneous mutations.

Just as the fatigable weakness of MG should not be confused with psychiatric disease, vague symptoms of "tiredness," which represent underlying depression, should not be considered evidence of MG. In my practice I have encountered patients with somatization disorders who were mislabeled with the diagnosis of MG. The incorrect diagnosis of MG may have devastating consequences. Depression may occur among patients with MG, which may complicate diagnostic assessment, and patients with MG often are mistakenly identified as having psychiatric disorders.

Evaluation and Diagnosis

Once MG is suspected based on clinical findings, the physician should attempt to confirm the diagnosis based on objective criteria. Diagnostic tests include the clinical tests, electrodiagnosis, and serology for AChR antibodies. Each has its pitfalls, which the clinician must be aware.

Improvement in strength after intravenous injection of edrophonium is the hallmark of a postsynaptic neuromuscular transmission disorder. Opinions as to the exact manner in which edrophonium should be administered vary, but in general for adults, a 1–2 mg test dose is given intravenously, and if no improvement occurs within 45 s, an additional 3 mg is given [46]. If improvement occurs in a single weakened muscle, the test is considered positive. If no clear increase in strength is appreciated, a total of 10 mg of edrophonium is given. A response is expected within 5 min. It is unnecessary to administer a larger dose, if the test has proven positive. This only increases adverse affects. The test is most useful if improvement in ptosis or the strength of an EOM is demonstrable because of the objective nature of this response. Difficulties arise in interpretation of the test when attempting to evaluate improvement in limb strength or bulbar function. Patients with bulbar muscle weakness may actually complain of worsened swallowing because of excess secretions produced by edrophonium. Additional, adverse affects include tearing, sweating, and gastrointestinal cramps. Rarely, diarrhea may occur as well as bradycardia with hypotension. Atropine should be immediately available to counteract significant bradycardia. Patients with asthma should be tested with caution. Injection of saline and edrophonium in a double-blind fashion is not useful given the obvious muscarinic side effects, which make blinding impossible for examiner and patient. False-positive edrophonium tests are described with motor neuron disease, LEMS, and intracranial mass lesions [47]. Physicians should not "talk themselves into" a positive response and should set clear standards for positive results. False-negative tests are relatively common, and repeated tests are of value. Within the proper clinical context, a single positive edrophonium test is strong support for the diagnosis of MG. Unfortunately, because of rare, severe adverse effects, edrophonium testing has become less popular in the United States leading to greater use of the rest and ice pack tests.

The ice pack test is performed by having a patient with ptosis. An ice pack is placed over the eyes for 5 min. Improvement in ptosis is appreciated and at times improvement in eye movement [48, 49]. Some patients may have difficulty tolerating the ice pack. For the rest test patients are asked to lie for 30 min with eyes closed and ptosis evaluated before and after [50]. The test is inconvenient for the busy outpatient practice, although clearly without risk. Both these tests lack the widespread clinical experience of the edrophonium test [51].

There are three AChR antibody tests and they should be performed in a selective manner. There is no need to perform all the varieties of AChR antibody tests or striational muscle antibody tests. When screening a patient for MG, the AChR binding antibody is the most sensitive test and, in my opinion, the only one that should be performed. The blocking antibody does not add significantly to the diagnostic yield, and the modulating antibody evaluation has a greater potential for false positives. About 85 % of patients with generalized MG will have elevated binding antibodies, while at best 50 % of ocular myasthenics will be positive [52, 53]. Repeat testing is useful in patients with recent symptom onset since the frequency for seropositivity increases with time. About three percent of patients with generalized MG and a very small number of ocular myasthenics will have antibodies against MuSK [54, 55]. I test for MuSK antibodies only in patients who are negative for AChR antibodies. The MuSK antibody test is about five times as expensive as the AChR binding evaluation. Serological testing is a useful adjunct to the diagnosis of MG; however, a large minority of patients will be seronegative, and confirmation of the diagnosis will rely on other diagnostic testing. Also, the clinician must be mindful that on rare occasions, AChR antibodies are detected in other conditions when there is no clinical or electrophysiological evidence of MG.

Striational antibodies are only present in patients with MG who are also positive for AChR antibodies [56] and, therefore, have no diagnostic value. Antistriational antibodies may

also be detected in LEMS, other autoimmune and paraneoplastic diseases, thymoma patients without MG, and the normal elderly. Therefore, there is the risk of confusing diagnosis by their identification in patients without MG. Antistriational muscle antibodies are a marker for thymoma. Elevation of antistriational antibodies among patients between the age of 20 and 50 increases the diagnostic likelihood of thymoma [57]. However, the gold standard for diagnosis of thymoma is imaging, and therefore, assessment of antistriational antibodies is of limited use even in thymoma assessment.

Patients seronegative for both AChR and MuSK antibodies and MG may represent a special subset of acquired autoimmune MG. Some of these patients likely harbor other autoantibodies. In 2011, antibodies were detected to LRP-4 in sera of "double-negative" patients; however, commercial testing for these autoantibodies as yet is not available, and evaluation of the pathogenic nature of LRP-4 antibodies is ongoing [13, 14]. Determination of autoantibody status is clinically important, not only for diagnosis but also guidance of treatment decision. MuSK-positive patients do appear to respond poorly to cholinesterase therapy and better to plasma exchange compared to the AChR-positive patients. It is likely that a portion of seronegative patients have high-affinity antibodies to neuromuscular junction proteins that are at such low levels in the serum that they cannot be identified by conventional assays [52].

Electrodiagnostic studies (Figs. 48.2 and 48.3) are critical in the evaluation of the patient with possible MG, and their performance is detailed elsewhere in this text. A decremental response of the compound muscle action potential with slow 2–3 Hz repetitive stimulation is identified in at least three-quarters of patients with MG [53]. Ocular myasthenics despite lack of generalized manifestations may also demonstrate a decremental response but in a lower percentage than generalized myasthenics [59]. As with serological testing, a decremental response with slow repetitive stimulation is observed in LEMS congenital myasthenias, botulism, and motor neuron disease. Therefore, electrodiagnostic testing needs interpretation in the context of clinical presentation. Single-fiber EMG is the most sensitive test for detecting abnormalities consistent with MG (Fig. 48.4) [61]. However, its usefulness is compromised by its time-intensiveness and requirement for specialized equipment and training. Therefore, it should be used only by experienced electromyographers in the definitive diagnosis of suspected MG patients, whose other diagnostic tests are normal and who do not harbor other neuromuscular diseases.

The evaluations above often confirm or refute the clinical impression of MG; however, there are a small minority of patients that prove difficult to diagnose. Some patients do not have clear fatigue or fluctuation in severity of weakness making recognition difficult. Serological testing and slow repetitive stimulation studies have a poor sensitivity further complicating diagnosis (Fig. 48.4).

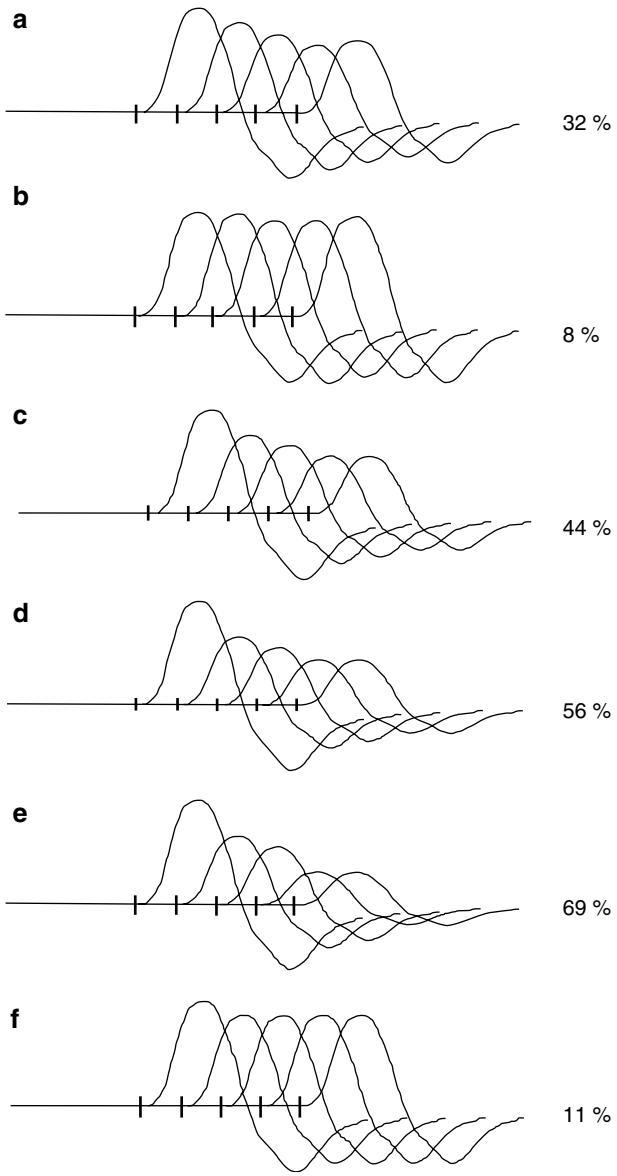

Fig. 48.2 Three Hz repetitive nerve stimulation in a patient with myasthenia gravis. (**a**) Decrement of compound muscle action potential (CMAP) amplitude at rest. (**b**) Postexercise facilitation: decrement of CMAP immediately following 10 s of maximal voluntary exercise. Decrement has repaired towards normal. (**c**, **d**, **e**) Postexercise exhaustion: decrements of CMAP 1, 2, and 3 min after 1 min of maximal voluntary exercise. Decrement becomes progressively more marked over the baseline decrement. (**f**) Postexercise facilitation after a decrement: immediately following another 10 s of maximal voluntary exercise, the decrement, which has worsened as a result of postexercise exhaustion, repairs towards normal (From Preston and Shapiro [58], with permission)

In addition to diagnostic testing, every MG requires evaluation of commonly associated diseases. Thyroid dysfunction is a frequent accompaniment of MG and may aggravate myasthenic weakness. Rheumatoid arthritis and systemic lupus erythematosus also occur more frequently among

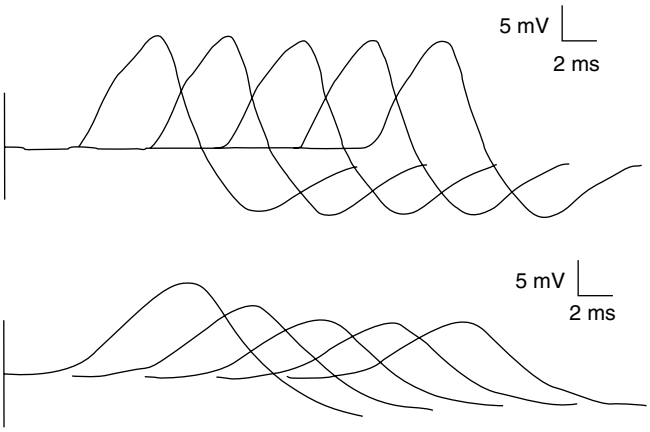

Fig. 48.3 Three Hz repetitive nerve stimulation of proximal and distal nerves in patient with myasthenia gravis. (*Top trace*) Normal decrement (4%) in the ulnar nerve. (*Bottom trace*) Markedly abnormal decrement (42%) in the spinal accessory nerve. In myasthenia gravis, the yield of an abnormal decrement is greater with proximal nerves (From Preston and Shapiro [58], with permission)

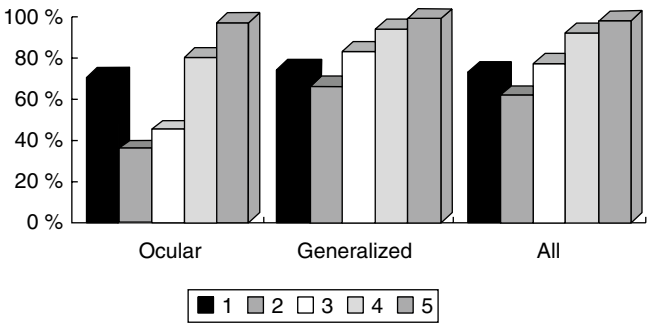

Fig. 48.4 Comparison of diagnostic techniques in myasthenia gravis. *1* AChR antibody positive, *2* Slow repetitive nerve stimulation (RNS) recording hand muscle, *3* Slow RNS recording shoulder muscle, *4* Single fiber EMG of forearm muscle, *5* Single fiber of EMG of facial muscle (Adapted from Oh et al. [53] and from Howard et al. [60])

patients with MG, and if clinically indicated patients, patients may require further evaluation for these disorders. Computed tomography or magnetic resonance imagining of the chest is needed to evaluate for thymoma. In patients with respiratory or bulbar manifestations, pulmonary function tests and barium swallowing studies are helpful in gauging the severity of the disorder. In anticipation of prednisone use, evaluation for tuberculosis and bone density measures are indicated. Screening for IgA deficiency is appropriate for those patients likely to receive intravenous immunoglobulin therapy.

Treatment

Care of the newly diagnosed myasthenic begins with a thorough discussion with the patient, family, and caregivers of the natural history, treatment options, and pathogenesis of the disease. Patients may be directed to the website of the MG Foundation of America or other international organizations, which provide excellent resources on various aspects of the disease. Support group services provided by these organizations are of particular benefit for many patients. Patients should receive a list of medications, which may exacerbate myasthenic manifestations and that such medications need to be used with caution. Because of the patient's special needs and unfamiliarity of primary care physicians with MG, the patient may wish to be provided by their primary care physician with information about MG. The patient should be educated on adverse effects of treatment and approaches to minimize severe side effects of treatment. Often a discussion of the costs of medication is necessary (Table 48.3). Psychological adjustment is difficult to a chronic illness in which definite predictions of outcome cannot be made and patients fear the development of incapacitating weakness. These fears may limit an individual's functional improvement despite significant resolution of myasthenic weakness. The neurologist should attempt to strike a balance between the difficulties in treating MG and the hope of complete remission.

Treatment choices must be individualized based on the severity of the disease, patient's lifestyle and career, associated medical conditions, and the patient's assessment of risk and benefit of various therapies. For example, an older individual with a sedentary lifestyle and mild general weakness may do well with cholinesterase inhibitors, while a young woman with an active career may require immunosuppressive treatment. Of course, the complications of immunosuppressive treatment need thorough explanation, and the patient and physician must work together to optimize the care plan.

Cholinesterase Inhibitors. ChE inhibitors, which retard the hydrolysis of ACh at the neuromuscular junction, are the initial treatment of MG. Pyridostigmine bromide is the only oral ChE inhibitor easily available in the United States. Initial therapy begins at doses of 30–60 mg with individual doses of greater than 120 mg rarely being affective. Dosing intervals of pyridostigmine are set at 3–6 h depending on symptoms. Timed-release forms are available but tend to have erratic absorption; however, they may be useful in some patients. Gastrointestinal complaints of nausea, diarrhea, and abdominal cramps are most common but may be controlled with administration of atropine and glycopyrrolate. Muscle twitches, fasciculations, and cramps are less common but may be particularly bothersome to patients. Rarely, patients may develop confusion from ChE inhibitor therapy. Respiratory secretions may be increased, which complicates treatment of patients with reactive airway diseases and may actually worsen breathing. Patients with dysphagia may have a worsening of symptoms from excess and thick saliva, especially when concomitant treatment with antimuscarinic medications is used. Such apparent paradoxical responses should

Table 48.3 Mechanism of action, cost comparison, and time of onset of clinical benefit for pharmacological agents used in myasthenia gravis

Drug	Mechanism of action	Cost in the USA[a]
Pyridostigmine 60 mg tablets	Reversibly binds to and inactivates acetylcholinesterase	$88 (120 tabs)
Pyridostigmine 180 mg controlled release (time span)		$126 (30 tabs)
Prednisone 20 mg tablet	Anti-inflammatory effects related to the following: (a) redistribution of lymphocytes and reduction of production and differentiation; (b) alterations of function of TNF, IL-1, and IL-2; (c) inhibition of antigen processing and presentation by macrophage	$12 (30 tabs)
Azathioprine 50 mg tablet	Inhibits T- and B-cell proliferation by reducing nucleic acid (purine) synthesis	$ 84 (120 tabs)
Mycophenolate mofetil 500 mg	Inhibits T- and B-cell proliferation by inhibition of guanosine nucleotide synthesis. Additional mechanisms include (a) apoptosis of activated T-lymphocytes, (b) decrease in cell adhesion molecules thus reducing lymphocyte recruitment, and (c) reduction of inducible NOS activity	$130 (100 tabs)
Tacrolimus 1 mg capsule	Calcineurin-mediated pathway inhibition of T-cell and IL-2 production. Modulates the activity of T-cells, increases their apoptosis, and may enhance T regulatory cells	$ 423(100 tabs)

[a]From Epocrates® online searched in July 2012

be appreciated, and a reduction of ChE inhibitor dose may improve symptoms. Patients frequently appreciated that effectiveness of pyridostigmine diminishes over time and this may be explained by expression of a soluble splice variant of the ChE gene, which is not effectively inhibited by pyridostigmine [62].

ChE inhibitor-induced weakness ("cholinergic crisis") is frequently discussed but is rarely encountered now that effective immunosuppressive treatment is available. The use of intravenous edrophonium to determine if muscle weakness is secondary to MG or ChE treatment is unreliable. Therefore, if cholinergic weakness is seriously considered, then ChE therapy should be temporarily discontinued and the patient monitored for improvement. In patients with myasthenic crisis, discontinuation of cholinesterase inhibitors is recommended to limit secretions while on artificial ventilation [63].

Glucocorticoids. Corticosteroids are usually recommended for patients with ocular and generalized or bulbar weakness which does not improve significantly with ChE inhibitor treatment. There is no consensus on the dose and manner of initiation of corticosteroid therapy [64–67]. Some advocate high-dose prednisone (80–100 mg) treatment until clinical improvement occurs followed by alternate-day steroid treatment with gradual tapering as tolerated [68]. Some patients may develop worsening of strength usually within the first few days, of treatment, which has lead to the recommendation for gradual initiation of corticosteroids [69]. For patient on a ventilator, there is no benefit delaying high-dose therapy, especially, if acute treatments, such as IV IG or plasma exchange, are being performed. Eighty percent of patients may expect significant improvement or resolution of weakness on such a regimen during the first months of therapy. However, prior to the widespread use of immunosuppressives used as "steroid-sparing" agents, few patients were able to stop corticosteroid treatments [68].

The clinical situation dictates the optimal treatment regimen. The patient in myasthenic crisis or hospitalized with severe general weakness or dysphagia requires acute treatment with IVIg or plasma exchange. Here, high-dose steroids should be started immediately since these other treatments, in my experience, limit the degree of steroid-induced exacerbation and the time of treatment response hastened. In contrast, patients with mild to moderate weakness may have corticosteroids initiated on a gradually escalating dosage regimen as outpatients [65, 70]. The potential complications of corticosteroids, as described elsewhere in this text, are legion and the patient must be made aware of them.

Azathioprine (Imuran®). Azathioprine is a purine analogue, which inhibits synthesis of nucleic acids. The primary effect on the immune system is interference with T- and B-cell proliferation. Azathioprine is used for treatment of patients with moderate to severe myasthenia alone or in combination with corticosteroids [71, 72]. It is critical to appreciate that azathioprine has a long onset to initial clinical response of at least 12 months. The efficacy of azathioprine in reducing the daily dose of corticosteroid and clinical outcome was demonstrated in a randomized trial. A steroid-sparing effect was only identified at 18 months of treatment. It is critical for the patient to receive a dose based on weight (1–3 mg/kg/day). Underdosing may lead to the false impression of a lack of efficacy. An increase of mean corpuscular

volume and decrease in lymphocyte counts are indicators of a biological effect of azathioprine [73].

About 10 % of patients upon initiation of therapy develop fever and flu-like symptoms necessitating discontinuation of the medication. Adverse reactions appear to be related to the activity of the thiopurine *S*-methyltransferase enzyme which metabolizes azathioprine [74]. Increased rates of lymphoma occur in patients treated with azathioprine, and this risk needs explanation to the patient. Monitoring of liver function tests and complete blood counts is necessary throughout the treatment course. Improvement tends to correlate with elevations of mean red blood cell volume.

Mycophenolate mofetil (CellCept®). Mycophenolate mofetil effects primarily T- and B-cell proliferation through inhibition of guanosine nucleotide synthesis. Initial evaluation of mycophenolate with brief follow-up indicated that it was effective in reducing corticosteroid dose and reduced AChR antibody levels leading to its common use [75]. Two randomized, controlled trials failed to demonstrate efficacy of mycophenolate for generalized MG [66, 76]; however, the trials have been criticized for several reasons, primarily their short duration [77, 78]. Mycophenolate mofetil is given at standard dose of 1 g twice daily, but I have increased the dose in patients with poor response and who are over 90 kg. Mycophenolate is generally well tolerated, except for initial minor gastrointestinal intolerance. Rarely, bone marrow depression may occur with anemia, thrombocytopenia, and leucopenia. Mycophenolate may increase the risk of malignancy, and occasional cases of progressive multifocal leukoencephalopathy have been reported, although not as yet in patients with MG.

Cyclosporine. Cyclosporine is derived from a fungus and is a cyclic undecapeptide with actions directed exclusively on T cells. Cyclosporine blocks T-helper-cell synthesis of cytokines, in particular interleukin (IL)-2 and IL-2 surface receptors. The agent also interferes with transcription of genes critical in T-cell function. Cyclosporine suppresses T-helper-cell-dependent function, maintains tolerance in transplant patients, and prevents experimental autoimmune MG. Cyclosporine has been used to treat myasthenics previously treated with thymectomy and corticosteroids with benefit [79, 80]. In the initial studies of treatment-resistant patients, doses of 5 mg/kg/day were used. Corticosteroids were discontinued or decreased in nearly all patients in clinical trials of the agent; however, 5 % of patients could not tolerate the drug. In general practice, adverse effects of hypertension and renal insufficiency limit its use, and in the last 10 years, use of the agent appears to have decreased among experts in the field.

Tacrolimus (Prograf®). Tacrolimus is a macrolide antibiotic, which inhibits calcineurin, as does cyclosporine. The agent may produce nephrotoxicity and hypertension as well as tremor and nausea. Tacrolimus has been evaluated in a randomized trial and large retrospective studies [81–83]. Taken together, the reports indicate efficacy and a safety profile superior to cyclosporine. The agent is provided in two divided doses of 0.075–0.1 mg/kg with an intention to achieve a trough level of 7–10 ng/ml.

Thymectomy. Since the popularization of thymectomy in 1940s and 1950s, the surgery has become a generally accepted treatment for patients with generalized MG. Rates of stable remission after thymectomy vary widely ranging from 15 to 90 % [7]. Comparison among studies is difficult because of variations in surgical approach (transcervical vs transsternal vs robotic vs videoscopic), time of follow-up, and population characteristics; however, the general consensus among experts is that thymectomy is an effective therapy [30, 84, 85], but a clinical trial is ongoing comparing patients randomized to thymectomy and prednisone versus prednisone alone [8]. No clear relationship among age, sex, thymic pathology, or severity of disease and clinical response to thymectomy is observed. With improvements in surgical technique, anesthesia, and respiratory care, operative morbidity and mortality approaches zero in recent reviews. Thymectomy is best performed within the first few years of diagnosis and usually recommended for patients without a significant contraindication to surgery and under age 65. The surgical method used to remove the thymus remains a point of controversy, but the greater the extent of thymic tissue removal, the better [86, 87].

Plasma Exchange. Although never subjected to a randomized control trial [88], plasma exchange is well established as treatment for severe exacerbations of MG and myasthenic crisis [89]. Typically exchanges are done to remove one to two plasma volumes three times per week up to six exchanges. In my experience, more than six exchanges are not beneficial. Patients may show improvement within 48 h while others may take up to 2 weeks [90, 91]. Treatment reduces immunoglobulin levels rapidly; however, rebound may occur in weeks, leading to clinical worsening, if concomitant immunosuppressive treatment has not begun. Its general usefulness is limited by its restriction to major medical centers and the frequent need for large-bore intravenous catheters, which leads to infectious complications. In rare patients, plasma exchange may be used as chronic therapy, but its use has not been studied.

Intravenous Immunoglobulin. Intravenous immunoglobulin IgG (IVIg) is used in similar clinical situations as plasma exchange. The primary mechanism of action is through anti-idiotype networks [92]. Treatment regimens range from 400 mg/kg/day dose for 5 days to 2 g/kg/day dose for 2 days. I prefer the latter. Treatment response may be rapid (days) but formal studies suggest 3 weeks as the expected time for a significant therapeutic benefit [93]. IVIg therapy may serve as an alternative to plasma exchange in individuals with poor vascular access or contraindications to plasma exchange [94]. IVIg may overall be a less-expensive treatment for hospitalized patients than plasma exchange [95]. IVIg is generally well tolerated with common adverse effects of headache

and nausea. However, the agent has been associated with life-threatening adverse effects of myocardial infarction, stroke, and pulmonary embolism. To date, no clear risk factors have been identified in patients for these complications. Among patients with congestive heart failure or renal insufficiency, IVIg may induce worsening of the underlying conditions. IVIg is used as chronic therapy in patients resistant to standard immunosuppressives to reduce the need for corticosteroids; however, such a practice has never undergone formal evaluation.

Other Treatments. Rituximab has been used for treatment of MG despite the lack of a significant database to warrant its use for AChR antibody-positive MG [96, 97]. In my opinion, it should only be used in treatment of patients who have failed several other immunosuppressive treatments. Cyclophosphamide is used to treat MG resistant to corticosteroids, and one study found half of the patients were asymptomatic after 1 year [98]. Some centers have utilized high-dose cyclophosphamide coupled with bone marrow reconstitution in an attempt to induce tolerance to the AChR, but in the few patients treated thus far, there have been patients that suffer recurrence of MG [99]. Methotrexate inhibits purine metabolism and thereby inhibits T-cell function. The agent has not been widely evaluated for therapy of MG. A blinded, controlled study, which was stopped prior to target recruitment, suggested the agent may have similar efficacy to azathioprine [100]. At the time of this writing, methotrexate is under study in a randomized controlled trial in the United States.

Prognosis

Generalized MG is no longer the grave disease it once was with life spans of patients being normal [101]. The natural history of MG moderates in severity after 5 years, but there is a subgroup of patients with chronic, moderate to severe disease. Improved outcome has occurred from the combination of modern critical care and immunosuppressive therapy. However, patients with severe weakness need to be identified and rapidly treated as mortality of patients hospitalized with MG exacerbations remains high [102]. Estimates vary but remission of weakness may occur in upwards of 80 % of patients. However, quality of life remains compromised [103], in large part due to immunosuppressive therapies with poor side effect profiles. Novel approaches are being taken to specifically target autoimmune pathology with some close to clinical trial evaluation [17, 104].

Special Situations

Treatment of Ocular Myasthenia. Care of patients with ocular myasthenia has its own special requirements [105–107]. The physician should appreciate that purely ocular manifestations, although not life-threatening, are often disabling, but that disability needs to be weighed against the complications of therapy. Some patients respond well to nonmedical therapy, such as ptosis crutches or tape although these are uncomfortable. Alternating eye patching will alleviate diplopia. Attempts may be made to treat ocular manifestations with ChE inhibitors which may improve symptoms adequately in some patients [107]. When diplopia or bilateral ptosis is disabling, corticosteroid treatment must be considered. Regimens for treatment of ocular myasthenia vary but, typically, involve starting at a dose of 10–20 mg with gradual increase every few days until symptoms are controlled. Half of the patients have a recurrence of manifestations with tapering of steroids. About 80 % of ocular myasthenics will develop generalized disease. There is a suggestion from a retrospective trial that corticosteroid treatment may reduce the risk of generalization, but a prospective trial is required to confirm this observation.

Myasthenia and Pregnancy. MG is not a contraindication to pregnancy [108, 109]. Women have highly variable course and the severity of MG may vary among pregnancies in the same individual [110]. The potential effect of MG treatments on the fetus is a concern. Mestinon and prednisone are safe, but all the immunosuppressives are potential teratogens and consideration needs to be given to the risk of harm to the fetus from the drug versus harm caused by significant myasthenic exacerbation. Despite the obvious concern of the parents, assessment of azathioprine use during pregnancy suggests that risk of birth defects is not increased [111]. There are no large studies of the effect of plasma exchange or IVIg in pregnant women but both appear to be safe. There is no reason to perform a thymectomy during pregnancy.

Approximately a third of infants of MG patients have neonatal myasthenia [112–114]. This is a transient disorder manifested by general weakness, difficulty feeding, and respiratory insufficiency in some. Such infants require supportive care and cholinesterase treatment. Weakness resolves over weeks without any residue or risk of development of MG later in life. Development of neonatal MG is independent of the clinical status of the mother and the mother may be asymptomatic. AChR antibody levels of the mother also do not predict occurrence of MG. An increased ratio of antibodies against the fetal AChR compared to the antibodies directed only against the adult AChR isoform correlates with the development of neonatal myasthenia. Commercial tests for this ratio are not available. Case reports exist in infants with arthrogryposis multiplex that were due to passage of antibodies against the fetal AChR, which severely compromised fetal muscle development [115, 116].

Treatment of the Myasthenia Gravis Patient with Thymoma. Ten percent of patients with MG have a thymoma. Usually, the thymoma is identified because of the manifestation of MG, but thymoma detection may predate and postdate the onset of MG by years. Such patients are more often men in the age range of 40–60 and are seropositive for AChR

and striational antibodies. Some studies suggest that thymoma-associated MG has a more severe clinical picture. Once a thymoma is detected, it should be removed, although the patient should be aware that the surgery is not to cure MG. If the tumor has broken through its capsule to involve adjacent tissue, local irradiation is necessary. Thymomas generally have good prognosis with surgical resection being curative. However, some thymomas are aggressive and produce widespread metastases. In the elderly patient with a contraindication to surgery, consideration may be given following the tumor radiologically, since many tumors are very slow growing [117–119].

Juvenile Myasthenia Gravis. The pathophysiology of children presenting with MG younger than 18 years is no different than the adult disorder. The incidence of juvenile MG is one per million with girls being more frequently affected with a ratio of 3:1. The disorder may be more common among the Chinese, Japanese, and African-American populations compared to Caucasians. Differential diagnosis and diagnostic methods are identical to adults; however, treatment considerations are more difficult. Prepubertal patients appear to have higher rates of spontaneous remission, and therefore, thymectomy has been recommended to be delayed by some. As in adults, treatment must be individualized and the parents educated regarding the complications of therapy. Care of the child with MG is more complex because of the complications of corticosteroids on growth and cosmetic changes. The risk of long-term immunosuppression is even a greater issue for the young compared to the elderly [120, 121].

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Lambert-Eaton Myasthenic Syndrome

49

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Introduction

Lambert-Eaton myasthenic syndrome (LEMS) is a neuromuscular transmission disorder, which was first recognized as a myasthenic-type illness in association with oat cell (small-cell) lung cancer in a 47-year-old man, who presented with fatiguable proximal leg weakness with absent tendon reflexes, swallowing difficulty, and arm fatigue [1]. Prolonged apnea followed succinylcholine administration during general anesthesia, and electrodiagnostic examination revealed a neuromuscular block. Manifestations of neuromuscular blockade reversed with intravenous injection of edrophonium.

After the introduction of more advanced, neurophysiological methods, Lambert, Eaton, and Rooke [2] (and reported fully by Eaton and Lambert [3]) distinguished six patients with lung cancer and myasthenic manifestations from patients with typical findings of myasthenia gravis. They described the classical electrophysiological abnormalities that are still used to determine the diagnosis of LEMS and identified the disorder as a "myasthenic syndrome." Two of their patients had small-cell lung cancer, and a further two had lesions identified on chest X-rays. Soon after the original reports, the clinical details of 30 patients were published from the same department [4, 5]. These papers highlighted the range of clinical and electrophysiological features of the syndrome. Included in these data were the first accounts of patients with "myasthenic syndrome" who had no signs of lung cancer, even after extended follow-up. Some patients with small-cell lung cancer had a marked improvement in myasthenic symptoms after successful treatment of cancer.

Etiology and Pathogenesis

The pathophysiology underlying the myasthenic syndrome was first described by Elmqvist and Lambert, [6] who later confirmed their findings in a larger series of patients [7]. Microelectrode recordings from intercostal muscle biopsies of patients with myasthenic syndrome revealed the nature of the neuromuscular transmission defect. Intracellular recordings from the end plate region of single muscle fibers showed that the miniature end plate potentials, produced by spontaneously released packets or "quanta" of acetylcholine, were normal in frequency and amplitude. However, the end plate potential amplitudes and the quantal content were reduced, increasing to normal with high-frequency nerve stimulation or increased calcium concentrations in the bathing solution. The defect in neuromuscular transmission was therefore discovered to be presynaptic, resulting in a reduction in the number of acetylcholine quanta released from the nerve terminal in response to a stimulus. The drug guanidine, capable of increasing the release of acetylcholine with each nerve impulse, improved neuromuscular transmission and symptoms of fatigue.

The suggestion of an autoimmune etiology in LEMS arose partly from the association between noncarcinomatous LEMS and other autoimmune disorders such as thyroid disease and pernicious anemia; [8] this link was also later established in a large series of LEMS patients in whom organ-specific autoantibodies were found in 24 % with

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small-cell lung cancer (SCLC) and 44 % with no detectable lung cancer [9]. Evidence of an autoimmune basis came additionally from the observations that (1) passive transfer by intraperitoneal injection of LEMS IgG into mice resulted in neuromuscular electrophysiological abnormalities identical to those seen in intercostal muscle in vitro studies on LEMS patients, [10–12] (2) passive transfer of LEMS from mother to child has been described, and (3) significant clinical and electromyographic improvement in LEMS patients without SCLC occurred after plasma exchange [10] and sustained benefit with immunosuppressive treatment [13]. Furthermore, LEMS is strongly associated with HLA-B8 and the Ig heavy chain marker Glm(2) [14, 15].

Subsequent studies suggested that the antibodies responsible for the characteristic electrophysiological abnormalities seen in LEMS patients were directed against voltage-gated calcium channels (VGCCs) at the motor nerve terminal. First, Lambert and Elmqvist had commented that in their electrophysiological recordings from intercostal muscle biopsy specimens from LEMS patients, the increase in end plate potential quantal content during repetitive nerve stimulation was similar to the low Ca^{2+} concentration effect at the neuromuscular junction [7]. Second, reduced evoked transmitter release at various extracellular calcium concentrations and smaller calcium currents were recorded in ex vivo nerve-muscle preparations from mice injected with LEMS IgG [16, 17]. Third, freeze-fracture electron microscopy of motor nerve terminals in LEMS patients [18] and in mice injected with LEMS IgG [18] showed the same quantitative loss of active zone particles, believed to be the morphological representation of VGCCs. Reduction in VGCC density appears to depend on the cross-linking of adjacent active zone particles by the divalent IgG. Loss of active zone particles was only seen in animal studies when divalent LEMS IgG or F(ab')2 aggregated and depleted the active zone particles, whereas monovalent Fab had no effect [19]. Later studies confirmed the presence of N-type anti-VGCC antibodies, detected by immunoprecipitation of radiolabelled Ca^{2+} channels, in about 90 % of patients with LEMS in one series [20] but only 44–52 % of patients in another [21]. Subsequently, antibodies to P/Q-type VGCCs were discovered in a greater proportion of LEMS patients (see below).

Neuronal VGCCs are multimeric proteins consisting of five subunits, α_1, β, α_2, δ, and γ [22]. The α_1-subunit, which consists of four homologous repeats, each having 6 transmembrane regions, forms the central ion pore. It is associated with the disulfide-linked α_2- and δ-subunits and a cytoplasmic β-subunit that modifies the channel's current amplitude, voltage dependence, and activation properties. Different subunit isoforms give rise to distinct channel subtypes.

Each VGCC subtype is identified by its specific pharmacological and electrophysiological properties, and the gene encoding the α_1-subunit differs for each VGCC subtype. Therefore, differences in functional properties between each VGCC subtype are in part due to differences in α_1-subunit structure [23, 24]. Both N- and P/Q-type VGCCs are located primarily on neurons, whereas L-type VGCCs are expressed not only in neural tissue but also on cardiac and endocrine cells [25]. The use of VGCC-blocking agents, such as dihydropyridine, nitrendipine, or the neurotoxins ω-agatoxin IVA and ω-conotoxin GV1A, demonstrates that neurotransmitter release at the mammalian neuromuscular junction is mediated principally by P/Q-type, rather than N- or L-type, VGCCs [26, 27]. Immunocytochemical experiments show that immunoreactivity to α_{1A}, the gene thought to encode for the pore-forming α_1-subunit in P/Q-type VGCCs, is localized presynaptically in areas thought to be motor nerve terminals, thereby providing further evidence of P/Q-type VGCCs at human neuromuscular junctions [28].

The antigenic target on the VGCC itself is not fully established. In addition, antibodies to other synapse-associated proteins can be found in the serum of LEMS patients. Antibodies to synaptotagmin, a synaptic vesicle protein, are found in LEMS patients [29], and immunization of rats with a synthetic peptide analogous to synaptotagmin induces physiological changes characteristic of LEMS [30]. The significance of these findings is not clear. Also, antibodies to the intracellular portion of the β-subunit of the VGCC were found in 55 % of patients with LEMS [31]. Probably, these determinants are not the primary target of the immune response, and these antibodies might arise because their antigens are released and presented due to immune-mediated attack on the VGCCs.

Two-thirds of LEMS patients with SCLC, and 43 % of SCLC patients without LEMS, have antibodies to one of the SOX or Hu proteins in their serum [32, 33]. SOX proteins are transcription factors that have critical roles in the regulation of developmental processes. Hu proteins are expressed in neurons and play an important role in the development and maintenance of the nervous system. Both proteins are also expressed in SCLC cells. Most likely, the immune response elicited by the SCLC is directed not only against VGCC but also to other tumor-related proteins like SOX and Hu proteins.

SOX antibodies had a sensitivity of 67 % and a specificity of 95 % to discriminate between LEMS with SCLC and nontumor LEMS. No difference in survival was observed between SOX positive- and SOX-negative SCLC patients [32, 34].

The functional effect of LEMS anti-VGCC antibodies on specific VGCC antigenic targets has been studied by recording calcium influx in human embryonic kidney cells transfected with different cloned α_1-subunits. LEMS serum most effectively blocked those cells expressing the α_{1A}-subunit type, as found in P/Q-type VGCCs, indicating that the α_{1A}-subunit of P/Q-type VGCCs may be a functionally important immunogen in LEMS [35]. Further studies found antibodies to recombinant peptides corresponding to the pore-forming S5-6 extracellular region of the 4 domains that form the α_{1A}-subunit of the P/Q-type VGCC in up to 30 % of patients with

LEMS [36]. Electrophysiological studies of rats immunized with the S5-6 peptide showed changes similar to previous studies of animal models of LEMS.

The presence of SCLC in over half of LEMS patients led to the hypothesis that this tumor, of presumed neuroectodermal origin [37], which express L-, N- and P-type VGCCs [38, 39], was capable of triggering a primary autoimmune response, where antibodies to tumor VGCCs cross-react with those at the motor nerve terminal, resulting in LEMS. Initial support for this theory came from Roberts et al. [40] who showed that LEMS IgG is capable of inhibiting K^+-stimulated Ca^{2+} flux in cultured human SCLC cell lines. Subsequent studies showed that LEMS IgG can block Ca^{2+} flux in SCLC cell lines by blocking more than one type of VGCC subtype [38, 41]. The clinical improvement, or even remission of LEMS, that can occur following successful antitumor therapy supports the theory that in SCLC-LEMS, the tumor is capable of triggering the autoimmune response. Immunocytochemical studies of SCLC tumors from patients with LEMS, compared to those without, show that tumor macrophage infiltration and MHC class I expression are less in the tumors of patients with LEMS [42]. This could imply that SCLC antigenic determinants trigger the autoimmune response resulting in immune-mediated tumor cell destruction in LEMS.

The autonomic dysfunction that occurs in LEMS also appears to be caused by anti-VGCC antibodies. To assess the effect of anti-VGCC antibodies on postganglionic autonomic neurons, mice were injected with IgG from LEMS patients or controls. The release of transmitter from parasympathetic and sympathetic neurons was recorded using muscle contraction amplitude in bladder strips and vas deferens [43]. LEMS IgG-treated mice showed impaired transmitter release principally through P/Q-type VGCCs.

Although VGCCs are important in stimulus-secretion coupling in endocrine tissues, pituitary hormone release or pancreatic β-cell function was not impaired in ten LEMS patients [44]. This result may be due to upregulation of non-P/Q-type VGCCs in pancreatic and pituitary cells or to antigenic differences between isoforms of P/Q-type VGCCs expressed in neurons and endocrine cells.

Pathology

Muscle biopsy is usually unhelpful in the diagnosis of LEMS, since a variety of mild, nonspecific changes occur, or normal muscle fibers are usually found. However, distinctive changes were reported in a muscle biopsy from one LEMS patient, which led to the diagnosis of LEMS in another patient with similar muscle biopsy findings [45]. Serial muscle biopsies showed progressive atrophy and type 1 muscle fiber loss, resulting in marked type 2 fiber predominance. The mechanism behind the alteration in fiber-type distribution is not known. Type 2 fiber predominance in LEMS was also reported by others [46, 47].

Clinical Presentation

The clinical features of LEMS, as first described in detail by Rooke and colleagues [4], were further defined as a syndrome in a large study by O'Neill et al. [9] and recently reviewed by Titulaer et al. [48].

Extremity Weakness

Leg weakness is universal and the presenting complaint in over three-quarters of LEMS patients [49]. The weakness is classically proximal, and patients have difficulty climbing stairs or walking uphill [4]. Pain in the weak muscles occurs much less frequently [9]. Classically, progressive augmentation of muscle strength is seen during the first few seconds of maximal voluntary contraction. Continued, prolonged voluntary effort, however, does lead to fatigue, as in myasthenia gravis. Muscle wasting is rare even after prolonged disease duration. Limb weakness can be worse in hot weather and improve in the cold [9]. Although less common than leg weakness, arm weakness occurs in over three-quarters of LEMS patients.

Oculomotor or Bulbar Weakness

During progression of the disease, weakness spreads proximally to distally and from caudal to cranial. Thus, in general, oculomotor and bulbar weakness appears later and only in more severely affected patients. This is in contrast to myasthenia gravis, where weakness most often starts in oculomotor or bulbar muscles and then descends. Isolated weakness of extraocular muscles in LEMS is rare [50].

Tendon Reflexes

Unlike myasthenia gravis, deep tendon reflexes are typically depressed or absent. LEMS patients can display posttetanic potentiation of reflexes, in that initially absent or depressed tendon reflexes can appear if tested directly after a brief voluntary contraction of the tested muscle. This is a unique and very useful clinical feature for diagnosing LEMS, although not very sensitive [51, 52].

Autonomic Manifestations

Although described in the original clinical descriptions of LEMS [4], dry mouth, impotence, blurred vision, and

constipation were first considered to be a specific cholinergic dysautonomia by Rubenstein et al. [53]. Of all autonomic disturbances seen in LEMS, by far the most common is dry mouth, present in about 75 % of patients, followed by erectile dysfunction and constipation [9, 48]. Patients may also have orthostatic hypotension, micturition difficulties, impaired sweating, dry eyes, and blurred vision [48].

Respiratory Insufficiency

LEMS may present with respiratory failure requiring assisted ventilation [54]. Occasionally, muscle relaxants, such as curare, during general anesthesia can produce prolonged apnea due to neuromuscular blockade [9].

Tumor Association

LEMS can occur at almost any age and has been reported in a 9-year-old child [55]. The mean age of onset of neurological manifestations for LEMS patients is about 50 years, but those with associated lung cancer tend to develop symptoms later (onset at about 58 years) [9, 48]. Over half of patients develop small-cell lung cancer (SCLC) [48] most commonly after the onset of LEMS, usually within 2 years. Some decades ago, a few cases were described with a latency of 5 or 6 years. Most likely this was due to less sensitive radiographical techniques for tumor screening. In recent series, screening with CT thorax or PET scans detected SCLC in 91 % of the patients within 3 months and in 96 % within 1 year after the diagnosis of LEMS. Using only chest X-ray is inadequate for the detection of an SCLC [56].

Patients with SCLC and LEMS have similar clinical features as those without lung cancer, but LEMS patients with an SCLC have a more progressive course of disease [49]. Based on this observation, a simple and sensitive clinical score was developed that predicts the presence of an SCLC. With this DELTA-P score, the probability for an SCLC can be calculated at the time of diagnosis of LEMS by solely using clinical criteria (Fig. 49.1) (Table 49.1) [57].

The overall prevalence of LEMS among SCLC patients is estimated to be about 1–3 % [58]. With such a prevalence of LEMS among a rather common cancer, many patients likely are not diagnosed, with muscle weakness probably being attributed to the underlying tumor or chemotherapy treatment. LEMS is reported with tumors other than SCLC (Table 49.2); however, some of these reports date to before VGCC antibody testing was available.

We feel that most of these tumors have co-occurred due to chance. However, it cannot be excluded that some of these tumors, like thymomas, prostate cancer, and lymphoproliferative disorders, may have a causal relationship with LEMS. Proof for this relationship can be obtained from histological studies, showing that the tumor has neuroendocrine characteristics [67].

Differential Diagnosis

LEMS patients are often initially given an inappropriate diagnosis. Over half of patients in one study were misdiagnosed, with the most common alternative diagnosis (in 20 %) being myasthenia gravis [9, 48]. Other diagnoses included primary myopathy, cervical myelopathy, polymyositis, and polymyalgia rheumatica. LEMS differs clinically from

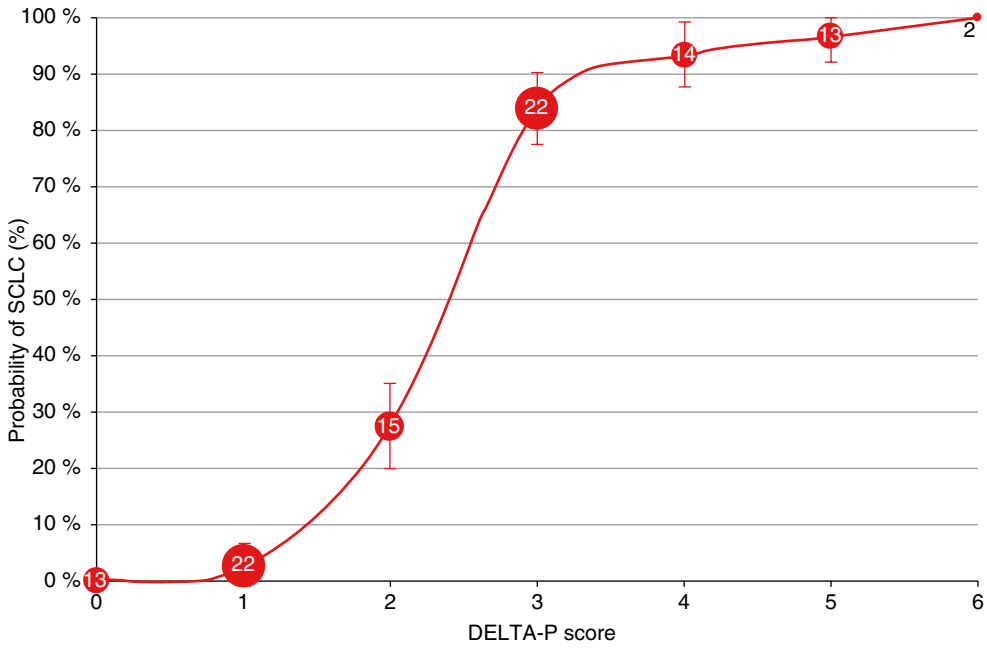

Fig. 49.1 DELTA-P score. Predicted percentage of SCLC in patients with LEMS, based on the Dutch-English LEMS Tumor Association Prediction (DELTA-P) score. Point sizes proportionate to the number of patients with a specific score also represented by the percentage inside the circle. Vertical bars indicate SEM(57) (Reprinted with permission from Titulaer et al. [57])

Table 49.1 Items of the DELTA-P score

	Categories		Score
D	**D**ysarthria, dysphagia, neck weakness: bulbar weakness	Absent	0
		Present	1
E	**E**rectile dysfunction	Female	0
		Male: absent	0
		Male: present	1
L	**L**oss of weight	Absent or < 5 %	0
		≥ 5 %	1
T	**T**obacco use at onset	Absent	0
		Present	1
A	**A**ge of onset	< 50 years	0
–		≥ 50 years	1
P	Karnofsky **p**erformance score	70–100	0
		0–60	1
	DELTA-P score		0–6

DELTA-P score. This score helps to estimate the chance for the presence of an SCLC in patients presenting with clinical signs and symptoms of LEMS (see also Fig. 51.1) [57]

Table 49.2 Malignancies other than SCLC reported to be associated with LEMS

Intrathoracic malignancies
Thymoma [59–62]
Carcinoid tumor [63]
Non-Hodgkin lymphoma [64]
Leukemia [65, 66]
Prostate cancer [67–69]
Breast cancer [9]
Cervical cancer [70]
Malignant bone tumor [71]
Transitional cell cancer of the bladder [72]

myasthenia gravis in that ocular manifestations are much less common at initial diagnosis and during the course of the disease, and the weakness ascends from the legs upward, while in myasthenia it develops in the opposite way [50]. Proximal leg weakness characteristically occurs in LEMS, where muscle power can be augmented after a brief voluntary contraction, a finding not displayed in myasthenia gravis. Also, most LEMS patients have absent or depressed reflexes and symptoms of dysautonomia. Thymectomy is not beneficial in LEMS, unlike myasthenia gravis [73], and the thymus is usually atrophic [9]. The different pattern of autoantibodies found and the incremental muscle responses following voluntary contraction on electromyography (EMG) should distinguish LEMS from myasthenia gravis. Rarely, LEMS and myasthenia gravis coexist in the same patient.

Predominant proximal weakness suggests a diagnosis of myopathy, and when associated with SCLC, the possibility of carcinomatous myopathy or polymyositis in association with cancer may be considered. Further confusion may arise when needle EMG demonstrates brief, small polyphasic units consistent with a myopathy; however, with sustained contraction, the interference pattern normalizes with increased motor unit action potential amplitudes. Type 1 muscle fiber atrophy on muscle biopsy also suggests the diagnosis of myopathy.

Incidentally, LEMS patients are misdiagnosed with neuropathy. Diminished compound muscle action potentials observed by nerve conduction studies may be inappropriately ascribed to a neuropathy, especially if the patient has received chemotherapy for treatment of cancer or thought to have a "carcinomatous neuropathy" [74]. The lack of sensory symptoms and the distribution of weakness to proximal muscles should alert the clinician.

Finally, the clinician must not confuse patients with LEMS and chronic fatigue syndrome. Such patients may demonstrate greater weakness by examination than expected by their level of function. Needle EMG may show a reduced or variable recruitment pattern, which may superficially resemble LEMS, but nerve conductions reveal normal compound muscle action potentials.

Diagnosis

The diagnosis of LEMS can often be made from the distinctive clinical features. The laboratory diagnosis of LEMS depends primarily on detection of specific antivoltage-gated calcium channel autoantibodies or characteristic electrodiagnostic findings.

Anti-Voltage-Gated Calcium Channel Antibodies

Using a standard radioimmunoassay, the detection of antibodies against ^{125}I-ω-CmTx MVIIC-labeled (P/Q-type) VGCCs in significant titers in 85–90 % of LEMS patients is possible [75]. About 33 % of these sera are also positive for ^{125}I-ω-CgTx GVIA-labeled (N-type) VGCC antibodies [75]. In the original study, anti-VGCC antibody titers were not significantly raised in healthy or disease control patients. In subsequent work, anti-P/Q-type VGCC antibodies were detectable in 1–4 % of patients with SCLC and no neurological symptoms [32, 76]. Also, 24 % of patients with SCLC and paraneoplastic cerebellar degeneration had anti-P/Q-type VGCC antibodies, half of whom had no manifestations of LEMS [77].

Electrodiagnostic Features

Eaton and Lambert first defined the classical electrophysiological characteristics of LEMS [3]. They demonstrated, unlike myasthenia gravis, the amplitude of the resting compound muscle action potential (CMAP) obtained by supramaximal nerve stimulation was reduced. Remarkably, transient further decrement was seen with slow repetitive

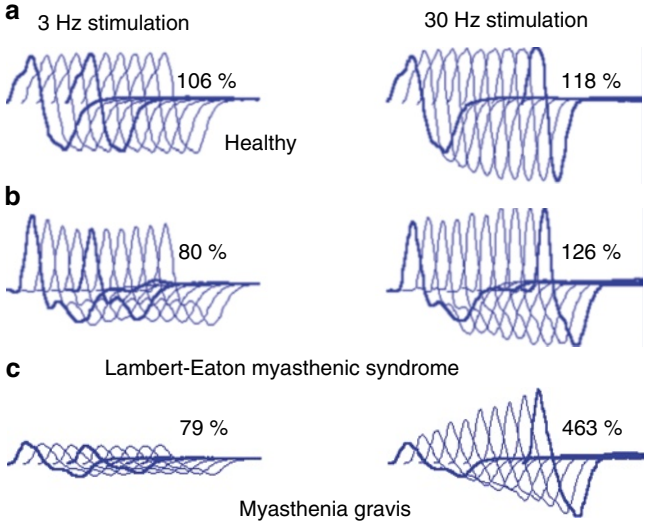

Fig. 49.2 Electrodiagnostic repetitive nerve stimulation studies. Electrodiagnostic repetitive nerve stimulation studies of the adductor digiti minimi muscle in a healthy person (**a**), in a patient with MG with acetylcholine receptor antibodies (**b**), or in a patient with LEMS (**c**). The *left-hand column* shows the results after low-frequency 3 Hz nerve stimulation. The *right-hand side* shows the recordings obtained directly after 20 s of maximal voluntary muscle contraction. Both patients with MG and LEMS show decrement at low-frequency stimulation (**b**, **c**). Only the patient with LEMS shows increment more than 60 % after maximal voluntary contraction (C) (Courtesy to prof. Gert van Dijk for providing these figures)

maximal nerve stimulation (RMNS) at rates less than 10 per second. However, following high-rate repetitive nerve stimulation (>10 Hz) or 10 s of maximal voluntary contraction, there was an increase in CMAP amplitude, typically over 100 % (see Fig. 49.2) [5].

These results suggested that the neuromuscular transmission disorder was presynaptic. The combination of a first lowered CMAP, decrement on low-rate RMNS, and increment after high-rate RMNS in a patient with acquired proximal muscle weakness is pathognomonic for LEMS.

RMNS may be abnormal in other neuromuscular disorders. Standard nerve conduction studies and needle EMG must be considered to exclude other muscle and anterior horn cell diseases. Needle EMG demonstrates increased low-amplitude, short-duration motor unit potentials. Amplitudes may enlarge with sustained contraction.

In one study of electrophysiological abnormalities of LEMS, the muscle most likely to detect the classical changes was the abductor digiti minimi (ADM). Although weakness predominates in proximal muscles, stimulating the ulnar nerve at the wrist with recording from the ADM is very sensitive in detecting typical electrophysiological abnormalities in LEMS [78]. All patients in this study had a reduced resting CMAP amplitude in at least one distal arm muscle. In another study, incremental responses of 60 % rather than 100 % were sufficient to diagnose LEMS with the same specificity over healthy control patients [52]. Overall, almost all LEMS patients are likely to have abnormal incremental CMAP responses over 100 % in ADM, abductor pollicis brevis, or anconeus after 10 s of voluntary contraction [78, 79]. One must appreciate that the increment of the CMAP is in fact a normalization of the previous low CMAP amplitude. For example, 300 % increment implies that the original CMAP was maximally 25 % of normal reference values. The higher the first original CMAP is, the less the increment that can be obtained.

In clinical practice, the differential diagnosis is often whether a patient has LEMS or MG, rather than having to distinguish between a patient with LEMS and a healthy subject. The postsynaptic disorder of myasthenia gravis characteristically shows a decremental response in CMAP amplitude. In myasthenia gravis, no significant incremental pattern is found, because the original CMAP is not or only marginally decreased. This is in keeping with the results from 18 myasthenia gravis patients [80], who showed that the incremental response in ADM seen after maximal voluntary contraction was under 40 % in 17 patients with only one outlier registering an increment of about 70 %. A 60 % increment was observed in only 4 of 538 patients with myasthenia gravis by high-rate stimulation testing and in none by postexercise electromyographic testing. The use of a 60 % increment showed a sensitivity of 97 % for the diagnosis of LEMS and a specificity of 99 % in excluding myasthenia gravis [52].

Single-fiber EMG, which detects defects of neuromuscular transmission with high sensitivity, has been used to diagnose LEMS. Abnormal jitter and blocking, typical of defective neuromuscular transmission, are seen in all LEMS patients [9, 81]. While this technique is highly sensitive, it lacks specificity. The degree of jitter and blocking seen in LEMS is usually less when high-frequency nerve stimulation is used, a finding more specific to LEMS [81, 82].

Treatment

The weakness of LEMS responds well to treatment with 3,4-diaminopyridine (3,4-DAP) [83, 84], which in animals has been demonstrated to block voltage-sensitive potassium channels, thereby increasing evoked transmitter release by prolonging the action potential duration [85, 86] and increasing calcium influx at the nerve terminal [87]. Most patients commence 3,4-DAP treatment at 10 mg four times daily, increasing up to a 100 mg maximum per day. Symptomatic improvement usually occurs within an hour of ingestion. A prospective, placebo-controlled, double-blind trial of 3,4-DAP in 12 LEMS patients (with and without associated SCLC) showed its effectiveness in increasing muscle strength and improving autonomic symptoms at doses up to 100 mg/day [83]. A Cochrane review described the results of four

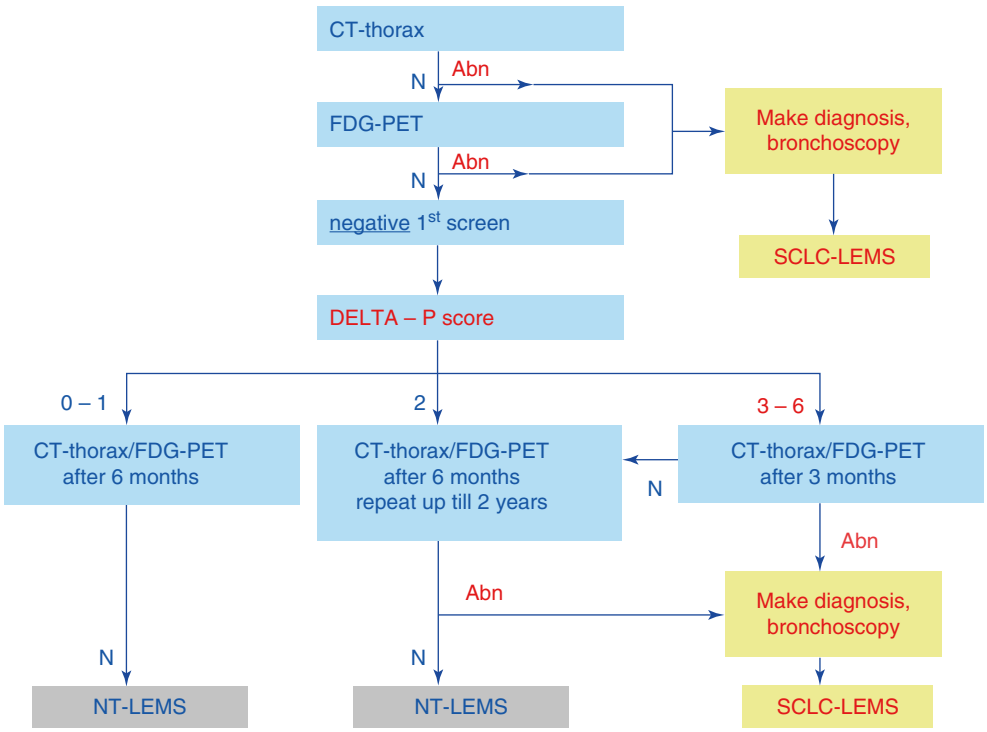

Fig. 49.3 Screening for SCLC. Scheme for screening for SCLC [56] (Reprinted with permission from Titulaer et al.[48]). To screen for SCLC, the DELTA-P score can help to estimate the chance that an SCLC might be present (see Fig. 49.1)

randomized trials in 54 patients with LEMS [88]. A significant improvement in muscle strength score, myometric limb measurement, or CMAP amplitude after treatment was reported. Common associated symptoms are perioral and distal paresthesias or less frequently gastrointestinal symptoms. In rare cases, an overdosage has caused epileptic attacks. At a dose around 100 mg a day, seizures have been described [89, 90].

Pyridostigmine, although not as effective as in myasthenia gravis, benefits some patients with LEMS [83, 91]. Guanidine has been used as an alternative symptomatic treatment of LEMS, although serious side effects such as bone marrow suppression and renal failure can occur [92]. Guanidine at doses of less than 1,000 mg/day in combination with pyridostigmine may be particularly useful with limited severity of side effects.

LEMS associated with SCLC should not modify treatment of the underlying cancer. Anticancer chemotherapy also has immunosuppressive effects which may contribute to the improvement of the neurological disorder. Following specific tumor therapy (chemotherapy, radiotherapy, or lung resection), seven of 11 LEMS patients who survived for more than 2 months had substantial and progressive neurological improvement [93]. One patient remained free of tumor recurrence and symptoms of LEMS over 12 years since lobectomy and radiotherapy for SCLC [94].

For all LEMS patients, thorough screening for SCLC is mandatory. CT of the thorax or 18 F-fluorodeoxyglucose (FGD)-PET or even an integrated FDG-PET/CT is these days available to screen for SCLC. Every patient with LEMS should be screened at least twice. A chest radiograph has insufficient sensitivity for diagnosis and should not be used for screening. After an initial negative screening, the DELTA-P score can be used to estimate the risk for an SCLC and help to decide how frequent further screening is necessary (Fig. 49.3) [57].

Although most patients benefit from symptomatic treatment (even after successful treatment of SCLC), often the response is incomplete, or limited, and other disease-modifying treatments are required (see treatment algorithm, Fig. 49.4).

For patients with severe symptoms requiring prompt treatment, a plasmapheresis course of five exchanges produces short-term clinical improvement [95]. Repeated exchanges result in similar improvement. This treatment is particularly useful in LEMS patients with initial respiratory depression [54]. In general, LEMS has a more indolent course of disease, and in contrast to autoimmune myasthenia gravis, the need for ventilatory support is rare.

Intravenous immunoglobulin (IVIg) was first reported to benefit an LEMS patient with clinical and electrophysiological improvement evident 2 weeks after treatment, which lasted for 10 weeks before relapse [96]. In a randomized, double-blind, placebo-controlled crossover trial of IVIg in nine LEMS patients, significant improvement occurred in strength that peaked at 2–4 weeks and lasted up to 8 weeks following 1 g/kg of IVIg given on two consecutive days [97]. There was also a significant reduction in mean P/Q-type VGCC antibody titers. This effect was not thought to be due to an anti-idiotypic neutralizing action as there was no

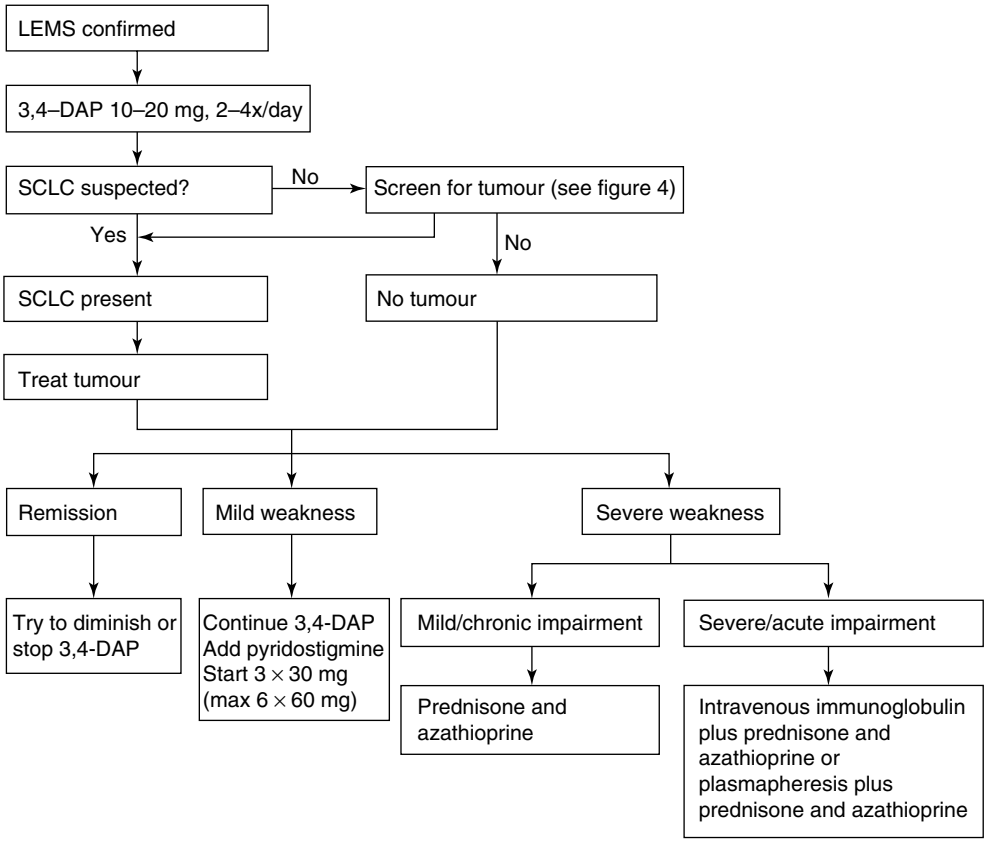

Fig. 49.4 Treatment of LEMS. A treatment algorithm to provide a guide to therapy in LEMS ((Ref. Lancet Neur); reprinted with permission from Titulaer et al.[48])

evidence of in vitro direct neutralization of VGCC antibodies by radioimmunoassay. From our experience, ongoing use of regular IVIg has been disappointing, with gradual reduction in clinical effectiveness occurring.

When disease remission does not occur after symptomatic or antitumor therapy, or after passive treatment such as plasma exchange, immunotherapy with prednisolone should commence. Alternate day prednisolone can result in full clinical remission in some patients, although the response is usually slow [95]. The initial prednisolone dose is up to 1–1.5 mg/kg on alternate days. For patients without detectable SCLC, concomitant daily azathioprine at doses up to 2.5 mg/kg can result in sustained remission, even allowing for reduction in the prednisolone dose [95]. Therefore, when clinical remission is achieved in LEMS patients taking both prednisolone and azathioprine, the prednisolone dose should be tapered to the minimum required to maintain remission. In patients intolerant of azathioprine, oral cyclosporine in doses up to 3 mg/kg body weight should be considered.

Prognosis

A longitudinal clinical, electrophysiological, and immunological study of 62 LEMS patients with and without SCLC during extended follow-up was matched for sex, age at diagnosis of SCLC, tumor extent (limited or extensive), and treatment (chemotherapy or radiotherapy). Survival data from 15 patients with SCLC and LEMS was compared with 81 patients with SCLC alone [98]. Median survival time from SCLC diagnosis was significantly longer in patients with SCLC and LEMS (17 months) compared with patients with SCLC alone (10 months), thus suggesting that the immunological response targeting tumor VGCCs in LEMS may retard SCLC growth. This prolonged survival was confirmed in a second study, comparing 138 SCLC patients to 53 patients with SCLC-LEMS (Fig. 49.5).

Further supportive evidence for this hypothesis arises from data [99] on cultured SCLC cells in vitro, which suggest that VGCC-blocking agents reduce tumor cell proliferation. However, this favorable prognosis may be related to lead-time bias, in that once LEMS is diagnosed, the vigilance for associated lung cancer may be increased.

In the 47 LEMS patients without SCLC, sustained clinical remission was achieved by 20 (43 %), almost all of whom still required significant doses of steroids and azathioprine (mean alternate day dose of prednisolone after 5 years' treatment and follow-up was 25 mg) [100]. Among clinical scores of muscle strength, anti-P/Q-type VGCC antibody titers, CMAP amplitudes and postexercise increments, and disease duration at first presentation, the only predictor of sustained clinical remission was muscle strength score, i.e., the stronger

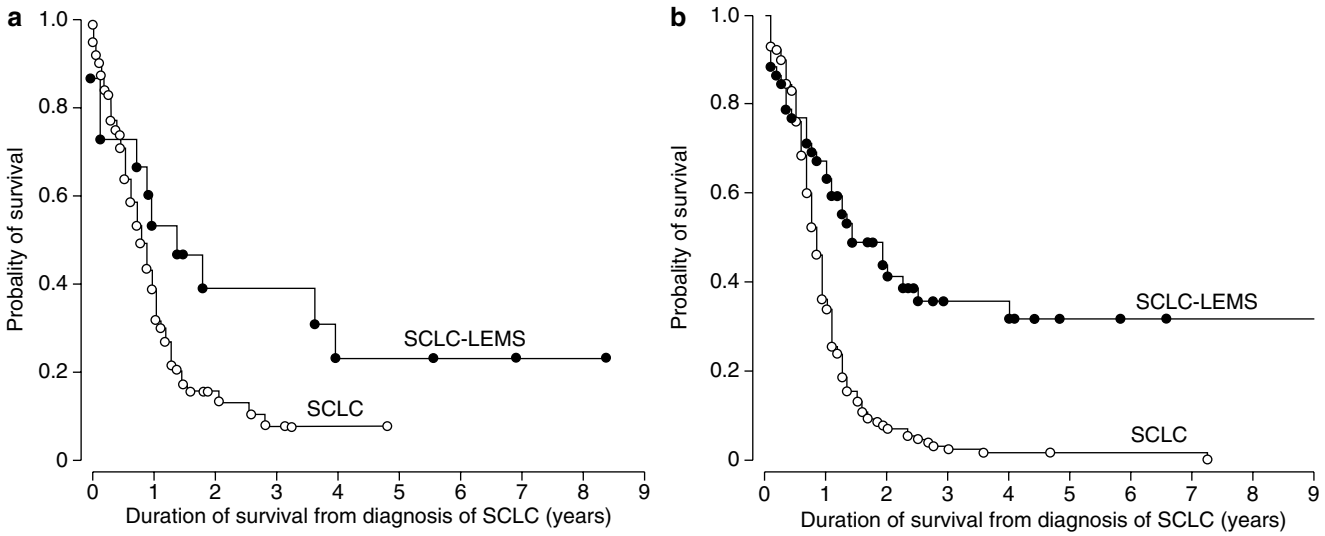

Fig. 49.5 Survival of LEMS patients with SCLC. Kaplan-Meier survival curves of small-cell lung cancer patients with (SCLC-LEMS) and without (SCLC) Lambert-Eaton myasthenic syndrome. Patients with LEMS and SCLC have a significantly longer median survival from the time of diagnosis of the lung tumor. At the *left side*, an English cohort ($p = 0.048$; reprinted with permission from Maddison et al., The Lancet [98]) and on the *right side*, a Dutch cohort of patients ($p < 0.0001$; reprinted with permission from Titulaer and Verschuuren, Ann N Y Acad Sci, 2008 [101])

the patient at initial presentation, the more likely the achievement of clinical remission. Conversely, ten patients (22 %) with markedly weak arms and legs required a wheelchair after a median 7 years' follow-up. Immunological and electrophysiological measurements are useful objective parameters for following disease progression and response to immunosuppression in individual patients but are not significant predictors of disease outcome in LEMS.

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Botulism

50

Mark Keezer, Ruba Benini, and Colin Chalk

Introduction

Although botulism was not formally described until the nineteenth century, evidence exists that as early as the tenth century, the disease was recognized when Emperor Leo IV of Byzantium outlawed the manufacture of blood sausage [1]. He did so after observing an outbreak of blood sausage-associated food poisoning which had proven fatal. In the early nineteenth century, the German physician and Romantic poet Justinus Kerner systemically described 76 patients with "lethal poisoning occurring… through the consumption of smoked sausages" [2]. As a result of his clinical and experimental observations, Kerner correctly proposed that this "sausage poisoning" occurred after the consumption of a biological toxin, which he referred to as a "fatty acid," a toxin which required an anaerobic environment to cultivate, that acted on both the motor and autonomic systems and that was lethal in even very small doses. Initially called Kerner's disease [2], the syndrome later became known as botulism (derived from *botulus,* the Latin word for sausage) due to its original gastronomic association [3]. Several decades later, in 1897, the microbiologist Emile Pierre-Marie van Ermengem isolated the responsible organism after an outbreak of botulism in the small Belgian village of Ellezelles [4].

Etiology and Pathogenesis

Botulism is an acute paralytic illness caused by a neurotoxin produced by the bacterium *Clostridium botulinum*, a sporulating, obligate anaerobic, gram-positive bacillus [5]. The bacterium and its spores are found ubiquitously in soil and aquatic sediment as well as in the gastrointestinal tracts of grazing livestock and animal wildlife [6]. Although *C. botulinum* is generally innocuous, it does produce regular outbreaks of disease in wildlife. Avian botulism generally leads to the death of 50,000, and on occasion as many as 1,000,000, wetland birds per year in North America during local epidemics [7].

There are seven types of *C. botulinum*, differentiated by the antigenicity of the neurotoxin produced (types A through G). Types A, B, and E are most often the cause of human botulism [8] although there are occasional cases of type F [9]. Types C and D are associated with disease in animals and birds, while type G has never been clearly implicated in either human or animal disease [10]. Rare cases of botulism due to toxigenic *Clostridium butyricum* and *Clostridium baratii* have occurred [11–14].

Botulinum neurotoxin (BoNT) is among the most potent known toxins. Estimates suggest that as little as 1 g of aerosolized BoNT could lead to the death of over 1.5 million people [15]. The potency of the toxin is enhanced by the resilience of *C. botulinum* spores. Temperatures of 120 °C are required to kill the spores [16]. *C. botulinum* spores can survive 30 years in a fluid medium, likely even longer in a dry medium [17], and have even been shown to survive 10 months in a simulated Martian environment [18].

Much of the detailed molecular pathophysiology of BoNT's actions is now understood (Fig. 50.1). BoNT is a 150 kDa protein which compromises the release of synaptic vesicles from presynaptic cholinergic nerve terminals into the synaptic cleft [20]. BoNT possesses a heavy and a light chain bound by a disulfide bond. The 100 kDa heavy chain is responsible for binding to an unknown receptor on the presynaptic cell membrane. Endocytosis ensues and dissociation of the heavy and light chains allows the 50 kDa light chain to cross the vesicular membrane and enter the neuronal cytoplasm. Having arrived in the axon terminal, the BoNT light chain, as a zinc-dependent endoprotease, interrupts neurotransmitter exocytosis into the synaptic cleft through

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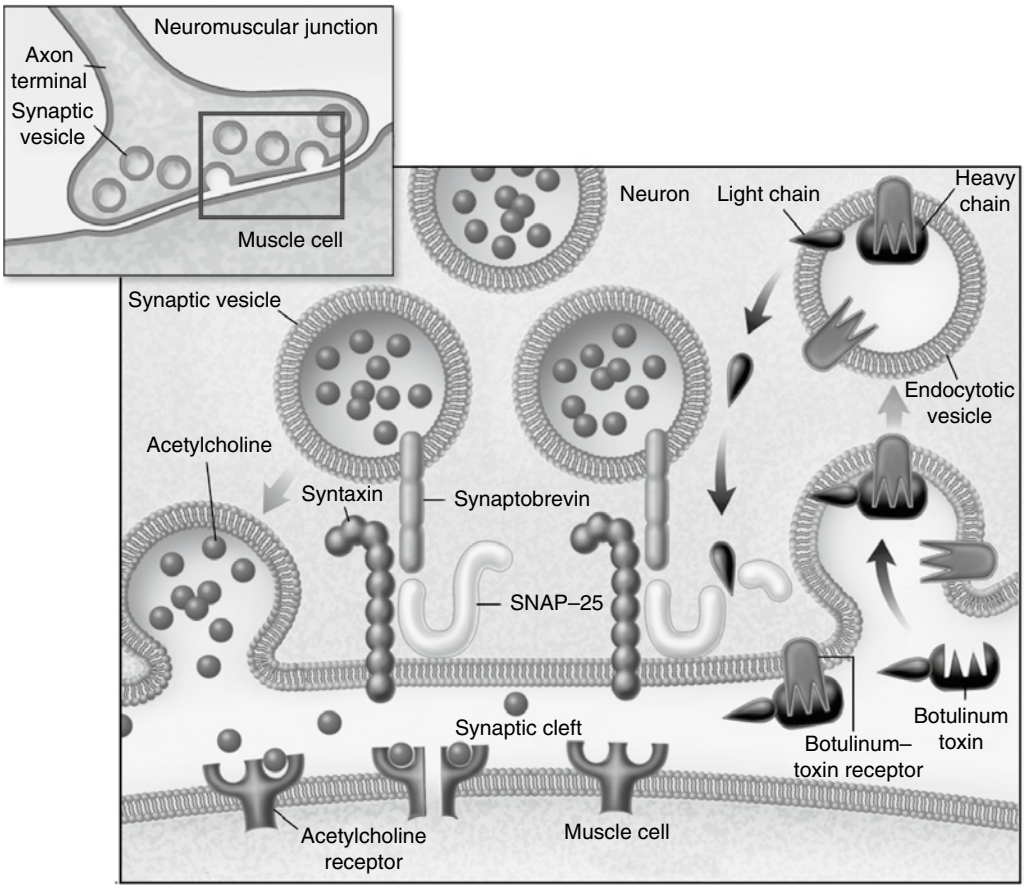

Fig. 50.1 Diagrammatic depiction of the neuromuscular junction and the action of *C. botulinum* neurotoxin (BoNT). BoNT, composed of a heavy and light chain, binds to an unknown receptor on the presynaptic cell membrane and is endocytosed; after which the BoNT light chain, a zinc-dependent endoprotease, interrupts neurotransmitter egress into the synaptic cleft through the cleavage of a number of different components of the synaptic vesicle docking and fusion complex. These targets include synaptosomal-associated protein (SNAP-25), synaptobrevin/vesicle-associated membrane protein (VAMP), and syntaxin (Reproduced with permission from Hallet [19])

the cleavage of a number of different components of the molecular complex responsible for the docking and fusion of synaptic vesicles with the axon terminal plasma membrane. Three targets have been described: synaptosomal-associated protein (SNAP-25) which is cleaved by BoNT A, C, and E; synaptobrevin/vesicle-associated membrane protein (VAMP) which is cleaved by BoNT B, D, F, and G; and syntaxin which is cleaved by BoNT C [21]. Failure of transmission at the level of peripheral cholinergic nerve terminals follows, resulting in both skeletal muscle paralysis and dysautonomia.

There are four major forms of human botulism: food-borne or "classical" botulism, infant botulism, wound botulism, and adult intestinal toxemia or "hidden" botulism. To these may also be added inhalational botulism and iatrogenic botulism, following the cosmetic or therapeutic injection of BoNT, but these remain exceedingly rare [22].

The pathogenesis of botulism differs among the various forms of the disease. Both infant and adult enteric toxemia botulism occur after the ingestion of *C. botulinum* spores which germinate in the host's gastrointestinal tract and subsequently produce BoNT in vivo [23]. Wound botulism occurs after the direct introduction of spores into devitalized flesh, classically after crush injuries to an extremity but increasingly among injection drug users [24]. Food-borne botulism differs from other types of botulism in that it occurs after the ingestion of preformed BoNT and does not involve an actual *C. botulinum* infection [22].

Clinical Presentations

Food-Borne Botulism (Classic Botulism)

More than 12,000 cases of food-borne botulism have been reported worldwide since 1951 [20]. Approximately 24 cases are reported annually to the Centers for Disease Control and Prevention (CDC) in the United States [25]. Although only 62 cases were reported in the United Kingdom between 1922 and 2005 [26], occasional outbreaks continue to occur. In 2006, four Americans and two Canadians suffered from food-borne botulism after consuming a commercially prepared carrot juice [27]. In the same year, 209 people in northern Thailand contracted botulism after having consumed the same home-canned bamboo shoots [28].

Food-borne botulism occurs with the ingestion of foods such as home-canned comestibles and salted, smoked, or fermented meats where *C. botulinum* spores have suitable anaerobic and alkaline environments to germinate and then

Table 50.1 Vehicles associated with food-borne botulism[a]

Home-canned or home-processed low-acid (pH >4.6) foods
Vegetables (including hummus)
Meats (including sausages and pâté)
Fish or seafood
Fermented or salted fish products
Whale or seal products
Relish or salsa
Chili peppers
Baked potatoes in aluminum foil
Garlic in oil
Sautéed onions kept under butter sauce
Cheese sauce

[a]Adapted from Shapiro et al. [25] and McClauchlin et al. [26]

produce BoNT (Table 50.1) [25, 26]. The median incubation period among humans after intoxication is between 1 and 2 days but may be as long as 8 days [28, 29].

The clinical course of food-borne botulism may be heralded by the onset of abdominal cramps, nausea, and vomiting, the exact mechanism of which is unclear. Cranial nerve symptoms and signs are consistently the initial neurological manifestation, presenting as blurred vision and photophobia, diplopia, ptosis, dysarthria, dysphonia, and dysphagia [28, 30]. These initial deficits are often followed by varying degrees of descending and symmetrical muscle paralysis, beginning with neck muscles and progressing to respiratory and limb muscles. In the 2009 outbreak of food-borne botulism in northern Thailand, from which BoNT type A was eventually isolated, 9 % of hospitalized patients were found to have weakness of the extremities, and 30 % required mechanical ventilation [31].

Autonomic dysfunction is often present, from involvement of both the parasympathetic and sympathetic nervous systems. The dysautonomia may be more severe and more persistent than the neuromuscular dysfunction [32, 33] and is typically characterized by orthostatic hypotension, xerostomia, ileus, and urinary retention. Mydriasis is less frequent, occurring in 1–44 % of patients [16, 28, 30]. Decreased heart rate variation and impaired sudomotor skin responses may also be demonstrable [32, 33].

> A 62-year-old Inuit man from northern Quebec, Canada, developed abdominal pain, vomiting, and abdominal distension 12 h after eating fermented beluga whale fat and oil, a local delicacy. He was initially suspected to have a small bowel obstruction, and he was flown to the Montreal General Hospital. In retrospect, the patient had already developed diplopia and dry mouth at this point. Over the next 48 h, the patient's blood pressure became increasingly labile, albeit without associated tachycardia. He became progressively obtunded and required intubation and ventilation for hypercapnic ventilatory failure. Neurological examination, limited by intubation and a language barrier, showed nonreactive, mid-position pupils and normal eye movements. There was mild tetraparesis and diffusely hypoactive tendon reflexes. Sensory examination was normal. Nerve conduction studies showed low-amplitude compound muscle action potentials in all four limbs, normal motor conduction velocities, and normal sensory nerve conduction studies. Two Hz repetitive stimulation of the left ulnar nerve showed a 12–14 % decrement; 50 Hz repetitive stimulation produced an increment of 22 %. Concentric needle examination of the left deltoid, first dorsal interosseous, and vastus lateralis was normal.
>
> A diagnosis of probable food-borne botulism was made, and equine-derived trivalent *C. botulinum* antitoxin was administered on the fourth day after the onset of his symptoms. Stool cultures were later positive for *C. botulinum* type E. The patient improved and he was extubated 11 days after symptom onset. He was discharged home 5 days later without apparent sequelae.

The rapidity of disease onset as well as disease severity likely vary depending on the inoculated dose of the neurotoxin [34]. Furthermore, the various types of BoNT appear to have different pathogenicity. Poisoning with BoNT type A results in a more severe clinical syndrome than poisoning with BoNT type B or E [29, 30]. BoNT type E appears to have a significantly shorter incubation period [29].

The differential diagnosis of food-borne botulism is generally limited to other disorders of the neuromuscular junction as well as acute peripheral neuropathies, in particular Guillain-Barré syndrome (GBS) and, its variant, Miller-Fisher syndrome (MFS). Prominent gastrointestinal symptoms accompanying acute flaccid paralysis might suggest arsenic or thallium poisoning as well as botulism. The descending pattern of weakness, beginning with the cranial nerves and only later involving the upper and then lower extremities, along with the frequent preservation of deep tendon reflexes, helps to distinguish botulism from most peripheral neuropathies. Likewise, in tick paralysis, weakness begins in the legs and ascends before cranial nerves are involved. Ophthalmoplegia and bulbar weakness may suggest myasthenia gravis, although onset of severe deficits in only a few days would be unusual, and pupillary paralysis does not occur in myasthenia. In an occasional patient with acute flaccid weakness, hypokalemia proves to be the cause, although cranial nerves are usually not affected. Diphtheria presents with prominent cranial neuropathies, but these develop over 1–4 weeks and are preceded by acute pharyngitis symptoms.

Electrophysiological studies are the most useful investigation to distinguish botulism from its mimics, although the electromyographer must be alerted to the possibility of botulism. Serological studies may also be helpful, although results may not be available sufficiently quickly in the acute setting. Up to 90 % of patients with myasthenia gravis are either acetylcholine receptor or muscle-specific tyrosine kinase (MuSK) antibody positive [35, 36]. In 95 % of Lambert-Eaton myasthenic syndrome (LEMS) patients, voltage-gated calcium channel antibodies can be found on serological testing [37] and 92 % of patients with

ophthalmoplegia in GBS or MFS are GQ1b antibody positive [38]. A dramatic response to intravenous anticholinesterase inhibitors such as edrophonium chloride favors myasthenia gravis, but some patients with mild botulism may also show a response [30, 39, 40].

Death from untreated botulism generally occurs because of respiratory arrest in the context of airway obstruction secondary to pharyngeal muscle paralysis as well as respiratory muscle and diaphragmatic failure [22]. Untreated, the mortality of food-borne botulism may be up to 60 % [25]. On the other hand, with the advent of mechanical ventilation, the mortality has dramatically decreased, with various authors reporting rates of zero to 18 % [28, 30, 41].

Up to 30 % of patients with botulism require mechanical ventilation, lasting days to weeks [41]. Once clinically stabilized, recuperation is usually complete, albeit prolonged. There is some evidence that recovery of autonomic function may be more prolonged than that of neuromuscular transmission [42].

Infant Botulism

Since its initial description in 1976 [43, 44], infant botulism is now recognized worldwide to be the most common form of botulism, surpassing both its food-borne and wound counterparts [25]. Perhaps due to increased physician awareness, the majority of cases have been diagnosed in the United States, where the incidence is estimated at 2.1 cases per 100,000 live births [45, 46].

Typically, affected infants are between the age of 2 weeks and 1 year (median age 10 weeks), with about 90 % of cases occurring before the age of 6 months [47, 48]. Although rare before the age of 2 weeks, cases of infant botulism within the first few days of life have been reported [49, 50], suggesting that the previously estimated incubation period for *Clostridium botulinum* of 3–30 days in infants [51] may need to be revisited.

Infants typically present with constipation, weak cry, lethargy, difficulty in feeding, poor sucking, and progressive weakness of limb and bulbar muscles developing over hours to several days [22, 44, 52–54]. Constipation and other signs of dysautonomia are present in up to 65 % of cases and may precede weakness by several weeks [53–55]. Weakness is a principal feature of infant botulism in up to 90 % of cases, beginning with poor head control and progressively evolving into a picture of descending flaccid paralysis with generalized hypotonia and hyporeflexia [53]. The severity of the clinical spectrum of infant botulism may range from mild hypotonia to flaccid paralysis to sudden unexpected death [56–58]. Respiratory distress, which can be exacerbated with the use of aminoglycosides, is often a late manifestation, with up to 70 % of infants requiring ventilatory support [53, 59, 60]. The mortality rate is reported to be as high as 5 % [47, 61]. Despite this, with timely and adequate supportive care, most infants with botulism have an excellent prognosis with complete recovery within weeks to months [45]. Relapse of symptoms is possible and usually occurs within 2 weeks.

> A 7-day-old baby boy presented to the emergency department (ED) with a 1-day history of decreased respiratory effort and cyanosis. He was the product of a spontaneous vaginal delivery at 37 weeks of gestation to a healthy mother. The pregnancy and delivery were unremarkable. Apgars were 5 and 10 at 1 and 5 min, respectively. He was initially fed with concentrated liquid formula and was waking up every 2–4 h to feed. Stools were normal and regular. At 4 days, he was switched to powdered infant formula, and the following day, he was noted to be constipated, with no stools since the switch in formula. He also became progressively sleepy and needed to be woken up for feeds. Feeding became difficult, with progressively weaker suck. He was found to be more floppy. On day 7, cyanosis and decreased respiratory effort were evident. He was brought to the ED, where he was found to be poorly responsive and hypopneic with an oxygen saturation (SpO2) of 43 %. He was afebrile and hemodynamically stable. A capillary blood gas revealed a pH of 7.2 and pCO2 of 60. He was promptly intubated and admitted to the intensive care unit (ICU).
>
> Initial investigations to rule out an infectious or metabolic etiology, including lumbar puncture, were unrevealing. Shortly after admission, the patient was noted to have fixed and dilated pupils (4 mm), with preserved corneal and gag reflexes. Suck was poor. Spontaneous movements were decreased, with marked axial and appendicular hypotonia. Moro reflex was absent. Deep tendon reflexes were diminished, but were bilaterally symmetrical with upgoing plantar responses. No tongue fasciculation was noted. The general examination was unremarkable. Brain MRI, cardiac and abdominal ultrasound, and ophthalmological assessment were unremarkable.
>
> During the second day in the ICU, the patient began to exhibit hemodynamic instability, with a labile BP requiring dopamine support for 48 h. At this point, infantile botulism was suspected and stool cultures were sent. Nerve conduction studies performed 5 days after onset of symptoms showed decreased ulnar, median, and tibial compound muscle action potential amplitudes, with normal motor conduction velocities and sensory nerve conduction studies. 2-Hz and 50-Hz repetitive stimulation of the median nerve showed neither increment nor decrement. Concentric needle examination of the deltoid, tibialis anterior, and vastus lateralis was normal.
>
> The patient received human-derived botulinum immunoglobulin (BIG) 8 days after admission. The following day, he began to trigger the ventilator, and 24 h later, he was extubated. Spontaneous movements increased and he began passing stool. Eleven days after symptom onset, he was feeding well. He was discharged home after 14 days. Stool culture and toxin assay demonstrated *C. botulinum* type F spores and toxin.

Due to the turnaround time of toxin assays (usually days), the clinical presentation and physical examination remain pivotal in making the diagnosis of infant botulism and in initiating treatment [22]. Importantly, other etiologies that commonly cause hypotonia in the infant need to be considered and appropriately ruled out including infectious, toxic,

metabolic, or other neuromuscular pathologies such as myopathies, spinal muscle atrophy, myasthenia gravis, Guillain-Barré syndrome, and poliomyelitis [54]. Electrodiagnostic tests can play a complementary role to the clinical presentation and allow for early diagnosis of botulism [62]. Notably, however, the characteristic electrodiagnostic findings of botulism (see below) are not reliably present in infants, and their absence does not rule out the diagnosis.

Although up to 85 % of cases of infant botulism have an unidentified source, epidemiologic studies have acknowledged a number of intrinsic and environmental factors that may predispose the infant to botulism [47, 63]. The absence of both protective bacterial flora as well as *Clostridium*-inhibiting bile acids renders the infant's gut particularly susceptible to colonization by the toxin-producing bacteria. Environmental exposure to *C. botulinum* spores, which are commonly found in soil and dust, may occur through inhalation of microscopic dust, particularly in infants who live in rural areas or through exposure to a parent who works with soil [58, 63]. Honey is a well-established source of *Clostridium botulinum* spores and has been implicated as a significant risk factor for infant botulism [64, 65]. As a result, avoidance of honey in infants younger than 1 year is recommended, and this practice has probably contributed to decreasing the incidence of honey-associated botulism to less than 5 % in the USA [46]. Breastfeeding as a risk factor remains controversial, with contradictory evidence for both an increased risk as well as a conferred protection [66, 67]. Nevertheless, botulism has been described in both breastfed and formula-fed infants.

Wound Botulism

Wound botulism was thought to be rare, reported in patients with traumatic and surgical wounds. More recently, however, it has become increasingly important since being recognized in illicit drug abusers [68]. In 1995 alone, 19 laboratory-confirmed cases of wound botulism among intravenous heroin users were reported to the California Department of Health Services [69].

It is generally held that wound botulism occurs with the introduction of *C. botulinum* spores at a site of injury followed by the in vivo formation of BoNT [70]. The major risk factor for wound botulism appears to be the frequent subcutaneous or intramuscular injection of illicit drugs [71] although cases have been reported after the inhalation of cocaine as well [72].

The neurologic features of wound botulism are largely similar to those in food-borne botulism although early abdominal cramps, nausea, and vomiting are conspicuously absent [22]. The clinical outcome is also similar between the two forms of botulism. There appears to be a relationship between wound botulism severity and the number of cutaneous abscesses [70].

Adult Intestinal Toxemia Botulism (Hidden Botulism)

In the majority of adults, *C. botulinum* cannot germinate in the generally acidic environment of the human gastrointestinal tract. It is likely thanks to this fortuitous circumstance, as well as to competitive inhibition from endogenous intestinal flora, that botulism is not more common in humans in spite of the fact that its spores are found ubiquitously in our environment.

Adult intestinal toxemia botulism occurs when *C. botulinum* spores successfully germinate in, and subsequently colonize, the gastrointestinal tracts of certain adults which then results in the in vivo production of BoNT. Not surprisingly, it is the comorbid abnormalities of the gastrointestinal tract that appear to predispose individuals to the condition including achlorhydria, whether due to medications or truncal vagotomy, Crohn's disease, as well as various abnormalities in small and large bowel anatomy, both spontaneous and iatrogenic [73–75]. Recent antibiotic therapy has also been associated with adult intestinal toxemia botulism, likely due to its effect on endogenous intestinal flora [73]. The clinical characteristics of this most rare form of botulism are again identical to those in food-borne botulism.

Iatrogenic and Inhalational Botulism

Since the first description in 1997, there have been a number of case reports and small case series of botulism that have occurred after the therapeutic and cosmetic injection of BoNT [76]. The majority of cases have occurred during the course of treating blepharospasm, dystonia, and spasticity where the average dose is up to 75 times larger than cosmetic applications [77–79]. There has been only one outbreak of iatrogenic botulism after the cosmetic use of BoNT [80]. On the other hand, it should be noted that in the aforementioned outbreak, the medical staff involved used an unlicensed form of BoNT type A and performed a dilution error which led to the inadvertent injection of more than 2,500 times the estimated human lethal dose into each of the four affected patients.

In addition to cases of frank botulism, patients who receive therapeutic injections of BoNT may have prolonged jitter and increased blocking on single-fiber electromyography of muscles distant to the site of injection, even in the absence of weakness [81]. Pathologic studies have also

demonstrated muscle fiber atrophy distant to the site of injection without any clear clinical significance [82].

A report in 1962 described three cases of inhalational botulism in a group of German laboratory technicians who had been participating in animal experiments that involved aerosolized BoNT [83]. Although there have been no further reports of inhalational botulism since then, it remains a concern among health agencies and governments alike due to its frightening potential as a biological weapon. It is thought that a number of countries have attempted to exploit botulism as a weapon over the last century, some expending considerable energy and resources on the endeavor [84]. There have also been fears that paramilitary groups might resort to biological weapons. In fact, there were a number of attempts by the religious group *Aum Shinrikyo,* later responsible for the 1995 sarin gas attack in Tokyo, to carry out assaults on civilian and American military targets in Japan during the early 1990s using aerosolized BoNT, all of which fortunately failed [85].

Evaluation and Diagnosis

Laboratory Findings

Laboratory confirmation of botulism may be established via a number of methods. The primary approach is to test the preformed BoNT in either gastric, serum, or stool samples using a bioassay [8]. This bioassay is available through a small number of laboratories and involves the intraperitoneal injection of various preparations of patient samples and BoNT type-specific antitoxins into a panel of mice. These mice are then observed for the development of botulism-specific manifestations, both to confirm the diagnosis of botulism as well as to establish the type of BoNT. Samples of the suspected food, if available, should be tested.

The sensitivity of bioassays for BoNT in food-borne botulism appears to be between 30 and 50 % although in one series it was as low as 18 % of stool samples [29, 86]. Samples collected within 2 days of symptom onset appear to be of greater sensitivity, reportedly as high as 60–70 % [29]. Interestingly, in these same studies involving what were ostensibly cases of food-borne botulism, up to 60 % of gastric and stool cultures were positive for *C. botulinum*. Such findings impress upon the clinician, the utility of investigating for both preformed toxin and *C. botulinum*. In addition, they suggest that our understanding of the pathogenesis of food-borne botulism is incomplete or that perhaps adult intestinal toxemia botulism is more frequent than currently appreciated. In cases of suspected infant botulism, stool samples for BoNT assay and bacterial culture are preferred [86]. In cases of suspected wound botulism, bacterial cultures of the wound may be helpful, with yields as high as 57 % [87]. Routine serologic examinations and cerebrospinal fluid analysis are normal in the majority of patients with botulism [25].

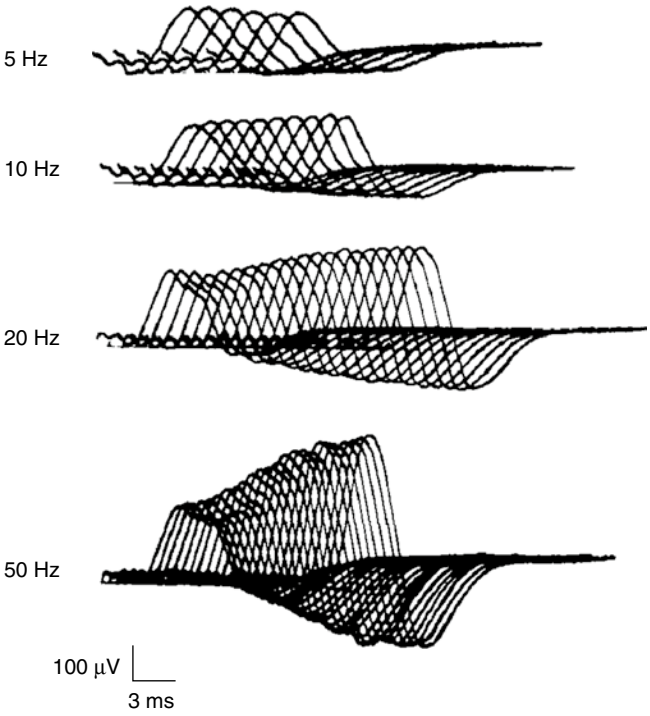

Fig. 50.2 Repetitive nerve stimulation in the left abductor pollicis brevis of a patient with infant botulism. The frequency of nerve stimulation is listed along the vertical axis. At 5 Hz, an 8 % decrement was seen. At higher frequencies, an increment was seen: 25 % at 10 Hz, 38 % at 20 Hz, and 94 % at 50 Hz (Reproduced with permission from Cornblath et al. [90])

Electrodiagnostic Findings

Due to the low sensitivity of laboratory testing as well as the time required to obtain their results, electrodiagnostic studies remain the cornerstone of botulism diagnosis.

Nerve conduction studies in botulism are characterized by decreased compound muscle action potential (CMAP) amplitudes in 85–92 % of patients, while conduction velocities and distal latencies remain relatively normal [88, 89]. Compound sensory nerve action potential amplitudes, conduction velocities, and latencies are normal. A decremental response to low-frequency (2–5 Hz) repetitive nerve stimulation (RNS) has been described in 56 % of patients with infant botulism [90]. Finally, an incremental response may be seen as a result of posttetanic facilitation (PTF), after either high-frequency (30–50 Hz) RNS or 10 s of isometric exercise.

In a study of 63 patients with food-borne botulism and 60 controls, an increment of only 25 % was shown to have both a sensitivity and specificity greater than 95 % [89]. This same study also reported a median increment of 97 % among patients with botulism. The increment is most evident at higher rates of RNS (50 Hz vs. 20 Hz) [90], and isometric exercise may be superior to RNS at eliciting this response [91]. A representative tracing of the RNS findings in botulism is shown in Fig. 50.2.

Conventional electromyography (EMG) studies occasionally reveal low-amplitude and polyphasic motor unit

potentials (MUP) and fibrillation potentials [92]. Such findings are described in up to 54 % of patients with infant botulism [90]. Increased jitter and blocking with single-fiber EMG are reported in a large proportion of patients [92–94]. Some argue that single-fiber EMG may be more sensitive for identification of botulism than RNS although clear evidence is lacking [94].

Findings in botulism are similar to those in Lambert-Eaton myasthenic syndrome (LEMS), since they are both presynaptic disorders of the neuromuscular junction. However, differences exist. Electrophysiological findings in botulism tend to be more variable among muscle groups and to change considerably over periods of days, whereas in LEMS they are more uniform from muscle to muscle and stable over months or longer [92]. It is also suggested that PTF in botulism is rather prolonged, lasting up to 20 min, while PTF in LEMS generally lasts only 30–60 s [95, 96].

Treatment

The most important advance in the treatment of botulism over the last century was the advent of modern intensive care, in particular mechanical ventilation. Vigilant surveillance and aggressive management of respiratory failure have dramatically decreased the mortality rate of botulism. Notably, there were no deaths in the 2006 outbreak that affected 209 individuals in Thailand [28].

A number of medical therapies have been developed over the last decades for botulism, although rigorous evidence supporting their efficacy is lacking. A Cochrane review examining medical therapy in botulism identified only one randomized controlled trial (RCT) [97]. The study involved 129 patients with infant botulism, of whom 65 were given a single infusion of human-derived botulism immune globulin (BIG) and 64 received a similar infusion of intravenous immune globulin (Gammagard or Gammagard S/D), both within 72 h of hospitalization [98]. Patients treated with BIG had significant decreases in the duration of hospitalization (3.3 weeks less), mechanical ventilation (2.6 weeks), and tube or parenteral feeding (6.4 weeks). There were no deaths in either group and no significant differences in adverse effects. An open-label extension of this study including 382 patients produced similar results and also suggested that administration of BIG within 3 days of hospitalization as opposed to 7 days conferred greater benefit [98]. There have not been any studies examining the efficacy of BIG in other forms of botulism.

Equine-derived botulinum antitoxin is widely considered to be the "standard of care" in the treatment of food-borne botulism, although the efficacy of antitoxin has not been demonstrated in an RCT. The best evidence supporting the use of antitoxin is derived from a retrospective observational cohort study that included 132 patients with laboratory-confirmed food-borne botulism [99]. One hundred fifteen patients (87 %) received trivalent (types A, B, and E) equine-derived botulinum antitoxin. Compared to untreated patients, those administered antitoxin had a 31–36 % decrease in mortality, depending on whether antitoxin was given within the first 24 h of symptom onset or later. There was also a 15–46-day decrease in the duration of hospitalization as well as a 7–28-day decrease in the duration of mechanical ventilation, again depending on the timing of antitoxin administration. Whether these findings were statistically significant was not reported and potential adverse effects of antitoxin were not addressed. In another small retrospective cohort study of 18 patients with food-borne botulism, administration of the antitoxin on day 4 as opposed to day 6 after exposure to BoNT resulted in a significant decrease in the duration of mechanical ventilation [100]. Equine-derived botulinum antitoxin has also been used in wound botulism, although the evidence of its efficacy is limited to small case series [101].

It must be emphasized that both acute and delayed hypersensitivity reactions frequently occur after the administration of equine-derived botulinum antitoxin. In a review of 268 patients reported to the CDC over a 10-year period, 24 (9 %) suffered from a hypersensitivity reaction, 5 (1.9 %) of which were anaphylaxis and 10 (3.7 %) of which were serum sickness [102]. These risks have been somewhat mitigated by the use of a horse serum skin test prior to the administration of the antitoxin although a negative skin test does not entirely rule out the possibility of anaphylaxis [103].

Other reported treatments for botulism have included guanidine and 3,4-diaminopyridine, both of which promote the presynaptic release of acetylcholine at the neuromuscular junction [104, 105]. Robust evidence of their efficacy in botulism is lacking, although the efficacy of 3,4-diaminopyridine in Lambert-Eaton syndrome was demonstrated in an RCT [106]. There are isolated reports describing the use of plasmapheresis in botulism [107].

In the case of wound botulism, debridement of any abscesses and removal of devascularized tissue is recommended to limit the further germination of spores and production of BoNT [5, 22, 108]. Treatment with antibiotics is also recommended, although this has not been formally studied [5, 22].

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Congenital Myasthenic Syndromes

51

Andrew G. Engel

Introduction

Congenital myasthenic syndromes (CMS) are inherited disorders of neuromuscular transmission in which the safety margin of neuromuscular transmission is compromised by one or more specific mechanisms. An understanding of the concept of the safety margin and of the mechanisms that can compromise it requires a brief overview of the anatomic and physiologic aspects of neuromuscular transmission [1].

At the motor endplate (EP), the nerve terminal is separated from the postsynaptic region of clefts and folds by primary and secondary synaptic clefts. The nerve terminal contains numerous synaptic vesicles that store quantal packets (5–10,000 molecules) of acetylcholine (ACh). Readily releasable vesicles abut on the active zones of the presynaptic membrane (Fig. 51.1). The acetylcholine receptor (AChR) is strategically deployed on the terminal expansions of the postsynaptic junctional folds at a density of about 10,000 molecules per μm^2. The EP species of acetylcholinesterase (ACHE) is concentrated in the synaptic space where it is anchored to the basal lamina. Exocytotic release of single quanta occurs spontaneously in the resting state. Depolarization of the nerve terminal by nerve impulse opens voltage-gated Ca^{2+} channels positioned in the active zones of the presynaptic membrane. The entry of Ca^{2+} ions triggers the release of multiple quanta. The number of released quanta (m) is a function of the probability of release (p), which depends mostly on the prevailing Ca^{2+} concentration near the intraterminal release sites, and the number of readily releasable quanta (n), so that $m = np$.

ACh released into the synaptic space diffuses toward the postsynaptic membrane. About 20 % of the released ACh is hydrolyzed by ACHE before it binds to AChR. Binding of ACh to AChR causes the cation-selective AChR channel to open for a period distributed exponentially from a fraction of a millisecond to several milliseconds, allowing Na^+, and, to a lesser extent Ca^{2+}, to enter the muscle fiber. After ACh dissociates from AChR, ACHE hydrolyzes it rapidly and completely to choline and acetate. Choline is taken up by the nerve terminal by Na^+-dependent active transport. ACh is resynthesized in the nerve terminal from choline and acetyl coenzyme A in a reaction catalyzed by choline acetyltransferase. The newly synthesized ACh is concentrated in synaptic vesicles by a proton-pump-dependent ACh transporter.

The postsynaptic depolarization and the concomitant current flow induced by a single quantum give rise to a miniature endplate potential (MEPP) and a miniature endplate current (MEPC), respectively. The amplitude of the MEPP depends on the number of ACh molecules per quantum; the EP geometry; the number of activatable AChRs, which is a function of postsynaptic AChR density; the depolarization per channel opening; and the input resistance of the muscle fiber. The duration of the MEPP depends on the mean open time of the AChR channel, the functional state of ACHE, and the cable properties of the sarcolemma. The amplitude and duration of the MEPC are independent of the cable properties of the sarcolemma but are otherwise determined by the same factors that determine the amplitude and duration of the MEPP.

Multiquantal release by nerve impulse generates an endplate potential (EPP). The EPP amplitude is a function of m and of the MEPP amplitude. When the EPP exceeds the threshold for activating perijunctional voltage-gated Na^+ channels, it triggers a muscle fiber action potential. *The safety margin of neuromuscular transmission is the difference between the actual EPP amplitude and the EPP amplitude required to trigger a muscle fiber action potential*. From the above discussion, it follows that the safety margin will be compromised by defects that affect the (1) number of ACh molecules per quantum, (2) quantal release mechanisms, and (3) quantal efficiency. Quantal efficiency depends on EP geometry, the functional state of ACHE in the synaptic space, and the density and kinetic properties of AChR.

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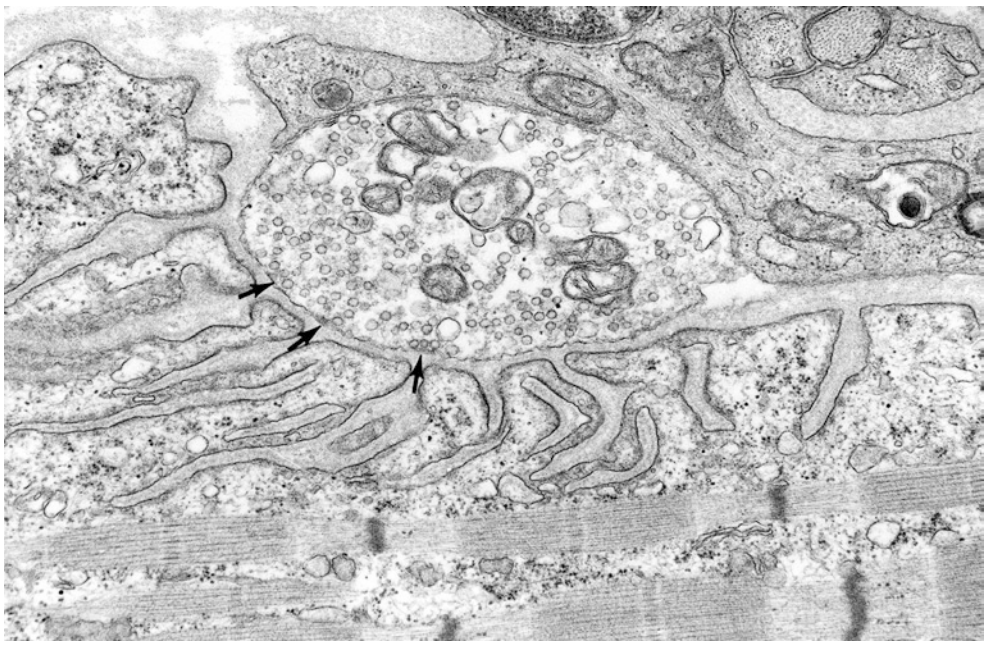

Fig. 51.1 Electron micrograph of a normal neuromuscular junction. The nerve terminal contains mitochondria, synaptic vesicles, and a few giant synaptic vesicles. *Arrows* indicate presynaptic active zones in register with the secondary synaptic clefts. The nerve terminal is covered by a Schwann cell process and faces the primary synaptic cleft (reduced from × 24,800)

Classification of the Congenital Myasthenic Syndromes

The CMS can be classified according to inheritance, the EP-specific protein that is altered, or the site of the defect (presynaptic, synaptic, or postsynaptic). A classification by inheritance is simple: the slow-channel syndromes are caused by autosomal dominant gain-of-function mutations; all other CMS recognized to date are caused by autosomal recessive loss-of-function mutations. Table 51.1 shows a classification of the CMS in 321 kinships investigated at the Mayo Clinic according to the site of the defect and according to mechanisms governing endplate (EP) development and maintenance. The classification is still tentative because additional CMS might yet be discovered or because, for some presynaptic CMS, the disease protein or gene is not yet known.

Table 51.1 indicates that the purely presynaptic CMS are least frequent, accounting for only 6 % of all cases. Of note, however, a defect in presynaptic quantal release is also present in EP ACHE deficiency [2], Dok-7 myasthenia [3, 4], β2-laminin deficiency [5], and in the CMS associated with centronuclear myopathy [6]. The purely postsynaptic CMS account for most patients in this group, and mutations in AChR subunits account for more than one-half of all cases.

Diagnosis of a Congenital Myasthenic Syndrome

Many CMS patients remain undiagnosed or are diagnosed incorrectly. A generic diagnosis of a CMS can be made from the features listed in Table 51.2. Also, in some CMS, there are

Table 51.1 Classification of the congenital myasthenic syndromes based on 321 kinships investigated at the Mayo Clinic[a]

Defect site	Index cases	Relative frequency (%)
Presynaptic (5.9 %)		
Choline acetyltransferase	17	5.3
Paucity of synaptic vesicles[b]	1	0.3
Congenital Lambert-Eaton-like syndrome[b]	1	0.3
Synaptic basal lamina (13.7 %)		
Endplate ACHE deficiency	43	13.4
β2-laminin deficiency	1	0.3
Postsynaptic (68 %)		
Primary AChR deficiency with/without kinetic abnormality	109	34
Primary kinetic abnormality with/without AChR deficiency	58	18.1
Rapsyn deficiency	48	15
Plectin deficiency	2	0.6
Na channel myasthenia	1	0.3
Defects in mechanisms governing endplate development and maintenance (12.5 %)		
Dok-7 myasthenia	31	9.7
Glutamine-fructose-6-phosphate transaminase deficiency (GFPT1)	8	2.5
Myasthenic syndrome associated with centronuclear myopathy[b]	1	0.3
Total	321	100

[a]Mutations in MuSK [107, 109, 110] and agrin [113] have been identified in few kinships at other medical centers
[b]No gene defect identified

Table 51.2 Generic diagnosis of a congenital myasthenic syndrome

Fatigable weakness involving ocular, bulbar, and limb muscles since infancy or early childhood
Similarly affected relative
Decremental EMG response at 2–3 Hz stimulation or abnormal jitter and blocking on single-fiber EMG[a]
Negative tests for anti-AChR antibodies
Exceptions and caveats
In some CMS, the onset is delayed
There may be no similarly affected relatives
EMG abnormalities may not be present in all muscles or are present only intermittently
Weakness can be restricted to selected muscle

[a]Single-fiber EMG has high sensitivity but can also be abnormal in myopathies and some neuropathies

Table 51.3 Clinical clues pointing to a specific diagnosis[a]

Endplate choline acetyltransferase deficiency
Recurrent apneic episodes, spontaneous or with fever, vomiting, or excitement
No or variable myasthenic symptoms between acute episodes
Stimulation at 10 Hz for 5 min causes marked decrease of CMAP followed by slow recovery over 10 min
EMG decrement at 2 Hz can be absent at rest but appears after stimulation at 10 Hz for 5 min and then disappears *slowly* over 10 min
EP ACHE deficiency
Repetitive CMAP
Refractoriness to cholinesterase inhibitors
Delayed pupillary light reflexes in some cases
Absence of cholinesterase reactivity from EPs in muscle specimens
Slow-channel CMS
Repetitive CMAP
Selectively severe involvement of cervical and wrist and finger extensor muscles in most cases
Dominant inheritance
Rapsyn deficiency
Multiple congenital joint contractures or dysmorphic features in ~30 %
Increased weakness and respiratory insufficiency precipitated by intercurrent infections
Ophthalmoparesis in ~25 %; strabismus relatively common
Dok-7 myasthenia
Predominantly limb-girdle and axial distribution of weakness, mild facial weakness, and ptosis are common; normal ocular ductions in most patients
Significant bulbar muscles involvement in some patients
Often worsened by pyridostigmine; responds to ephedrine and albuterol
Can present with stridor and vocal cord paralysis in neonates and infants
GFPT1 (GFAT) myasthenia
Tubular aggregates in muscle in most patients[b]
Predominantly limb-girdle and axial distribution of weakness
Responds to pyridostigmine
Laminin-β2 myasthenia
Nephrotic syndrome, ocular abnormalities (Pierson syndrome)
Refractoriness to cholinesterase inhibitors

Abbreviations: *ACHE* acetylcholinesterase, *CMAP* compound muscle fiber action potential, *CMS* congenital myasthenic syndrome, *EP* endplate, *GFPT1* glutamine-fructose-6-phosphate transaminase 1

[a]There are no specific clues to the diagnosis of the fast-channel congenital myasthenic syndrome, primary endplate AChR deficiency, and many cases of rapsyn deficiency

[b]Not all CMS patients with tubular aggregates have GFPT1 myasthenia

strong phenotypic clues pointing to a specific diagnosis, and these are listed in Table 51.3. In other CMS, the phenotypic features do not suggest a specific diagnosis or site of defect. In these patients, molecular genetic studies alone, or sometimes in combination with specialized morphologic and electrophysiologic investigations, are required to determine the etiology. Table 51.4 lists the differential diagnosis of the CMS.

Genetic Analysis

This is greatly facilitated when clinical, physiologic, or morphologic studies point to a candidate protein or gene. For example, a kinetic abnormality of AChR detected at the single-channel level [7] or severe EP AChR deficiency revealed by α-bungarotoxin binding studies [8] predicts mutations in

Table 51.4 The differential diagnosis of congenital myasthenic syndromes

Neonatal period, infancy, childhood
Spinal muscular atrophy
Morphologically distinct congenital myopathies (central core disease, nemaline myopathy, myotubular myopathy, fiber-type disproportion-related syndromes)
Congenital muscular dystrophies
Infantile myotonic dystrophy
Mitochondrial myopathy
Brain stem anomaly
Möbius syndrome
Infantile botulism
Seropositive and seronegative autoimmune myasthenia gravis[a]
Older patients
Motor neuron disease
Radial nerve palsy[b]
Peripheral neuropathy[b]
Limb-girdle or facioscapulohumeral dystrophy
Mitochondrial myopathy
Chronic fatigue syndrome
Seropositive and seronegative autoimmune myasthenia gravis

[a]Not reported in the first year of life
[b]This diagnosis has been made in some cases of the slow-channel CMS

an AChR subunit gene. However, only few highly specialized laboratories can perform these studies.

Genetic testing for CMS is now commercially available and facilitates diagnosis and management by neuromuscular specialists. It is also best used in a targeted manner based on specific clinical features, as listed in Table 51.3, or beginning with the most frequently mutated genes, as shown in Table 51.1. However, this approach has a number of drawbacks: (1) it is expensive, especially if used in a shotgun manner; (2) it does not establish that recessive mutations are heteroallelic unless they are homozygous; therefore, DNA from both parents also must be analyzed; (3) it will miss intronic mutations not close to exons; (4) evaluation of pathogenicity is based on software programs whose reliability is still debated; (5) it does not inform on kinetic consequences of mutations in AChR or ChAT or on pathogenicity of mutations that render the disease protein structurally unstable; and (6) negative results do not exclude the diagnosis of a CMS because only previously identified disease genes are sequenced.

Another approach is linkage analysis if a sufficient number of informative relatives are available. If successful, it will point to a candidate chromosomal locus. If the physical map of the locus shows an attractive candidate gene, then mutation analysis by direct sequencing becomes feasible. This approach seldom works for CMS because large informative CMS kinships are seldom available; however, it has been successful in inbred populations with multiple consanguineous families [9].

A direct and efficient approach is the use of microarrays specifically designed for screening multiple candidate disease loci in known CMS genes. One publication finds that this approach has a 73.3 % overall sensitivity and a 95.5 % sensitivity for missense mutation, but it is not recommended for detecting insertion or deletion mutations [10]. Also, this approach will miss mutations in novel CMS disease genes.

A novel approach to mutation discovery is whole-exome sequencing that searches for mutations in exons. This technique is still evolving. A discussion of its use and limitations is beyond the scope of this chapter.

Endplate Choline Acetyltransferase (ChAT) Deficiency

The disease is characterized by sudden episodes of apnea precipitated by infections, fever, excitement, or no apparent cause [11–13]. In some patients, the disease presents at birth with hypotonia and severe bulbar and respiratory weakness requiring ventilatory support. In some children, an acute attack is followed by respiratory insufficiency that lasts for weeks [14]. Few patients are apneic, respirator dependent, and paralyzed since birth, and some develop cerebral atrophy after episodes of hypoxemia [13]. The symptoms gradually improve, but are followed by recurrent apneic attacks associated with bulbar paralysis in later life. Other patients are normal at birth and experience their first apneic attack during infancy or early childhood. Variable ptosis and fatigable weakness may persist between the attacks. After the first decade, the apneic crises become less frequent. The external ocular muscles are frequently spared. The clinical diagnosis is established by the clues listed in Table 51.3.

Endplate studies reveal no AChR deficiency and the postsynaptic regions show no structural abnormality. The amplitude of the evoked compound muscle action potential (CMAP), the EPP, and the MEPP is normal in rested muscle, but decreases abnormally during 10 Hz stimulation for 5 min and then returns to the baseline slowly over the next 10–15 min. Quantal release by nerve impulse is not depressed after 10 Hz stimulation for 5 min [15]. These findings point to a defect in the resynthesis or vesicular packaging of ACh.

The muscle weakness, when present, responds well to small or modest doses of anticholinesterase drugs. Some patients are asymptomatic or have only minimal weakness, except during exacerbations. These patients require anticholinesterase drugs only on an emergency basis. Patients with frequent apneic attacks are best treated prophylactically with anticholinesterase medications. Parents of affected children must be taught to anticipate sudden worsening of the weakness and possible apnea with febrile illnesses, excitement, or overexertion. Parents must also be familiar with the use of a hand-assisted ventilatory device and should be able to administer appropriate doses of prostigmine intramuscularly during

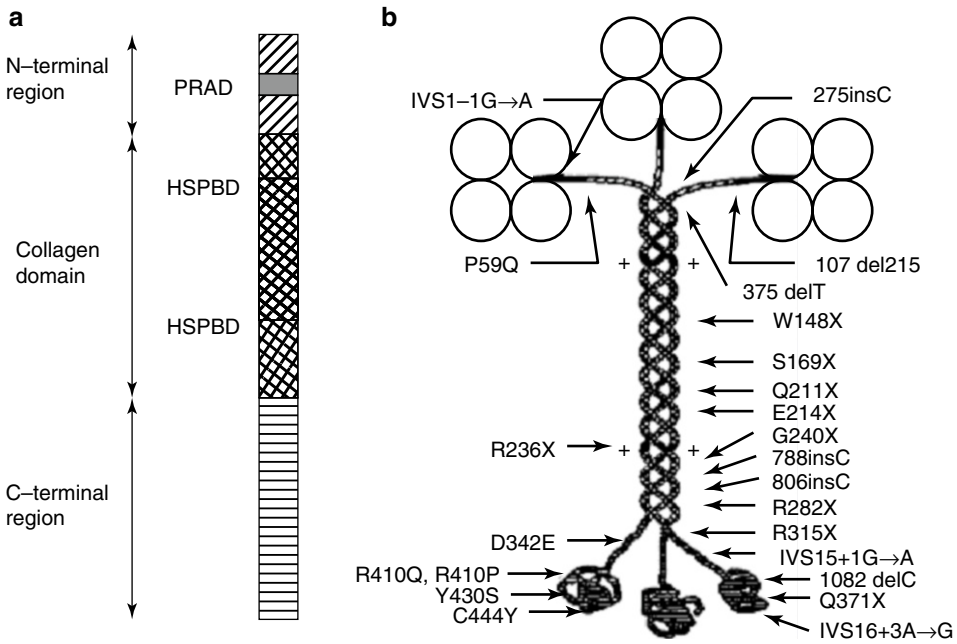

Fig. 51.2 (**a**) Schematic diagram showing domains of a COLQ strand with identified COLQ mutations and (**b**) components of the A_{12} species of asymmetric ACHE. The N-terminal region of each COLQ strand contains a proline-rich attachment domain (PRAD) that binds a homotetramer of the catalytic $ACHE_T$ subunit. The triple helical collagenic domain contains two positively charged heparan sulfate proteoglycan binding regions (HSPBD) that participate in anchoring the tail subunit in the synaptic basal lamina. The C-terminal region of COLQ is essential for the assembly of the triple helix of the collagen domain in a C- to N-terminal direction and also participates in anchoring the tail subunit

such crises. Patients with a febrile illness and a previous history of crisis should be hospitalized for close observation and for ventilatory support as needed.

Paucity of Synaptic Vesicles and Reduced Quantal Release

The clinical features of this syndrome closely mimic those of autoimmune MG, but EP studies reveal no AChR deficiency. A presynaptic defect is indicated by a severe decrease (to ~20 % of normal) in the number of ACh quanta (*m*) released by nerve impulse. The decrease in *m* is due to a decrease in the number of readily releasable quanta (*n*), and this decrease is associated with a comparable decrease (to ~20 % of normal) in the numerical density of synaptic vesicles. The putative defect resides in the synthesis or axonal transport of vesicle precursors from the anterior horn cell to the nerve terminal or, less likely, is related to impaired recycling of the synaptic vesicles [16]. A generic diagnosis of a CMS is easy to establish (see Table 51.2), but a specific diagnosis requires in vitro studies of neuromuscular transmission and quantitative electron microscopy examination of the EP. The disorder responds partially to anticholinesterase medications.

CMS Resembling the Lambert-Eaton Myasthenic Syndrome

In this CMS, repetitive nerve stimulation shows marked facilitation of the compound muscle action potential (CMAP) at physiologic rates of stimulation [17]. In a single patient investigated by the author, the number of quanta released by nerve impulse was decreased due to a decreased probability of quantal release. EP ultrastructure was normal [18]. The patient failed to respond to 3,4-diaminopyridine (3,4-DAP), which enhances quantal release in the acquired forms of the Lambert-Eaton syndrome.

Endplate Acetylcholinesterase Deficiency

The EP species of ACHE is an asymmetric enzyme composed of catalytic subunits encoded by $ACHE_T$ and a collagenic structural subunit encoded by *COLQ*. No spontaneous mutations have been observed in $ACHE_T$. The COLQ protein anchoring the complex in the synaptic basal lamina is composed of three identical strands. The N-terminal residues of each strand bind a catalytic homotetramer. Mutations in the N-terminal region of COLQ prevent its association with the catalytic subunits; frameshift or nonsense mutations in collagenic midsection of COLQ produce an insertion incompetent single-stranded enzyme. Mutations of critical residues in the globular C-terminal region of COLQ prevent COLQ insertion into the synaptic basal lamina or hinder the triple helical assembly of the COLQ strands [19, 20] (Fig. 51.2).

This CMS is caused by absence or marked reduction of ACHE from the synaptic space [2]. Absence of ACHE from the EP prolongs the lifetime of ACh in the synaptic cleft because each ACh binds multiple AChRs before leaving the synaptic space by diffusion. This prolongs the duration of the MEPP and EPP, and when the EPP outlasts the absolute refractory period of the muscle fiber, it generates a second (or repetitive) muscle action potential, reflected by a repetitive compound muscle action potential (CMAP) that is not affected by edrophonium.

Cholinergic overactivity at the EP results in cationic overloading of the postsynaptic region and causes degeneration of the junctional folds with loss of AChR. The nerve terminals are abnormally small and often encased by Schwann cells, which reduces the number of releasable quanta. The safety margin of neuromuscular transmission is compromised by decreased quantal release, loss of AChR from degenerating junctional folds, altered endplate geometry, and desensitization of AChR from overexposure to ACh [2, 21].

The clinical course is variable [19, 20, 22]. Most patients present in early infancy and are severely disabled. These patients typically harbor mutations in the N-terminal or rod domain of COLQ which abolish the expression of ACHE in the synaptic space. Patients with the C-terminal missense mutations that do not abolish the triple helical assembly or the insertion of the COLQ into synaptic basal lamina present later in childhood and have a milder course.

Therapy is still unsatisfactory, but ephedrine has had a significant beneficial effect in some patients [23–25]. More recently, albuterol was found to be as or more effective than ephedrine [26].

CMS Associated with β2-Laminin Deficiency

β2-laminin, encoded by *LAMB2*, is a component of the basal lamina of different tissues and is highly expressed in kidney, eye, and the neuromuscular junction. Synaptic β2-laminin governs the appropriate alignment of the axon terminal with the postsynaptic region and, hence, pre- and postsynaptic trophic interactions. Defects in β2-laminin result in Pierson syndrome with renal and ocular malformations. A patient carrying heteroallelic missense and frameshift mutations in *LAMB2* had Pierson syndrome with severe ocular, respiratory, and proximal limb muscle weakness [5]. The renal defect was corrected by renal transplant at age 15 months. In vitro microelectrode studies revealed decreased quantal release by nerve impulse and a reduced MEPP amplitude. Electron microscopy showed that the nerve terminals were abnormally small and often encased by Schwann cells, accounting for the decreased quantal release. The synaptic space was widened and the junctional folds were simplified, accounting for the decreased MEPP amplitude.

Mutations in the AChR

Because more than one-half of all CMS are caused by mutations in AChR and because understanding the consequences of the mutations requires grasp of the structural features of the receptor, we will first focus on this topic. The AChR is a ligand-gated ion channel with a pentameric structure consisting of four homologous subunits with a stoichiometry of $\alpha_2\beta\delta\gamma$ in the fetal and $\alpha_2\beta\delta\varepsilon$ in the adult receptor. Each subunit is composed of two extracellular domains at its N- and C-terminal ends, an intracellular domain, and four transmembrane (M) domains connected by intra- and extracellular linkers [27]. Two agonist-binding pockets of AChR are present at the α/δ and α/ε subunit interfaces (Fig. 51.3a, b). The principal face of each binding site is formed by the α-subunit [28]. In each binding pocket, the cationic agonist ACh is stabilized by interaction with conserved aromatic residues. The transmembrane domains are connected by an extracellular M2/M3 linker and by intracellular M1/M2 and M3/M4 linkers. The M3/M4 linker forms a long cytoplasmic loop that likely serves as an attachment site for cytoskeletal elements (Fig. 51.3b). Cryoelectron microscopy studies in 2005 provided a structural model of the *Torpedo* AChR at 4 Å resolution at near physiological conditions [29] (Fig. 51.3d–f). Additional information came from multiple studies: solution at 2.7 Å of the structure of snail AChR-binding protein that corresponds to the extracellular domain of vertebrate nicotinic (n) AChRs [30], homology modeling based on the structure of the human nAChR-binding domain [31], resolution of the crystal structure of the nAChR α1 subunit bound to α-bungarotoxin at 1.94 Å resolution [32], and the recent report of the X-ray crystal structure of the ligand-binding domain of the eukaryotic α7 nAChR bound to epibatidine at 2.8 Å [33]. These studies pave the way to deciphering the molecular events triggered by agonist binding and the subsequent coupling of agonist binding to channel opening.

Primary AChR Deficiency with or Without Minor Kinetic Abnormalities

CMS with severe EP AChR deficiency result from different types of homozygous, or more frequently heterozygous, recessive mutations in AChR subunit genes. The clinical symptoms range from mild to very severe and resemble those of autoimmune MG. A generic diagnosis of a CMS is readily made from the criteria listed in Table 51.2**,** but muscle biopsy studies are needed to demonstrate the EP AChR deficiency for mutations that do not alter the open reading frame, and in vitro microelectrode studies are required to prove or disprove an associated significant kinetic abnormality of AChR [7, 34].

Mutations causing severe EP AChR deficiency are concentrated in the ε subunit. The main reason for this is that expression of the fetal-type γ- subunit, although at a low level, partially compensates for absence of the ε- subunit [35–37], whereas patients harboring null mutations in subunits other than ε might not survive for lack of a substituting subunit (Fig. 51.4). Different types of recessive mutations causing severe EP AChR deficiency have been identified. These mutations are frameshifting [8, 36, 38–40], occur at a

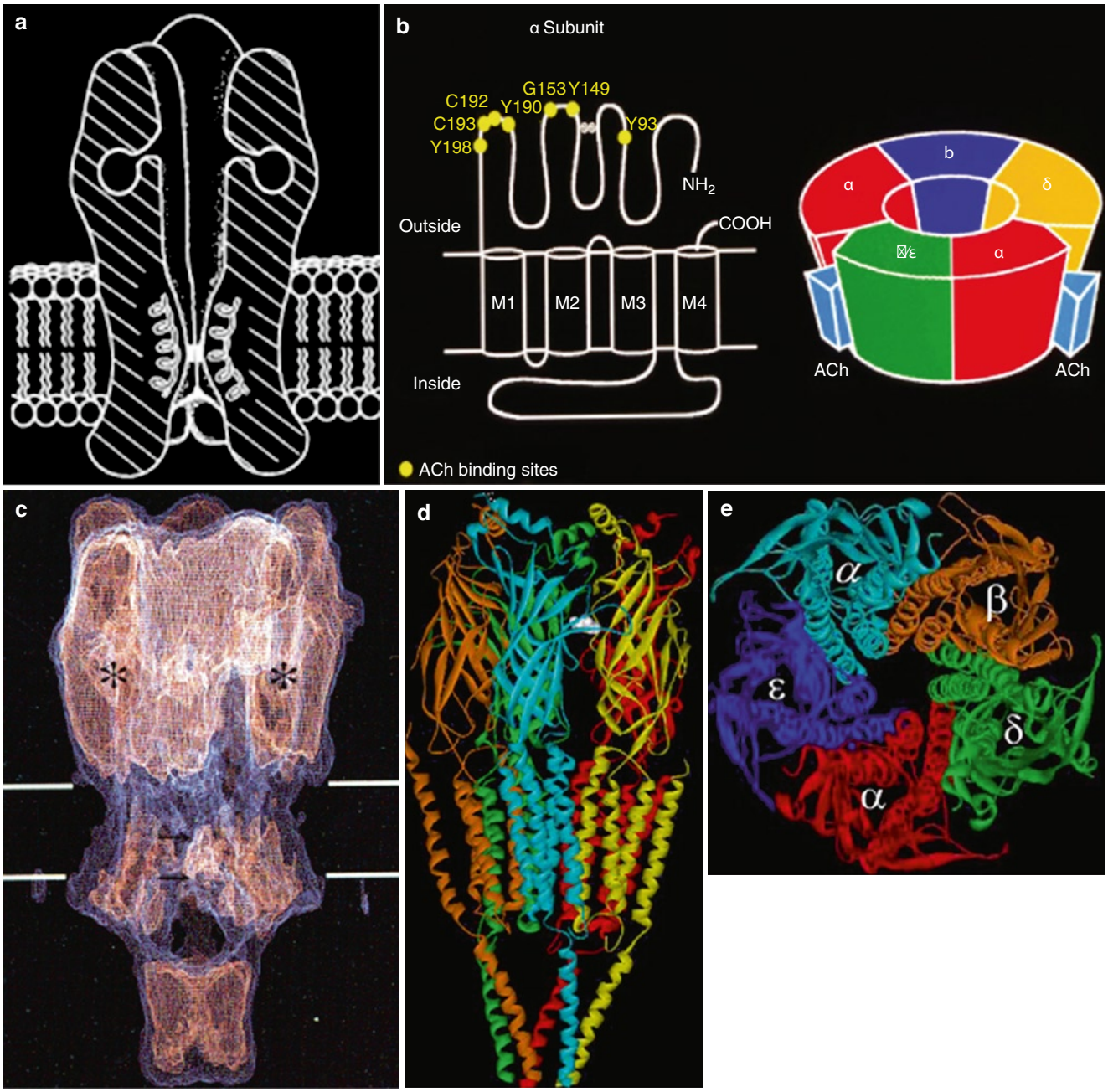

Fig. 51.3 Schematic diagrams: (**a**) AChR in lipid bilayer showing putative ACh-binding pocket and the central pore of the channel. (**b**) Folding pattern of the of α subunit; residues indicated on 3 peptide loops are implicated in governing affinity for ACh. (**c**) Cross section of AChR at the level of the ACh-binding pocket. Note that the circular arrangement of AChR subunits and that the ACh-binding pockets appear at the interfaces between α and ε/γ subunits, and between the α and δ subunits. (**d** and **e**). Structure of the *Torpedo* AChR as determined at 4 Å resolution (PDB2BG9) showing side view (**d** and **e**) and top view (**d**) of the receptor. For each subunit, the extracellular domain contains predominantly β-sheets, the transmembrane domains contain four α helices, and the cytoplasmic domain contains an α-helix and unresolved structure

splice site [8, 39], produce a stop codon directly [36], or arise from a chromosomal microdeletion [41]. An important mutation in this group is ε1369delG because it results in loss of a C-terminal Cys470 residue crucial to maturation and surface expression of the adult receptor [42]. Thus, any mutation that truncates the ε subunit upstream of Cys470 abrogates expression of the ε- subunit. Some missense mutations affect both AChR expression and kinetics. For example, εR311W in the long cytoplasmic loop between M3 and M4 decreases, whereas εP245L in the M1 domain increases the open duration of channel events [36]. In the case of εR311W and εP245L, the kinetic consequences are modest and are overshadowed by the reduced expression of the mutant gene.

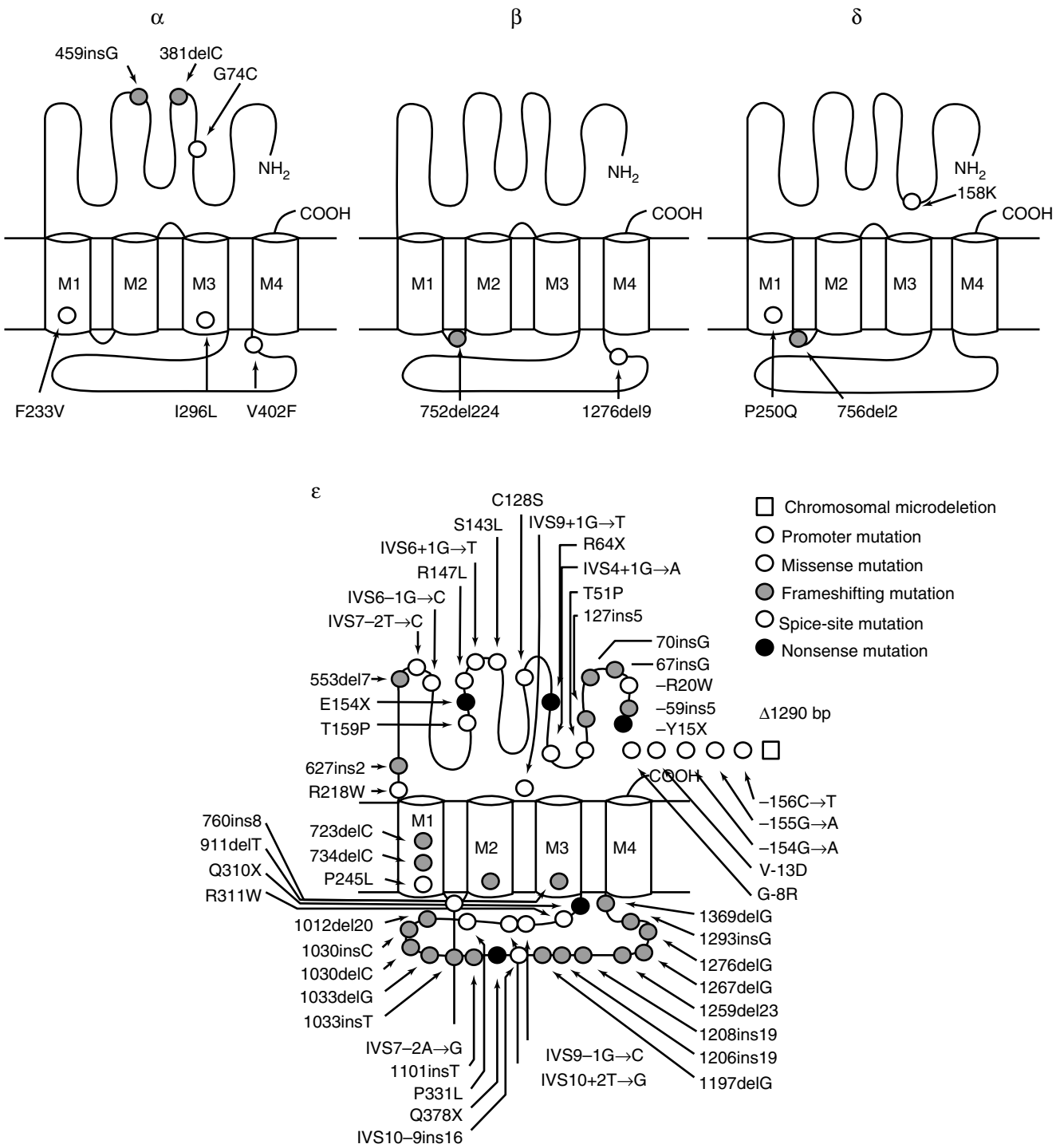

Fig. 51.4 Mutations in AChR subunits. Most mutations occur in the ε subunit of the receptor, but only few appear in the α, β, or δ subunits

Morphologic studies show an increased number of EP regions distributed over an increased span of the muscle fiber. The integrity of the junctional folds is preserved, but AChR expression on the folds is patchy and faint. Compared to normal, some EP regions are simplified and small, and some display a reduced number of secondary synaptic clefts (Fig. 51.5). The MEPP and MEPC amplitudes are small, but quantal release by nerve impulse is often higher than normal.

Most patients respond favorably but incompletely to ACHE inhibitors. The additional use of 3,4-DAP results in further improvement, but the limited ocular ductions, pronounced in most patients with AChR deficiency, are typically refractory to any therapy. Recently, albuterol was found

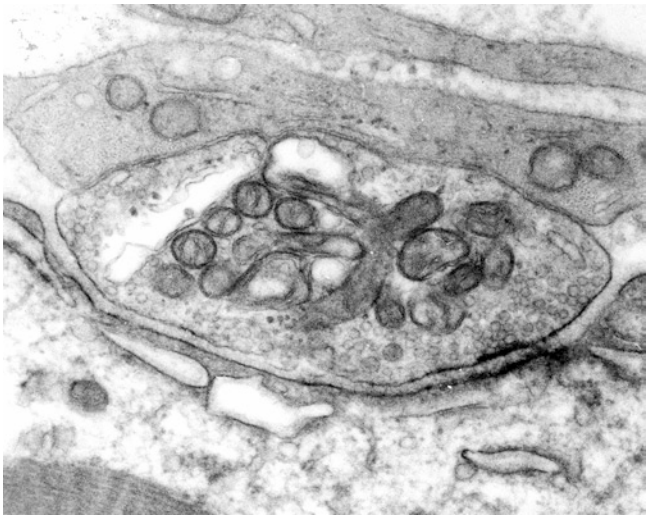

Fig. 51.5 Ultrastructural localization of AChR with peroxidase-labeled α-bungarotoxin at an endplate (EP) from a patient harboring two heteroallelic low-expressor mutations in the AChR ε- subunit (ε127ins5 and P245L). The postsynaptic region is simplified and lacks connections between the primary and secondary clefts in the plane of sectioning. The reaction for AChR is attenuated and the length of the postsynaptic membrane reacting for AChR is markedly is reduced × 25,900

Table 51.5 Kinetic abnormalities of the AChR

	Slow-channel syndromes	Fast-channel syndromes
Endplate currents	Slow decay	Fast decay
Channel opening events	Prolonged	Brief
Open states	Stabilized	Destabilized
Closed states	Destabilized	Stabilized
Mechanisms[a]	Increased affinity	Decreased affinity
	Increased β	Decreased β
	Decreased α	Increased α
		Mode-switching kinetics

β = channel opening rate; α = channel closing rate
[a]Different combinations of mechanisms operate in the individual slow- and fast-channel syndromes

to be effective in two patients responding poorly to pyridostigmine and 3,4-DAP [43].

Kinetic Abnormalities of the AChR

These result from missense mutations that may or may not reduce AChR expression. Two major and physiologically opposite syndromes are recognized. We refer to them as the slow-channel and fast-channel syndromes. Table 51.5 compares the two syndromes.

The Slow-Channel Syndromes

The clinical phenotypes vary. Some slow-channel CMS present in early life and cause severe disability by the end of the first decade; others present later in life and progress slowly, resulting in little disability even in the sixth or seventh decade [7, 44, 45]. Most patients show selectively severe involvement of cervical and wrist and finger extensor muscles. The clinical diagnosis of a slow-channel syndrome is based on the clues listed in Table 51.3. It can be confirmed by excluding EP ACHE deficiency which also causes repetitive CMAPs by histochemical demonstration of AChE activity at the patient endplates.

The phenotypic consequences stem from prolonged opening episodes of the AChR channel on exposure to ACh (see Fig. 51.6, panels b and c). Moreover, choline, present in serum at ~10 μM/L, also opens the mutant channels and renders them leaky in the resting state [46]. These factors cause cationic overloading of the junctional sarcoplasm and an EP myopathy. The EP myopathy comprises degeneration of the junctional folds with loss of AChR, widening of the synaptic space, and subsynaptic alterations consisting of degeneration of organelles, apoptosis of nuclei, and vacuolar change [7, 44, 45] (Fig. 51.7). The prolonged channel activation episodes prolong the EP potential, so that a single nerve stimulus elicits one or more repetitive CMAPs. During physiologic activity, the markedly prolonged EP potentials undergo staircase summation producing a depolarization block.

The slow-channel mutations occur in different AChR subunits and in different functional domains of the subunits [7, 45, 47–56] (Fig. 51.6a). Each is dominant, causing a pathologic gain of function. Patch-clamp studies at the EP, mutation analysis, and expression studies in human embryonic kidney (HEK) cells indicate that mutations near extracellular ACh-binding sites [48, 51] and in the N-terminal part of M1 [49] act mainly by enhancing affinity for ACh, which promotes channel reopenings, and mutations in M2, which lines the channel pore, promote the open state by affecting gating and may or may not enhance affinity [7, 45, 47] .

Therapy depends on the use of long-lived open-channel blockers of AChR, such as quinidine [57–59] or fluoxetine [60]. While these agents have a beneficial effect in the slow-channel syndrome, they are liable to worsen all other CMS. Therefore, they must not be used in a CMS unless the diagnosis of a slow-channel syndrome is firmly established.

The Fast-Channel Syndromes

The fast-channel syndromes are caused by recessive loss-of-function mutations that decrease affinity for ACh, or reduce gating efficiency, or destabilize channel kinetics, or act by a combination of these mechanisms. Each of these derangements

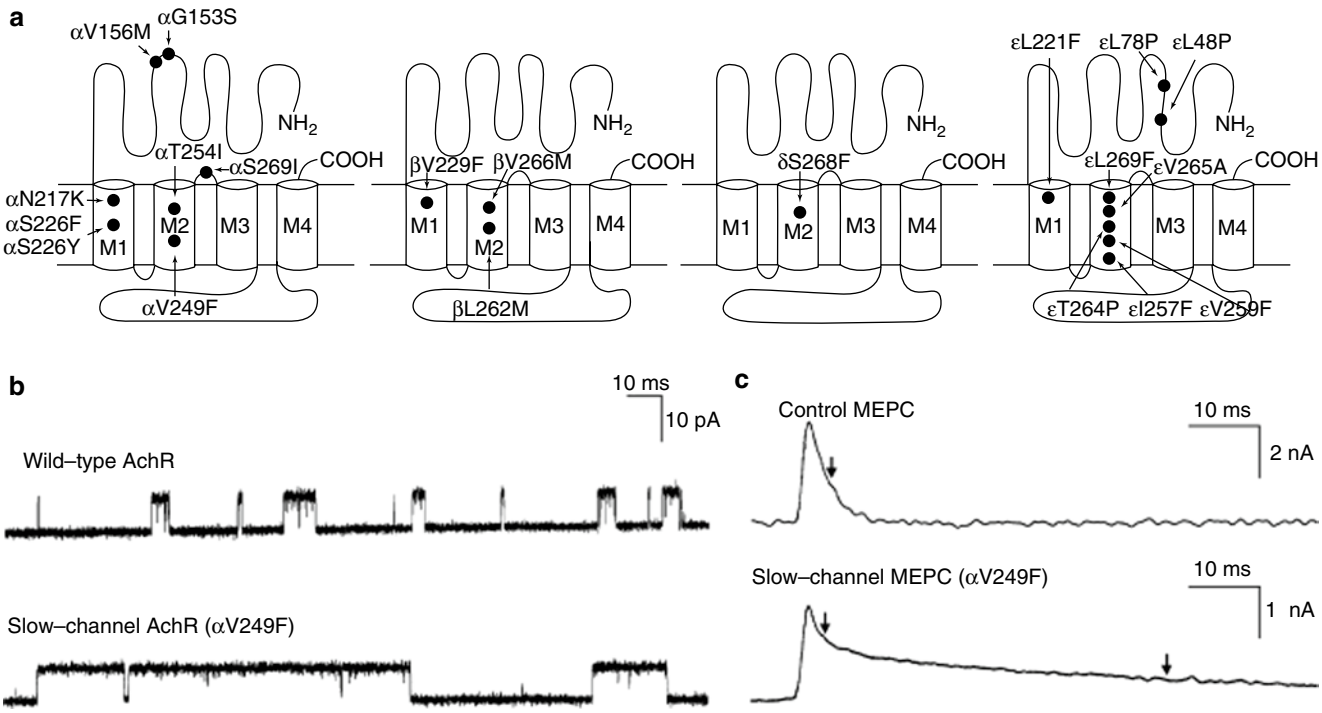

Fig. 51.6 Slow-channel syndromes. (**a**) Schematic diagram of AChR subunits with slow-channel mutations. (**b**) Single-channel currents from wild-type and slow-channel (αV249F) AChRs expressed in HEK cells. (**c**) MEPCs recorded from endplates of a control subject and a patient harboring the αV249F mutation. The slow-channel MEPC decays exponentially due to expression of both wild-type and mutant AChRs at the endplate (Reproduced from Engel and Franzini-Armstrong [1]. By permission)

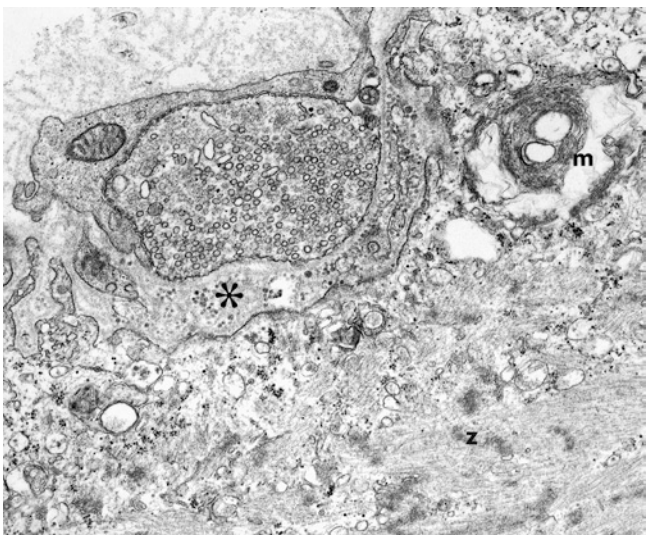

Fig. 51.7 Severe endplate myopathy in a patient harboring the εL269F slow-channel mutation. All junctional folds facing the nerve terminal have degenerated, and the synaptic space here contains only globular debris (*asterisk*). The junctional sarcoplasm harbors dilated vesicles and a myeloid structure (*m*). The nearby myofibrils are disorganized and their Z-disks (*z*) are disintegrating. Compare with normal endplate imaged in Fig. 51.1 × 21,500

results in abnormally brief channel opening events that are reflected by an abnormally fast decay of the synaptic response (Fig. 51.8a, b). A fast-channel mutation dominates the clinical phenotype when the second allele harbors a null mutation or if occurs at homozygosity. Some fast-channel mutations also reduce the expression of the mutant receptor [37, 61, 62].

The fast-channel mutations occur in different domains of different subunits (Fig. 51.8c). The mutated residues affecting affinity or gating efficiency are positioned near or at the agonist-binding site [34, 63], or are involved in isomerization of the receptor in the transient interval between the closed and open states [64, 65], or appear in a gating domain [62]. Still other mutated residues appear in the long cytoplasmic loop between the third and fourth transmembrane domains and are required to stabilize channel kinetics [37, 66].

The symptoms resemble those of autoimmune myasthenia gravis. They can be mild when the main effect is on gating efficiency [62, 64], moderately severe when channel kinetics are unstable [37, 66], and severe when affinity for ACh, or both affinity and gating efficiency, is impaired [34, 67–69] . In each syndrome, a generic diagnosis of a myasthenic disorder can be made on the basis of the criteria listed in Table 51.2, but there are no clinical or EMG clues that can point to the specific diagnosis of a fast-channel syndrome.

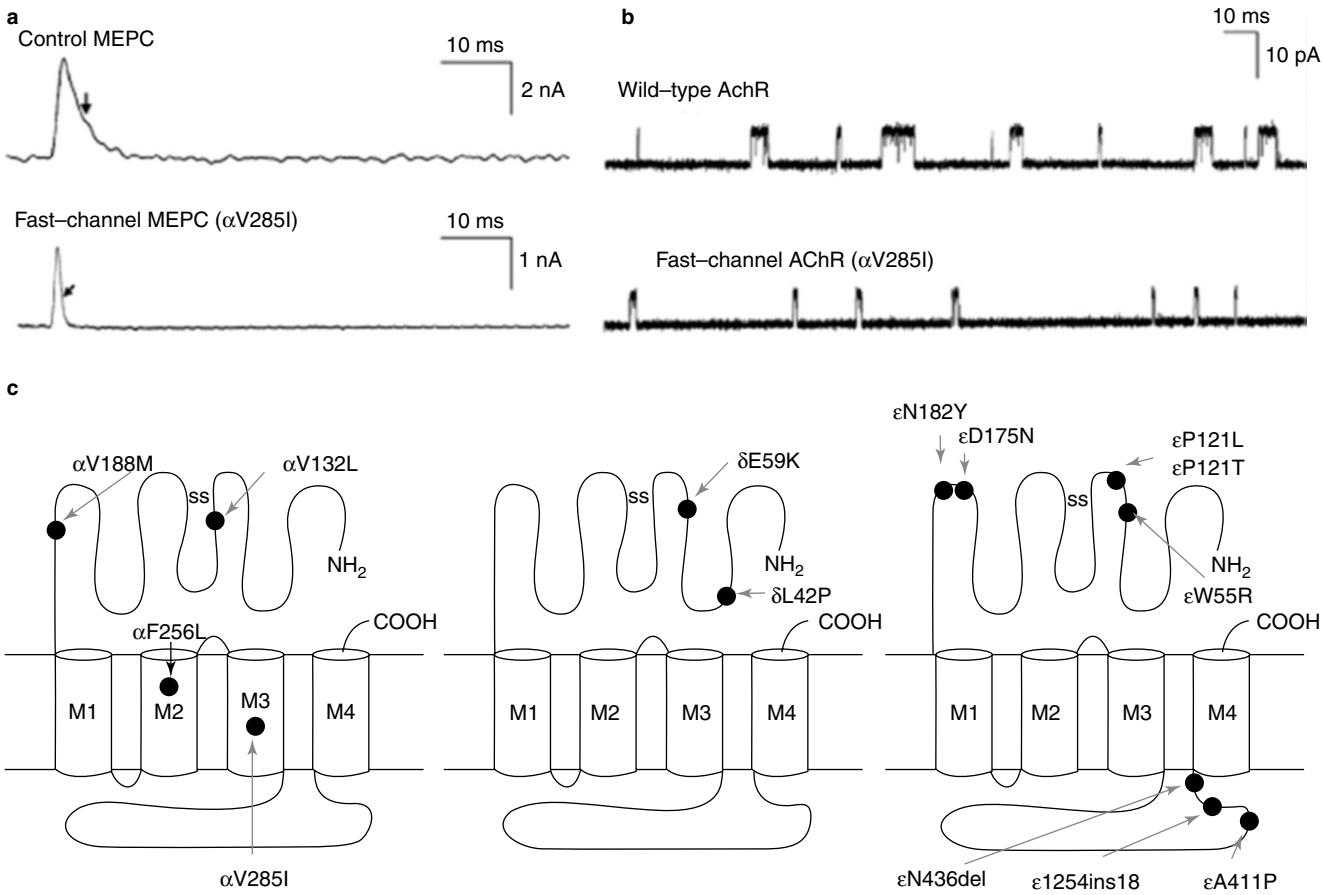

Fig. 51.8 (**a**) Fast-channel mutations result in endplate currents that decay abnormally fast due to abnormally brief channel opening events. *Arrows* point to the MEPC decay time constants. (**b**) Schematic diagram of fast-channel mutations identified in our patients. The mutations appear in different subunits of AChR and in different functional domains of the subunits (Reproduced from Engel and Franzini-Armstrong [1]. By permission)

A definitive diagnosis requires in vitro microelectrode studies to analyze the decay time constant of the miniature EP currents at voltage-clamped EPs, or patch-clamp analysis of the kinetic properties of AChRs expressed at patient EPs, or patch-clamp analysis of AChRs harboring identified mutations engineered into fibroblasts.

Treatment consists of pyridostigmine in doses similar to those used in autoimmune MG and 3,4-DAP, 1 mg/kg/day given in divided doses. 3,4-DAP increases the number of quanta released by nerve impulse, and pyridostigmine increases the number of AChRs activated by each quantum.

CMS Caused by Defects in Rapsyn

Rapsyn, under the influence of agrin, LRP4, MuSK, and Dok-7, concentrates AChR in the postsynaptic membrane and links it to the subsynaptic cytoskeleton through α-dystroglycan [70–74]. Nearly all Indo-Europeans harbor a common N88K mutation in *RAPSN* [75], but one patient carried 2 heteroallelic non-N88K mutations [76]. Expression studies in different cell lines reveal that different rapsyn mutations hinder rapsyn colocalization with AChR, prevent formation of agrin-induced AChR clusters, impede rapsyn self-association, or reduce rapsyn expression [77, 78]. Despite these differences, there are no consistent genotype-phenotype correlations except in Near Eastern Jewish patients with homozygous E-box mutation (−38A>G) who have prominent masticatory and facial muscle weakness, ptosis, prognathism, and hypernasal speech with sparing of the cervical, axial, and limb muscles [79].

In most patient, myasthenic symptoms present at birth or infancy with only few presenting after the age of 10 years [80]. Arthrogryposis at birth and other congenital malformations occur in nearly one-third [77, 80, 81] but are not associated with specific mutations. Respiratory infections or other febrile illnesses precipitate increased weakness and respiratory crises and can cause an anoxic encephalopathy [77, 80, 82, 83].

The distribution of weakness resembles that in autoimmune myasthenia gravis except ophthalmoparesis is less common [80]; in the Mayo Clinic series, 9 of 39 patients had constant or episodic involvement of the extraocular muscles [81]. Out-of-proportion weakness of the foot dorsiflexors was reported to be a feature of the late-onset phenotype [80].

The morphologic features of the EP and the factors that impair the safety margin of neuromuscular transmission are the same as in primary AChR deficiency, but the EP AChR deficiency is relatively mild in most patients. In some patients, single-fiber EMG is required to demonstrate a defect in neuromuscular transmission.

Most patients respond well to ACHE inhibitors; some derive additional benefit from the use of 3,4-DAP [82], and some patients observed by the author benefited from the added use of ephedrine or albuterol.

CMS Associated with Plectin Deficiency

Plectin, encoded by *PLEC*, is a highly conserved and ubiquitously expressed intermediate filament-linking protein. Owing to tissue- and organelle-specific transcript isoforms, plectin is a versatile linker of cytoskeletal components to target organelles in cells of different tissues [84–86]. It is concentrated at sites of mechanical stress, such as the postsynaptic membrane lining junctional folds, the sarcolemma, Z-disks in skeletal muscle, hemidesmosomes in skin, and intercalated disks in cardiac muscle. In skeletal muscle, multiple alternatively spliced transcripts of the exon preceding a common exon 2 link cytoskeletal intermediate filaments to specific targets: the outer nuclear membrane (isoform 1), the outer mitochondrial membrane (isoform 1b), Z-disks (isoform 1d), and the sarcolemmal costameres (isoform 1f) [86]. Pathogenic mutations in plectin result in epidermolysis bullosa simplex (EBS), a progressive muscular dystrophy in many patients, and a myasthenic syndrome in some patients (reviewed in Refs. [87, 88]). Heteroallelic nonsense, frameshift, or splice-site mutations in *PLEC* were recently reported in four unrelated patients with documented defects in neuromuscular transmission [88–90]. In two patients investigated by the author, microelectrode studies of intercostal muscle EPs showed low-amplitude MEPPs. Morphologic studies revealed dislocated and degenerating muscle fiber organelles, plasma membrane defects resulting in Ca^{2+} overloading of the muscle fibers as in Duchenne dystrophy, and extensive degeneration of the junctional folds, all attributable to lack of cytoskeletal support [88]. One patient harbored homozygous frameshift mutations in both *PLEC* and in *CHRNE* [90]. Interestingly, a recent study identified a homozygous deletion mutation in isoform 1f that caused limb-girdle muscular dystrophy but neither EBS nor myasthenia [91].

Na Channel Myasthenia

Only a single patient has been reported to date [92]. She had abrupt attacks of respiratory and bulbar paralysis since birth lasting 3–30 min similar to those caused by ChAT deficiency. Detailed electrophysiology analysis of patient EPs revealed that suprathreshold EPPs failed to generate muscle action potentials pointing to Nav1.4, encoded by *SCN4A*, as the culprit. EP structure and Nav1.4 expression at the EPs were normal, but *SCN4A* harbored 2 mutations (S246L in the S4/S5 linker in domain I and V1442E in S4/S5 linker in domain IV). Recombinant V1442E-sodium channels expressed in HEK cells showed marked enhancement of fast inactivation close to the resting potential and enhanced use-dependent inactivation on high-frequency stimulation; S246L had only minor kinetic effects and is likely a benign mutation. The safety margin in this congenital myasthenic syndrome is impaired because a large fraction of the Nav1.4 channels are inexcitable in the resting state.

Dok-7 Myasthenia

After the discovery in 2006 of Dok-7 as a muscle-intrinsic activator of MuSK [73], numerous CMS-related mutations were indentified in *DOK7* [3, 4, 93–95], and Dok-7 myasthenia is now recognized as a common cause of CMS. Dok-7 is strongly expressed at the postsynaptic region of the skeletal muscle and in the heart. It harbors an N-terminal pleckstrin homology domain (PH) important for membrane association, a phosphotyrosine-binding (PTB) domain, and C-terminal sites for phosphorylation. The PTB and PH domains are required for association with and phosphorylation of MuSK. Phosphorylation of two of the C-terminal residues is a requisite for Dok-7 activation by Crk and Crk-L [96]. A recent review lists all Dok-7 mutations reported since 2006 [95].

Nearly all patients carry a common 1124_1127dupTGCC mutation in exon 7. This and other mutations upstream of the C-terminal phosphorylation sites abrogate the ability of Dok-7 to associate with Crk1/Crk1L and hence its activation [96, 97]. Other mutations disrupt or eliminate the PH and PTB domains of Dok-7 or cause exon skipping due to intronic mutations.

The weakness in Dok-7 myasthenia typically has a limb-girdle distribution, but mild ptosis and facial weakness are not infrequent [4, 93–95, 98–100]. Severe bulbar symptoms are uncommon except for laryngeal stridor in infants [101] but were present in a patient who carries a readthrough mutation in the last codon of *DOK7* [4]. In 16 patients investigated by us, the age at onset ranged from birth to 5 years (mean, 1.6 years; median, 1 year) [4]. The clinical course varied from mild static weakness limited to the limb-girdle

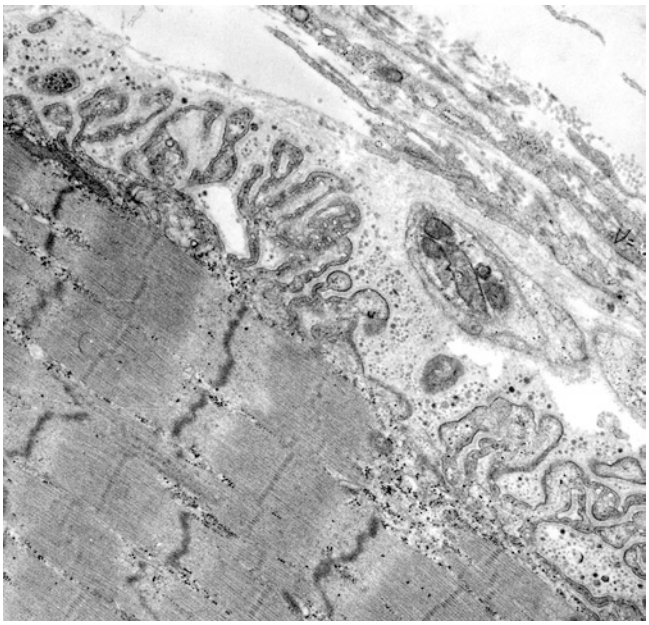

Fig. 51.9 Abnormal endplate region in Dok-7 myasthenia. There is extensive destruction of the junctional fold causing accumulation of globular remnants of the folds in the synaptic space. The junctional folds on the left are denuded of nerve terminal. A small nerve terminal on the right is enveloped by Schwann cell processes (× 10,000)

muscles to severe generalized progressive disease with conspicuous muscle atrophy. All had short-term fatigability on exertion. Ten patients experienced intermittent worsenings lasting from days to weeks, as also observed by others [93, 99]. Seven patients had significant respiratory embarrassment. The overall course was progressive in 12 of the 16 patients.

Morphologic studies often show type 1 fiber preponderance, type 2 fiber atrophy, and frequently minor myopathic features. The synaptic contacts are small relative to fiber size and are single or multiple on a given fiber. Most EPs lack the normal pretzel shape indicating impaired differentiation of the postsynaptic region [4, 98]. Electron microscopy shows ongoing destruction of existing endplates (Fig. 51.9) and attempts to form new endplates, indicating that Dok-7 is essential not only for the development but also for maintaining the structural integrity of the neuromuscular junction throughout life [4]. In vitro microelectrode studies indicate impaired quantal release or impaired postsynaptic response to the released quanta or both.

Most studies found that pyridostigmine worsened the disease either immediately or gradually [4, 93, 95, 99]. In contrast, treatment with ephedrine is beneficial in Dok-7 myasthenia [4, 98, 100, 102, 103]. Because ephedrine is no longer available in the USA, we use albuterol sulfate instead with good and sometimes strikingly beneficial results in doses of up to 4 mg three times daily in adults and appropriate pediatric dosages in children [26].

CMS Caused by Defects in MuSK

MuSK (muscle-specific receptor tyrosine kinase), under the influence of agrin mediated by LRP4 and in concert with Dok-7, plays a role in maturation and maintenance of the EP and in directing rapsyn to concentrate AChR in the postsynaptic membrane [104–106]. Only three reports describe myasthenic syndromes caused by defects in MuSK. One kinship harbored c.220insC and V790M mutations. The missense mutations did not affect the catalytic kinase activity of MuSK but decreased its expression and stability [107]. Expression studies in mice revealed reduced synaptic AChR expression and aberrant axonal outgrowths as observed in the patient [108]. The safety margin in this patient is likely compromised by the AChR deficiency.

A second report describes heteroallelic M605I and A727V mutations in MuSK in a patient with severe myasthenic symptoms since early life that improved after puberty but worsened after menstrual periods. The MEPP and MEPC amplitudes in anconeus muscle were reduced to about 30 % of normal and the EPP quantal content was half normal. Synaptic contacts were small and the postsynaptic regions had poorly differentiated secondary clefts. The patient failed to respond to pyridostigmine, ephedrine, or 3,4-DAP but responded partially to albuterol [109].

A third kinship harbored a homozygous P344R missense mutation in the cysteine-rich extracellular domain of MuSK. The clinical course was progressive. Low doses of pyridostigmine and 3,4-DAP led to gradual improvement; ephedrine or higher doses of pyridostigmine were not tolerated [110].

CMS Caused by Defect in Agrin

Agrin, encoded by *AGRN*, is a multidomain proteoglycan secreted into the synaptic basal lamina by the nerve terminal. The muscle isoform of agrin harbors A and B regions near its C-terminal. Agrin phosphorylates and thereby activates MuSK by way of its receptor LRP4 [111, 112]. Two siblings with eyelid ptosis but normal ocular ductions and only mild weakness of the facial and hip-girdle muscles carried a homozygous missense mutation in *AGRN* at codon 1709 (G1709R). The mutation is in the laminin G-like 2 domain, upstream of the *y* and *z* inserts of neural agrin required for MuSK activation and EP formation. AChR and agrin expression at the EP were normal. Structural studies showed EPs with misshaped synaptic gutters partially filled by nerve endings and formation of new EP regions. The postsynaptic regions were preserved. Expression studies revealed that the mutation did not affect activation of MuSK by agrin or agrin binding to α-dystroglycan. Forced expression of a mutant mini-agrin gene in mouse soleus muscle showed changes similar to those at patient EPs suggesting that the observed

mutation perturbs the maintenance of the EP without altering the canonical function of agrin to induce the development of the postsynaptic compartment. The index patient failed to respond to a cholinesterase inhibitor and 3,4-DAP but responded partially to ephedrine [113].

Myasthenic Syndrome Associated with Centronuclear Myopathy

Centronuclear myopathies (CNM) are clinically and genetically heterogenous congenital myopathies in which the predominant pathologic alteration is centralization of the muscle fiber nuclei. The implicated disease proteins/genes are myotubularin (*MTM1*), dynamin 2 (*DNM2*), amphiphysin 2 (*BIN1*), and the ryanodine receptor (*RYR1*) [114]. Features suggesting a myasthenic disorder, ptosis, ophthalmoparesis, abnormal fatigability, decremental EMG response [115], or abnormally increased jitter [116] have been observed in clinically and genetically different CNM patients.

A recently investigated 39-year-old man with CNM and a myasthenic syndrome [117] had a 19–35 % EMG decrement and responded partially to pyridostigmine. Serologic tests for AChR and MuSK antibodies were negative. No mutations were detected in *MTM1*, *DNM2*, *BIN1*, and *RYR1*. Intercostal muscle EP studies revealed simplified postsynaptic regions and mild AChR deficiency. The safety margin of neuromuscular transmission was compromised by reduction of the MEPP amplitude to 60 % and of quantal release to 40 % of normal [117]. Four other CNM patients with myasthenic features responding to pyridostigmine with no known mutation were also reported, but EP structure and parameters of neuromuscular transmission were not evaluated [118].

CMS Caused by Mutations in *GFPT1*

GFPT1 encodes glutamine-fructose-6-phosphate transaminase-1. GFPT1 controls the flux of glucose into the hexosamine pathway and thus the formation of hexosamine products and the availability of precursors for *N*- and O-linked glycosylation of proteins. The disease gene was discovered by linkage and homozygosity analysis studies of multiplex kinships with a limb-girdle CMS associated with tubular aggregates in skeletal muscle [9]. The affected patients harbored no mutations in Dok-7 and, unlike patients with Dok-7 myasthenia, responded favorably to ACHE inhibitors. Among the 13 reported patients, most presented in the first decade, about one-fourth had elevated serum CK levels, some had distal as well as proximal weakness, but very few had ptosis or respiratory muscle involvement. Immunoblots of muscle of affected patients revealed decreased expression of O-*N*-acetylglucosamine residues on numerous muscle proteins. One patient was shown to have a decreased number of EP AChRs. The effects of the different mutations on EP fine structure and the extent to which they alter parameters of neuromuscular transmission have not yet been determined [9].

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Toxic Neuromuscular Transmission Disorders

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James F. Howard Jr.

Introduction

The neuromuscular junction (NMJ) is uniquely sensitive to the effects of neurotoxins. While the blood–brain barrier protects the brain and spinal cord and the blood-nerve barrier protects peripheral nerve, there are no barriers to protect the NMJ from the deleterious effects of these agents. Several forms of neurotoxins are directed against the NMJ. Many occur as natural substances of plants or animals, others result from the actions of widely prescribed pharmaceutical compounds, and still others are environmental hazards. In nearly all instances of NMJ neurotoxicity, there is a reduction in the safety factor of neuromuscular transmission by one of several mechanisms. These neurotoxins may affect either the presynaptic or the postsynaptic elements of the NMJ. The clinical features of these neurotoxins are quite varied as many have associated toxicity of other parts of the central, peripheral, or autonomic nervous systems. Many will have other systemic effects as well. While feared as the purveyor of morbidity and mortality, many of these neurotoxins have led to significant advances in our understanding of the molecular mechanisms of pharmacology and physiology and their associated diseases. For example, was it not for the recognition that α-bungarotoxin binds to the acetylcholine receptor (AChR), and omega-conotoxin binds to the voltage-dependent calcium channel (VDCC) our advances in the diagnosis and treatment of myasthenia gravis (MG) and the Lambert-Eaton syndrome (LES) would have been delayed [1, 2]. Worldwide, the most common neurotoxicity of the neuromuscular junction results from envenomation. More concern to the clinical neurologist are those situations that result from the direct effects of various pharmacologic agents routinely used in the practice of medicine that produce significant aberrations of neuromuscular transmission in susceptible individuals. The potential for environmental intoxication has been limited by the stringent regulation of federal and international regulatory agencies.

All forms of NMJ neurotoxicity are characterized by progressive, typically symmetrical, muscle weakness. Muscles of eye movement or the eyelid are most often involved as well as the muscles of neck flexion and the pectoral and pelvic girdles. There may be involvement of bulbar and respiratory musculature depending upon the toxin involved, the dose acquired, and the duration of toxin exposure. Cognition and sensation are spared, unless other elements of the central nervous system are simultaneously involved. Muscle stretch reflexes are often preserved or only minimally diminished particularly during the early phases of the illness but may be lost if the weakness is severe.

Pharmacological Neurotoxicity

The adverse reaction of drugs on synaptic transmission may be classified either as acting *presynaptically*, with a reduction in acetylcholine (ACh) release secondary to local anesthetic-like activity on the nerve terminal, alteration or impairment of calcium flux into the nerve terminal, or a hemicholinium effect; *postsynaptically*, with antibody blockade of ACh receptors, curare-like effects, or potentiation of depolarizing or nondepolarizing neuromuscular blocking agents; or, in varying degrees, *both*. Each of these pharmacological interactions may result in any of the clinical situations described above. Since the publication of the summaries of Barrons, Howard, and Kaeser, describing disorders of neuromuscular transmission occurring as the result of adverse drug reactions, many more reports have surfaced adding to the list of potentially dangerous drugs [3–7]. An up-to-date list of these potential drug-disorder interactions is maintained on the web site of the Myasthenia Gravis Foundation of

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America (http://www.myasthenia.org/portals/0/draft_medications_and_myasthenia_gravis_for_MGFA_website_8%). Unfortunately, much of the literature is anecdotal and there are only a few comprehensive in vitro studies of drug effects on neuromuscular transmission in animal or human nerve-muscle preparations. The potential adverse effects of these medications must be taken into consideration when deciding which drugs to use in treating patients who have disorders of synaptic transmission.

With the exception of telithromycin and the possible exceptions of D-penicillamine, α-interferon, and botulinum toxin, there are no drugs that are absolutely contraindicated in patients with MG and Lambert-Eaton syndrome (LES). There are, however, numerous drugs that interfere with neuromuscular transmission and will make the weakness of these patients worse or prolong the duration of neuromuscular block in patients receiving muscle relaxants. Drug-induced disturbances of synaptic transmission resemble MG with varying degrees of ptosis, ocular, facial, bulbar, respiratory, and generalized muscle weakness. Treatment includes discontinuation of the offending drug and when necessary reversing the neuromuscular block with intravenous infusions of calcium, potassium, or cholinesterase inhibitors. In rare instances, these drugs may induce an autoimmune form of MG (D-penicillamine and interferon alpha). In these situations, the treating physician must utilize therapies that are typically used for other forms of autoimmune MG.

While it is most desirable to avoid drugs that may adversely affect neuromuscular transmission, in certain instances, they must be used for the management of another illness. In such situations, a thorough knowledge of the deleterious side effects can minimize their potential danger. If at all possible, it is wise to use the drug within a class of drugs that has been shown to have the least effect on neuromuscular transmission. Unfortunately, studies, which allow such comparisons, are quite few.

The most frequently encountered problems are the effects of antibiotics (macrolides, fluoroquinolones, and aminoglycosides) and β-adrenergic blocking agents acutely worsening the strength of patients with MG. Less commonly encountered are prolonged muscle weakness and respiratory embarrassment postoperatively in patients with disorders of neuromuscular transmission.

Antibiotics

Two classes of antibiotics carry the FDA Black Box Warning designation. The ketolide, telithromycin, and the fluoroquinolone class of antibiotics received this designation due to repeated reports of myasthenic exacerbation and death following their use [8, 9]. The aminoglycoside antibiotics may produce neuromuscular weakness irrespective of their route of administration [10]. The weakness is related to serum levels of the drug and is reversible in part by cholinesterase inhibitors, calcium infusion, and the aminopyridines [11]. These drugs have pre- and postsynaptic actions; many have elements of both. Neuromuscular toxicity data exist for several of the antibiotics including amikacin, gentamicin, kanamycin, neomycin, netilmicin, streptomycin, and tobramycin [12]. Of the group, neomycin is the most toxic, tobramycin the least. Clinically, gentamicin, kanamycin, neomycin, tobramycin, and streptomycin have been implicated in producing muscle weakness in non-myasthenic patients [5]. Neuromuscular blockade is not limited to the aminoglycoside antibiotics. Myasthenic patients given the macrolides, erythromycin, or azithromycin will often report a mild to moderate exacerbation of their weakness [13, 14]. Myasthenic crisis has also been reported [15]. The newly recognized ketolide, telithromycin, has produced abrupt and severe worsening in MG or unmasked previously undiagnosed MG [Howard JF, 2003, personal observation] [16–19]. The polypeptide and monobasic amino-acid antibiotics, penicillins, sulfonamides, tetracyclines, and fluoroquinolones, cause transient worsening of myasthenic weakness, potentiate the weakness of neuromuscular blocking agents, or have theoretical reasons for blocking synaptic transmission [20]. Lincomycin and clindamycin can cause neuromuscular blocking which is not readily reversible with cholinesterase inhibitors [21, 22]. Polymyxin B, colistimethate, and colistin are also reported to produce neuromuscular weakness particularly in patients with renal disease or when used in combination with other antibiotics or neuromuscular blocking agents [10, 23]. These drugs, ampicillin, the tetracycline analogs, oxytetracycline and rolitetracycline, and, more recently, ciprofloxacin [24], exacerbate MG, although the mechanisms for each medication are not fully understood [25, 26].

Cardiovascular Drugs

Many cardiovascular drugs are implicated in adversely affecting the strength of patients with MG and LES, and they (along with the antibiotics) account for the majority of adverse drug reactions in patients with neuromuscular disorders. Beta-adrenergic blockers may cause exacerbation of MG, or their use may coincide with the onset of myasthenic manifestations [4, 27]. Even those drugs instilled topically on the cornea are capable of producing such weakness [28, 29]. Atenolol, labetalol, metoprolol, nadolol, propranolol, and timolol cause a dose-dependent reduction in the efficacy of neuromuscular transmission in normal rat skeletal muscle and human myasthenic intercostal muscle biopsies [27]. Different ß-blockers have reproducibly different pre- and postsynaptic effects on neuromuscular transmission. Of the group, propranolol is most effective in blocking

neuromuscular transmission and atenolol the least. The effects of calcium channel blockers on skeletal muscle are not understood fully, and studies have provided conflicting information. Some demonstrated neuromuscular blockade with postsynaptic curare-like effects, presynaptic inhibition of ACh release, and both pre- and postsynaptic effects [30–32]. The oral administration of calcium channel blockers to cardiac patients without neuromuscular disease does not produce altered neuromuscular transmission by single-fiber electromyography (SF-EMG) measures [33]. Acute respiratory failure was temporally associated with administration of oral dose of verapamil in a patient with LES and small-cell carcinoma of the lung [34]. One patient with moderately severe, generalized MG developed acute respiratory failure following verapamil initiation (author's observations). Low doses of verapamil and its timed-release preparation have been used successfully for the treatment of hypertension in patients with MG receiving cyclosporine (author's observations).

Procainamide may produce acute worsening of strength in patients with MG [35]. The rapid onset of neuromuscular block and the rapid resolution of symptoms following discontinuation of the drug suggest the drug has a direct toxic effect on synaptic transmission rather than the induction of an autoimmune response against the neuromuscular junction. The postulated mechanism of action is primarily at the presynaptic membrane with impaired formation of ACh or its release, although it is known to have postsynaptic blocking effects as well. Two case reports suggest that the antiarrhythmic P-glycoprotein inhibitor, propafenone, may cause acute exacerbations of myasthenic weakness [36, 37]. Like the effects of procainamide, the rapid onset of worsening and resolution following the discontinuation of the drug implicates a direct toxic effect on neuromuscular transmission.

The earliest report of quinidine (the stereoisomer of quinine) administration aggravating MG was by Weisman [38]. There are several reports of the unmasking of previously unrecognized MG following treatment with quinidine [39, 40]. The neuromuscular block is both presynaptic, impairing either the formation or release of ACh, and, in larger doses, postsynaptic with a curare-like action [41]. It has been claimed the ingestion of small amounts of quinine, for example, in a gin and tonic, may acutely worsen weakness in a myasthenic patient, although this cannot be substantiated with objective reports.

Cholesterol-Lowering Agents

Several published works suggest that the statin cholesterol-lowering agents may be causal in the exacerbation of myasthenic weakness [42–48] The mechanism(s) for this worsening is not clear, but several postulates have been proposed. It is well recognized that HMG-CoA reductase therapy may produce a myopathy [49–52]. Is it possible the myasthenic worsening could be due to a coexisting disorder of the muscle membrane? Statins have immunomodulatory properties, with the ability to induce production of the Th2 cytokines interleukin (IL)-4, IL-5, and IL-10 [53]. Animal and human studies suggest that these Th2 cytokines play a role in the development of MG [54]. Therefore, it is possible that upregulation of Th2 cytokine production could lead to worsening MG. Statins have been postulated to cause mitochondrial dysfunction by depleting endogenous coenzyme Q10 [55]. Statin-induced mitochondrial failure in the nerve terminal has been proposed as a mechanism to impair neuromuscular transmission given the high content of mitochondria in the nerve terminal [44]. There is no evidence to suggest that HMG-CoA reductase is known to directly interfere with neuromuscular transmission [56].

Magnesium

Hypermagnesemia is an uncommon clinical complication from the use of magnesium-containing drugs [57]. Renal failure predisposes to hypermagnesemia and is the reason to avoid magnesium-containing antacids and laxatives [58, 59]. Excessive use of enemas containing Mg^{++} may produce hypermagnesemia, but this is usually in patients with underlying gastrointestinal (GI) tract disease [60, 61]. Hypermagnesemia commonly results from administration of high doses of parenteral $MgSO_4$ for treatment of eclampsia, at times resulting in serious side effects to the mother or the newborn [62–64]. The clinical manifestations of hypermagnesemia correlate with serum Mg^{++} levels [61, 65, 66]. Muscle stretch reflexes become reduced when the serum Mg^{++} level exceeds 5 mEq/L; levels of 9–10 mEq/L are associated with absent reflexes and muscle weakness. During treatment of preeclampsia, muscle stretch reflexes are monitored and Mg^{++} administration is discontinued if the reflexes disappear [64]. Fatal respiratory failure can occur at levels greater than 10 mEq/L [62, 64]. Serum levels greater than 14 mEq/L can induce acute cardiac arrhythmia, including heart block and arrest. Symptoms of autonomic dysfunction in hypermagnesemia include dry mouth, dilated pupils, urinary retention, hypotension, and flushing and are thought to result from presynaptic blockade at autonomic ganglia [67]. The muscles of ocular motility tend to be spared and the clinical findings of hypermagnesemia resemble those of LES rather than MG [68]. Magnesium inhibits release of ACh by competitively blocking calcium entry at the motor nerve terminal [69]. There may also be a milder postsynaptic affect. Magnesium also potentiates the action of neuromuscular blocking agents, and this must be considered in women undergoing cesarean section after receiving Mg^{++} for preeclampsia [70, 71]. Patients with underlying junctional disorders are more sensitive to Mg^{++}-induced weakness. Patients

with MG and LES may become weaker after receiving Mg^{++} even when serum Mg^{++} levels are normal or only slightly elevated [72–75]. Reports exist of the uncovering of previously unrecognized MG following treatment of preeclampsia with magnesium salts (Howard JF, unpublished observation) [76]. Increased MG symptoms most often occur when Mg^{++} is administered parenterally but on occasion is seen with oral use [75]. Therefore, parenteral Mg^{++} administration should be avoided and oral Mg^{++} preparations should be used with caution in patients with known disorders of synaptic transmission, such as MG, LES, and botulism. Patients with MG or LES respond poorly to calcium and may respond better to cholinesterase inhibitors [72].

Recreational Drugs

Several cases of MG exacerbation following recreational use of cocaine have been reported [77–80]. These attacks frequently include respiratory insufficiency requiring ventilatory support [79, 80] and improve with therapeutic apheresis [80] (D.B. Sanders – unpublished observations) or high-dose intravenous immunoglobulin [80]. Myasthenic exacerbations have been associated with elevated serum creatine kinase in some patients [79]. Cocaine reduces the skeletal muscle response to repetitive nerve stimulation in mice by decreasing the muscle and nerve excitability but without apparent effect on NMT [80]. Cocaine inhibits nicotinic AChR in cultured muscle cells [81].

Rheumatologic Drugs

D-penicillamine (D-P) is used in the treatment of rheumatoid arthritis (RA), Wilson's disease, and cystinuria. A number of autoimmune diseases occur in patients receiving D-P of which MG is most frequent [82–84]. The MG induced by D-P is usually mild and may be restricted to the ocular muscles. In many patients, the symptoms are not recognized, and it may be difficult to demonstrate mild weakness of the limbs in the presence of severe arthritis. It is unlikely that D-P has a direct effect on neuromuscular transmission as MG begins after prolonged D-P therapy in most patients and has a relatively low incidence in patients receiving D-P for Wilson's disease compared with those receiving it for RA [85]. It is more likely that D-P induces MG by stimulating or enhancing an immunological reaction against the neuromuscular junction. When MG begins while the patient is receiving D-P, it remits in 70 % of patients within 1 year after the discontinuation of the drug [86]. In a few patients, the MG persists after D-P is discontinued, implying that a subclinical myasthenic state existed prior to the initiation of the D-P (author's observations).

Chloroquine is used primarily as an antimalarial drug, but in higher doses, it is also used in the treatment of several collagen vascular disorders including RA, discoid lupus erythematosus, and porphyria cutanea. It may produce a number of neurological side effects among which are disorders of neuromuscular transmission. Reported mechanisms of action for this have been both pre- and postsynaptic, but chloroquine may also alter immune regulation producing a clinical syndrome of MG similar to that reported with D-P. One patient with RA and another with systemic lupus erythematosus developed the typical clinical, physiological, and pharmacological picture of MG following prolonged treatment with chloroquine. Antibodies to the AChR were identified and subsequently slowly disappeared, as did the clinical and electrophysiological abnormalities, with discontinuation of the drug [46, 48]. A patient is described with a transient postsynaptic disorder of neuromuscular transmission following 1 week of chloroquine therapy that was thought to be due to a direct toxic effect on the neuromuscular junction rather than a derangement of immune function [87].

Others

Interferon Alpha

Generalized MG may occur after starting interferon alpha therapy for leukemia, during interferon alpha-2b treatment for malignancy, and during treatment for chronic active hepatitis C [88–91]. Myasthenic crisis may even develop with interferon alpha therapy [92]. The mechanism of interferon-induced MG is not known. Expression of interferon gamma at motor endplates of transgenic mice results in generalized weakness and abnormal NMJ function, which improves with cholinesterase inhibitors. Immunoprecipitation studies identified an 87-kD target antigen recognized by sera from these transgenic mice and from human MG patients. Such studies suggest that the expression of interferon gamma at the motor endplates provoked an autoimmune humoral response, similar to that which occurs in human MG [93].

Botulinum Neurotoxin

Botulinum neurotoxin, when used therapeutically for focal dystonia, has unmasked subclinical LES and MG [94, 95]. Worsening of weakness or crisis has also been reported in MG following injections of botulinum toxin [96–99]. A known defect of NMT is considered to be a relative contraindication to the use of botulinum toxin, although others have reported its successful use in patients with MG [100].

Numerous other drugs may interfere with neuromuscular transmission. Many local anesthetics, certain anticonvulsants, magnesium, iodinated contrast dyes, and, of course, the neuromuscular blocking agents used by anesthesiology during surgery are included in this list. Newly reported

Table 52.1 Clinical classification of botulism

Classic form
Infantile form
Wound botulism
Traumatic or surgical
Drug abuse
Intranasal
Intravenous
Hidden form

adverse drug-disorder interactions are reported frequently. It is beyond the scope of this chapter to discuss them all in detail, and the reader is referred to a more comprehensive review of the topic [4] or to the web address of the Myasthenia Gravis Foundation of America.

Biological Neurotoxins

Botulism

Botulism is caused by a clostridial neurotoxin that blocks the release of ACh from the motor nerve terminal[1] [101]. The result is a long-lasting, severe muscle paralysis. Botulism may be classified clinically according to presentation as noted in Table 52.1. Of eight different types of botulinum toxins, types A and B cause most cases of botulism in the United States. Type E is transmitted in seafood and type A is thought to produce the most severe manifestations. The classic form of the disease usually follows ingestion of foods that were contaminated by inadequate sterilization. Not all persons ingesting contaminated food become symptomatic. Nausea and vomiting are the first symptoms and the neuromuscular features begin 12–36 h after exposure. The clinical findings are stereotypical. Ptosis, blurred vision, dysphagia, and dysarthria are the presenting features. The pupils may be dilated and poorly reactive to light. Descending weakness progresses for 4–5 days and then plateaus. Respiratory paralysis may occur rapidly. Most patients have autonomic dysfunction, such as dry mouth, constipation, urinary retention, and cardiovascular instability.

Infantile botulism is caused by the chronic absorption of toxin from *Clostridium botulinum* growing in the infant gastrointestinal tract [102]. Honey is a common source of contamination. The onset of symptoms, constipation, lethargy, and poor suck, usually occurs between 1 week and 12 months of age, most commonly between 2 and 8 months of age. The majority of reported cases occur with type A or B toxin. A descending pattern of weakness occurs and may produce widespread cranial nerve and limb muscle involvement. The pupils are poorly reactive and the tendon reflexes are hypoactive. Most babies will require ventilatory support.

Wound botulism occurs due to the contamination of a wound with *Clostridium botulinum*. Its rarity may be related to the difficulty of spore germination in a wound environment. The clinical presentation of wound botulism is similar to the classical form of the disease as noted above. It may occur as a complication of intranasal and parenteral use of cocaine [103].

Hidden botulism refers to those cases in which no source of botulism can be identified and in whom no apparent source or exposure is known [104, 105]. Some argue that these cases represent adult forms of infantile botulism [106]. This is suggested by the high prevalence of colonic diverting procedures, achlorhydria, Crohn's disease, or recent antibiotic treatment among these patients [107].

Response to antitoxin treatment is generally poor probably because once toxin binds to the nerve terminal, it is no longer accessible to the antitoxin. Antibiotic therapy is not effective unless the botulism is the infantile or hidden form of the disease. Otherwise, treatment is supportive with respiratory assistance when necessary. Cholinesterase inhibitors are not usually beneficial; guanidine or 3,4-diaminopyridine (3,4-DAP) may improve strength but not respiratory function. Recovery takes many months but is usually complete.

EMG abnormalities evolve as the disease progresses and may not be present at onset of symptoms. CMAP amplitude is decreased in affected muscles, but motor and sensory nerve conduction is normal. Some patients demonstrate a decremental pattern, and most have post-tetanic facilitation in some muscles of 30–100 % at some time to low-frequency stimulation. These findings are similar to LES but have a more restricted distribution. SF-EMG shows markedly increased jitter and blocking. The organism can be recovered from the stool of infected infants or in the hidden form of the disease.

Envenomation

Most biological toxins of animal origin affect the cholinergic system and either facilitate the release of neurotransmitter from the presynaptic nerve terminal or block the AChR. In general, bites from snakes, scorpions, and ticks are more common during summer months when they are inadvertently encountered. In contrast, exposure to marine toxins may occur at any time as they are acquired through ingestion and less rarely by injection or penetration. Specific geographic

[1]While tetanus toxin also binds to the neuromuscular junction, its mechanism of action is distinctly different. This toxin is translocated into the nerve terminal and then moves in a retro-axonal fashion to the synaptic space between the alpha motoneuron and inhibitory neurons. There it inhibits exocytosis resulting in paresis. Because it does not directly involve the motor nerve terminal, it will not be discussed further.

Table 52.2 Mechanisms of arthropod blockade of synaptic transmission

Facilitation of ACh release with subsequent exhaustion of neurotransmitter
Facilitation of ACh release without subsequent exhaustion of neurotransmitter
Depletion of ACh release with subsequent exhaustion of neurotransmitter

loci can be demonstrated for each of these vectors. For example, tic envenomation predominates in States west of the Rocky Mountains, the western provinces of Canada, and in Australia. The geography of snake envenomation is species specific. The cobras are found in Asia and Africa, the kraits in Southeast Asia, the mambas in Africa, the coral snake in North America, and the sea snakes in the waters of the Pacific near Australia and New Guinea.

Arthropods

The venoms of the phylum Arthropod are used to incapacitate prey for feeding or as a defense against predators [108]. An observation made in antiquity. Few of the arthropods, however, produce toxicity at the NMJ, but when produced, it is by three mechanisms (Table 52.2). In the first, there is an initial augmentation of ACh release followed by presynaptic depletion of neurotransmitter. The second leads to a facilitation of ACh release without a subsequent presynaptic depletion of neurotransmitter. The third mechanism causes a depletion of ACh release without a subsequent presynaptic depletion of neurotransmitter.

Spider Bites

Only a few spider venoms affect the neuromuscular junction. The funnel web spider and the redback spider of Australia are the most dangerous spiders in this group. In North America, only the bite of the black widow spider is of concern. The usual victim of a black widow spider bite is a small boy, perhaps the result of their inquisitiveness of nooks and crannies.

Latrotoxins found in the venoms from the spider genus *Latrodectus* (black widow spider) cause systemic latrodectism. These toxins produce a marked facilitation in neurotransmitter release by depolarization of the presynaptic nerve terminal and increasing Ca^{++} influx into the nerve terminal at all neurosecretory synapses including the neuromuscular junction [109–111]. There is a subsequent depletion of neurotransmitter from the nerve terminal resulting in a blockade of synaptic transmission. This toxin exerts its effects on the presynaptic nerve terminal by several mechanisms. The toxin binds to neurexin and thereby activates the presynaptic protein complex of neurexin, syntaxin, synaptotagmin, and the N-type calcium channel to massively facilitate ACh release [112]. Neurotransmitter release in nerve-muscle preparations, as measured by MEPP frequency, increases several hundredfold within a few minutes [113]. There is a subsequent depletion of synaptic vesicles, disruption of the highly organized active zone region of the presynaptic nerve terminal, thus inhibiting the docking of synaptic vesicles to the terminal membrane and effective recycling of vesicular membrane [114–119].

Signs of a black widow spider bite begin within minutes of the bite and reflect the massive release of neurotransmitter from peripheral, autonomic, and central synapses [120]. Severe muscle rigidity and cramps precedes generalized muscle weakness due to the depolarizing neuromuscular blockade. The black widow spider bite is rarely fatal but cardiovascular collapse may occur in the elderly or in young children. Treatment is primarily supportive. The administration of calcium gluconate may be helpful in alleviating muscle cramps and rigidity [121]. Magnesium salts may be beneficial by reducing neurotransmitter release [120]. The administration of horse-serum antivenom is effective and rapidly reverses the neurotoxic effects [122].

Tick Paralysis

Tick paralysis, a worldwide disorder, was first described at the turn of the twentieth century in North America and Australia although there is vague reference to an earlier case in the early 1800s [123–126]. It is one of several kinds of neuromuscular disorders that result from tick venom exposure [127]. Tick paralysis results from the introduction of a neurotoxin from one of more than 60 tick species [128, 129]. In North America, the *Dermacentor andersoni, D. variabilis, D. occidentalis, Amblyomma americanum, and A. maculatum* species are toxic. The vectors in Europe and the Pacific are *Ixodes ricinus* and *I. cornuatus* and in Australia, it is *I. holocyclus.* Geographically, tick paralysis is more common in States west of the Rocky Mountains and in British Columbia and Alberta [130].

The symptoms are stereotypical. Within 5–6 days of attachment, there is a prodrome of paresthesia, headache, malaise, nausea, and vomiting. The prodromal period parallels the feeding pattern of the tick. Over the next 24–48 h, an ascending paralysis occurs. It begins symmetrically in the lower extremities and progresses to involve the trunk and arms. In most instances when a tick is found, it is fully engorged. In contrast to the vectors found most commonly in North America (*Dermacentor* and *Amblyomma species),* the weakness of the Australian tick is more severe and much slower to resolve. In these patients, there is often a worsening of clinical signs 24–48 h following the removal of the tick [131]. Sensation is preserved but muscle stretch reflexes are often diminished or not present suggesting the Landry-Guillain-Barré syndrome (Table 52.3), a common

Table 52.3 Comparative features of ascending paralysis

Clinical and laboratory features	Tick paralysis	Landry-Guillain-Barré syndrome
Rate of progression	Hours to days	Days to 1–2 weeks
Sensory loss	Absent	Mild
Muscle stretch reflexes	Diminished or absent	Diminished or absent
Time to recovery	<24 h after tick removal	Weeks to months
CSF WBC count	<10 per mm^2	<10 per mm^2
CSF protein	Normal	Elevated

CSF cerebrospinal fluid, mm^2 per square millimeter, < less than

misdiagnosis [132]. There is no demonstrable response to cholinesterase inhibitors [133, 134]. There is some indication of an association between the proximity of the site of attachment to the brain and the severity of the disease. Antitoxin may be of benefit in some situations, but the high frequency of acute allergic reactions makes its widespread use less useful [135]. Resolution of manifestations is dependent in part on how quickly the tick is removed, suggesting that the amount of muscle weakness is a dose-dependent process. Often, improvement begins within hours of removing the tick. Paralyses due to the *Dermacentor* species may continue over several days. However, prolonged weakness is reported [136]. Death may occur due to respiratory failure from severe bulbar and respiratory muscle weakness, and the clinical picture may be clouded by the presences of central nervous system manifestations [130, 137].

Where once, these envenomations carried a 12–25 % mortality; the improvement in critical care over the latter half of the twentieth century makes these intoxications rarely fatal [123, 138]. Children are more prone to the disorder than adults. This may be due in part to their play habits and their lower body mass relative to the amount of toxin acquired. The head and neck are the most common sites for tick attachment, although any part of the body may be bitten. Some studies suggest that girls are more often affected because they have, on average, longer hair than boys that allows the tick to remain hidden for longer periods and therefore allows prolonged feeding [132, 139]. The identification of a tick bite is often delayed resulting in misdiagnosis. Tic paralysis may be confused with Landry-Guillain-Barré syndrome, myasthenia gravis, spinal cord disease, periodic paralysis, diphtheria, heavy-metal intoxication, insecticide poisoning, porphyria, and hysteria [132, 140]. In many instances, the tick is located by the nurse, the house officer, the mortician, or autopsy personnel [132, 138, 141]. Careful, systematic inspection of the scalp, neck, and perineum, often with a fine-toothed comb, is necessary to locate the tick.

The mechanisms of paralysis following tick envenomation remain controversial. The most potent toxin is from the Australian tick, *Ixodes holocyclus*. Holocyclotoxin, isolated from the salivary glands of female ticks causes a temperature-dependent blockade of neuronally evoked release of ACh [142]. Others have suggested a postsynaptic block of neuromuscular transmission [143]. The tick paralysis of the *Dermacentor* species is understood less clearly, and no direct abnormality of synaptic transmission may occur. Rather, the abnormality may be due to impaired depolarization of the nerve terminal with the consequence of decreased ACh release [144, 145]. Prolonged distal motor latencies, slowed nerve conduction velocities, and reduced compound muscle action potential (CMAP) amplitudes are described [128, 133, 146–148].

Scorpion Bites

The peptides contained in scorpion neurotoxins may cause a variety of neurological effects, the most significant of which are those that modulate Na^+ and K^+ channel function. Some, however, affect the neuromuscular junction and produce an enhanced presynaptic depolarization resulting in neurotransmitter release [149]. Increased excretion of catecholamines is demonstrated after scorpion sting and may relate to the primary effect of the venom or to a secondary sympathetic adrenergic surge. Treatment is nonspecific and focuses on maintaining respiratory, cardiac, and coagulation function. Antivenom appears not to be efficacious [150, 151].

Snakebites

Envenomation by snakebite occurs from four major groups: *Viperidae* (true vipers), *Crotalidae* (rattlesnakes and pit vipers), *Elapidae* (American coral snake, cobras, kraits, mambas), and *Hydrophiidae* (sea snakes). Neuromuscular blockade occurs primarily from the *Elapidae* and *Hydrophiidae* species [152–154]. One *Crotalidae* species, *Crotalus durissus terrificus*, a South American rattlesnake, has a very potent neuromuscular blocking venom. Other rattlesnakes and pit vipers act through hematological and cardiovascular mechanisms. Venom is produced and stored in salivary glands, and inoculation occurs through fangs or modified premaxillary teeth [152].

Snake toxins may act by presynaptic or postsynaptic mechanisms. Presynaptic toxins, β-neurotoxins (β-bungarotoxin, notexin, and taipoxin), act to inhibit the normal release of acetylcholine from the presynaptic cell of the neuromuscular junction. Often, there is an initial augmentation of acetylcholine release followed by presynaptic depletion of neurotransmitter. They tend to be more potent than postsynaptic toxins. Postsynaptic neurotoxins, α-neurotoxins, produce a curare-mimetic, nondepolarizing neuromuscular block and vary in the degree of the reversibility of the block in experimental preparations.

Most venoms are a mixture of the two types of neurotoxin, although one type may predominate in a given venom. For example, the venom of the Thai cobra is composed

primarily of a single postsynaptic neurotoxin [155]. In contrast, the venom of *Bungarus multicinctus* contains β-bungarotoxin, four other presynaptic toxins, α-bungarotoxin, and two other postsynaptic toxins [156]. The venom of *Hydrophiidae* species is more toxic than land snakes although the amount of toxin injected by sea snakes is smaller than that of land-based snakes [157, 158]. The α-neurotoxins (postsynaptic), like curare, bind to the muscle nicotinic AChR. They have a slower onset of action and a longer duration of effect and are 15–40 times more potent than d-tubocurarine [159, 160]. There are numerous subforms of β-neurotoxins (presynaptic). Most have a phospholipase component that is essential for the presynaptic effects of the toxin. All suppress the release of ACh from the nerve terminal although there is some variability in the precise mechanism by which this occurs. In experimental preparations, toxins from different species potentiate each other suggesting different binding sites at the neuromuscular junction [161]. Taipoxin from the Australian and Papua New Guinean taipan snake is unique. In addition to its potent presynaptic blockade of synaptic transmission, it also has a direct myotoxic component. This produces rapid muscle necrosis and degeneration. There is species variation in the susceptibility to toxin exposure. The venom of the Australian mulga snake is fatal in man, produces ptosis in monkeys, and does not produce a neuromuscular block in the rabbit [162, 163].

The clinical course of snake envenomation follows a specific pattern. After the bite of a pit viper or cobra, there is local pain, which is often absent following the bite of other *Elapidae* (mambas, kraits, coral snakes) and *Hydrophiidae*. Swelling typically follows within an hour of the bites from *Viperidae, Crotalidae*, or the cobra but is not seen following bites from other *Elapidae* and *Hydrophiidae.* A preparalytic stage develops with headache, vomiting, loss of consciousness, paresthesias, hematuria, or hemoptysis [164]. These manifestations are not common after envenomation by cobras or mambas. The time between snakebite and paralysis may vary from 0.5–19 h [165]. The first signs of neuromuscular toxicity are usually ptosis and ophthalmoparesis though these are absent following the bite of the South American rattlesnake. Facial and bulbar weakness develops over hours following the ocular signs [166]. For 2–3 days, limb, diaphragmatic, and intercostal weakness follows and may continue to evolve [152, 167], and without appropriate treatment, cardiovascular collapse, seizures, and coma ensue. There is no sensory abnormality other than that from the bite itself. Other systemic effects of neurologic importance relate to coagulation deficits. Cerebral and subarachnoid hemorrhage may occur after bites from many species and is the leading cause of death following viper bites in several regions of the world [168, 169].

Treatment consists of antivenom which is most effective in bites that do not contain significant amounts of phospholipase, a component of presynaptic neurotoxins [166, 170–172]. If the type of snake is known, a high-titer monovalent type is administered, but more often, snake variety is not known necessitating the use of polyvalent antivenom. The goal of antivenom is to shorten the duration of weakness, and frequently, the addition of respiratory, cardiovascular, and hematological support is required. Supportive measures are the mainstay of care for most victims of coral snakebite. Intensive care treatment and airway maintenance is similar to patients with myasthenia gravis. Some authors recommend treatment with cholinesterase inhibitors in cases that are predominantly caused by a postsynaptic abnormality and suggest that electrodiagnostic testing may be useful in determining their effectiveness [173, 174].

Marine Toxins

The rapid rise in marine pollution has spurred a renewed interest in marine toxins. Previously they were only of interest to the physiologist and pharmacologist who use them in the investigation of biological systems. Examples of marine neurotoxicology are scattered throughout the literature dating to biblical times (Exodus 7:20–21). The reader is referred to Southcott's paper for an excellent review of the subject [175]. Marine neurotoxins affecting the neuromuscular junction are rare and occur primarily from poisonous fish, a few mollusks, and perhaps dinoflagellates. Unlike the poisoning from arthropods and snakes, the majority of marine intoxications occur as the result of ingestion. Unique to some marine toxins is that the increase in concentration of toxin through successive predatory transvection up the food chain.

Dinoflagellates are single-celled, biflagellated, algae-like organisms. Diatoms, similar to dinoflagellates, are not flagellated and are encased by a silica shell. The toxins produced by these organisms cause a variety of systemic and neurological effects, but neuromuscular junction effects are rare and indirect. Paralytic shellfish poisoning results from neurotoxins produced by less than 1 % of the 2,000–3,000 species of known dinoflagellates and diatoms [176]. These toxins are rapidly absorbed through the gastrointestinal tract, and symptoms begin within 30 min of ingestion. Characteristically, there is an initial burning or paresthesia of the face and mouth, spreading quickly to involve the neck and limbs. These sensations slowly abate and are replaced with numbness, some ataxia, and, in severe cases, progressive generalized weakness and respiratory failure. Overall, the mortality approaches 10 %. Most neurotoxins from dinoflagellates and diatoms are sodium channel blockers (e.g., saxitoxin and tetrodotoxin). Brevetoxin, a milder neurotoxin that causes the nonlethal neurotoxic shellfish poisoning, depolarizes cholinergic systems, by opening sodium channels and resulting in neuromuscular transmission

alterations indirectly [177, 178]. The cyclic imine group of toxins, gymnodimine and spirolides, are potent antagonists of both cholinergic and muscarinic nicotinic acetylcholine receptors [179]. Recently isolated from New Zealand shellfish, these toxins are rapid in onset and lethal. Ciguatoxin, from *Gambierdiscus toxicus*, is commonly found in the Caribbean, Australia, and South Pacific Island Countries and Territories. The incidence is rapidly increasing and is now considered a major health hazard [180, 181]. This heat-stable lipid enhances the release of ACh from the neuromuscular junction by prolonged sodium channel opening. Onset of symptoms is within hours of ingestion, and respiratory muscle paralysis may occur quickly. Recovery usually occurs within a few weeks.

Conotoxins are a diverse group of toxins from predatory cone snails that inject their venom through a small harpoon-like dart [182]. It is only the fish predatory species (*Conus geographus*, *C. textile*, *C. marmoreus*, *and C. omaria*) of this mollusk that appear dangerous to humans [183–185]. The effects of these toxins are variable among species and within a single species, and several have direct effects on the neuromuscular junction. α-Conotoxins block the binding of ACh to the ligand binding site [186–188]. These venoms function similarly to the snake α-neurotoxins described earlier. The ω-conotoxins block the voltage-gated calcium channel of the presynaptic nerve terminal [189]. The latter toxin has played an important role in understanding of the LES and serves as the basis for the currently used antibody assay [2, 190]. Following the injection of toxin, there is intense local pain quickly followed by malaise, headache, and, within 30 min, progressive generalized weakness. Respiratory failure often occurs within 1–2 h. Most cone shell bites are preventable. These shells should be handled carefully with forceps and thick gloves. The proboscis protrudes from the small end of the shell, but it is flexible and long enough to sting the holder at the other end. The live shells should never be placed in a pocket as the dart may penetrate cloth [175]. Treatment is directed toward respiratory and cardiovascular support. There is no available antivenom. There is no literature discussing the potential efficacy of cholinesterase inhibitors. More than 60 % of stings are fatal [185, 191].

The most venomous fish is the stonefish, *Synanceia horrida, S. trachynis, and S. verrucosa*, found in the Indo-Pacific oceans and Red Sea as well as the genus *Inimicus* found off the coast of Japan [192]. The toxin, stonustoxin, is inflicted by injection through the 13 dorsal spines when the victim steps on the small fish that is buried in the sand [193]. Neuromuscular blockade results from induced neurotransmitter release with depletion of ACh stores, similar to that of other presynaptic toxins [194, 195]. Envenomation results in immediate, excruciating pain that may last for 1–2 days. Severe edema occurs due to the actions of hyaluronidase that promotes the rapid spread of venom through the tissue, and tissue necrosis may occur [175]. In addition to gastrointestinal, autonomic, and cognitive effects, the victim may experience generalized muscle weakness due to the mechanism noted above. Death occurs from cardiotoxicity. Treatment is supportive and in some patients, a specific antitoxin may be administered.

Plant Toxins

Rarely, plant neurotoxins affect the human NMJ, but more toxic effects are observed in animals. Neurotoxicity is dependent upon the potency, concentration, and interaction with other toxins or substrates in the victim. Many are alkaloids. Coniine, the neurotoxin from the herb, *Conium maculatum* (poison hemlock), produces a rapidly ascending paralysis often resulting in death. Sensory abnormalities are common and prominent [196]. The death of Socrates is attributed to hemlock [197]. The mechanisms of action of this piperidine alkaloid neurotoxin are not completely understood. There is evidence that the toxin acts as a curare-mimetic [198]. Many of these alkaloid neurotoxins are teratogenic to the fetus and by desensitizing nicotinic acetylcholine receptors produce arthrogryposis, scoliosis, kyphosis, and lordosis [199].

Occupational Neurotoxins

Heavy Metals

Numerous polyvalent cations affect neuromuscular transmission and are often used to study basic mechanisms of synaptic transmission. These include barium, erbium, cadmium, cobalt, gadolinium, lanthanum, manganese, nickel, praseodymium, triethyltin, and zinc [200–212]. Nearly all of these intoxicants have multiple effects on synaptic transmission, but they predominantly block the release of ACh as well as facilitating spontaneous quantal release of neurotransmitter. They exert their effects by the block of the flux of Ca^{++} through voltage-gated calcium channels and disrupt intracellular stores of Ca^{++} [213].

Heavy-metal intoxication is a rare cause of clinical NMJ toxicity. Interest in this topic arose from the 1971 contamination of grain in Iraq with a methylmercury fungicide. Despite appropriate warnings, the grain was fed to animals, ground for flour, and used for making bread [214]. Symptoms began within one month of consumption ultimately affecting more than 6,500 people and killing nearly 8 % [215]. Patients experienced ataxia, fatigue, generalized muscle weakness, and occasionally optic atrophy. While one of the expected abnormalities following mercurial poisoning is a peripheral neuropathy (based on the Minamata experience), extensive electrodiagnostic examinations of the affected population

Table 52.4 Neuromuscular syndromes of organophosphate poisoning

Acute cholinergic crisis
Intermediate syndrome
Myopathy
Delayed toxin-induced neuropathy

did not demonstrate this [216, 217]. Repetitive nerve stimulation studies demonstrated a decremental response that was partially reversible with cholinesterase inhibitors [218]. Similar abnormalities were demonstrated in experimental animals [219].

Organophosphate and Carbamate Poisoning

The earliest use of a cholinesterase inhibitor as a neurotoxin is attributed to tribesman in Africa who used the Calabar bean as a right of passage or an "ordeal poison" [220, 221]. Organophosphates (OP) are a class of more than 20,000 compounds that irreversibly inhibit cholinesterases including acetylcholinesterase (AChE) [222]. They are widely used in the agricultural, manufacturing, and pharmaceutical industries as well as a weapon of mass destruction [223, 224]. Exposure to OP compounds occurs in the workplace, in food, drinking water, and in the environment. OP intoxication is infrequent in the United States because OP-containing insecticides are not readily available. However, these are used commonly in many other countries, where intoxication most commonly results from attempted suicide by ingestion of insecticides, indiscriminate handling, and storage by poorly informed workers [225–229].

The physiochemical properties of these compounds vary. They may be solid, liquid or gaseous, and soluble in various media. Some are highly corrosive, others are not; some highly volatile, others not. Dermal contact, respiratory inhalation, and gastrointestinal absorption may lead to OP absorption. These various physiochemical properties lend themselves to the wide range of applications noted above as well as to the inherent danger of their use [230].

Four neuromuscular toxicological syndromes occur from OP poisoning: an acute cholinergic crisis (types 1 and 2), an intermediate syndrome, a myopathy, and a delayed induced neuropathy (Table 52.4) [231]. Only the type 2 cholinergic crisis and the intermediate syndrome are the result of NMJ toxicity. OP compounds exert their NMJ toxicity by the irreversible inhibition of AChE. This results in the excessive accumulation of ACh at the NMJ as well as other cholinergic synapses of the central, peripheral, and autonomic nervous systems [232]. The excessive accumulation of ACh produces a depolarizing neuromuscular block at the NMJ that is followed by desensitization of the AChR [233–236]. Electrodiagnostic studies demonstrate normal nerve conduction studies, reduced CMAP amplitudes, a decremental response to repetitive nerve stimulation, and CMAP afterdischarges to a single nerve stimulus [227, 237].

Carbamate salts and esters, which are primarily used as pesticides, are synthetic analogs of the alkaloid physostigmine (eserine). They may directly or indirectly affect the NMJ. Like the OP compounds, carbamates also inhibit the action of AChE at cholinergic synapses. They are easily absorbed into the central nervous system because of their lipid solubility characteristics. Unlike OP compounds, the effects of carbamate agents are reversible. However, the manifestations of carbamate poisoning are indistinguishable from OP poisoning. Neurotoxicity occurs rapidly following significant exposure to both classes of compounds. Mortality rates are high with death usually occurring from respiratory paralysis, which develops in 40 % of poison victims [238].

Pesticides

OP chemistry had its origin around 1820 when Lassainge synthesized triethyl phosphate, but not until the turn of the century did they become commonly used for their insecticidal properties. The OP insecticides are all derivatives of phosphoric acid. There are many subclasses within this group of compounds, and their various moieties (e.g., sulfur, amides) confer variation in overall toxicity. Despite recognition of their toxicity, their use continues to rise, particularly in developing countries where demand was predicted to more than double in the 1990s [239]. Most fatal intoxications result from suicidal ingestion [225–228, 240–243]. Reports of carbamate NMJ toxicity are few [244]. The largest episode of carbamate poisoning occurred in 1985 when aldicarb was illegally used as an insecticide on watermelons [245]. Seventy-seven percent of 1,376 exposed individuals were poisoned, each exhibiting a dose-related spectrum of nicotinic and muscarinic cholinergic receptor toxicity. Fatalities are rare and only occur at high exposure levels [246–249]. Symptoms appear rapidly, often within an hour, peaking in 2–3 h with full recovery within 72 h [250].

Agents of War and Terrorism

The highly dangerous toxicity of OP compounds was recognized in 1932 leading to the development of a series of G-agents (G = German). These compounds, GA (Ethyl N,N-dimethylphosphoramidocyanidate; tabun) in 1936, GB (O-Isopropyl methylphosphonofluoridate; sarin) in 1938, GD (O-Pinacolyl methylphosphonofluoridate; soman) in 1944, and CF (Cyclohexyl methylphosphonofluoridate; cyclosarin), were developed specifically as agents of war [251]. The V-series (V=venomous) followed and include 4 compounds: VE (S-(Diethylamino)ethyl O-ethyl ethylphosphonothioate), VG (O,O-Diethyl-S-[2-(diethylamino)ethyl] phosphorothioate; also called Amiton or Tetram), VM (Phosphonothioic

Table 52.5 Comparative human LCt_{50} and LD_{50} to nerve agents

Nerve agent	Aerosolized (LCt_{50})	Percutaneous (LD_{50})
VX vapor	10 mg·min/m^3	6–10 mg
Soman vapor	50 mg·min/m^3	350 mg
Sarin vapor	100 mg·min/m^3	1,700 mg
Tabun vapor	400 mg·min/m^3	1,000 mg

Abbreviations: LCt_{50} – the dose of vapor necessary to cause death in 50 % of the exposed population where *C* is concentration and *t* is time; LD_{50} – the dose of cutaneous exposure necessary to cause death in 50 % of the exposed population; mg – milligram; min/m^3 – minutes per meter squared

acid, methyl-, S-(2-(diethylamino)ethyl) O-ethyl ester), and VX (O-ethyl-S-[2(diisopropylamino)ethyl] methylphosphonothioate; venom X) in 1952. Little is known about a Russian agent, coded VR-55 [252]. Great Britain ceased nerve gas weapons research in 1959, and the USA transiently discontinued their efforts between 1969 and 1981 [253]. Other countries continue to develop their weapons programs. It is speculated that GA was used in the 1980s during the Iraq-Iran conflict causing innumerable deaths [252]. G-agents share a number of similar characteristic properties. They are highly volatile in room air. As a result, their toxicity may be from either inhalation or by contact. These compounds are soluble in fat and water. This allows ready absorption through the skin eyes and mucous membranes. Vapor agents are absorbed initially through the eyes producing local irritation and then through the respiratory tree. Liquid agents penetrate through the skin at the point of contact and are able to produce more severe and generalized symptoms.

The V-series toxins are the most highly toxic chemical warfare agents. These agents of war are termed persistent agents as they remain active on skin, clothes, and other surfaces for prolonged periods of time. VX was synthesized by the British in 1957. Other agents in the series (Ve, Vg, Vm, and V-gas) are less well-known as information about them is very limited.

Local effects (sweating, mucosal irritation) occur within seconds and paralysis, and apnea may occur as quickly as 1–2 min of exposure. Comparative inhalation toxicities are summarized in Table 52.5. Absorption may be through inhalation, ingestion, or cutaneous contact. VX is the most potent and GA the least. Terrorist attacks in Japan resulted in the exposure of civilians to GB and VX [254–258].

Pathophysiology

The G- and V-series nerve agents inhibit the hydrolysis of acetylcholine by acetylcholinesterase by binding to and phosphorylating the active site of AChE [259]. The resulting depolarizing neuromuscular block leads to rapid and profound muscle weakness. Death occurs by respiratory failure. The inhibition of AChE by these agents becomes irreversible, a phenomenon known as "aging." The aging half-time is variable, as short as 2 min for GD and as long as 48 h for VX [260]. Aging is an irreversible phenomenon. Prior to this reaction, the enzyme can be reactivated with the use of oximes which remove the neurotoxin from the AChE molecule. Oximes dissociate the toxic phosphate moiety from the esteratic site on AChE, thus reactivating esterase and restoring normal NMT [261, 262]. Following attachment of the nerve agent to AChE, a portion of the nerve agent, called the leaving group, is cleaved from the bound molecule. This is followed by a second reaction during which an alkyl group leaves the nerve agent. This results in an aged complex for which oximes have no effect [263].

Treatment

Treatment is directed toward the prevention of chemical exposure by appropriate clothing and the decontamination of exposed victims [264, 265]. Aggressive cardiopulmonary support is necessary. Atropine is an effective antidote to block excessive cholinergic activity at muscarinic receptors in both organophosphate and carbamate intoxications. AChE reactivators (oximes, e.g., 2-PAM) and anticholinergics are often helpful for acute OP intoxications but appear to have little effect to reverse weakness caused by the intermediate syndrome. Oximes dissociate the toxic phosphate moiety from the esteratic site on AChE, thus reactivating esterase and restoring normal neuromuscular transmission [261]. Soman is the least responsive of the nerve agents to oxime therapy because the agent-enzyme complex rapidly undergoes "aging." This refers to the compound undergoing a time-dependent conformational change that is no longer responsive to reactivators [266]. In contrast to OP intoxications, oxime reactivators are contraindicated in carbamate poisoning as these compounds enhance the effects of the carbamate and promote further junctional toxicity [267]. In cases where the offending compound is not known, it is possible to assay the reactivation of AChE activity in vivo and possibly differentiate between OP and carbamate poisoning [268]. Neuromuscular blockade with curariform drugs blocks repetitive discharges although it is not clear whether there is any clinical benefit to their use [269]. The carbamate pyridostigmine was used as a "pretreatment" for organophosphorous poisoning during the Gulf War, but their use is controversial. While studies showed that a 40 % inhibition in AChE activity by physostigmine protected experimental animals from acute cholinergic toxicity following exposure to soman, such findings have not been conclusively demonstrated for pyridostigmine [270].

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Part VII

Neuromuscular Disorders: Muscle Ion Channel Disorders

Disorders of Skeletal Muscle Membrane Excitability: Myotonia Congenita, Paramyotonia Congenita, Periodic Paralysis, and Related Syndromes

53

Robert L. Ruff and Barbara E. Shapiro

Introduction

The disorders of skeletal muscle membrane excitability comprise a group of diseases characterized by muscle stiffness, pain, and sometimes weakness, which may be intermittent or fixed. Myotonia occurs in several of these disorders. Patients with myotonia may describe an inability to relax their muscles after contraction, such as during handgrip. In addition, patients may experience the myotonia as muscle stiffness. Traditionally, the myotonic muscle disorders have been classified into those with dystrophic changes on muscle biopsy, such as the myotonic dystrophies, resulting in weakness, and those without dystrophic changes, such as myotonia congenita and paramyotonia congenita, where progressive weakness is generally not a feature. Furthermore, the dystrophic disorders also manifest extramuscular abnormalities, including cataracts, cardiac defects, and pulmonary or endocrine dysfunction [1]. The dystrophic myotonic muscle disorders are covered elsewhere in this book (see Chap. 59). *Neuromyotonia*, a rare phenomenon associated with peripheral nerve as opposed to muscle disorders, may also result in a delay in muscle relaxation. However, this is distinguished from myotonia by its association with disorders of peripheral nerve origin (see Chap. 70).

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Physiology

To understand disorders of skeletal muscle membrane excitability, it is necessary to review the following: (1) factors that alter membrane excitability, (2) the contributions of different ion conductances to the resting membrane potential, (3) ion conductances during an action potential, and (4) the need for skeletal muscle fibers to have high chloride conductances to counteract the destabilizing effect of the transverse tubular system on membrane excitability. There are many types of ion channels. We will consider four classes of ionic channels: (1) voltage-gated sodium channels; (2) two forms of potassium channels, inward rectifier (also called anomalous rectifier) and voltage-gated delayed rectifier potassium channels; (3) skeletal muscle chloride channels; and (4) a subset of voltage-gated calcium channels called L-type or dihydropyridine (DHP)-sensitive calcium channels. Several important features of sodium channel gating are also considered.

Factors Contributing to Skeletal Muscle Membrane Excitability

Directions of Ion Movements and Equilibrium Potentials

Two factors determine the net flow of ions across an open ionic channel: (1) the membrane potential and (2) the differences in ion concentrations between the intracellular and extracellular spaces. Since cells have negative intracellular potentials, the electrical force will tend to direct positively charged ions (cations such as sodium, potassium, and calcium) to flow into a cell. Hence, electrical forces will direct an inward flow of sodium, potassium, and calcium ions and an outward flow of chloride ions. The direction of ion movement produced by the "concentration force" depends on the concentration differences for the ion between the intracellular and extracellular compartments. Sodium, calcium, and chloride ions have higher extracellular concentrations

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Table 53.1 Equilibrium potentials for ions in skeletal muscle

Sodium	+65 mV
Potassium	−105 mV
Calcium	>+100 mV
Chloride	−95 mV (resting potential)
Resting potential	−95 mV

compared with intracellular concentrations. The intracellular concentration of potassium is greater than the extracellular concentration. "Concentration forces" direct an inward flow of sodium, calcium, and chloride ions and an outward flow of potassium ions. The membrane potential at which the electrical and "concentration" forces are balanced for a given ion is called the *equilibrium or Nernst potential* for a given ion. At the equilibrium potential, inward and outward current movements are balanced for a specific ion due to balancing of the electrical and "concentration" forces. For a given cation, at membrane potentials that are negative compared with the equilibrium potential, ions flow into the cell. At membrane potentials that are more positive than the equilibrium potential, current carried by the specific ion will flow out of the cell. *The direction of current movement for a specific ion always tends to bring the membrane potential back to the equilibrium potential for that specific ion.* Examples of approximate equilibrium potentials for ions in skeletal muscle are shown in Table 53.1.

The Contributions of Different Ion Conductances to the Resting Membrane Potential

The membrane potential represents a balance among the equilibrium potentials of the ions that the membrane is permeable to. The greater the conductance of an ion, the more that ion will influence the membrane potential of the cell. The principal conductances responsible for establishing the resting membrane potential are chloride conductance, potassium conductance, and sodium conductance.

Chloride conductance is mediated by skeletal muscle chloride channels. *Chloride is the dominant membrane conductance, accounting for about 80 % of the resting membrane conductance*. Chloride channels in skeletal muscle are unusual in that they are gated by the presence of ions at the intracellular and extracellular orifices, rather than by the membrane potential. Thus, the channel is likely to open when a chloride ion presents itself at either the intra- or extracellular opening of the chloride channel. The unique gating properties of chloride channels result in the chloride ions being distributed across the membrane in accord with the membrane potential. Consequently, chloride conductance does not set the membrane potential. Instead, chloride conductance acts as a brake or damper that makes it harder for the membrane potential to change. Therefore, chloride conductance provides an important stabilizing influence on the membrane potential. Another important feature of skeletal muscle chloride channels is that they gate (open and close) slowly. Consequently, chloride channels do not respond to transient changes in membrane potential, such as that occurring during an action potential. *Therefore, chloride conductance is well suited to inhibit slow alterations in membrane potential without greatly inhibiting action potentials*.

The dominant ion in setting the resting membrane potential is potassium. Potassium conductance accounts for about 20 % of the resting membrane conductance. The small amount of sodium conductance in the resting skeletal muscle membrane results in the resting membrane potential being slightly positive or depolarized compared to the equilibrium potential for potassium (Table 53.1). The specific class of potassium channels that determines the resting membrane potential is the inward or anomalous rectifier potassium channel. The ATP-dependent potassium channel is one of several types of inward rectifier potassium channels. Resting calcium conductance is exceedingly small. Therefore, calcium does not contribute to determining the resting membrane potential.

Ion channel normally conducts ions only through a central pore or ion channel. However, some mutations of calcium or sodium channels result in the appearance of a secondary new pathway for conducting ions. This alternative pathway is referred to as a gating pore because it appears only with mutations of segments of the calcium or sodium channels that involve the gating mechanism. The gating mechanism of an ion channel consists of segments of that channel containing charged amino acids. Under the influence of the transmembrane potential, these segments with charged amino acid partially translate across the membrane when the membrane potential changes. The translation of charged portions of the ion channel when the membrane potential changes results in a charge movement, called a gating charge [2–4]. Some mutations that occur in segments of sodium or calcium channels involved in gating can result the formation of an alternative pathway for ion current flow that is independent of the normal ion channel. The alternative pathway created by mutations in the channel segments involved in gating is referred to as a gating pore [5–10].

Important Properties of Ion Channels in Skeletal Muscle

As mentioned above, the skeletal muscle chloride channel is gated by chloride ion concentrations. The other important skeletal muscle ion channels are gated by membrane potential. We discuss the voltage-gated sodium channel first.

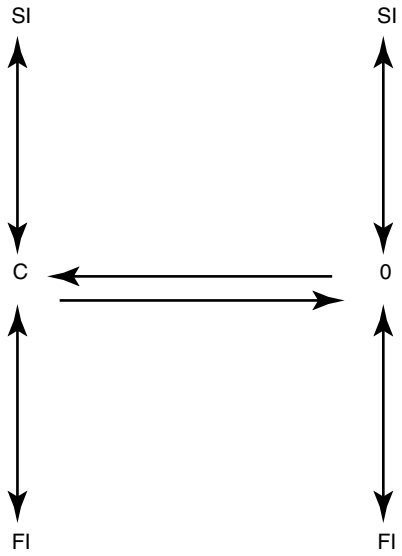

Fig. 53.1 Possible transitions that the sodium channel can undergo. *FI* fast inactivated, *SI* slow inactivated, *C* closed, *O* open

Table 53.2 States that the sodium channels are in at different membrane potentials

Hyperpolarized resting potential (<−90mv) – most in closed state, some in SI state
Depolarized resting potential (>−80 mV) – most in SI state, some in closed or FI state
Rising phase of action potential – open state with channels beginning O→ FI transition
Falling phase of the action potential – most are in the FI state

FI fast inactivated, *SI* slow inactivated, *O* open

Sodium Channel Gating Properties

Membrane depolarization activates sodium channels via conformation changes from closed, nonconducting states to an open, current-conducting state [2, 11–13]. The declining portion of I_{Na} elicited by prolonged depolarization results from late openings of sodium channels and transition of open channels to a nonconducting fast inactivated state [12, 14, 15]. Sodium channels can also transit directly between closed and fast inactivated states [2, 11, 12, 14]. Inactivated channels do not open when the membrane is depolarized. The transition rate from the open to the fast inactivated state is independent of voltage over part of its operative range, [14] and the transition rate increases with depolarization at potentials more positive than about −30 mV [12]. The transition rate from the closed to the fast inactivated state increases with depolarization (Fig. 53.1) [16].

Mammalian skeletal muscle sodium channels have two inactivation processes with different kinetics and voltage dependence [12]. Fast inactivation closes channels on a ms time scale, whereas slow inactivation takes seconds to minutes. In *rat and human skeletal muscle, fast inactivation helps to terminate the action potential* [17, 18]. Slow inactivation is too slow to affect action potential termination. However, *slow inactivation operates at more negative potentials than fast inactivation, so that the distribution of channels between the closed and slow inactivated state regulates the number of excitable sodium channels as a function of the membrane potential* (Table 53.2) [12, 16, 19, 20]. Gating charge studies show that fast and slow inactivated states are distinct conformations of the sodium channel [16, 21]. Protease treatment of the intracellular membrane surface or other chemical treatments may selectively alter slow inactivation or fast inactivation [22–24]. Sodium channel mutations can independently change fast or slow inactivation [12, 25, 26]. Therefore, the slow and fast inactivated states probably represent independent sodium channel conformations. Slow inactivation represents the accumulation of sodium channels into the inexcitable slow inactivated state [12]. Slow inactivation changes the number of excitable channels, but does not change the single-channel conductance or open time [12].

Potassium Channel Gating Properties

Different potassium channels are responsible for the resting membrane conductance and for terminating the action potential. The potassium channel that is responsible for the resting membrane conductance is called the *inward rectifier or anomalous rectifier potassium channel*. This channel has unique properties that enable it to provide the resting membrane conductance for potassium without resulting in excessive potassium loss during an action potential [2, 11]. The inward rectifier potassium channel gets its name from having a larger conductance for inward potassium currents. When the membrane is depolarized more than 10–15 mV with respect to the equilibrium potential for potassium, the conductance of the inward rectifier potassium channel decreases. Consequently, once the membrane has depolarized to about the threshold for triggering an action potential, the conductance of the inward rectifier potassium channel decreases and little potassium exits the cell during the rising phase of the action potential. The nonlinear conductance properties of the inward rectifier potassium channel enable it to set the membrane potential and not cause excessive potassium loss during an action potential. Since the cell has to utilize ATP to pump potassium back into the cell, the conductance properties of the inward rectifier potassium channel reduce the energy expenditure of the muscle cells. Note that in skeletal muscle cells, an action potential indirectly triggers a great deal of ATP breakdown to fuel the movement of the contractile proteins and the reuptake of calcium released from the sarcoplasmic reticulum.

The second potassium channel in skeletal muscle is the *delayed rectifier potassium channel*. This voltage-gated channel gets its name because at physiological temperatures, the delayed rectifier potassium channel opens slower than

the voltage-gated sodium channel. *Delayed rectifier potassium channels are opened by the membrane depolarization produced by the action potential. However, due to the delay in their openings, most of the delayed rectifier channels do not open until after the rising phase of the action potential has completed. The delayed opening of these potassium channels enables them to assist in terminating the action potential without hindering the rising phase of the action potential*. Hence, the gating properties of the delayed rectifier potassium also conserve intracellular potassium [2, 11].

The Course of Events During an Action Potential

The first step in generating an action potential is membrane depolarization, which in skeletal muscle is initiated by the endplate potential. The depolarization causes some voltage-gated sodium channels to open, which augments the membrane depolarization. The process of depolarization causing more sodium channels to open continues until threshold is reached. *At threshold, the sodium conductance just exceeds the combined chloride and potassium conductances that are resisting membrane depolarization*. The factors that contribute to determining threshold membrane potential for triggering an action potential are the voltage dependence of sodium channel opening and the decreasing conductance of the inward rectifier potassium channel with depolarization. *Once threshold is reached, the membrane potential depolarizes very quickly during the rising phase of the action potential. During the rising phase of the action potential, most of the voltage-gated sodium channels are in the open state* (Table 53.2). The large membrane conductance for sodium results in the membrane potential approaching the equilibrium potential for sodium (Table 53.1).

The declining phase of the action potential results from two processes: (1) the membrane depolarization triggers sodium channels to undergo conformation changes from the open state to the fast inactivated state and (2) the delayed rectifier potassium channels begin to open. The membrane repolarizes because the sodium conductance decreases and potassium conductance increases resulting in the membrane moving toward the potassium equilibrium potential (Table 53.1). *Immediately after an action potential, most sodium channels are still in the fast inactivated state*. Consequently, there are not enough excitable sodium channels to trigger a second action potential immediately after the first action potential.

The period during which the population of excitable sodium channels (those in the closed state) is too small to support an action potential (i.e., there are not enough excitable sodium channels to overcome the chloride and inward rectifier potassium conductances) is referred to as the *absolute refractory period*. During this period, an action potential cannot be triggered by even a very large depolarization. The period of time from the end of the absolute refractory period until the sodium channels have redistributed among their possible states to return to the steady-state population of channels in the closed and inactivated states is referred to as the *relative refractory period*. In this period, a larger than usual stimulus is needed to trigger an action potential. During the refractory periods, sodium channels are changing from the fast inactivated to the closed state.

Perturbation of the fast inactivation process can make the muscle membrane hyperexcitable. The membrane becomes hyperexcitable if some sodium channels do not undergo fast inactivation, producing a persistent inward sodium current that can trigger repeated action potentials during the relative refractory period. The refractory periods are shortened if sodium channels rapidly recover from the inactivated state. The effect of potassium accumulation in the transverse tubules on membrane electrical stability is discussed below.

Skeletal Muscle Needs a Large Resting Chloride Conductance to Counter the Destabilizing Effect of the Transverse Tubule System

Skeletal muscle membrane has a transverse tubule (T-tubule) system. The T-tubules are relatively thin and long. They serve to conduct the action potential into the muscle fiber. The T-tubules are essential for coupling surface membrane action potentials with release of calcium from the sarcoplasmic reticulum inside a muscle fiber. Because they are very thin, potassium leaving the muscle fiber during an action potential can accumulate in the T-tubule. The elevated extracellular potassium concentration in the T-tubules makes the equilibrium potential for potassium across the T-tubule membrane less negative. For example, increasing the potassium concentration in the T-tubule space to 12 mM, which likely happens after a series of action potentials, would result in the potassium equilibrium potential depolarizing by more than 40 mV to become −64 mV. The membrane potential of the T-tubules remains depolarized after an action potential until the sodium-potassium pumps are able to remove the excess extracellular potassium. Under physiological conditions, sodium channels recover from inactivation faster than the sodium-potassium pump can remove the excess potassium in the T-tubules. The depolarized T-tubules can depolarize adjacent membrane and trigger repeated action potentials. Therefore, the T-tubules provide a depolarizing current that could trigger subsequent action potentials. Muscle needs to have a high resting chloride conductance to hinder the ability of the T-tubules to depolarize the muscle membrane and to prevent repeated action potentials from developing after a single depolarizing stimulus. If one removes the T-tubules by chemically disrupting them, one inhibits the muscle membrane from generating a string of action potentials in

response to a depolarizing stimulus. In addition, muscle studied under conditions where chloride channels do not contribute to membrane stability – blocking chloride channels or studying the skeletal muscle in a bathing solution that does not have chloride – will result in a muscle membrane hyperexcitable state [27].

Clinical Disorders

Having reviewed the relevant physiology, discussion focuses next on the mechanism by which different disorders of membrane excitability result from alterations of (1) chloride conductance, (2) sodium channel gating, (3) the density of sodium channels, (4) the gating of potassium channels, or (5) the presence of a pathological depolarizing current. Mutations in a calcium channel that is present in the surface membrane result in the most common forms of hypokalemic periodic paralysis. However, the membrane pathology in hypokalemic periodic paralysis is a complex consequence of the calcium channel mutations. The altered calcium channels induce membrane pathology by changing the properties of other ion channels and by showing a gating pore current.

Chloride Channel Disorders: Autosomal Dominant Myotonia Congenita (Thomsen's Disease) and Recessive Generalized Myotonia Congenita (Becker-Type Myotonia)

Introduction and Clinical Presentation

Two forms of myotonia congenita are classically recognized. An autosomal dominant form, *Thomsen's disease*, was first described in 1876 by the Danish physician Julius Thomsen who was himself affected [28]. An autosomal recessive form was described by Becker in the 1950s, which is also called *Becker-type myotonia* or *recessive generalized myotonia congenita* [29]. Both disorders arise from mutations in the skeletal muscle voltage-gated chloride channel gene (CLC1) on chromosome 7q [30]. The recessive generalized form occurs much more frequently than the dominant form [29, 31]. A potassium-sensitive form of myotonia congenita has also been recognized, associated with mutations in the α-subunit of the voltage-gated sodium channel on chromosome 17q. The sodium channel myotonias are discussed below along with the other sodium channel disorders including hyperkalemic periodic paralysis (HyperPP) and paramyotonia congenita.

The myotonia congenitas are differentiated from the myotonic dystrophies by the lack of weakness in most patients and the absence of extramuscular abnormalities such as cataracts, cardiac defects, and pulmonary or endocrine dysfunction [1].

Autosomal Dominant Myotonia Congenita (Thomsen's Disease)

Onset is generally in infancy or early childhood in dominant myotonia congenita. Patients present with painless myotonia resulting in muscle stiffness (Table 53.3). *The hallmark clinical finding in myotonia congenita is stiffness that manifests when the patient attempts to initiate movement and diminishes with repeated muscle contractions. The stiffness is seen especially with a forceful muscle contraction after a period of rest* [33, 34]. Thus, patients describe a "warm-up" period during which they can work through the muscle stiffness by continued exercise. For example, the patient may find it difficult to arise from a chair after sitting for a few minutes or to climb the first few steps of a stairway. However, once movement is initiated, such as climbing the first few steps, the stiffness lessens and movement is easier. Some patients describe worsening of symptoms in the cold. Stiffness is not progressive over time, and there is no associated weakness. In fact, patients are often quite strong. Muscle hypertrophy is common, probably due to the almost constant state of muscle contraction. It is often noted in the proximal arms, thighs, calves, and facial muscles, giving rise to the characteristic "Herculean" appearance (Fig. 53.2). Grip and percussion myotonia and the lid lag phenomenon are easily elicited.

Autosomal Recessive Myotonia Congenita (Becker-Type Myotonia, Recessive Generalized Myotonia Congenita)

The autosomal recessive form of myotonia congenita is more common than the dominant form. Onset is usually later in childhood compared to the dominant form, although may rarely occur in the first 2–3 years of life (Table 53.3). As in the autosomal dominant form, stiffness is most prominent with muscle contractions after a period of rest and diminishes with further activity. Some patients describe worsening of symptoms in the cold. The stiffness typically appears initially in the lower extremities and slowly progresses over the first several years before stabilizing. Males are more severely affected than females, and stiffness may be more severe than in the dominant form, especially in the lower extremities. While weakness is not a feature of autosomal dominant myotonia congenita, minor progressive weakness and wasting of distal muscles may occur in the recessive form [35–37]. Furthermore, some patients experience transient attacks of true weakness that tend to occur after initiating a sudden movement after rest and are relieved with exercise [37, 38]. This transient weakness may be quite disabling as it is often generalized. Muscle hypertrophy is common in the legs and gluteal muscles, while the upper extremities may appear underdeveloped in contrast [30, 39]. Grip and percussion myotonia and the lid lag phenomenon are easily elicited.

Table 53.3 Clinical features of myotonic and periodic paralysis disorders

	Myotonic dystrophy, type I	Myotonical dystrophy, type II	Myotonia congenita – dominant	Myotonia congenita – recessive	Sodium channel myotonia	Paramyotonia congenita	Hyperkalemic periodic paralysis	Hypokalemic periodic paralysis, types I, II
Age of onset	Teens to early adult	Teens to early adult	Infancy	Early childhood	Childhood to early teens	Infancy	Infancy to early childhood	Early teens
Inheritance	Aut. dominant	Aut. dominant	Aut. dominant	Aut. recessive	Aut. dominant	Aut. dominant	Aut. Dominant	Aut. Dominant
Gene defect	Protein kinase, chr. 19q	Unknown, chr. 3q	Chloride channel, chr. 7q	Chloride channel, chr. 7q	Sodium channel, chr. 17q	Sodium channel, chr. 17q	Sodium channel, chr. 17q	Calcium channel, chr. 1q – type I sodium channel, chr. 17q – type II
Myotonia	Yes	Yes	Yes	Yes	Yes (painful)	Yes	Yes	No
Distribution of myotonia	Distal > proximal	Proximal and distal	Generalized	Generalized	Proximal > distal	Face, hands, thighs	Generalized, if present	None
Periodic weakness	No	No	No	Yes, in some patients	No	Yes	Yes	Yes
Duration of periodic weakness	None	None	None	Minutes	None	Minutes to days	Minutes to days	Hours to days
Progressive weakness	Distal > proximal	Proximal and distal	No	Rarely	No	No	Variable	Yes
Extramuscular involvement	Yes	Yes	No	No	No	No	No	No
Provocative factors	None	None	Exercise after rest Cold	Exercise after rest Cold	Potassium Rest after exercise Fasting	Cold Repeated exercise Fasting	Cold Rest after exercise Fasting Potassium Ingestion	Cold Rest after exercise Carbohydrates
Alleviating factors	None	None	Repeated exercise	Repeated exercise		Warming	Carbohydrates Exercise	Potassium Exercise

Adapted from Preston and Shapiro [32], with permission

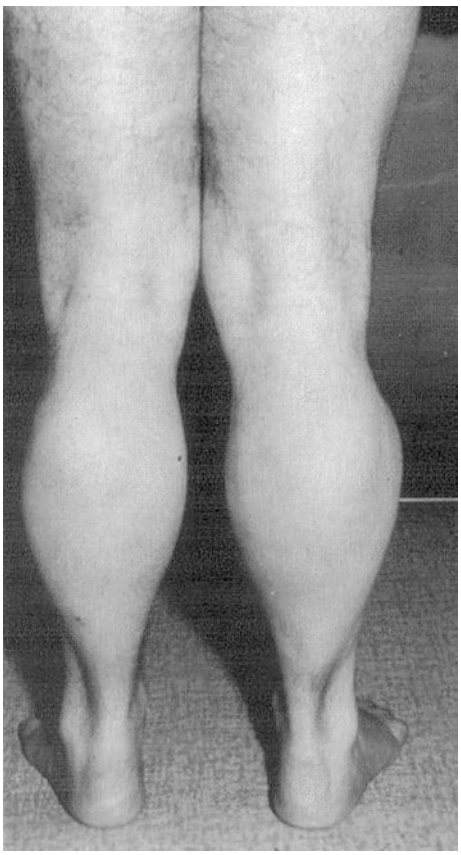

Fig. 53.2 Muscle hypertrophy of calf muscles in myotonia congenita associated with chloride channel mutations

Etiology and Pathogenesis

In both the autosomal dominant (Thomsen's disease) and the autosomal recessive (Becker-type) forms of myotonia congenita, the primary membrane defect is *reduced chloride conductance* [40–44]. The chloride channel is formed as a polymer of one subunit, but the exact stoichiometry is unknown. In both forms of myotonia congenita, chloride conductance is reduced due to a fewer functional chloride channels in the skeletal muscle membrane. The autosomal recessive form is believed to result when both copies of the subunit are defective. The subunit mutation responsible for the recessive form of myotonia congenita produces a nonfunctional subunit that is poorly expressed. In the case of a heterozygote, the normal subunit is expressed in great excess compared with the mutant subunit so that normal chloride channels form. The mechanism for the dominant form of myotonia congenita is not well understood. A possible explanation is that the dominant mutation produces a subunit that is well expressed and which when combined with a normal subunit results in a nonfunctional channel [30, 45–48].

The reduction in chloride conductance may result in removal of a major portion of the inhibition against membrane depolarization. The chloride conductance would normally counter the depolarizing current from the T-tubules and, thereby, prevent a string of action potentials from developing after the muscle fiber has fired one or more action potentials. The interplay between chloride conductance and the T-tubules is demonstrated experimentally as follows: if chloride conductance is lowered by using a chloride channel blocking agent, such as 9-anthracene carboxylic acid, or by replacing chloride with an impermeant anion, such as methane sulfonate, then the muscle membrane becomes hyperexcitable and manifests myotonic behavior. The myotonic membrane behavior can be blocked by chemically disrupting the T-tubules. *Thus, reduced chloride conductance will produce myotonic membrane behavior only if the T-tubules are intact.*

Differential Diagnosis

The differential diagnosis of myotonia congenita is limited, including other disorders associated with myotonia as a prominent symptom. Other diseases to consider include sodium channel myotonia, paramyotonia congenita, HyperPP, the myotonic dystrophies, and rarer neurologic disorders with myotonia including Schwartz-Jampel syndrome (chondrodystrophic myotonia). Myotonia congenita can usually be distinguished from these disorders based on characteristic clinical features; distribution of myotonia; factors that provoke, worsen, or alleviate symptoms; findings on electrodiagnostic (EDX) and exercise testing; and, where appropriate, DNA testing (Tables 53.3 and 53.4).

Patients with myotonia congenita usually describe muscle stiffness present from childhood. The neurologic exam reveals diffuse easily elicited myotonia. There may be muscle hypertrophy. Physical exam should include a search for grip and percussion myotonia, eyelid myotonia, lid lag phenomenon, muscle hypertrophy, distinctive physical features, and extramuscular manifestations (e.g., frontal balding, cataracts, endocrine dysfunction). Distinguishing the dominant from recessive form of myotonia congenita may be difficult. Family history should be studied in detail to determine the mode of inheritance. Since the recessive form of myotonia congenita is more common than the dominant form, there may be no family history. In the recessive form, the stiffness may be quite prominent, and males are more severely affected than females. Patients with the recessive form may have minor progressive distal weakness, and attacks of periodic weakness brought on by movement after rest, not seen in the dominant form. The distinction between chloride and sodium channel myotonia (see below) may be difficult based on clinical grounds, but the following clues are helpful (Table 53.3). There is a characteristic worsening of symptoms with potassium ingestion in patients with sodium channel myotonia, not seen in chloride channel myotonia. Some patients with

Table 53.4 Electrodiagnostic findings in myotonic and periodic paralysis disorders

	Myotonic dystrophy, type I	Myotonia congenita – dominant	Myotonia congenita – recessive	Sodium channel myotonia	Paramyotonia congenita	Hyperkalemic periodic paralysis	Hypokalemic periodic paralysis, types I, II
Nerve conductions	Normal or ↓ distal CMAPs	Normal	Normal	Normal	Normal	Normal between attacks. ↓ CMAP amplitude during attack of weakness	Normal between attacks. ↓ CMAP amplitude during attack of weakness
EMG							
Myotonia	++ (D>P)	+++ (P and D	+++ (P and D)	+ to ++++ (P and D, depending on variant)	++ (P and D)	++ (P and D, esp, during attack)	No myotonia
MUAPs	Myopathic D	Normal	Usually NL, +/− myopathic	Normal	Normal	Myopathic late in course	Myopathic late in course
Effect of muscle cooling (20 °C) on EMG	No effect	May lead to ↑ duration of myotonic bursts, easier to elicit	No effect	No effect	1. Transient dense fibrillations that disappear below 28 °C 2. Myotonic bursts disappear below 20 °C 3. Electrical silence, long-lasting muscle contracture when cooled to 20 °C	No effect	No effect
Short exercise	1. Drop in CMAP amplitude 2. Quick recovery over 2 min 3. Drop does not persist on subsequent trials	1. Variable drop in CMAP amplitude 2. Quick recovery over 2 min	1. Large drop in CMAP amplitude 2. Quick recovery over 2 min 3. Drop persists on subsequent trials	Unknown	With muscle cooling: 1. Drop in CMAP amplitude 2. Very slow recovery over an hour	No effect or transient increase in CMAP amplitude during an attack of weakness	No effect or transient increase in CMAP amplitude during an attack of weakness
Prolonged exercise	Small decrement immediately after exercise, with recovery over 3 min	Unknown	Small decrement immediately after exercise, with recovery over 3 min	Unknown	Moderate decrement immediately after exercise, maximal at 3 min, with slow recovery over an hour	Most with initial increase in CMAP amplitude (~35 %). Progressive drop in CMAP amplitude (~50 %) over 20–40 min with slow recovery over an hour	Most with initial increase in CMAP amplitude (~35 %). Progressive drop in CMAP amplitude (~50 %) over 20–40 min with slow recovery over an hour

Adapted from Preston and Shapiro [49], with permission
NL normal, *D* distal, *P* proximal, *CMAP* compound muscle action potential

sodium channel myotonia display the phenomenon of *exercise-induced delayed-onset myotonia*, whereby muscle contractions induce myotonia after a period of delay. This is in contrast to the "warm-up" phenomenon seen in chloride channel myotonia congenita, whereby repeated muscle contractions alleviate the myotonia. Additionally, many patients with sodium channel myotonia have painful myotonia, not seen in chloride channel myotonia congenita. Since fluctuating symptoms were reported in some patients with chloride channel myotonia congenita [31], this is not a reliable method of distinguishing these patients from the subset of patients with sodium channel myotonia with a fluctuating course (myotonia fluctuans).

Distinguishing myotonia congenita from paramyotonia congenita may be difficult, as both conditions present with generalized stiffness, and muscle hypertrophy is common in both. Furthermore, some patients with myotonia congenita note worsening of symptoms in the cold. However, patients with paramyotonia congenita display *extreme cold sensitivity resulting in severe stiffness followed by true weakness*, features not seen in myotonia congenita. In contrast, the attacks of weakness in recessive generalized myotonia are provoked by movement after rest, rather than cold temperature. Additionally, patients with the dominant and recessive forms of myotonia congenita display a "warm-up" phenomenon whereby myotonia is relieved with repeated muscle contractions, in contrast to the *worsening* of symptoms with repeated muscle contractions noted in paramyotonia congenita.

Patients with recessive generalized myotonia who experience periodic weakness may be confused with the subgroup of patients with HyperPP and myotonia. However, exercise testing can be helpful in this regard. With short exercise testing (see below), patients with myotonia congenita show a drop in the compound muscle action potential (CMAP) amplitude with a quick recovery, not seen in periodic paralysis. In contrast, with prolonged exercise testing, patients with periodic paralysis show a progressive decline in the CMAP amplitude over 20–40 min, which is not seen in myotonia congenita (see below).

Hypokalemic periodic paralysis (HypoPP) and Andersen-Tawil syndrome (ATS), both of which are associated with periodic weakness, should be considered in the differential diagnosis of patients with recessive generalized myotonia and attacks of weakness. However, both disorders can usually be eliminated from consideration based on the lack of myotonia on physical examination and the lack of myotonic discharges on needle electromyography (EMG). Furthermore, patients with ATS have distinctive facial and skeletal features and a prolonged QT interval on electrocardiogram (EKG), not seen in myotonia congenita (see below).

The myotonic dystrophies should be considered in the differential diagnosis of myotonia congenita (see Chap. 59). However, these disorders can usually be eliminated based on the history and physical examination, looking for extramuscular manifestations such as early cataracts, cardiac conduction and pulmonary defects, endocrine dysfunction, hypersomnia, and in some patients mild to moderate cognitive impairment (Table 53.3). Furthermore, the myotonic dystrophies are associated with a progressive myopathy, not seen in myotonia congenita, except for those patients with recessive generalized myotonia and mild distal weakness. Some patients with myotonic dystrophy type I have only a small expansion of the cytosine-thymine-guanine (CTG) trinucleotide repeat associated with the disorder and thus only minor distal weakness and subtle extramuscular manifestations at the time of presentation. In such patients, the diagnosis may be unclear, and DNA testing for myotonic dystrophy type I is warranted. It is important to distinguish the myotonic dystrophies from myotonia congenita since the extramuscular manifestations have important implications for management and treatment. Myotonia congenita is easily distinguished from Schwartz-Jampel syndrome by the characteristic facial and skeletal features associated with Schwartz-Jampel syndrome (see below).

Myotonic discharges, seen on EDX testing, occur in various metabolic, inflammatory, and congenital myopathies (Table 53.5 III). These disorders can usually be easily distinguished from myotonia congenita by their associated proximal weakness and lack of clinical myotonia (grip, percussion, or lid lag). Some drugs can precipitate or unmask electrical myotonia (Table 53.5 IV) and should be questioned, especially if onset of symptoms is later than childhood, there is no family history of myotonia, and muscle hypertrophy and other typical features of myotonia congenita are not present.

Diagnosis and Evaluation

Electrodiagnostic Testing (Table 53.4)

EDX findings in several of the disorders of muscle membrane excitability are noted in Table 53.4. In myotonia congenita, routine motor and sensory nerve conduction studies are normal. Needle EMG generally shows widespread myotonic discharges that are easily elicited with minimal needle movement or muscle contraction in proximal and distal muscles. In the dominant form, the motor unit action potentials (MUAPs) and recruitment pattern are normal. In the recessive form, the MUAPs may be small, short, and polyphasic with early recruitment in distal muscles, consistent with a mild myopathy.

Muscle Cooling

The responses to muscle cooling and the short exercise test can differentiate myotonia congenita from paramyotonia congenita [50, 51]. Muscle cooling is best accomplished by wrapping the limb in a plastic bag and submerging it in ice water

Table 53.5 Classification of myotonic and periodic paralysis disorders

I. Inherited myotonic muscle/periodic paralysis disorders
A. Dystrophic myotonic myopathies
Myotonic dystrophies, types I and I
B. Non-dystrophic myotonic myopathies
Autosomal dominant myotonia congenita (Thomsen's disease)
Autosomal recessive myotonia congenita (Becker-type myotonia)
Paramyotonia congenita (Eulenburg disease)
Sodium channel myotonia
C. Hyperkalemic periodic paralysis (+/– myotonia)
D. Hypokalemic periodic paralysis, types I and II
E. Andersen's syndrome (periodic paralysis with cardiac arrhythmias)
II. Acquired periodic paralysis disorders
A. Secondary hyperkalemic periodic paralysis (may be associated with myotonia)
May be seen in association with:
Renal failure
Adrenal failure
Hypoaldosteronism
Metabolic acidosis
Potassium-sparing diuretics
B. Secondary hypokalemic periodic paralysis (not associated with myotonia)
May be seen in association with:
Thyrotoxicosis – especially in Asian adults
Primary hyperaldosteronism (Conn's syndrome)
Bartter's syndrome
Potassium-depleting diuretics
Inadequate potassium intake
Excessive potassium loss through sweat
Gastrointestinal or renal potassium wasting
Chronic licorice ingestion
Steroid use
Alcoholism
Lithium
III. Muscle disorders associated with myotonic discharges on needle EMG
A. Metabolic – acid maltase deficiency
B. Inflammatory – polymyositis
C. Congenital – myotubular myopathy
D. Associated with systemic disorders – malignant hyperpyrexia
IV. Drugs that unmask or precipitate clinical myotonia or myotonic discharges on needle EMG
Propranolol
Fenoterol
Terbutaline
Colchicine
Penicillamine
Cyclosporin
Clofibrate
HMG-CoA reductase inhibitors (lipid-lowering agents)

Adapted from Preston and Shapiro [32]

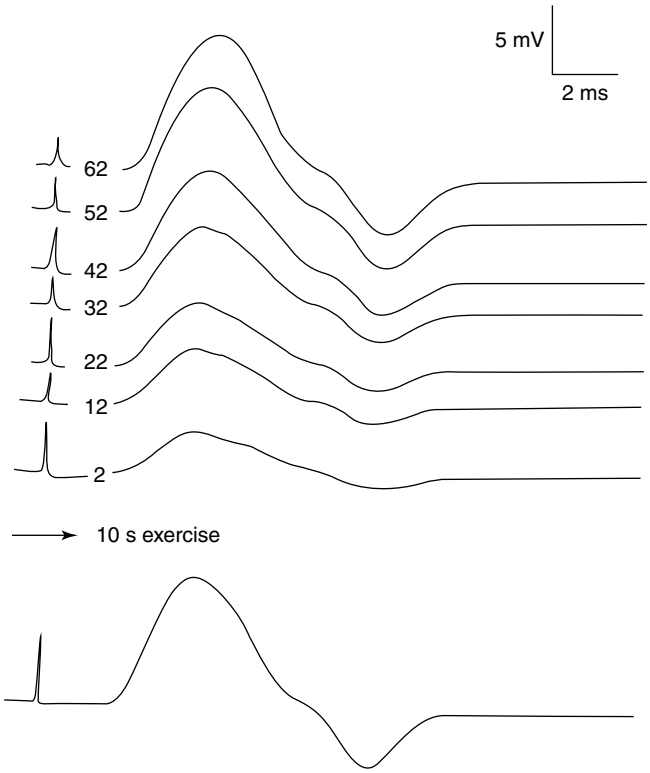

Fig. 53.3 Short exercise testing in the myotonias

for 10–20 min. After the skin temperature is lowered to 20 °C, needle EMG of the extremity is repeated. In dominant myotonia congenita, muscle cooling to 20 °C may produce myotonic bursts that are longer in duration and more easily elicited than at room temperature. In paramyotonia congenita, muscle cooling to 20 °C produces electrical silence as the muscle goes into a prolonged contracture, which is pathognomonic for paramyotonia congenita (Table 53.4).

Short Exercise Test

To perform the short exercise test [1], a routine distal CMAP is evoked with supramaximal stimulation (e.g., stimulating the ulnar nerve at the wrist, recording the abductor digiti minimi). The nerve is then stimulated at 1-min intervals for several minutes to ensure a stable baseline. The patient is then asked to perform maximal voluntary contraction for 5–10 s. Immediately afterwards, a CMAP is evoked. If a decrement in amplitude is seen, a CMAP is then recorded every 10 s until the CMAP recovers to baseline (typically 1–2 min) (Fig. 53.3). If a decrement occurs after brief exercise and then recovers, the same procedure is repeated several times to see if the decrement continues to occur or habituates to help differentiate among the myotonic syndromes [1].

In chloride channel myotonia congenita, the short exercise test produces a drop in CMAP amplitude immediately follow-

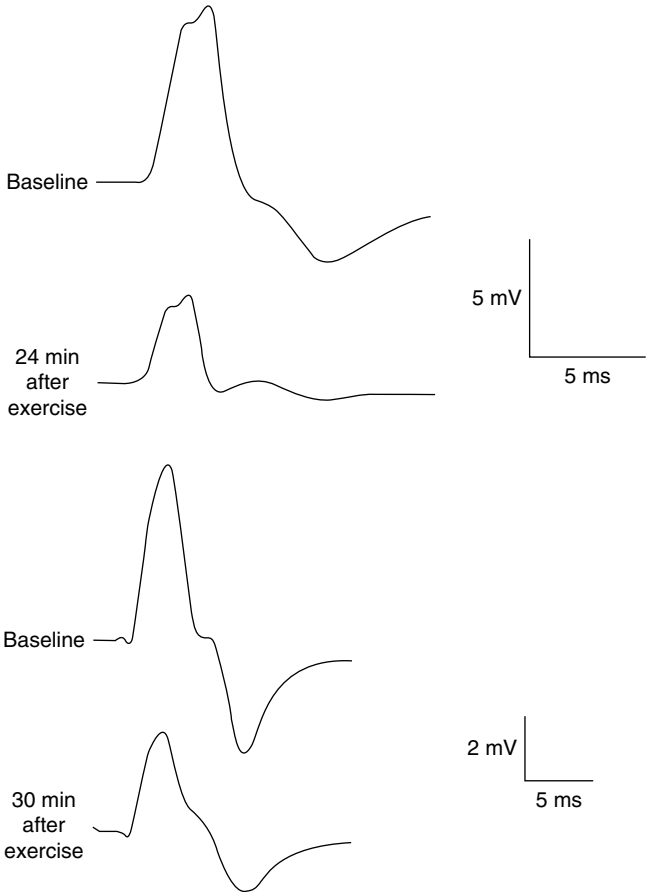

Fig. 53.4 Prolonged exercise test in periodic paralysis

ing exercise, which recovers over 1–2 min with repeated recording of the CMAP every 10 s. In the recessive form of myotonia congenita, the initial drop in amplitude is often profound and is more likely to continue to show an initial decremental response on repeated trials of the short exercise test [1]. This is unlike paramyotonia congenita, where a decremental response occurs that recovers very slowly over many minutes, if the short exercise test is done when the muscle is cooled (Table 53.4).

The responses to the short exercise test can also differentiate recessive myotonia congenita, where weakness may be present, from myotonic dystrophy type I. The short exercise test in myotonic dystrophy type I produces a drop in the CMAP amplitude immediately after exercise, which recovers to baseline over 2 min. If short exercise is then repeated, the decremental response habituates after one or two cycles. In recessive myotonia congenita, the decremental response does not habituate over repeated trials (Table 53.4) [1].

Prolonged Exercise Test

The prolonged exercise test helps distinguish recessive myotonia congenita, where periodic weakness may be present, from the periodic paralyses [1, 52, 53]. The recording procedure is the same as for the short exercise test. However, for the prolonged exercise test, after ensuring a stable baseline, the patient is asked to voluntarily contract their muscle maximally for 3–5 min, resting for a few seconds every 15 s. After the 5 min of exercise are over, the patient relaxes completely. A CMAP is evoked immediately and then every 1–2 min for the next 40–60 min. No decline of the CMAP is seen in myotonia congenita. In contrast, in the periodic paralysis syndromes, the CMAP amplitude may be unchanged or slightly larger immediately after prolonged exercise and then declines substantially over the next 20–40 min (Fig. 53.4).

Laboratory Testing

Serum creatine kinase (CK) level in the dominant form of myotonia congenita may be slightly elevated and in the recessive form, moderately elevated. Muscle biopsy in myotonia congenita may show a lack of type IIB fibers [54].

Treatment and Management

The choice of treatment depends on whether symptoms require daily versus intermittent treatment and on the side effect profile of the various medications. Some patients with minor complaints may need no treatment at all and learn to accommodate their activities and lifestyle to reduce symptoms. When treatment of myotonic stiffness is required, medications that stabilize the muscle membrane are most effective. The mainstay of treatment is the lidocaine derivative mexiletine, beginning at 150 mg bid by mouth and increasing slowly as needed up to 300 mg tid by mouth [55, 56]. The most common potential side effects include gastrointestinal distress, lightheadedness, and tremor which are reversible with dose reduction. Rash has been reported. Although tocainide, another lidocaine derivative, is useful in reducing myotonia in some patients at a dose of 400–1,200 mg a day, who may not respond to mexiletine, it should be used with extreme caution because of the potential for bone marrow suppression [57]. Alternatively, procainamide or quinine can be used and may be used intermittently as needed. Phenytoin 300–400 mg a day by mouth is often effective and can be used on a daily basis with few side effects [34].

Less commonly used medications include dantrolene, which has shown benefit in some severe cases [55, 58]. However, fatal and nonfatal hepatotoxicity have been reported, and the risk-benefit ratio must be weighed on an individual basis. Liver function studies must be measured at baseline and at appropriate intervals during therapy. Dantrolene must be discontinued if abnormal values are obtained. Acetazolamide is also beneficial in some

patients [59]. Doses generally begin at 125 mg by mouth twice a day, slowly increasing to 250 mg by mouth three times a day, as required and as tolerated by the patient. Common side effects include nausea, anorexia, and paresthesias, and patients must be warned about the formation of kidney stones [60]. Rash has been reported, and liver function studies and blood count should be monitored. As with other myotonic disorders, care must be taken with the use of depolarizing muscle relaxants during anesthesia, which aggravate myotonia and may cause adverse anesthesia-related events.

Prognosis

Patients with chloride channel myotonia congenita have a normal life span. As noted above, autosomal recessive myotonia congenita may be associated with minor progressive weakness and wasting of distal muscles. Rare patients experience disabling progressive weakness. Transient attacks of weakness experienced by some patients with recessive myotonia congenita may be disabling as it is often generalized. These tend to occur after initiating a sudden movement after a period of rest, and patients learn to avoid precipitating factors.

Sodium Channel Disorders: Sodium Channel Myotonia (Potassium-Aggravated Myotonia), Paramyotonia Congenita (Eulenburg Disease), and Hyperkalemic Periodic Paralysis

Patients with skeletal muscle sodium channel disorders present with a variety of symptoms including myotonia, stiffness, pain, and weakness. Those with sodium channel myotonia experience painful stiffness and spasms secondary to myotonia but do not experience true weakness. There may be day to day variation in the severity of myotonia, and symptoms are worsened or provoked by potassium [39]. In contrast, patients with paramyotonia congenita and HyperPP experience periodic weakness, and symptoms are worsened or provoked by the cold. Those with paramyotonia congenita and some patients with HyperPP experience stiffness secondary to myotonia. Sodium channel mutations involving the positively charged arginines in S4 segments of the sodium channel can produce a phenotype of hypokalemic periodic paralysis (HypoPP) [5, 8, 61], which is described below along with the more frequently seen form of HypoPP associated with calcium channel mutations that are substitutions of uncharged amino acids for positively charged arginines in S4 segments [62–64]. The mechanisms underlying these phenotypic differences are discussed below. There is not a strict relationship of the sodium channel mutation to the phenotype. For example, within a given family, some members may manifest only myotonia and others myotonia and paramyotonia or HyperPP [39].

The phenotypic variations associated with many mutations suggest that several as yet unrecognized factors may modify the phenotype. Only a few families with HyperPP without myotonia have been studied. Consequently, the single-channel defects associated with this phenotype are not known. There are some alterations in single sodium channel behavior that can predict the phenotype. Impaired sodium channel slow inactivation is usually associated with HyperPP [39, 65–68], while impaired deactivation has only been associated with paramyotonia and myotonia [69].

Sodium Channel Myotonia (Potassium-Aggravated Myotonia)

Introduction and Clinical Presentation

Several variants of sodium channel myotonia, also referred to as potassium-aggravated myotonia, have been described. These variants include *myotonia fluctuans*, *myotonia permanens*, and *acetazolamide-responsive myotonia* [70–72]. They are all associated with mutations in the α-subunit of the human skeletal muscle voltage-gated sodium channel gene (SCN4A) on chromosome 17q23 and inherited in an autosomal dominant fashion. Like recessive generalized myotonia, sodium channel myotonia is much more common than Thomsen's myotonia congenita [73].

Patients present in childhood or adolescence with episodes of generalized stiffness secondary to myotonia. Distinguishing features include painful myotonia which is quite potassium sensitive, with worsening of symptoms induced by potassium ingestion (Table 53.3), hence the designation "potassium-aggravated myotonia." Patients do not experience true episodic weakness, and in most patients, there is no worsening of symptoms with cold. There is considerable overlap in the clinical presentations of the different variants of sodium channel myotonia discussed below.

Myotonia Fluctuans

Patients present in adolescence with muscle stiffness that fluctuates in frequency and severity, sometimes not occurring for days or weeks [72]. The myotonia may be painful and has a peculiar feature of being *exercise induced and delayed in onset,* i.e., the myotonia is exercise induced but with a delay in onset for several minutes after exercise [74, 75]. This is not to be confused with *paramyotonia*, where myotonia occurs immediately after exercise (see below). The myotonia is worsened by the intake of potassium but not by the cold.

The fluctuating myotonia is such that on some days, patients experience no stiffness at all, while on other days myotonic stiffness of the bulbofacial, extraocular, or distal hand muscles may incapacitate a patient [74, 75]. On examination, patients may have well-developed musculature but without hypertrophy. Percussion and grip myotonia, and lid lag phenomenon may be present. There is no weakness.

Myotonia Permanens

In myotonia permanens, patients present in childhood with severe and unremitting generalized myotonia, hence the term *myotonia permanens*. Examination reveals marked hypertrophy of the neck and shoulders. Worsening of symptoms with potassium intake may be very severe and may affect thoracic muscles, resulting in hypoventilation, cyanosis, and loss of consciousness, which can be life-threatening [76]. To date, all reported cases have been de novo mutations [72, 76].

Acetazolamide-Responsive Myotonia

In the acetazolamide-responsive variant, also known as *atypical myotonia congenita*, patients experience intermittent painful myotonia beginning in childhood [77]. The myotonia has a predilection for axial and proximal limb musculature. The painful stiffness may be so marked at times that it results in severe disabling spasms and acute lumbar scoliosis [33], while on other days symptoms are barely present. Symptoms are provoked or worsened by fasting, infection, and intake of potassium. Cold temperature may worsen the myotonia but does not induce paralysis. Symptoms are markedly reduced with acetazolamide, although mexiletine is also effective. As with the other sodium channel myotonias, there is no periodic weakness. Percussion and grip myotonia are noted on neurologic examination [70, 71, 77].

Etiology and Pathogenesis

To better understand how the sodium channel mutations produce myotonia, the structure of the skeletal muscle voltage-gated sodium channel is reviewed (Fig. 53.5). The sodium channel from mammalian skeletal muscle is a glycopeptide composed of a large 260 kDa α-subunit and a smaller β-subunit [78, 79]. The gene (SCN4A) encoding the adult isoform of the sodium channel α-subunit of skeletal muscle (SKM1 or μ-1) which is sensitive to tetrodotoxin (TTX) is located on chromosome 17q in humans. The gene for the fetal isoform of the human α-subunit (SKM2), which is insensitive to TTX and is also expressed in denervated muscle fibers, is located on chromosome 3. The human and rat α-subunits contain 1,836 amino acids. The α-subunit contains 4 internally homologous repeating domains. Within each domain, a stereotypic pattern of 6 relatively hydrophobic segments exists, which theoretical models predict may form from 6 to 8 membrane-spanning

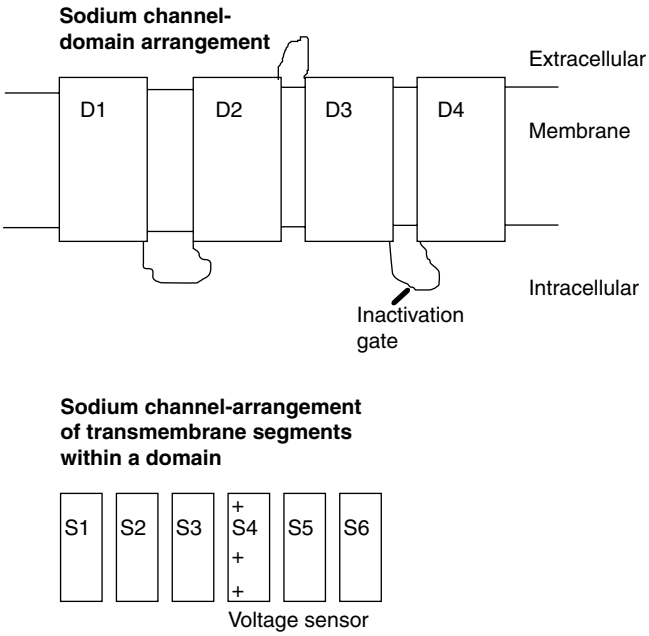

Fig. 53.5 Schematic of the structure of the sodium channel

alpha helices. Each of the 4 domains of the α-subunit contains a positively charged S4 segment which may function as a voltage sensor. Changing the net charges in the S4 segments alters the sodium channel activation-voltage relationship.

The channel pore is guarded by intra- and extracellular charged vestibules. Altering amino acids within the putative vestibules or changing amino acids within the pore itself can alter sensitivity to TTX or change the permeability characteristics of the channel [80].

The intracellular peptide between domains 3 and 4 of the sodium channel α-subunit is associated with fast inactivation and has been postulated to be part of the "ball and chain" that binds to the intracellular channel orifice and blocks current flow [78, 79]. Antibodies specific for, or disruption of, the intracellular peptide between domains 3 and 4 caused a reduction in the rate of fast inactivation without appreciably changing activation.

Fast inactivation can be disrupted in several different ways to produce myotonia

1. The voltage dependence of fast inactivation can be shifted (alone or along with the voltage dependence of activation) so that a voltage range exists over which channels can be opened and not develop fast inactivation. In the range of membrane potentials over which activation occurs with incomplete fast inactivation, persistent sodium currents can develop. Such sodium currents are often referred to as window currents, because they develop within a window of membrane potential values.
2. The development of fast inactivation can be inhibited so that many mutated channels do not enter the fast inactivated state in response to membrane depolarization.

3. Mutated sodium channels can develop a gating pattern (referred to as modal gating) in which the channels repeatedly jump between the open state and the inactivated state without having the channel persistently close.
4. Channels can recover from the fast inactivated state very quickly so that the channels rapidly transit from the inactivated state to the excitable closed state during membrane repolarization.

The first three types of disruption result in an inward sodium current that will augment the depolarizing effect of potassium accumulation in the T-tubules and result in sufficient membrane depolarization to trigger repeated action potentials. The fourth type of disruption greatly shortens the absolute and relative refractory periods allowing repeated action potentials to fire at high frequency. Many mutations result in a combination of these disruptions [39, 78, 79].

For a given site in the sodium channel protein, the severity of functional alteration of inactivation may relate to the amino acid that was substituted by the mutation. Amino acids with larger side chains such as valine or tryptophan may interfere with conformation changes to a greater extent than smaller amino acids such as glycine or alanine. Hence, altered behavior such as impaired ability to enter the fast inactivated state or instability of the fast inactivated state may be more pronounced when a larger amino acid substitutes for the native amino acid [39].

Differential Diagnosis

The differential diagnosis of sodium channel myotonia is limited and similar to that of chloride channel myotonia congenita. Disorders that should be considered include myotonia congenita associated with chloride channel mutations, paramyotonia congenita, the myotonic dystrophies, and Schwartz-Jampel syndrome. Precipitating or relieving factors, distribution of myotonia, the presence of extramuscular findings, distinctive facial or skeletal features, and findings on EDX and exercise testing are useful in distinguishing among these disorders (Tables 53.3 and 53.4).

The distinction between sodium and chloride channel myotonia can usually be made based on the characteristic worsening of myotonia with potassium ingestion in patients with sodium channel myotonia. Additionally, the myotonia in sodium channel myotonia is painful, unlike chloride channel myotonia. While fluctuating symptoms are characteristic of myotonia fluctuans and acetazolamide-responsive myotonia, fluctuating symptoms were also reported in patients with myotonia congenita associated with chloride channel mutations [31] and cannot necessarily be used to distinguish these disorders. Patients with myotonia fluctuans display the characteristic phenomenon of exercise-induced, delayed-onset myotonia, not seen in myotonia congenita associated with chloride channel mutations. The marked relief of symptoms with acetazolamide in patients with acetazolamide-responsive myotonia helps differentiate these patients.

Patients with sodium channel myotonia and paramyotonia congenita experience generalized stiffness and worsening of symptoms in the cold. However, patients with paramyotonia congenita display *extreme cold sensitivity resulting in true weakness*, not seen in sodium channel myotonia. Additionally, the exercise-induced, *delayed-onset* myotonia noted in myotonia fluctuans differs from the *immediate* worsening of myotonia with exercise noted in patients with paramyotonia congenita (see below). Patients with sodium channel myotonia do not experience periodic weakness and are therefore unlikely to be confused with any of the periodic paralyses.

Patients with sodium channel myotonia congenita lack the characteristic facial and skeletal features seen in Schwartz-Jampel (see below). The myotonic dystrophies can also be excluded because of their association with extramuscular manifestations (frontal balding, early cataracts, cardiac conduction and pulmonary defects, endocrine dysfunction, hypersomnia, and in some patients mild to moderate cognitive impairment). Additionally, patients with dystrophic disorders develop a progressive myopathy, not seen in sodium channel myotonia.

Various metabolic, inflammatory, and congenital myopathies may be associated with myotonic discharges on needle EMG (Table 53.5 III). These can usually be easily distinguished from sodium channel myotonia by associated features such as proximal weakness and lack of generalized myotonia. Certain drugs can precipitate or unmask electrical myotonia (Table 53.5 IV) and should be questioned, especially if onset of symptoms is later than childhood, there is no family history of myotonia, and painful myotonia and potassium sensitivity, typical features of sodium channel myotonia, are absent.

Diagnosis and Evaluation

Electrodiagnostic Testing (Table 53.4)

On EDX testing, routine motor and sensory nerve conduction studies are normal. Needle EMG examination generally shows myotonic discharges which are elicited in proximal and distal muscles. In myotonia permanens, the myotonic discharges are continuous. In contrast, in myotonia fluctuans and acetazolamide-responsive myotonia, the degree of myotonic discharges varies depending on the patient's symptoms. The MUAPs are normal in amplitude and duration with normal recruitment. In contrast to paramyotonia congenita, muscle cooling does not induce electrical silence with contracture [81]. In one family with the acetazolamide-responsive variant, there was no decrease in the CMAP amplitude with

cooling, as seen in paramyotonia congenita [70]. However, in another family with sodium channel myotonia, a decrease in CMAP amplitude was noted during motor conduction testing when the limb was cooled [81].

Short and prolonged exercise testing are not well studied in the sodium channel myotonias. Short exercise testing in one patient produced no decrement in CMAP amplitude at room temperature but a 10 % decrement after potassium administration and cooling of the limb [81].

Laboratory Testing

Serum CK level may be normal or slightly elevated. Muscle biopsy may be normal or show generalized fiber hypertrophy in the acetazolamide-responsive variant [77].

Treatment and Management

Symptomatic treatment with acetazolamide, especially in those patients with acetazolamide-responsive myotonia, helps reduce stiffness and pain. Doses generally begin at 125 mg by mouth twice a day, slowly increasing to 250 mg by mouth three times a day, as required and as tolerated by the patient. Common side effects include nausea, anorexia, and paresthesias, and patients must be warned about the formation of kidney stones [60]. Rash has been reported. Liver function studies and blood count should be monitored. Membrane-stabilizing agents including mexiletine and tocainide are also helpful. Mexiletine is especially helpful in patients with myotonia fluctuans, starting at 150 mg bid by mouth, increasing slowly as needed up to 300 mg tid by mouth [55, 56]. Common side effects include gastrointestinal distress, lightheadedness, and tremor which are reversible with dose reduction. Rash has been reported. Muscle relaxants may be helpful and necessary if the stiffness is severe, as in some patients with acetazolamide-responsive myotonia. Nonsteroidal anti-inflammatory medications are helpful adjuncts in reducing severe muscle pain in some patients.

General anesthesia may produce worsening of stiffness and myotonia, even in patients with normal contracture testing for malignant hyperthermia. Care must be taken with the use of depolarizing muscle relaxants during anesthesia, which aggravate myotonia and may cause adverse anesthesia-related events, especially in patients with myotonia fluctuans [82].

Prognosis

Patients in general have a normal life span. Those with continuous myotonic stiffness or severe spasms can be quite disabled, especially patients with myotonia permanens who experience severe stiffness of thoracic muscles resulting in hypoventilation. Some patients can learn to avoid triggering factors such as fasting, intake of potassium, and in some cases cold temperature.

Paramyotonia Congenita (Eulenburg Disease)

Introduction and Clinical Presentation

Paramyotonia congenita is an autosomal dominant inherited disorder that was first described by Eulenburg in 1886 [83]. The disorder arises from mutations in the α-subunit of the human skeletal muscle voltage-gated sodium channel gene (SCN4A) on chromosome 17q23, with complete penetrance in both sexes. In *paramyotonia*, muscle stiffness is brought on by repeated muscle contractions or exercise and is extremely cold sensitive. This is in contrast to *myotonia* where a warm-up period of repeated muscle contractions alleviates the muscle stiffness. Thus, the designation paradoxical, myotonia, or "*paramyotonia*."

Patients with paramyotonia congenita present in infancy with muscle stiffness primarily affecting bulbofacial, neck, and hand muscles. The stiffness is brought on by repeated muscle contractions (exercise) and worsened by exposure to cold, especially during repeated muscle contractions (Table 53.3). Indeed, parents often note the first signs of muscle stiffness in their infants when they observe prolonged eye closure after crying, or when they sleep near a fan with cool air blowing on them, or when they wash the infant's face with cool water. In most patients, cold induces attacks of stiffness followed by true weakness, especially during prolonged exercise in cold temperatures. Despite warming, it may take hours to regain strength. Patients learn to avoid those situations that trigger myotonia, such as eating ice cream or drinking a cold drink. Similar to patients with myotonia congenita, patients are often very muscular. Grip and percussion myotonia and the lid lag phenomenon are easily demonstrated on examination [39].

Paramyotonia congenita has appreciable overlap with sodium channel myotonia and HyperPP. Different mutations are associated with different presentations that may include periodic weakness or stiffness not precipitated by cold. For example, in one variant, patients experience spontaneous attacks of flaccid weakness resembling HyperPP (hyperkalemic periodic paralysis with paramyotonia), which can be provoked by potassium loading but is unprovoked by cold or exercise. Attacks of weakness appear during the teen years. Patients eventually develop fixed weakness between attacks [39, 84, 85]. In another variant, exercise-induced stiffness is not provoked by cold and may occur at room temperature, which is quite disabling. The clinical presentations of affected family members, with the same mutation, may also vary.

Etiology and Pathogenesis

Paramyotonia congenita is an autosomal dominant disorder of skeletal muscle membrane excitability [78, 79, 86]. It overlaps clinically with HyperPP and is associated with mutations of the sodium channel gene, SCN4A. While patients with paramyotonia congenita may have myotonia at normal temperature, they differ from myotonia congenita patients in three ways: (1) in paramyotonia, the myotonia is aggravated or elicited by cooling, (2) cold-induced weakness follows myotonia, and (3) there is worsening of myotonia by exercise (paradoxical myotonia). As stated above, paramyotonia refers to the development of muscle stiffness when a muscle is cooled. Paramyotonia results from repeated action potentials in muscle fibers. The distinction between myotonia and paramyotonia is not precise, and the two conditions overlap. For example, patients with paramyotonia congenita usually have myotonia when studied in a warm environment, and patients with myotonia often note that their muscle stiffness is more severe in a cold environment.

Paramyotonia usually results from sodium channel mutations that alter fast inactivation [78, 79]. *Consequently, paramyotonia congenita joins sodium channel myotonia and HyperPP as a sodium channelopathy* [87]. Muscle biopsies from paramyotonia congenita patients demonstrate normal membrane properties at 37 °C, but cooling to 27 °C triggers depolarization to about −40 mV. A pathological persistent inward sodium current causes the depolarization [78, 79, 86, 88]. Single-channel studies of mutant sodium channels usually demonstrate alterations in fast inactivation. *The defects in sodium channel gating present in most sodium channel mutations associated with paramyotonia are similar to those that produce myotonia*. However, physiological studies of sodium channel mutations that are associated with paramyotonia do not explain why the pathological persistent sodium current and paralysis are elicited by cooling.

One suggestion for the paramyotonia congenita mutations is that mutant channels can directly transit from the fast inactivated state to the open state, thereby enabling a fraction of channels to be open at depolarized potentials [88]. However, the hypothesis that depolarized mutant channels would transit between fast inactivated and open channel states does not consider that unless slow inactivation is perturbed, depolarized mutant channels would accumulate in the slow inactivated state, which would terminate the pathological sodium current. Two mutations associated with paramyotonia congenita have gating abnormalities that are distinct from those found in mutations associated with HyperPP or sodium channel myotonia [89, 90]. *One paramyotonia congenita mutation has impaired deactivation in addition to impaired inactivation* [89]. Deactivation refers to the conformation change of channels changing from the open state to the closed state when the membrane is hyperpolarized. Impaired deactivation coupled with impaired inactivation results in many mutant channels remaining open as the membrane repolarizes during the falling phase of the action potential. The open mutant channels provide a depolarizing current that triggers a chain of action potentials. *The second mutation does not affect fast inactivation and is speculated to alter slow inactivation* [90]. Plassart-Schiess et al. [90] found that fast inactivation was not appreciably altered by the Ile 693 Thr mutation, which was associated with the clinical manifestation of cold-induced weakness with myotonia. They suggested that the cold-induced weakness might result from altered slow inactivation.

Study of mutant channels has not elucidated how reducing temperature increases membrane excitability in paramyotonia congenita. One of the practical problems is that it is difficult to perform electrical recordings from single cells at physiological temperatures. Most physiological studies are performed at room temperature (20 °C or 68 °F). Consequently, a difference in sodium channel gating associated with cooling from a physiological to a subphysiological temperature would not be detected.

Possible Role of Slow Inactivation in Paramyotonia

Alteration in the temperature dependence of slow inactivation of sodium channels could result in increased membrane excitability at reduced temperatures. Skeletal muscle membrane excitability is a complex interplay of sodium, potassium, and chloride conductances. At a physiological temperature of 37 °C, most skeletal muscle sodium channels are excitable at the resting potential because most channels are in the closed state. At lower temperatures, the voltage dependence of slow inactivation shifts so that more than half of the channels of fast twitch skeletal muscle fibers are in the slow inactivated state at 19 °C [12, 91]. In contrast, the voltage dependence of fast inactivation and sodium channel opening have much less temperature sensitivity. Reducing the population of excitable sodium channels at lower temperature may help to prevent membrane hyperexcitability. At 37 °C, the kinetics of mammalian skeletal muscle delayed rectifier potassium channels are sufficiently fast to assist in terminating the action potential [92]. In contrast, at 23 °C mammalian skeletal muscle delayed rectifier potassium channels open too slowly compared to sodium channels to affect action potential termination [17]. Consequently, reducing the numbers of excitable sodium channels at lower temperatures may compensate for the slower opening of delayed rectifier potassium channels and allow the muscle membrane to maintain an appropriate level of excitability.

A reduction in the effect of temperature on the voltage dependence of slow inactivation would prevent depolarized

mutant channels from entering the slow inactivated state at reduced temperatures. Normal sodium channels are more susceptible to slow inactivation with cooling, which would facilitate the ability of a pathological persistent sodium current produced by the mutant channels to render the membrane inexcitable due to inactivation of the normal sodium channels. The pathological depolarizing current would initially trigger a string of action potentials, cold-induced myotonia. As the normal sodium channels accumulated in inactivated states, the membrane would become inexcitable producing clinical weakness. Consequently, a pathological depolarizing current could produce myotonia followed by paralysis. The theme of a pathological current producing myotonia followed by paralysis is echoed in the discussion of HyperPP. Richmond et al. [93] suggested mutations associated with weakness in addition to myotonia may have altered slow inactivation that allows a paralyzing persistent sodium current to exist.

Differential Diagnosis

The differential diagnosis of paramyotonia congenita comprises a small group of diseases with prominent myotonia. These include myotonia congenita associated with chloride channel mutations, sodium channel myotonia, HyperPP, the myotonic dystrophies, and Schwartz-Jampel syndrome. Paramyotonia congenita can usually be distinguished from these disorders based on characteristic clinical features including *the extreme cold sensitivity resulting in stiffness followed by true weakness*, as well as the phenomenon of *worsening of symptoms with repeated muscle contractions* (Table 53.3). Family history, distribution of myotonia, and pathognomonic findings on needle EMG with muscle cooling and exercise testing are also helpful.

The distinction between paramyotonia congenita and chloride channel myotonia congenita may be somewhat difficult, since generalized stiffness and muscle hypertrophy are common to both disorders. Furthermore, some patients with myotonia congenita may note worsening of symptoms in the cold. However, patients with paramyotonia congenita display *extreme cold sensitivity resulting in true weakness*, while those with myotonia congenita associated with chloride channel mutations rarely experience weakness. Furthermore, in paramyotonia congenita there is *worsening of symptoms with repeated muscle contractions*, in contrast to the "warm-up" phenomenon noted in chloride channel myotonia congenita.

In sodium channel myotonia and a subset of patients with paramyotonia congenita, potassium ingestion may worsen symptoms; however, patients with sodium channel myotonia do not experience weakness as in paramyotonia congenita.

Patients with paramyotonia congenita who experience attacks of weakness unprovoked by cold or exercise are clinically indistinguishable from the subset of patients with HyperPP and clinical myotonia including those with HyperPP with paramyotonia. With muscle cooling, most patients with paramyotonia congenita show a characteristic finding of paralysis of the cooled limb, accompanied by electrical silence with contracture at 20 °C, not seen in periodic paralysis (Table 53.4) [1, 50, 51]. However, it is not clear whether this finding is also seen in the subset of patients with paramyotonia congenita who develop attacks of weakness unprovoked by cold.

Paramyotonia congenita can be distinguished from patients with ATS, who experience periodic paralysis, and Schwartz-Jampel syndrome, where myotonia is prominent, by the lack of characteristic facial and skeletal features associated with these two disorders (see below). Furthermore, ATS is not associated with myotonia. Paramyotonia congenita can be differentiated from the myotonic dystrophies by their extramuscular manifestations and progressive weakness, not seen in paramyotonia congenita. In fact, patients with paramyotonia congenita are often quite muscular and strong.

Various metabolic, inflammatory, and congenital myopathies associated with myotonic discharges on EMG are noted in Table 53.5 III. These can be easily distinguished from paramyotonia congenita by associated features including proximal weakness and lack of generalized myotonia. Drugs that precipitate or unmask electrical myotonia (Table 53.5 IV) should also be questioned, especially if onset of symptoms is later than childhood, there is no family history of myotonia, and muscle hypertrophy and other typical features of paramyotonia congenita are not present.

Diagnosis and Evaluation

EDX Testing (Table 53.4)

Routine motor and sensory nerve conduction studies are normal. Needle EMG generally shows easily elicited myotonic discharges in proximal and distal muscles, although not as easily elicited as in the myotonia congenitas. The myotonic discharges may be more prominent in distal muscles. The MUAPs are normal in amplitude and duration with a normal pattern of recruitment.

Muscle Cooling

Muscle cooling to 20 °C may have a profound effect on the needle EMG, which is pathognomonic for paramyotonia congenita. Transient dense fibrillation potentials appear with cooling which eventually disappear below 28 °C. As the muscle cools down further, the myotonic discharges completely disappear below 20 °C, giving way to muscle paralysis. At this point, the muscle is inexcitable to electrical or mechanical stimulation and goes into a long-lasting

electrically silent contracture. This state may last over an hour after the muscle is warmed to room temperature [1].

Short Exercise Test

If the short exercise test is performed with the muscle cooled, there is a drop in CMAP amplitude, with a marked delay in recovery to the baseline CMAP amplitude with repeated recording of the CMAP up to an hour [1]. This is unlike the myotonic dystrophy type I or the chloride channel myotonia congenitas, where short exercise produces a drop in CMAP amplitude that rapidly recovers to baseline over a minute or two (Fig. 53.3).

Laboratory Testing

Serum CK level is often mildly to moderately elevated. Potassium level during attacks of weakness may be low, normal, or elevated, depending on the phenotype. In patients with cold-induced weakness, the potassium level is usually low or normal. In those with periodic weakness that is not temperature related (HyperPP with paramyotonia), the potassium level may be elevated, and attacks may be provoked by potassium ingestion. It is important to make this distinction through careful questioning of what factors induce weakness, as well as measuring the potassium level during weakness, since this may have important implications for treatment, discussed below.

Treatment and Management

Many patients with paramyotonia congenita do not require daily treatment, as they learn to avoid situations such as exposure to the cold, especially during exercise, that provoke symptoms of stiffness and weakness. For patients who require treatment, the lidocaine derivative mexiletine is helpful in preventing or alleviating stiffness and weakness induced by cold, as well as the periodic weakness experienced by some patients [94]. Doses beginning at 150 mg bid by mouth are used, increasing slowly as needed up to 300 mg tid by mouth. Common potential side effects include gastrointestinal distress, lightheadedness, and tremor which reverse with dose reduction. Rash has been reported.

Patients with spontaneous attacks of periodic weakness that are not related to temperature usually require treatment and may benefit from a combination of mexiletine with hydrochlorothiazide (HCTZ). The mexiletine is used to reduce the cold-induced stiffness, and the HCTZ is used to prevent spontaneous attacks of weakness not precipitated by cold or exercise, presumably by lowering the potassium level [95, 96]. Tocainide can reduce stiffness and weakness in some patients with paramyotonia congenita, at doses of 400–1,200 mg a day [1, 97]. However, it should be used only with extreme caution because of the potential for bone marrow suppression [57]. Acetazolamide, either alone or in combination with mexiletine, has proved beneficial in some patients with temperature-independent periodic weakness [59, 98]. Doses generally begin at 125 mg by mouth twice a day, slowly increasing to 250 mg by mouth three times a day, as required and as tolerated by the patient. Common side effects include nausea, anorexia, paresthesias, and rash, and patients should be warned about the formation of kidney stones [60]. Liver function studies and blood count should be monitored. It should be noted, however, that acetazolamide has also provoked weakness in some patients with paramyotonia congenita with cold-induced weakness, probably by lowering the potassium level [59, 98]. Thus, it is crucial to determine whether weakness is temperature dependent, as there are clear implications regarding treatment options. As with other myotonic disorders, care must be taken with the use of depolarizing muscle relaxants during anesthesia, which aggravate myotonia and may cause adverse anesthesia-related events.

Prognosis

Patients with paramyotonia congenita have a normal life span. Most learn to refrain from situations, such as cold exposure and exercise, that provoke symptoms of stiffness and weakness. However, those patients who experience spontaneous periodic weakness, unprovoked by cold, can be quite disabled by these and usually require daily treatment.

Hyperkalemic Periodic Paralysis

Introduction and Clinical Presentation

Hyperkalemic periodic paralysis (HyperPP) was initially described in the 1950s and differentiated from hypokalemic periodic paralysis (HypoPP) by the elevated potassium during attacks [99–101]. Gamstorp used the term *adynamia episodica hereditaria* to refer to the disorder. HyperPP arises from mutations in the α-subunit of the human skeletal muscle voltage-gated sodium channel gene (SCN4A) on chromosome 17q23. There is usually complete penetrance for both sexes, though rare patients were described with mutations where penetrance was incomplete [102, 103].

Three variants are described as follows: (1) HyperPP without myotonia, (2) HyperPP with clinical or EMG evidence of myotonia, and (3) HyperPP with paramyotonia (discussed in the previous section). Patients present in early childhood with attacks of periodic weakness that commonly occur in the morning after awakening from sleep. Attacks of weakness are usually brief, lasting from minutes to hours, and are generally accompanied by hyporeflexia. However, rare patients experience prolonged attacks of weakness.

Weakness is usually generalized but spares the facial and respiratory muscles. Some patients report focal limb or hemibody weakness, perhaps secondary to cold exposure confined to those limbs. Attacks vary in frequency, occurring daily in some patients and weekly or monthly in others. Myotonia, if present, can be variable. In some patients, the myotonia is detected only on needle EMG, while in others myotonia is elicited on physical examination. The frequency of attacks generally lessens in middle age, and some patients develop fixed progressive proximal weakness in adulthood [104].

Provocative factors include rest after exercise, fasting, emotional stress, cold, and potassium loading. Patients often anticipate an attack by a sense of muscle discomfort. The potassium level is usually elevated during attacks, though rarely reaches life-threatening levels. In some patients, the potassium level is normal during attacks of weakness. In all cases, the potassium level returns to normal after the attack. Symptoms are relieved by ingesting carbohydrates or inhaling a β-adrenergic agent [105]. Some patients can forestall an attack for a while with mild exercise, though an attack will eventually occur. During an attack, if exercise is possible, the attack may be shortened.

Etiology and Pathogenesis

Sodium channels from HyperPP patients with myotonia or from rat channels mutated to resemble one of the HyperPP mutants demonstrate abnormal sodium channel gating with repeated channel openings during depolarization that resembles the "slow" or "modal" gating discussed above, in which channels repeated flip between the inactivated state and the open state [106–108]. Single-channel conductance of the abnormally gating channels was reduced in one case [108] and was normal in others [12, 106, 107, 109–111]. Several mutations producing HyperPP and myotonia showed persistent inward sodium current attributed to (1) disrupted fast inactivation with an excessive amount of "slow" gating [66, 106, 112–114] or (2) "window" currents created by shifting the voltage dependence of activation [25, 26, 115] or activation and inactivation [116] resulting in a voltage range over which some channels will open and do not fast inactivate.

Possible Role of Slow Inactivation in Hyperkalemic Periodic Paralysis

As discussed in the section on myotonia, inhibition of fast inactivation is sufficient to produce myotonia [117, 118]. Disrupting slow inactivation enables a persistent depolarizing current that can facilitate the genesis of a HyperPP phenotype. Inhibiting slow inactivation enables the HyperPP phenotype by permitting the pathological persistent sodium current associated with HyperPP to last for minutes and therefore enables depolarization-induced paralysis to last for minutes to hours, the typical duration of paralytic attacks [12, 65, 119–121]. If slow inactivation is not disrupted, the depolarized mutant sodium channels will accumulate in the inexcitable slow inactivated state, which will terminate the pathological depolarizing current. Cummins demonstrated that slow inactivation was disrupted in the human Thr704Met mutation [26], which is the most common sodium channel mutation associated with HyperPP, and in the rat Thr698Met mutation, which is the rat analog of the human Thr704Met mutation producing HyperPP with myotonia [25]. Additional physiological evidence supports the importance of impaired slow inactivation in HyperPP [119, 120].

The difference between sodium channel mutations that produce only myotonia and those that produce prolonged depolarization-induced paralysis and myotonia may be that disrupting slow inactivation can produce prolonged depolarization [12, 25, 67, 119]. Slow inactivation was disrupted in three of four mutations of sodium channels associated with HyperPP including the most common mutations, Thr704 Met and Met 1592 Val [25, 119, 120]. One mutation, Met 1360 Val, displayed the same pattern of slow inactivation of I_{Na} as wild-type channels when studied at room temperature [119].

The slow inactivation results for the Met 1360 Val mutation can be reconciled in two ways. First, slow inactivation may be incomplete in vivo so that it need not be disrupted for mutant sodium channels to produce persistent depolarizing sodium current [119]. The second way of reconciling the Met 1360 Val slow inactivation data is to note that the mutation produced HyperPP with cold-induced weakness [122]. Consequently, the Met 1360 Val mutation could have abnormal temperature dependence for slow inactivation that would reduce the impact of slow inactivation at normal and slightly subnormal body temperatures with slow inactivation at room temperature being similar to wild-type channels. For example, the voltage dependence of slow inactivation of the mutant channels at 37 °C could have a positive voltage shift, meaning that very large depolarizations would be needed to have channels enter the slow inactivated state, and a larger temperature dependence compared with normal channels. Consequently, at normal and slightly subnormal temperatures, larger-than-usual depolarizations would be required to slow inactive mutant sodium channels. Hence, slow inactivation would not terminate the pathological persistent sodium current. A larger temperature dependence could result in slow inactivation for the mutant sodium channels being similar to normal channels at room temperature. Thus far, there does not seem to be a discernible pattern in either the mutation location or in the channel behavioral change that can predict which mutation will be associated with progressive weakness.

Differential Diagnosis

The differential diagnosis of HyperPP is limited, including HypoPP, ATS, and secondary hyperkalemic periodic paralysis disorders. These can usually be differentiated based on factors that provoke, worsen, or alleviate symptoms, findings on needle EMG, muscle cooling and exercise testing, and DNA testing when appropriate.

The distinction between HyperPP and HypoPP can usually be made based on age of onset, factors that provoke or alleviate an attack (Table 53.3), and determining the potassium level during an attack. Patients with HyperPP generally present in early childhood, in contrast to HypoPP, which usually manifests in adolescence. HyperPP attacks are provoked by fasting or ingestion of potassium, while attacks in HypoPP are provoked by carbohydrates. In contrast, carbohydrate ingestion prevents or relieves attacks in HyperPP, while potassium ingestion prevents or relieves attacks in HypoPP. Cold and rest after exercise may provoke attacks in both conditions. The prolonged exercise test produces a decremental response in both conditions and cannot distinguish between them. Clinical DNA diagnostic screening for the sodium or calcium channel mutations associated with HyperPP and HypoPP can be done in specialized laboratories.

Patients with HyperPP and myotonia may be confused with patients with recessive generalized myotonia who experience periodic weakness. However, exercise testing can be helpful in this regard. With prolonged exercise testing, patients with periodic paralysis show a progressive decline in the CMAP amplitude over 20–40 min, not seen in myotonia congenita (Table 53.4) [1, 52]. With short exercise testing, patients with myotonia congenita show a drop in the CMAP amplitude with a quick recovery, not seen in periodic paralysis. HyperPP can usually be distinguished from ATS by the lack of characteristic facial and skeletal features and prolonged QT interval that are found in ATS (see below). However, EKG may be a useful screening test in all patients with periodic paralysis even without distinctive facial and skeletal features, which may be lacking in some patients with ATS.

Secondary causes of HyperPP should be considered in those patients with later age of onset, no family history, or an atypical presentation. In such cases, appropriate laboratory screening should be done to screen for disorders associated with acquired hyperkalemic periodic paralysis (Table 53.5 II).

Diagnosis and Evaluation

EDX Testing (Table 53.4)

Routine motor and sensory nerve conduction studies are normal in HyperPP if performed between attacks of weakness. During an attack of weakness, the CMAP amplitudes may decline proportionate to the degree of weakness. Needle EMG exam between attacks may be normal, but in some patients, myopathic MUAPs may be found. In patients with HyperPP with myotonia, myotonic discharges may either increase or appear for the first time during an attack of weakness. Myotonic discharges are seen early in the attack but then disappear as weakness progresses. During an attack of weakness, there is a reduction in the size and number of MUAPs recruited in weak muscles.

Exercise Testing and Muscle Cooling

The prolonged exercise test often produces an immediate increase in the CMAP amplitude, especially if the initial amplitude is low. This is followed by a progressive decline in the CMAP amplitude by about 50 % over 20–40 min, with most of the decline occurring in the first 20 min [52]. A similar drop in the CMAP amplitude may also be noted by simply immobilizing the muscle without exercise. If there is a decline in the CMAP amplitude with rest, then exercise may produce a brief increment in the CMAP amplitude. The drop in CMAP amplitude with prolonged exercise does not distinguish HyperPP from HypoPP. However, as noted above, if myotonic discharges are noted on needle EMG, the diagnosis of HyperPP must be considered. The short exercise test produces no decrement, and muscle cooling has no appreciable effect on the needle EMG exam.

Laboratory Testing

Serum CK level may be mildly elevated. Serum potassium level is usually elevated during attacks of weakness. Muscle biopsy may show a vacuolar myopathy with fiber necrosis and degeneration. Tubular aggregates may be present. Clinical DNA diagnostic screening for HyperPP can be done in specialized laboratories. If the diagnosis cannot be established by the above methods, provocative testing can be done by administering potassium chloride after fasting and exercise, in an attempt to induce an attack of weakness [123]. This should not be done in patients who are already hyperkalemic nor in those with impaired renal or cardiac function and must be done under strict supervision with close EKG and serum electrolyte (including potassium) monitoring.

Treatment and Management

Management of HyperPP is directed toward preventing or decreasing the frequency of attacks and treating major paralytic attacks once they occur. To prevent attacks, patients are advised to eat regular meals, especially carbohydrate-rich and low-potassium meals, and to avoid situations that precipitate attacks, such as strenuous activity followed by rest. Many patients can forestall an impending attack, at least for a while, by engaging in mild exercise, ingesting carbohydrates

such as a candy bar, or inhaling a β-adrenergic agent once they note an impending attack [105].

Thiazide diuretics, such as hydrochlorothiazide (HCTZ), or the carbonic anhydrase inhibitor acetazolamide is effective in reducing the frequency and severity of attacks in the majority of patients. Patients are often unaware of minor daily attacks of weakness until beginning daily preventative therapy, when they note improvement in daily functioning. However, it is unclear whether preventing attacks will preclude later development of fixed proximal weakness [104].

Diuretics can be taken daily or intermittently as needed, using the lowest dose and frequency needed to prevent attacks. A reasonable starting dose of acetazolamide is 125 mg orally twice a day that can be slowly increased as tolerated to 250 mg orally four times a day, though some patients may require a higher dose, up to 1,500 mg a day, to prevent attacks or reduce the severity of attacks. Side effects include nausea, anorexia, and paresthesias. Rash has been reported. Patients should be warned about the formation of kidney stones [60]. Liver function studies and blood count should be monitored. A randomized double-blind placebo-controlled trial showed that dichlorphenamide, a potent carbonic anhydrase inhibitor, reduced the frequency and severity of attacks in HyperPP [124]. Dichlorphenamide can be used at a starting dose of 25 mg by mouth twice a day and slowly increased to 25–50 mg two to three times a day. The side effect profile is similar to acetazolamide. Some patients report confusion.

Rarely, acute paralytic attacks require more aggressive treatment than ingesting carbohydrates or inhaling a β-adrenergic agent if they are severe or associated with life-threatening hyperkalemia. Intravenous glucose and insulin can be used to lower the potassium level but must be done under strict supervision, with EKG and serum electrolyte monitoring. Finally, care must be taken with the use of depolarizing muscle relaxants during anesthesia, which aggravate myotonia and may cause adverse anesthesia-related events.

Prognosis

The elevated potassium levels during attacks are generally not life-threatening in terms of cardiac manifestations. Respiratory and bulbar involvement is exceedingly rare. Progressive fixed weakness may occur in adulthood.

Hypokalemic Periodic Paralysis: Types I and II

Introduction and Clinical Presentation

Hypokalemic periodic paralysis (HypoPP) type I is the most common of the inherited periodic paralyses. It is an autosomal dominant inherited disorder with reduced penetrance in women. The first genetic linkage of HypoPP (type I) was with mutations in the S4 segments of the α-subunit of a voltage-sensitive muscle calcium channel gene (CACNA1S) on chromosome 1q [125]. Calcium and sodium channels are close cousins with similar structures of four domains each containing six transmembrane spanning segments [126]. A few point mutations can convert the conductance properties of a sodium channel into those of a calcium channel [80].

In 1994, Plassart et al. [127] reported a large French family with HypoPP that did not link to the calcium channel gene on chromosome 1q32. The subjects were clinically indistinguishable from patients in whom HypoPP was associated with calcium channel mutations. Subsequently, mutations were identified in the α-subunit of the sodium channel gene on chromosome 17q accounting for this phenotype, and the term HypoPP type II was used to designate patients with HypoPP associated with sodium channel mutations [128, 129]. Because of the similarities in clinical presentation and pathogenesis, these disorders are discussed together below.

Patients generally present in adolescence with periodic attacks of weakness, although rare patients present in childhood or in their twenties. Attacks are provoked by cold, carbohydrate ingestion, alcohol, emotional stress, and rest after exercise. Some patients report a peculiar sensitivity to Chinese food, precipitating attacks of weakness. Typical attacks occur upon awakening from sleep, especially after strenuous physical activity or a large carbohydrate meal the day before. Patients may have a warning of an impending attack, describing muscle discomfort or stiffness [130]. Minor attacks can be forestalled for at least a short period of time by exercise or potassium ingestion. Untreated, attacks of weakness may be quite prolonged, lasting from several hours to days, generally occurring upon awakening from sleep. Weakness is usually generalized and often accompanied by hyporeflexia. Some patients experience focal limb weakness, perhaps if that limb was exposed to the cold during sleep.

In some patients, the weakness may be quite severe, resulting in flaccid quadriplegia with loss of reflexes. Major attacks may be preceded by diaphoresis and followed by oliguria. In rare individuals, bulbar and respiratory muscles are involved, which can be life-threatening during prolonged attacks. The potassium level is usually low during attacks (2.0–3.0 mEq/l) [98]. This may lead to bradycardia or sinus arrhythmias if the hypokalemia is profound [39, 130, 131]. In some patients, the potassium level is normal during attacks. Myotonia is not present either clinically or electrically, with the exception of eyelid myotonia in few patients.

Attacks are more frequent in males than females. It is not uncommon for females to be asymptomatic or so minimally affected by periodic weakness that they are unaware of their disorder. Even patients with attacks of periodic weakness

may be unaware of minor daily attacks until they are treated, when they note improvement in daily functioning. While the frequency of attacks tends to diminish in adulthood, most patients invariably develop progressive proximal weakness during adulthood, whether they have had attacks of periodic paralysis or not [132, 133].

Etiology and Pathogenesis

Hypokalemic Periodic Paralysis Results from Loss of Muscle Membrane Excitability

Muscular weakness in HypoPP develops in parallel with reduced surface membrane excitability [134]. Skeletal muscle membrane excitability is reduced in HypoPP, and membrane hyperexcitability is not typically associated with HypoPP. HypoPP muscle fibers have normal excitation contraction coupling [135]. Paralysis in HypoPP is caused by membrane depolarization triggering inactivation of sodium channels [39, 136]. Insulin administration may trigger a paralytic attack without appreciable hypokalemia [39, 136]. Muscle fibers in HypoPP are very susceptible to depolarization-induced inexcitability [39, 136] and have slow conduction velocities [137].

Hypokalemic Periodic Paralysis Is Linked to Sodium or Calcium Channel Mutations

HypoPP has been linked to mutations in a skeletal muscle calcium channel (HypoPP type I) or a sodium channel (HypoPP type II). The first recognized linkage of HypoPP was to chromosome 1q31-32 [125, 138]. The defective gene (CACNA1S) encodes a skeletal muscle dihydropyridine (DHP)-sensitive or L-type calcium channel, with a structure similar to that of the sodium channel (Fig. 53.5). Two mutation sites are on segment 4 of domain 2 (D2/S4, R528H) and D4/S4 (R1239H/G) of the α-subunit of the skeletal muscle L-type calcium channel [39, 138]. The other mutation sites are R879S, R900S, and V876E (Fig. 53.6) [64, 139].

Following identification of the calcium channel gene as a locus for HypoPP, studies demonstrated that point mutations in the SCN4A gene affecting D2/S4 of the α-subunit of the skeletal muscle sodium channel can also produce the phenotype of HypoPP [128, 129]. About 60 % of people with HypoPP have type I, 20 % have type II, and 20 % have undefined mutations.

The Sodium and Calcium Channel Mutations Have Similar Phenotypes

HypoPP associated with calcium channel mutations (HypoPP type I) or sodium channel mutations (HypoPP type II) is clinically indistinguishable [128, 129]. Bulman et al. [128] and Jurkat-Rott et al. [129] demonstrated that both types share the following four salient clinical features: (1) reduced membrane excitability, (2) depolarization in response to hypokalemia, (3) insulin-induced paralysis, and (4) episodic hypokalemia (Table 53.6).

Some Alterations in Membrane Excitability Are Directly or Indirectly Explained by the Sodium or Calcium Channel Mutations

A challenge in HypoPP is to understand how the sodium or calcium channel mutations produce the membrane abnormalities that lead to the clinical phenotype. Table 53.6 lists four important physiological features of HypoPP. Some of the pathological properties of skeletal muscle membrane in HypoPP muscle are directly understood from the sodium channel mutations for HypoPP type II. In contrast, several of the membrane abnormalities in HypoPP type I probably result from alteration of sodium or potassium channels. Because the membrane pathology associated with the calcium channel mutations do not result directly from the mutations, HypoPP type I has been called an *indirect channelopathy* [140, 141].

The Sodium Channel Mutations Directly Explain Reduced Membrane Excitability

Susceptibility to depolarization-induced paralysis and slow muscle fiber conduction velocities both suggest impaired sodium channel function in HypoPP. Jurkat-Rott et al. [129] explained the slow skeletal muscle fiber conduction velocities for patients with HypoPP with sodium channel mutations by demonstrating reduced action potential rates of rise due to lower sodium current density on isolated muscle fibers. The reduced sodium current resulted from two factors. First, mutant sodium channels did not conduct current because they were in an inactivated state at the resting membrane potential, due to a shift in the voltage dependence of fast inactivation. Second, the density of normal (wild type) sodium channels was only 50 % of the usual density. The pattern of insertion of wild-type sodium channels was what would be expected if the mutant channels were expressed at a similar rate to wild-type sodium channels and the mutant channels competed on an equal basis with the wild-type channels for membrane insertion. Skeletal muscle fibers did not upregulate sodium channel production or membrane insertion of wild-type sodium channels to accommodate for the reduced current carried by the mutant channels. The sodium current density in the muscle fibers of patients with HypoPP was about 50 % of that in normal muscle fibers.

Calcium Channel Mutations May Indirectly Explain Reduced Membrane Excitability in Hypokalemic Periodic Paralysis

The reduced excitability of muscle fibers from patients with HypoPP due to the R528H calcium channel mutation

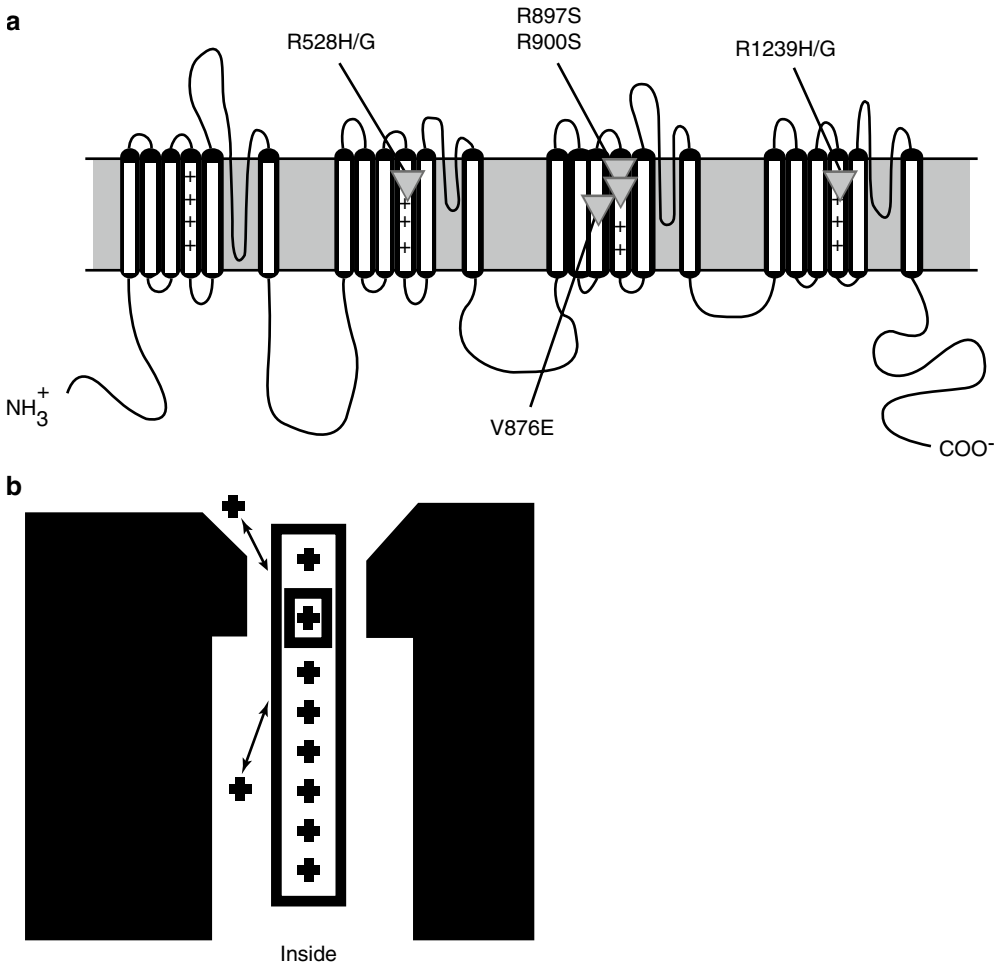

Fig. 53.6 Calcium channel mutations involved in HypoPP. (**a**) A cartoon of the calcium channel mutations identified in HypoPP and (**b**) a cartoon to suggest that mutations in which a positively charged arginine is replaced by an uncharged or negatively charged ion could create a binding site for cations on the S4 segment and enable the S4 segment to form an alternative pathway for ions to travel across the membrane – i.e., a "gating pore"

Table 53.6 Characteristics of hypokalemic periodic paralysis caused by sodium or calcium channel mutations

Characteristic of HypoPP	Present with calcium channel mutations	Present with sodium channel mutations	Explained by calcium channel mutations	Explained by sodium channel mutations
Reduced interictal skeletal muscle membrane excitability	Yes	Possibly – studies done before mutations were recognized	Indirectly via reduced sodium channel density	Yes
Muscle membrane depolarizes in response to reduced extracellular K^+	Yes	Yes	No	No
Insulin potentiates depolarization	Yes	Yes	Indirectly via altered impact of insulin on potassium conductance	No
Episodic hypokalemia	Yes	Yes	No	No

is associated with reduced sodium current amplitude [141, 142]. Reduced sodium current amplitudes result from a lower density of sodium channels without any alteration in the voltage dependence of sodium channel activation, fast inactivation, or slow inactivation. Consequently, the R528H calcium channel mutation reduced the expression or membrane trafficking of normal sodium channels via an undetermined mechanism. The commonality of reduced sodium current amplitude in HypoPP types I and II suggests that reduced sodium current may be an important pathophysiological change needed to produce the phenotype of HypoPP.

How do the calcium channel mutations alter the regulation of other ionic channels to produce the membrane changes present in HypoPP? One possibility is that the steady-state intracellular calcium levels may be altered in response to the mutations. The change in intracellular calcium may alter the production and membrane insertion of voltage-gated sodium

channels [143]. Hence, intracellular calcium concentration can modulate surface membrane sodium channel density, which provides a way for altered calcium channels to influence sodium channels [142].

Gating Pore Current Causes Muscle Fibers to Depolarize

Normal skeletal muscle fibers hyperpolarize in response to hypokalemia (Table 53.7). Paradoxically, muscle fibers from patients with HypoPP due to sodium or calcium channel mutations depolarize in response to hypokalemia (Table 53.7). The depolarization of muscle fibers is due in part to a depolarizing current arising from gating pore channels that are created by mutations in the charged S4 segments of mutated calcium or sodium channels (Fig. 53.6) [5, 8, 61, 64, 144–146]. An additional factor is that reduced activity of inward rectifier potassium channels enables a small current to produce a large depolarization [142].

The pathological depolarizing was initially recognized as resulting from an abnormal cationic-specific ion current that was not impaired by blockers of skeletal muscle sodium or calcium channels is and that was opened by reduced extracellular potassium concentration [140]. Thus, the depolarizing current was not carried through the normal ion channel pore of sodium or potassium channels. The genesis of the pathological depolarizing current was explained by the observation that mutations which replaced positively charged amino acids in the charged S4 segments of sodium channels produced a gating pore pathway for current flow (Fig. 53.6) [5–8]. Evaluation of comparable S4 mutations in potassium channels showed the positively charged arginines prevented gating pore currents [9, 10]. The presence of gating pore currents with mutations of arginines in S4 segments of either sodium or calcium channels partially explains why mutations of S4 segments of either skeletal muscle sodium or calcium channels can produce a similar phenotype.

The finding of gating pore currents associated with both forms of HypoPP raises the question of whether the gating pore currents are sufficient to produce the HypoPP phenotype [61, 147]. Types 1 and 2 HypoPP are associated with reduced voltage-gated sodium channel current and reduced inward rectifier potassium channel current [129, 140, 142, 148, 149]. In addition, reducing the conductance of inward rectifier potassium channels can result in an HypoPP-like skeletal muscle behavior [150, 151]. However, increasing membrane leak, which simulates the impact of gating pore currents, also produces HypoPP-like muscle behavior [152]. Thus, the extent to which gating pore currents cause the clinical HypoPP phenotype remains to be determined.

Table 53.7 The resting membrane potentials, percent of muscle fibers that could generate an action potential with a peak amplitude that reached or exceeded 0 mV, and the membrane potentials (mV) at which action potentials were triggered (action potential thresholds) in bathing solutions with different K^+ concentrations and with or without insulin (12 mU/ml) for intercostal muscle fibers from patients with hypokalemic periodic paralysis associated with the Arg-528-His Ca^{2+} channel mutation and control subjects

Solution	Control	HypoPP
Resting membrane potentials (mV)		
4.0 mM K^+	−93.4 ± 1.2 (n = 16)	−87.9 ± 1.5 (n = 16)
4.0 mM K^+ + insulin	−97.2 ± 1.1 (n = 16) p < 0.01	−74.9 ± 1.3 (n = 15) p < 0.001
2.5 mM K^+	−97.2 ± 1.0 (n = 16)	−83.3 ± 1.1 (n = 15)
2.5 mM K^+ + insulin	−99.8 ± 1.0 (n = 16) p < 0.05	−65.0 ± 1.4 (n = 15) p < 0.001
Percent of fibers that can produce an action potential		
4.0 mM K^+	100 %	100 %
4.0 mM K^+ + insulin	100 %	33 % p = 0.00014
2.5 mM K^+	100 %	67 % p = 0.0177
2.5 mM K^+ + insulin	100 %	0 % p < 0.0001
Action potential thresholds of excitable fibers (mV)		
4.0 mM K^+	−58.4 ± 2.0	−52.2 ± 2.2 p < 0.01
4.0 mM K^+ + insulin	−60.2 ± 1.9	−44.1 ± 4.5 p < 0.001 p < 0.05
2.5 mM K^+	−60.3 ± 1.8	−49.1 ± 3.9 p < 0.001
2.5 mM K^+ + insulin	−60.8 ± 2.1	None

Data obtained from Ruff [140] with permission of the journal *Neurology*

Insulin-Induced Depolarization Results from Altered Potassium Channel Response to Insulin: An Indirect Consequence of the Calcium Channel Mutations

Insulin hyperpolarizes normal fibers and depolarizes fibers from patients with both types of HypoPP. Insulin hyperpolarizes normal muscle fibers by activating the electrogenic sodium/potassium-ATPase and by altering the resting membrane sodium and potassium conductances so that the membrane is biased more toward the potassium equilibrium potential to produce hyperpolarization [136, 140, 148]. The effects of insulin on the membrane K_{ATP} channels are dramatically altered in type 1 HypoPP. Insulin markedly reduces the conductance of the inward rectifier class of potassium channels, particularly the K_{ATP} channels [140, 148]. The reduced potassium channel conductance produced by insulin

shifts the balance of membrane conductances so that the membrane potential moves away from the potassium equilibrium potential and closer to the sodium equilibrium potential, which causes membrane depolarization. Because insulin reduces the membrane potassium conductance, insulin will augment the hypokalemia-induced depolarization associated with activation of a depolarizing inward current. The impact of the gating pore current is increased when the potassium conductance is reduced.

It Is Not Known How the Calcium or Sodium Channel Mutations Make Patients with Hypokalemic Periodic Paralysis Have Episodic Hypokalemia

Insulin appears to induce excessive potassium uptake by muscle and other cells in both types of HypoPP. The pathophysiology of excessive cellular uptake of potassium is not known.

Summary of the Pathophysiology of HypoPP

HypoPP is a muscle disease with the following four cardinal features: (1) there is reduced membrane excitability, (2) muscle fibers depolarize in response to hypokalemia, (3) insulin potentiates depolarization, and (4) patients experience episodic hypokalemia. HypoPP is linked to mutations in the skeletal muscle L-type calcium or sodium channel. The HypoPP mutations produce gating pore currents in sodium and calcium channels that contribute to the paradoxical depolarization. Sodium channel mutations provide a direct explanation for reduced membrane excitability in HypoPP. Calcium channel mutations may reduce membrane excitability by reducing the expression of sodium channels. In association with calcium channel mutations, membrane depolarization in response to hypokalemia results from reduced conductance of inward rectifier potassium channels, especially K_{ATP} channels, and gating pore currents which produce a depolarizing inward current. Insulin potentiates depolarization in type 1 HypoPP by reducing the conductance of inward rectifier potassium channels, particularly K_{ATP} channels. For either class of ion channel mutation, the origin of episodes of hypokalemia is not known.

Differential Diagnosis

The differential diagnosis of HypoPP is limited, including HyperPP, ATS, and secondary HypoPP disorders. These can usually be differentiated based on factors that provoke, worsen, or alleviate symptoms, findings on EDX and exercise testing, and when appropriate DNA testing. Family history should always be questioned. However, because sporadic cases are not uncommon, likely representing new mutations, family history is not always helpful [125].

The distinction between HypoPP and HyperPP can often be made by age of onset, factors that provoke or alleviate an attack (Table 53.3), and measuring the potassium level during an attack. Patients with HypoPP generally present in adolescence, while those with HyperPP have a younger age of onset, in childhood. Weakness in HypoPP is triggered by carbohydrates, and symptoms are relieved with potassium ingestion. In contrast, in HyperPP weakness is provoked by fasting or potassium ingestion, and carbohydrate ingestion prevents or relieves attacks. Cold and rest after exercise provoke attacks in both conditions. Serum potassium levels are generally low during attacks in patients with HypoPP and elevated during attacks in patients with HyperPP.

The prolonged exercise test produces a decremental response in both conditions and is not useful in distinguishing between the two conditions. However, the finding of myotonic discharges on needle EMG, which can be seen in a subset of patients with HyperPP, excludes the diagnosis of HypoPP. Clinical DNA diagnostic screening for HypoPP can be done in specialized laboratories.

While patients with recessive generalized myotonia congenita (Becker-type myotonia) may also experience periodic weakness, they can be easily distinguished from HypoPP by the myotonic discharges on needle EMG, not seen in HypoPP. Furthermore, patients with recessive generalized myotonia congenita do not display the progressive decline in CMAP amplitude with prolonged exercise testing noted in HypoPP. HypoPP can be distinguished from ATS by the lack of characteristic facial and skeletal features and prolonged QT interval associated with ATS (see below). However, EKG may be a useful screening test in patients with periodic paralysis even without distinctive facial and skeletal features, which may be lacking in some patients with ATS.

Some patients with HypoPP never experience periodic paralysis yet develop a progressive proximal myopathy in adulthood. This is especially common in females. Such patients may be confused with inflammatory myopathy. However, muscle biopsy specimen in such patients reveals no inflammation. Nevertheless, it may be difficult to distinguish such patients from inclusion body myositis because of the vacuolar changes present in muscle biopsy specimens in both populations. However, other histologic findings in inclusion body myositis are distinctive, including endomysial inflammation, rimmed vacuoles lined with granular material, and intranuclear and cytoplasmic tubulofilaments noted on electron microscopy, not seen in HypoPP (see Chap. 65). Family history may also be helpful, since HypoPP is

dominantly inherited. Careful questioning for family members with periodic paralysis is crucial, especially in females with progressive weakness but without episodes of periodic weakness.

Secondary causes of HypoPP should be considered in those patients with later age of onset, no family history, or an atypical presentation. In such cases, appropriate laboratory screening should be done to screen for disorders and medications associated with acquired HypoPP (Table 53.5 II, IV).

Diagnosis and Evaluation

EDX Testing (Table 53.4)

Routine motor and sensory nerve conduction studies are normal. During an attack of weakness, the CMAP amplitudes generally decline proportionate to the degree of weakness. There are no myotonic discharges on needle EMG. The MUAPs and recruitment pattern are normal in the early stages of the disorder. There is a reduction in the size and number of MUAPs recruited in weak muscles during a paralytic attack. As patients develop fixed proximal weakness, small, short-duration MUAPs with early recruitment are noted in proximal muscles. In end-stage myopathy, the MUAPs may be large and of long duration, with poor recruitment, resembling MUAPs associated with chronic neurogenic disorders.

Exercise Testing and Muscle Cooling

The prolonged exercise test often produces an immediate increase in the CMAP amplitude, especially if the initial amplitude is low. This is followed by a progressive drop in the CMAP amplitude by about 50 % over 20–40 min, with most of the decline occurring in the first 20 min. A similar decline in the CMAP amplitude may also be noted by just immobilizing the muscle without exercise. If there is a decline in the CMAP amplitude with rest, then exercise may produce a brief increment in the CMAP amplitude. The decrement in CMAP amplitude with prolonged exercise does not distinguish between HyperPP and HypoPP. However, as noted above, if myotonic discharges are noted on needle EMG, the diagnosis of HypoPP is eliminated. The short exercise test produces no decrement, and muscle cooling has no appreciable effect on the needle EMG exam.

Laboratory Testing

Laboratory findings may show an elevated serum CK level. The potassium level is usually low during attacks of weakness. Muscle biopsy shows a vacuolar myopathy, characterized by large, central vacuoles, that may be present in patients with or without fixed weakness. Muscle fiber necrosis and degeneration may also be seen. Thyroid function tests as well as screening for secondary causes of HypoPP (Table 53.5 II) should be done, particularly when there is no family history or with late age of onset. Clinical DNA diagnostic screening for HypoPP can be done in specialized laboratories.

If the diagnosis cannot be established by the above methods, infusion of glucose with insulin can be used to provoke an attack. Several methods have been described [123]. However, provocative testing with glucose and insulin should only be used as a measure of last resort when the diagnosis cannot be otherwise established. Testing should not be done in patients who are already hypokalemic or in patients with known cardiac conduction defects. Since this testing can provoke a severe attack, it should only be done under the strict supervision of a knowledgeable physician, with continuous EKG monitoring as well as sequential monitoring of electrolytes, including potassium and glucose levels.

Treatment and Management

Management of HypoPP is directed toward preventing attacks and aggressively treating major paralytic attacks once they occur. To prevent attacks, patients are advised to follow a low-carbohydrate, low-sodium diet and avoid situations that precipitate attacks, such as strenuous activity or a high-carbohydrate meal or alcohol followed by rest. Most patients require some form of maintenance therapy to prevent attacks. Patients may be unaware of minor daily attacks of weakness until beginning preventative therapy, when they note improvement in daily functioning.

Acetazolamide is effective in reducing the frequency and severity of attacks and reducing inter-attack weakness in 50–60 % of patients [153–155]. A reasonable starting dose is 125 mg orally twice a day that can be slowly increased as tolerated to 250 mg orally four times a day, to prevent attacks or reduce the severity of attacks. Common side effects include nausea, anorexia, and paresthesias. Rash has been reported. Patients should be warned about the formation of kidney stones [60]. Liver function studies and blood count should be monitored. There have been few reports of patients with HypoPP who worsen with acetazolamide [156]. A randomized double-blind placebo-controlled trial showed that dichlorphenamide, a potent carbonic anhydrase inhibitor, reduced the frequency and severity of paralytic attacks in HypoPP [124]. Dichlorphenamide can be used at a starting dose of 25 mg by mouth twice a day and slowly increased to 25–50 mg two to three times a day. The side effect profile is similar to acetazolamide. Some patients report confusion.

Patients who do not respond to carbonic anhydrase inhibitors may respond to potassium-sparing diuretics, such as triamterene or spironolactone, although these must be used with caution in patients who are also taking oral potassium supplements [156]. Daily maintenance therapy with oral potassium chloride, either alone or in conjunction with a

carbonic anhydrase inhibitor, is useful in preventing or reducing the frequency and severity of attacks.

Acute paralytic attacks are treated with oral potassium chloride, 0.25 mEq/kg body weight, repeating every half hour until weakness improves. Electrolyte monitoring should be done during severe attacks requiring extensive potassium supplementation. Intravenous potassium is best avoided, unless oral potassium cannot be administered, and should always be done with close monitoring of the EKG and serum potassium level. Intravenous potassium may exacerbate the hypokalemia when mixed in a solution of glucose and saline or may cause acute hyperkalemia when given as a continuous infusion.

Prognosis

The lowered potassium levels during attacks are generally not life-threatening in terms of cardiac manifestations. However, respiratory and bulbar involvement may occur and may be life-threatening. Close monitoring during prolonged severe attacks involving respiratory and bulbar muscles is warranted. A mortality rate as high as 10 % was reported, but this was prior to modern medical care [157]. Progressive fixed weakness may occur in adulthood, even in those patients with no prior history of periodic weakness [133].

Thyrotoxic Periodic Paralysis

Thyrotoxic periodic paralysis (TPP) is seen in a subset of patients with thyrotoxicosis [153, 158]. Patients present with attacks of weakness associated with hypokalemia [159, 160]. The syndrome is clinically indistinguishable from primary HypoPP, except age of presentation, which is generally in adulthood [136, 139, 161]. Similar to primary HypoPP, attacks may be provoked by a high-carbohydrate meal, rest after exercise, or cooling of the limb. It occurs more commonly in males than females, despite the fact that thyrotoxicosis is more prevalent in females. Just as in the primary periodic paralyses, the prolonged exercise test results in a progressive decline in the CMAP amplitude.

The incidence of TPP is highest in adults of Asian origin, although it has been reported in all races [162, 163]. Susceptibility to developing TPP may be transmitted in an autosomal dominant fashion [164, 165]. Periodic paralysis and hypokalemia may be the initial presentation of thyrotoxicosis, without any of the usual features of hyperthyroidism. Patients with TPP manifest periodic paralysis associated with muscle fiber membrane depolarization when they are thyrotoxic, but not when euthyroid [142]. In spite of the similarities between TPP and either forms of HypoPP, patients with TPP do not have any of the sodium or calcium channel mutations associated with HypoPP [166–168]. Rather TPP is associated with a loss-of-function mutation of an inward rectifier potassium channel [169].

Treatment consists of correcting the thyrotoxicosis. In some patients, propranolol may prevent attacks of weakness. Acetazolamide is not effective in preventing periodic weakness in TPP [170]. As in primary HypoPP, acute attacks are treated with oral potassium. Untreated, TPP may result in progressive myopathy. The etiology of the paralysis is thought to be sodium channel inactivation secondary to sarcolemmal depolarization, which leads to loss of membrane excitability [18, 171]. Membrane depolarization is likely abetted by the reduced inward rectifier potassium channel current, and loss of membrane excitability is fostered by overall reduced sodium channel conductance (which may reflect fewer channels) [142, 169].

Related Syndromes

Andersen-Tawil Syndrome (ATS)

Introduction and Clinical Presentation

In 1971, Andersen described a syndrome characterized by the triad of *periodic paralysis, ventricular arrhythmias, and dysmorphic facial features* [172], though there were a few previous reports of patients with periodic paralysis and cardiac arrhythmias. In 1994, Tawil et al. reported four patients with autosomal dominant inherited periodic paralysis [173], ventricular ectopy, and dysmorphic features similar to Andersen's original description [174].

Patients present in childhood or adolescence with all or some features of the clinical triad of (1) periodic paralysis, (2) prolonged QT interval and ventricular arrhythmias, and (3) characteristic physical features [174, 175]. Clinical heterogeneity is noted within families. The periodic paralysis may be accompanied by hypokalemia, normokalemia, or hyperkalemia. Attacks may occur spontaneously or triggered by rest after exercise or alcohol. Some patients report intermittent muscle pain without attacks of weakness. As with other types of periodic paralysis, some patients can work through the muscle pain by continuing with mild exercise. Prolonged QT interval is the most consistent cardiac manifestation, present in about 80 % of patients, and may be the only finding in some individuals from a family with typical ATS [175]. In some patients, the long QT interval may be asymptomatic. However, patients may present in childhood with cardiac arrest, with no history of periodic paralysis, though they may experience periodic paralysis in later years. Others with periodic paralysis and characteristic facial features do not have a prolonged QT interval at rest, although other EKG findings may occur, such as a prominent U wave in the chest leads.

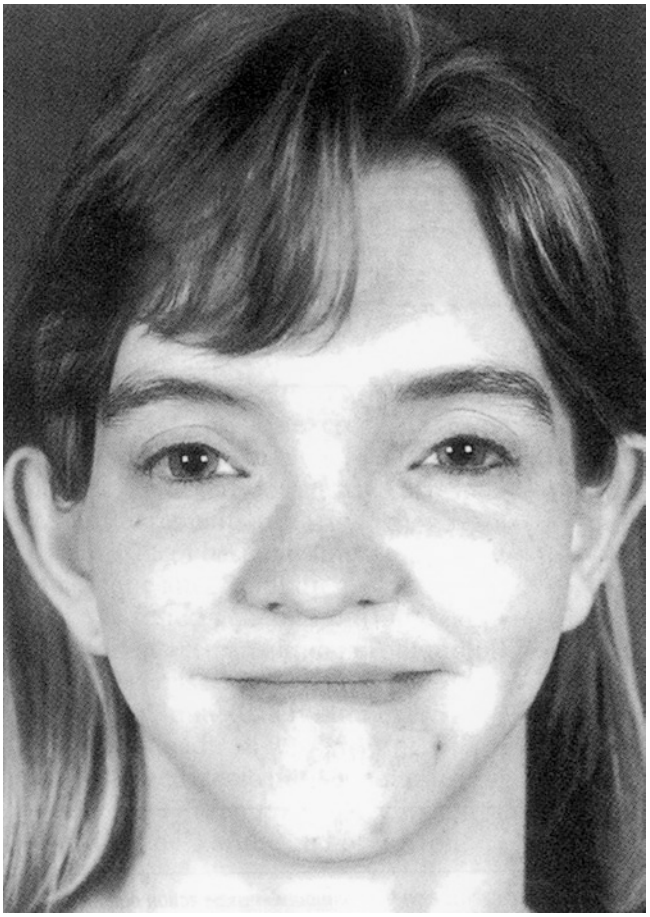

Fig. 53.7 Characteristic facial features in Andersen-Tawil's syndrome. Note low-set ears, broad nose, and hypertelorism

Characteristic physical features include short stature, high-arched palate, low-set ears, broad nose, micrognathia, hypertelorism, clinodactyly of the fingers, short index finger, and syndactyly of the toes (Fig. 53.7) [174, 175]. Scoliosis may be present. Neurologic examination between paralytic attacks may reveal generalized limb and neck flexor weakness, without grip or percussion myotonia.

Etiology and Pathogenesis

The etiology and pathogenesis of ATS are beginning to emerge. It is inherited in an autosomal dominant fashion with incomplete penetrance. The responsible gene encodes an inward rectifier potassium channel $K_{IR}2.1$ [176, 177]. That mutations of inward rectifier channels are involved with both TPP and ATS suggests that disturbing inward rectifier potassium channel function likely contributes to periodic paralysis.

Differential Diagnosis

The differential diagnosis of ATS includes HyperPP and HypoPP, as well as recessive generalized myotonia congenita with periodic weakness. However, the presence of distinctive facial and skeletal features and a long QT interval usually differentiate ATS from the other primary periodic paralyses and recessive generalized myotonia congenita. If myotonic discharges are noted on needle EMG, the diagnosis of ATS is excluded, in favor of recessive generalized myotonia congenita or the subset of patients with HyperPP and myotonia. In patients who report muscle pain with exertion and in whom it is unclear whether the pain is accompanied by true weakness, metabolic myopathies should be considered. However, the distinctive facial and skeletal features will usually differentiate ATS from these other disorders.

Evaluation and Diagnosis

EDX Testing

Routine motor and sensory nerve conduction studies are normal. There are no myotonic discharges on needle EMG, even with muscle cooling.

Exercise Testing

The short exercise test produces no decrement. The prolonged exercise test often produces an immediate increase in the CMAP amplitude, especially if the initial amplitude is low. This is followed by a progressive drop in the CMAP amplitude by about 45 % over 20–30 min [178]. Although there may be minor differences in the degree and time course of the decrement in CMAP amplitude with prolonged exercise, one cannot use this test to definitively distinguish among ATS, HyperPP, and HypoPP.

Laboratory Testing

Serum CK level is mildly to moderately elevated. Muscle biopsy may be normal, or there may be mild chronic myopathic changes, often with tubular aggregates [175]. Evaluation should include an EKG looking for evidence of a long QT interval and 24-h Holter monitoring looking for evidence of arrhythmias. In some cases, exercise stress testing may be needed to bring out a prolonged QT interval or other cardiac abnormalities and should be done under the strict supervision of a knowledgeable cardiologist. *Provocative hyperkalemic and hypokalemic challenges, as described above, should be avoided in patients suspected of ATS because of the possibility of precipitating a life-threatening arrhythmia by exacerbating an underlying prolonged QT interval.*

Management and Treatment

Treatment of ATS is empiric and complicated by the fact that both skeletal and cardiac muscle are involved, and treatment of one set of symptoms may exacerbate the other through paradoxical responses to changes in potassium levels. Additionally, cardiac arrhythmias may be refractory to standard antiarrhythmic agents. Treatment with carbonic anhydrase inhibitors (acetazolamide, dichlorphenamide) may be

helpful in controlling periodic weakness while only minimally lowering the potassium level. A reasonable starting dose of acetazolamide is 125 mg orally twice a day that can be slowly increased to the lowest dose needed to prevent or reduce the severity of attacks, while monitoring cardiac function closely. Common side effects include nausea, anorexia, and paresthesias. Rash has been reported, and patients should be warned about the formation of kidney stones. Liver function studies and blood count should be monitored. Dichlorphenamide can be used at a starting dose of 25 mg by mouth twice a day and slowly increased to the lowest dose needed to control paralytic attacks while monitoring cardiac function. The side effect profile is similar to acetazolamide, though some patients report confusion.

Arrhythmias are poorly responsive to commonly used antiarrhythmic agents, including tocainide, procainamide, flecainide, quinidine, sotalol, and amiodarone, which may also worsen the weakness or prolong the QT interval [174]. Imipramine, a mild antiarrhythmic, was used in some patients to treat the arrhythmias without causing further weakness [174, 179]. Patients should be evaluated by a cardiologist for close cardiac monitoring and coordination of treatment of arrhythmias.

Prognosis

The major complication of ATS is sudden death from cardiac arrhythmias, and close cardiac monitoring is warranted.

Schwartz-Jampel Syndrome (Chondrodystrophic Myotonia)

Introduction and Clinical Presentation

Schwartz-Jampel syndrome (SJS) is a rare, inherited myotonic disorder characterized by short stature, skeletal deformities, facial anomalies, and muscle stiffness [180]. Dwarfism and prominent facial and skeletal anomalies distinguish SJS from other myotonic disorders. SJS has several synonyms including chondrodystrophic myotonia, chondrodystrophica myotonica, osteochondromuscular dystrophy, spondyloepimetaphyseal dysplasia with myotonia, and Aberfield syndrome. The syndrome is usually transmitted as an autosomal recessive condition, but in occasional families, the inheritance pattern suggests an autosomal dominant disorder [181, 182].

The characteristic skeletal anomalies that contribute to dwarfism include bony dysplasia with metaphyseal enlargement and cortical thickening, bowing and shortening of the long bones of the upper and lower extremities, arachnodactyly, hip dysplasia with abnormalities of the acetabulum, kyphoscoliosis, and pectus carinatum. Facial anomalies include small mouth with micrognathia and pursed lips, upward slanting eyes, blepharophimosis, exotropia, microcornea, low-set ears, and prominent eyebrows (Fig. 53.8). Other dysmorphic features include hypoplastic larynx, short neck, and hypertrichosis. Patients with SJS may have prominent proximal upper and lower extremity muscle hypertrophy and distal predominant generalized weakness and atrophy [182, 183]. In contrast to the pseudohypertrophy seen in dystrophinopathies, proximal limb muscles in SJS are genuinely enlarged. Approximately 20 % of people with SJS have some degree of cognitive impairment [184]. Other features associated with SJS include malignant hyperthermia and susceptibility to carpal tunnel syndrome.

The clinical manifestations may vary among affected members of the same family. However, there are three common presentation patterns for families with SJS: type 1A, 1B, and 2 [184]. SJS type 1A manifests in childhood with moderate bone dysplasia, muscle enlargement, myotonia, and dysmorphic facial features. SJS type 1B is similar to type 1A but is recognizable at birth and has more prominent bone dysplasia. SJS type 2 is the most severe and manifests at birth with contractures, severe long bone bowing (campomelia), prominent myotonia, and severe facial and pharyngeal deformities that preclude normal feeding and lead to infantile death. SJS type 2 is very similar to the Stuve-Wiedemann syndrome. Some authors suggested that Stuve-Wiedemann syndrome and SJS type 2 may be the same disease [185]; however, the underlying genetic abnormalities differ [186, 187].

Etiology and Pathogenesis

SJS is autosomal recessive and characterized by skeletal dysplasia with varying degrees of myotonia and chondrodysplasia, with close to normal survival. The variability in the severity of SJS within a family and between families suggests that the SJS phenotype is modified by several genes. SJS type 1 is linked to chromosome 1q34-36 or 1p34-36 in different families [184, 188]. SJS type 1 is associated with mutations of the gene encoding perlecan (HSPG2). Perlecan is a large heparan sulfate proteoglycan and is a component of the basement membrane and other extracellular matrices and has been implicated in multiple biological functions. Mutations in HSPG2 cause two classes of skeletal disorders: the relatively mild SJS and severe neonatal lethal dyssegmental dysplasia, Silverman-Handmaker type. At least some of the skeletal dysmorphic features such as campomelia and pectus carinatum may result from increased muscle tone associated with myotonia. Reducing myotonia appears to reduce the severity of campomelia and pectus carinatum [189].

Muscle fiber hyperexcitability is prominent, with spontaneous individual muscle fiber activity occurring even during sleep [180, 183]. The excessive muscle fiber contraction likely contributes to skeletal muscle hypertrophy [189].

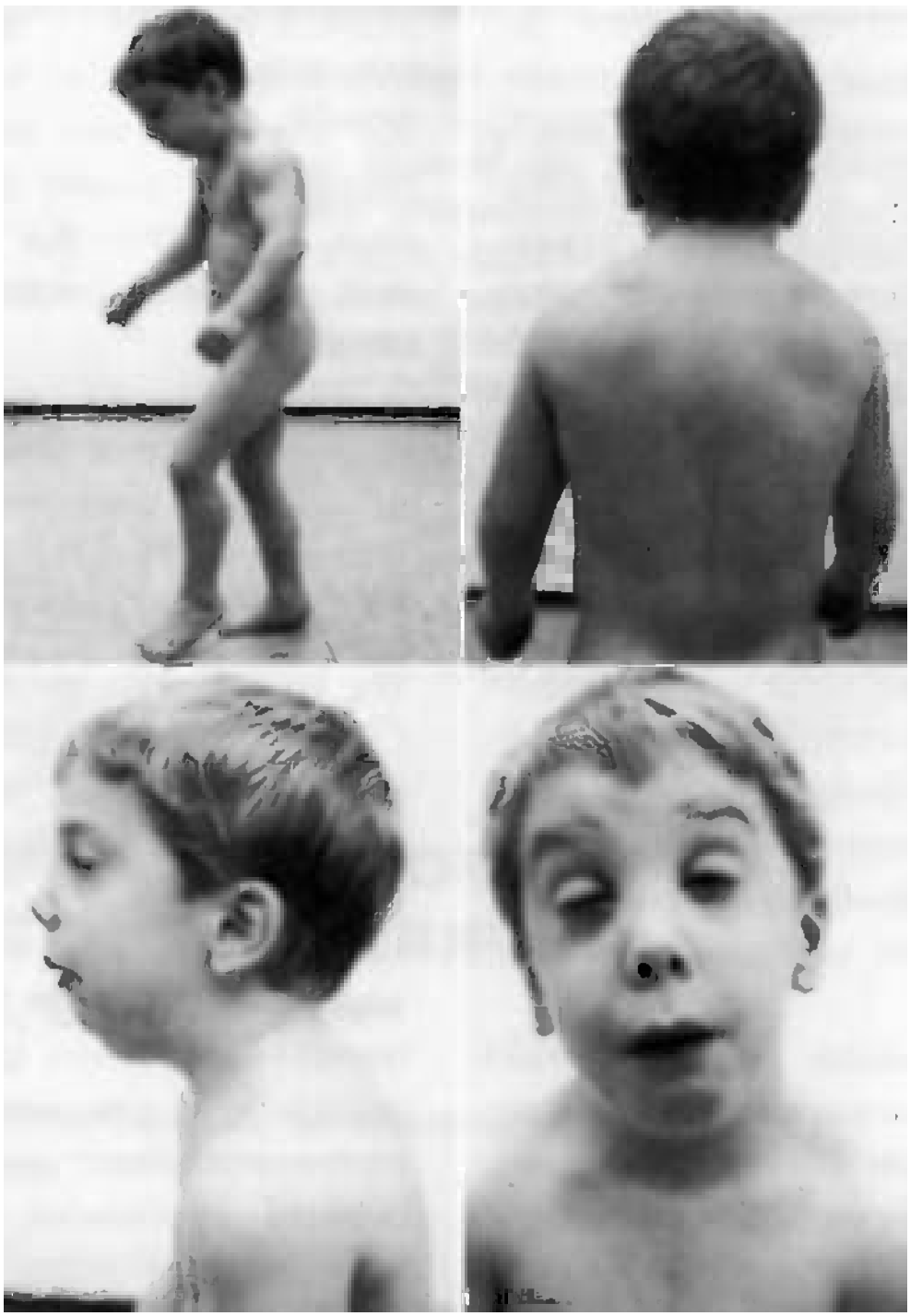

Fig. 53.8 Characteristic facial and skeletal features in Schwartz-Jampel syndrome. Note skeletal and facial anomalies including short neck, small mouth, micrognathia, pursed lips, upward slanting eyes, blepharophimosis, low-set ears, and prominent eyebrows. Patients with SJS may have prominent proximal upper and lower extremity muscle hypertrophy and distal predominant generalized weakness and atrophy

The physiological basis for myotonia in SJS is complex. The single fiber hyperexcitability raised the possibility that SJS was associated with abnormal function of skeletal muscle membrane ion channels. However, SJS is not associated with sodium or chloride channel mutations. Chloride conductance is not sufficiently altered to produce myotonia [190]. Sodium channel gating is altered. In response to membrane depolarization, sodium channel openings are delayed and the channels open repeatedly during the depolarization. The delayed openings indicate that the transition from the closed to the open state of the sodium channel is altered. The repeated openings during depolarization indicate destabilization of the fast inactivated state so that channels can repeatedly jump between the inactivated and open channel states [190].

More recent studies following identification of the HSPG2 mutations underlying SJS type 1 demonstrated peripheral nerve hyperexcitability and suggest that myotonic behavior is in part due to neuromyotonia [191]. Schwann cell basement

membrane and its molecular interactions with axons are critical for proper myelination and node of Ranvier structure. Perlecan-deficient mice had shorter internodes, more numerous Schmidt-Lanterman incisures, and a higher density of internodal delayed rectifier potassium channels [192]. The increased number of intermodal potassium channels would oppose hyperexcitability. Thus, the increased potassium channel number is perhaps a cellular adaptation in response to peripheral nerve hyperexcitability [192]. The origin of the hyperexcitability of skeletal muscle and peripheral nerve membranes in SJS is likely due to altered function of membrane ion channels related to altered basement membrane.

Differential Diagnosis

The clinical presentation of SJS is so characteristic that the differential diagnosis is quite limited. The diagnosis of SJS is usually established by the combination of characteristic dysmorphic features, dwarfism, and myotonia accompanied by muscle enlargement. SJS differs from myotonia associated with chloride and sodium channel mutations by the prominent dysmorphic features characteristic of SJS. Skeletal anomalies and blepharophimosis distinguish SJS from the myotonic dystrophies. In addition among the myotonias, the combination of proximal muscle enlargement and generalized muscle weakness is unique to SJS [182, 183]. The skeletal and facial anomalies of SJS are similar to those found in the Marden-Walker syndrome. However, Marden-Walker syndrome is not associated with myotonia or proximal muscle hypertrophy [181, 184, 185]. As discussed above, SJS type 2 and Stuve-Wiedemann syndrome have very similar clinical patterns [181, 184, 185].

Diagnosis and Evaluation

EDX Testing

Routine motor and sensory nerve conduction studies are normal. Needle EMG shows continuous spontaneous high-frequency, low-voltage discharges in proximal and distal extremity muscles that wax and wane in frequency and amplitude (myotonic discharges) as well as high-frequency discharges with no change in frequency and amplitude (complex repetitive discharges) [180, 182, 183, 189, 193]. Myotonia is present in patients with SJS type 1A and 1B but is more prominent in SJS type 1B. The abnormal electrical activity represents spontaneous action potentials arising from individual muscle fibers. These can be found during sleep or general anesthesia. Electrical activity persists after motor nerve block and after neuromuscular block with curare, indicating that the abnormal electrical activity arises from primary hyperexcitability of skeletal muscle membrane [182, 183]. Procainamide [190] or carbamazepine [189] reduces the spontaneous electrical activity.

In one family where both father and son were affected, spontaneous rhythmic bursts of motor unit action potentials (myokymia) were described, indicating peripheral nerve involvement in this family [182].

Laboratory Testing

Serum CK level may be mildly to moderately elevated. Skeletal muscle is usually normal on light microscopy [182, 183, 189]. Occasional patients have mild myopathic features including excessive variability in fiber size [194]. Electron microscopic studies may reveal subsarcolemmal membrane abnormalities and mild changes in intracellular organelles [183, 189]. The myofibrils have a normal configuration, but the distributions of isoforms of myosin, myosin light chains, and other contractile or structural proteins are slightly altered in SJS [195].

Management and Treatment

Management is primarily symptomatic. Plastic surgery may be needed for severe blepharophimosis. Both procainamide [183, 190] and carbamazepine [189] can reduce myotonia and muscle stiffness in SJS. Early and aggressive treatment of myotonia during infancy and childhood may reduce the severity of some of the skeletal anomalies such as bowing of the long bones [189]. As with patients with other myotonic syndromes, patients with SJS may be subject to malignant hyperthermia, and depolarizing muscle relaxants are best avoided during anesthesia [196].

Prognosis

For SJS type 1A, the skeletal anomalies and dysmorphic features progress during childhood and reach a plateau in adolescence. For SJS type 1B, some skeletal anomalies and dysmorphic features are present at birth or early infancy and progress during childhood. Both type 1A and 1B patients have delayed acquisition of gait, slowness of gait, and reduced walking stability. Gait impairment is more severe in patients with type 1B SJS due to greater severity of hip dysplasia. Patients with SJS type 1A and 1B develop visual impairment due to the blepharophimosis, lens anomalies, and small corneas. Infants with type 2 SJS, the most severe form, have extreme difficulty feeding owing to severe micrognathia and laryngeal hypoplasia [181, 184].

The life expectancy of patients with SJS type 1A appears to be normal, while those with SJS type 2 usually die in infancy or childhood. The life expectancy of patients with SJS type 1B has not been clearly established but is probably reduced [181, 184].

Rippling Muscle Disease

Introduction and Clinical Presentation

Rippling muscle disease (RMD) is a very rare autosomal dominant inherited disorder of skeletal muscle originally described in 1975 by Torbergsen [197]. In 1989, Ricker, Moxley, and Rohkamm used the term "rippling muscle disease" to describe several members of two German families with the disorder [198]. Subsequently, two large families from the United States and two other German families were described [199, 200]. Rare sporadic cases associated with myasthenia gravis were also described [201, 202].

Patients present in childhood or adolescence with stiffness and intermittent pain and cramps induced by exercise, though rare patients present in adulthood. Mechanical percussion of muscle or muscle stretch after contraction induces continuous rolling, "rippling" waves of muscle contractions that begin in the proximal portion of the muscle and spread laterally across the muscle. The rippling can be induced again after a few minutes of rest. The quadriceps and biceps brachii were the most commonly affected muscles in two families [203]. Direct percussion of muscle produces two other phenomena: a distinctive rapid muscle contraction and a mounding up of the muscle with direct percussion which may be painful. Direct percussion of the muscle may also produce a prolonged muscle contraction identical to the percussion myotonia seen in the myotonic disorders. Ricker et al. [198] showed that the speed of the muscle waves during a contraction was 0.6 m/s, about ten times slower than the speed of a muscle fiber action potential, with the direction of the ripple at right angles to the long axis of the muscle fiber. The contractions are accompanied by needle EMG silence. Muscle hypertrophy, especially of the calves, is common. In one family, mild weakness of facial and proximal muscles was noted [200].

RMD has incomplete penetrance. Not all patients exhibit all of the clinical findings. In some of the families reported, males appear to be more severely affected than females, who may lack the rippling muscle phenomenon altogether. Muscle contraction and mounding of the muscle with percussion appear to be more constant features than muscle rippling in most affected individuals. In one family, a cardiac conduction defect was noted as part of the clinical picture [198]. In another family, some affected members reported recurrent pigmenturia precipitated by exercise [203].

Etiology and Pathogenesis

The etiology and pathogenesis are unknown. Genetic linkage was made to the distal end of the long arm of chromosome 1 (1q41) in a large family from Oregon [199, 204], while the German families studied by Ricker et al. [198] and Vorgerd et al. [203] and a large family from the United States described by So et al. [200] did not map to this locus, thus demonstrating genetic heterogeneity. However, the gene responsible for the disease is not known.

The mechanism by which abnormal contractions are induced by percussion or stretch is not clear. Some have postulated involvement of mechanosensitive or stretch-activated human skeletal muscle channels [201]. Direct percussion or stretch of muscle may induce intracellular events leading to the abnormal contractions. Defective regulation of calcium transport and homeostasis may be responsible for the abnormal cellular events [203]. Mechanically induced calcium release from the sarcoplasmic reticulum may be extremely high, uncompensated for by calcium reuptake, leading to abnormal accumulation of calcium in the cytosol and abnormal muscle contractions [203]. Extracellular communication may then initiate a similar train of events in neighboring muscle, given that thousands of muscle fibers act concurrently [199]. There is also an autoimmune form of RMD associated with myasthenia gravis, with or without thymoma, that resembles the inherited form [201, 202].

Diagnosis and Evaluation

The presentation of RMD is so idiosyncratic that the diagnosis is made when the distinctive characteristics are recognized. A search for associated cardiac abnormalities is warranted. If there is no family history, and presentation occurs in adulthood, an evaluation for myasthenia gravis is indicated. Needle EMG shows slightly increased insertional activity at rest and electrical silence during the rippling muscle movements. Muscle biopsy shows mild nonspecific abnormalities including increased variability in fiber size and increased central nuclei [198, 203]. Serum CK level may be slightly to markedly elevated [198].

Treatment and Prognosis

In general, there is little to no disability associated with RMD, although stiffness and cramps can be bothersome, and patients learn to avoid situations that cause painful mounding of the muscles. The subset of patients with cardiac conduction defects needs close cardiac monitoring. Some patients responded to dantrolene sodium or benzodiazepines to reduce stiffness, but tocainide was not helpful in reducing cramps or stiffness [199, 203, 204]. In the rare reported patients with RMD associated with myasthenia gravis, symptoms improved with immunosuppressive therapy or thymectomy.

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Malignant Hyperthermia

54

Tulio E. Bertorini

Introduction

Malignant hyperthermia (MH) is a condition that manifests acutely by rigidity, increased body temperature, and muscle necrosis. This usually occurs during surgery under exposure to certain inhalable anesthetics, such as ether, or halogenated compounds such as halothane usually but not always together with depolarizing relaxants, such as succinylcholine. The syndrome, which was initially described by Denborough in 1960 [1], produces acidosis, hypermetabolism, and myoglobinuria with excessive intracellular calcium accumulation and muscle necrosis. The reported incidence of MH varies from approximately 1 of every 5,000 to 10,000 to 1 of every 50,000 to 100,000 surgeries [2]. It occurs more frequently in males than in females, and the incidence is higher in children [3–8].

Pathogenesis

MH is believed to be caused by an excessive release of calcium from the sarcoplasmic reticulum (SR) in subjects at risk because of specific genetic mutations. MH also has been reported sporadically in patients with certain neuromuscular disorders, but in some of these patients, the attacks are atypical. The typical syndrome usually has an autosomal-dominant inheritance pattern, most often associated with genetic mutations of the ryanodine receptor (RYR1) calcium channel gene [9–11] in muscles, and less frequently, the dihydropyridine (DHP) voltage-gated calcium channel gene [12, 13]. Both of these proteins are involved in muscle calcium release by the SR [10, 11, 13, 14], and the mutations appear to lower the threshold for calcium release for electrical contraction coupling [15]. A similar condition, known as the *porcine stress syndrome*, occurs in pigs and is also caused by a RYR1 gene mutation.

Located in the SR, the RYR1 receptor, so named because of its binding to the alkaloid of ryanodine, is a large protein with a molecular weight of 2,200 kd, with 5,000 amino acids [16]. Intimately connected with the RYR1 at the triads of the SR and the T tubules is the DHP receptor calcium channel, which acts as a voltage sensor for the RYR1 receptor, and gets its name for its sensitivity to DHP [16] (Fig. 54.1). The actions of

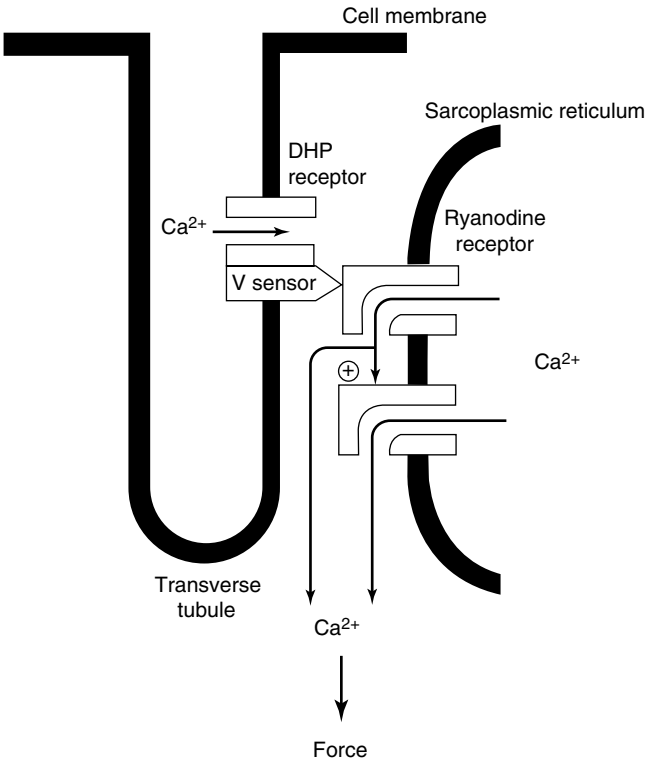

Fig. 54.1 The triadic junction between a transverse tubule and the sarcoplasmic reticulum: position of the two calcium (Ca^{2+}) channels of skeletal muscle, the dihydropyridine (DHP) receptor, and the ryanodine receptor (Reproduced from [19], p. 137, figure 6.1. With permission from Butterworth Heinemann)

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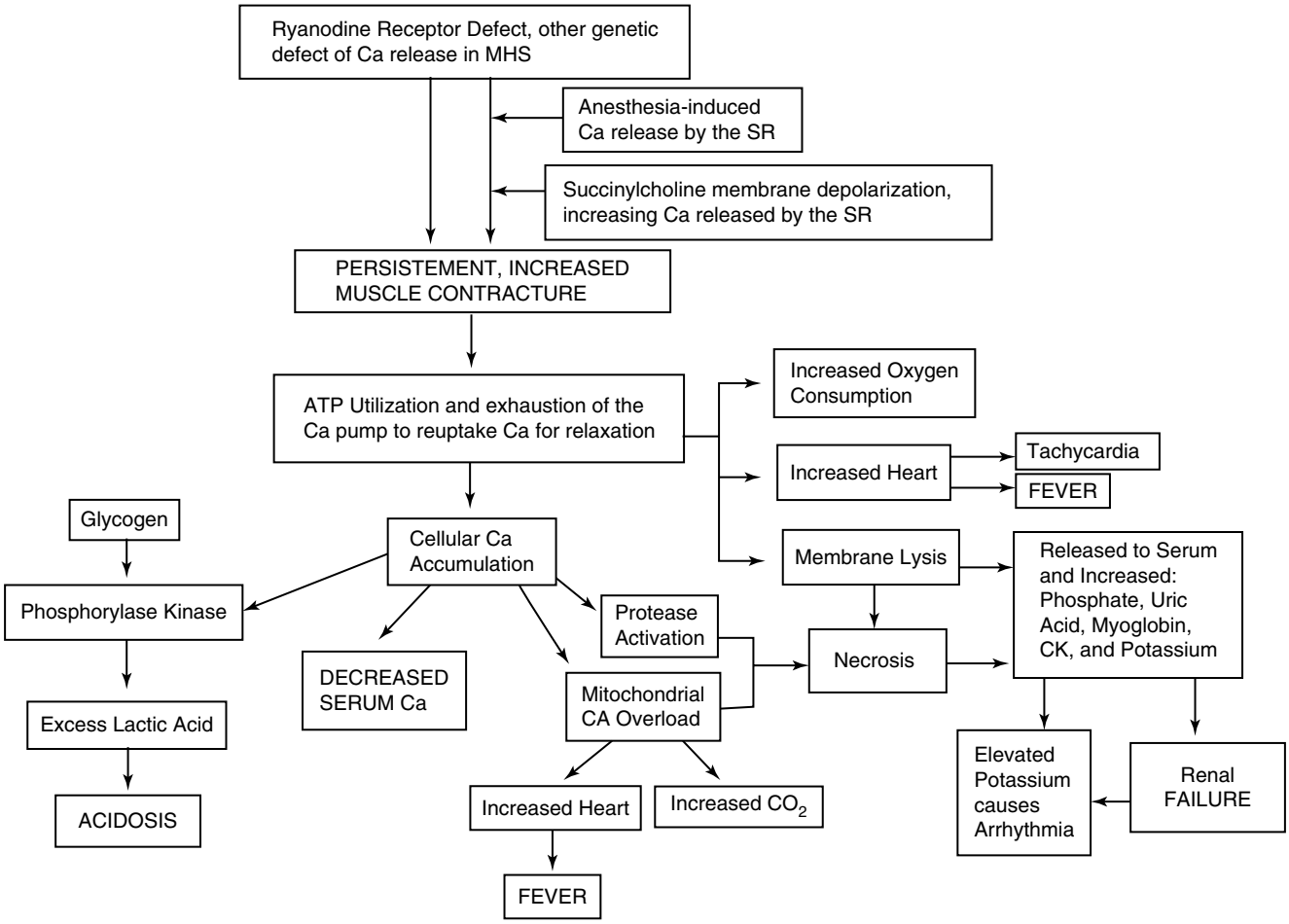

Fig. 54.2 Possible mechanisms of clinical and laboratory abnormalities in malignant hyperthermia syndrome (Data from [24], p. 658, figure 3. Modified with permission from W.B. Saunders)

these receptors are closely coupled by mechanisms that are not fully understood, but it is believed that the opening of the DHP channel stimulates the RYR1 channel to release calcium. This channel is regulated by adenosine 5′-triphosphate and calmodulin and is activated by caffeine and ryanodine [17, 18].

In MH-susceptible individuals, the RYR1 receptor is activated by lower than the typical calcium concentrations, and higher than normal calcium levels are required to inhibit the channel opening during special circumstances that cause excessive calcium release [19]. The exact mechanism by which some anesthetics trigger excessive calcium release and the association of MH with the RYR1 and DHP receptors mutations have not been seen completely elucidated [14, 18, 20], but it appears that the effects of anesthetics is dose related. The additional use of succinylcholine increases the risk of MH, likely because this drug increases membrane depolarization [21, 22], but the causative effect of the drug when used alone is not clear [21]. The role of other drugs in the development of the syndrome is controversial and based only on individual reports [21, 23]. An excessive muscle calcium release also causes increased contractures during the muscle in vitro muscle contracture test, which is used to identify individuals predisposed to MH attacks in susceptible muscle.

During MH attacks, the excessive muscle contractions [14, 20] lead to elevated oxygen consumption, glycogenolysis with depletion of high-energy phosphates in muscle, and elevation of body temperature (Fig. 54.2). The energy exhaustion limits reuptake of calcium into the SR impairing muscle relaxation and resulting in a further increase of intracellular calcium causing necrosis [24]. The necrosis leads to a leak of phosphates, potassium, and uric and lactic acids into the blood stream, and severe systemic acidosis develops. Creatine kinase (CK) and other muscle constituents, including myoglobin, are also released, and myoglobinuria ensues.

In genetically predisposed pigs, stress (e.g., when they are confined to small pens before slaughter) also causes spontaneous muscle contractions leading to the devastating metabolic cascade of events as is seen in humans [25, 26]. MH also may occur in humans during extreme stress or excessive exercise [27–31]. The similarity of the swine and the human

Table 54.1 Individuals at risk of malignant hyperthermia or malignant hyperthermia-like syndromes

Family history of malignant hyperthermia
King-Denborough syndrome
Evans myopathy
Central core disease
Multicore disease
Muscular dystrophy (dystrophinopathy, myotonic dystrophy)
Periodic paralysis
Myotonia congenita
Carnitine palmitoyl transferase deficiency
Phosphorylase deficiency, possible other glycogen storage myopathies
Brody's disease
Idiopathic hyperCKemia
Exercise-induced myoglobinuria
Statin myopathy

diseases allows the pig to be an excellent animal model for the study of the human condition [25, 26].

Variations of the syndrome, manifesting by muscle rigidity during anesthesia, occur in some hereditary myopathies (Table 54.1), and it also has been suggested that some patients with neuroleptic malignant syndrome, heat stroke, sudden infant death syndrome, or frequent muscle cramps may have genetic defects that predispose them to MH [30, 32]. There is, however, no evidence of MH-associated mutations in patients with malignant neuroleptic syndrome, which is caused by dopamine deficiency or blockade myoglobinuria could also occur in MH-susceptible individuals during stress and exercise.

Genetics

Most patients with MH have mutations of the RYR1 gene located on chromosome 19q13.1 [4, 19], and this has been classified as *malignant hyperthermia syndrome 1* or *MHS1* [4, 32–36]. False exclusion of linkage to the RYR1 locus in some families, however, cannot be excluded [16]. The gene expands 158 kb and contains 106 exons and transcribes an RNA molecule of 15 kb length [37]. Another locus is located at chromosome 17q11-224 on the gene of the sodium channel a-subunit or *MHS2* [38]. A third locus maps to chromosome 7q21-q22, which encodes to the α2/d-subunit of the L-type DHP voltage-gated calcium channel receptor (CACNL2A); this is considered *MHS3* [12, 13]. Mutations of a gene in chromosome 3q13.1 also have been reported in some families [39], and these are classified as *MHS4*. A mutation of the α1-subunit of the calcium channel receptor (CACNL1A3) in chromosome 1q31-q32, found in about 1 % of patients [13, 40], is designated *MHS5*. *A* mutation in chromosome 5p also has been identified, and this has been called *MHS6* [41] (Table 54.2). Patients with King-Denborough syndrome can manifest MH, and some but not all might also have a mutation in the RYR gene [42]. Finally, the calsequestrin gene in chromosome 1q21 has been suggested as a candidate gene [43]. Calsequestrin is a calcium-binding protein of the terminal cysterna of muscle that also regulates calcium release [44]. This group could be considered *MHS7*.

Table 54.2 Genetic classification of malignant hyperthermia susceptibility syndrome (MHS)

Classification	Gene location	Gene product
MHS1[a]	19q13.1	Ryanodine receptor
MHS2	17q11.2-q24	Close to α subunit of the sodium channel
MHS3	7q21-q22	Unknown but close to α2/δ subunit of the L-type dihydropyridine calcium channel
MHS4	3q13.1	Unknown
MHS5	1q31-q32	α1 subunit of the dihydropyridine calcium channel
MHS6	5p	Unknown

[a] 70–80 % of all MHS cases

Attacks of MH occur in multicore disease and central core disease [45, 46], and most patients with this disorder have mutations of the RYR 1 gene [47–49].

It has been suggested that some patients with idiopathic hyperCKemia might also have MH and mutations of the RYR1 gene [50]. Furthermore, important research also has been done on patients with statin myopathies who appear to be at risk of MH [51], and some of these have a positive caffeine-halothane contracture test [52], suggesting that statins might have an effect on the regulation of calcium function. These drugs have been suggested to upregulate genes connected with muscle calcium regulation homeostasis and membrane repair [53, 54]. A similar effect has been detected with the use of fluoroquinolones, which increase susceptibility to myotoxicity and cause alteration of calcium metabolism associated with abnormal contraction tests [55]. Patients with exercise-induced myoglobinuria might be suspected to be at risk to develop MH and should be tested for this disorder [28].

The MH-like attacks that occur in various myopathies without RYR1 gene mutations are atypical in most. These may be associated with muscle rigidity, usually without fever, during anesthesia caused by excessive muscle depolarization or elevations of baseline cytosolic calcium levels from different mechanisms. Those disorders include myotonia congenita, myotonic dystrophy, dystrophinopathies, phosphorylase deficiency, Brody's disease, periodic paralysis, and carnitine palmitoyl transferase deficiency [56–61].

Clinical Characteristics

MH attacks are characterized by muscle spasms and contractures, a rapid rise in temperature, tachycardia, hypoxemia, cyanosis, hypermetabolism, acidosis, and sometimes cardiac

Table 54.3 Criteria used in the clinical grading scale for malignant hyperthermia

Clinical finding	Manifestation
Respiratory acidosis	End-tidal CO_2 > 55 mmHg: $PaCO_2$>60 mmHg.
Cardiac involvement	Unexplained sinus tachycardia, ventricular tachycardia, or ventricular fibrillation
Metabolic acidosis	Base deficit >8 m/Eql, pH <7.25
Muscle rigidity	Generalized rigidity: severe masseters muscle rigidity
Muscle breakdown	Serum creatine kinase concentration >20,000/L units: cola-colored urine, excess myoglobin in urine or serum, plasma [K+] >6 mEq/L
Temperature increase	Rapidly increasing temperature: T >38.8°C
Other	Rapid reversal of MH signs with dantrolene. Elevated resting serum creatine kinase concentration
Family history	Consistent with autosomal-dominant inheritance

Source: Reproduced from [71]. With permission

Table 54.4 Testing protocols for malignant hyperthermia

Designation[a]	North American protocol	European protocol
MHS	Contracture of >0.7 g to 3 % halothane	Contracture of ≥0.2 g to ≤2 % halothane
	OR	AND
	Contracture of >0.3 g to 2.0 mmol/L caffeine	Contracture of ≥2 g to ≤2.0 mmol/L caffeine
MHE[b]	Contracture of 0.5–0.7 g to 3 % halothane	Contracture of halothane only or caffeine only
	No contracture	
	OR	
MHN	Contracture of <0.5 g to halothane	No significant contractures with either agent
	OR	
	Contracture of <0.3 g to 2.0 mmol/L caffeine	

Note: (1) Studies to determine the sensitivity and specificity of the contracture test show that both protocols have a sensitivity of about 100 %. Specificity is generally between 80 % and 97 %, according to several studies with these protocols malignant hyperthermia susceptibility [85]. (2) Some laboratories employ 1.0 or 1.0 micromolar ryanodine or 4-chloro-m-chlorocresol in addition to halothane and caffeine to clarify equivocal results; however, these agents have not been incorporated into the standardized test

[a]MHS, malignant hyperthermia susceptible; MHE, malignant hyperthermia equivocal; MHN, malignant hyperthermia negative

[b]In the North American protocol, the MHE designation is "optional," and most centers report results as either MHN or MHS using a threshold of 0.5 g

arrhythmia [3, 24]. Muscle necrosis causes a markedly elevated serum CK, potassium, lactic acid, and myoglobinuria, which may result in renal failure [3, 7, 24, 62, 63] (Table 54.3).

Anesthesiologists usually are suspicious of an attack early when patients develop excessive masseter muscle contractures or elevation of end-tidal carbon dioxide (CO_2) during induction of anesthesia. Masseter contractures are not always present and may occur in patients who never develop MH [64]; therefore, their presence is not a reliable indicator of MH [65].

Because MH occasionally occur during the postoperative period, patients at risk should be monitored for at least 24 h in the intensive care unit, even after minor surgery or minimally invasive procedures such as muscle biopsy [66].

The muscle histology in classic MH patients includes variation in muscle fiber size, "moth-eaten" and opaque fibers, and an increased number of internal nuclei. These are nonspecific findings that are not diagnostic [67]. The histologic features on muscle biopsy of patients with central core disease show central areas devoided of oxidative enzyme activity in type I fibers. These areas have a decreased number or an absence of mitochondria on electron microscopy. In minicore disease, these are small and multiple in individual muscle fibers.

Other than those patients with classical central core or minicore disease, the phenotype or histology in most MH patients has no distinct features. Those with the King-Denborough syndrome, however, are identified by short stature, undescended testes, high-arched palate, small chin, low-set ears, ptosis, dislocated shoulders, lordosis, scoliosis, kyphosis, and pectus carinatum [68, 69]. Another group of patients have Evans myopathy, with nonspecific features of proximal muscle wasting; hypertrophy of some muscles, such as the sternocleidomastoid; partial ptosis; elevated CK; and nonspecific muscle biopsy findings [30].

Diagnosis

The diagnosis of MH is suggested by a rise in end-tidal CO_2, an elevated temperature, tachycardia, or acidosis and prominent contractures [2, 20, 30, 62]. Any of these events should alert the anesthesiologist to suspect the condition and treat it properly before the development of the complete syndrome.

Recognition of susceptible patients before surgery is most important in order to take preventive measures. A family history of an abnormal reaction to anesthesia or death associated with anesthesia should raise concern for MH.

The muscle contracture test is based on the increased susceptibility of an MH patient's muscle to electrical stimuli that cause calcium release and contractions [70]. To perform the test, which is done at only a few medical centers, a fresh muscle biopsy is required. A strip of muscle is stimulated, and contractures are produced with varying concentrations of halothane or caffeine [70–73] (Table 54.4). Other compounds, such as ryanodine and 4-chloro-m-cresol, also appear promising substances to be used in the test [7, 16, 73, 74]. Muscle tension is measured with a strain gauge, and an

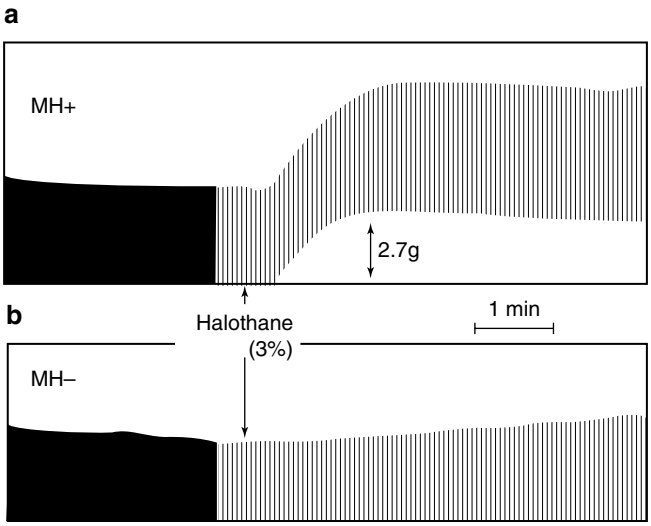

Fig. 54.3 Muscle contracture test after halothane (**a**) in a patient at risk of malignant hyperthermia; normal test (**b**) (Reproduced from [85], p. 13. With permission)

abnormal response is detected – for example, when tension exceeds 0.2–0.7 g during 3 % halothane administration (Fig. 54.3). These excessive contractions occur in those predisposed to MH, and the same test detects swine at risk for the porcine stress syndrome [75].

Standardization of the technique allows for a more accurate diagnosis and eliminates the occurrence of false-positives [76, 77]. The standardized American and European protocols differ somewhat, but both produce adequate recognition of at-risk individuals [77, 78]. The test should be performed on patients with a family history of MH or those with a previous abnormal reaction to anesthesia. A novel, promising screening test is the use of in vivo magnetic resonance spectroscopy [74], although its value in a large population of patients has not been proven.

Individuals at risk may have a baseline elevation of serum CK, which is useful in recognizing an increased risk for surgery in individuals with an affected family member. However, this is not a sensitive indicator because baseline CK values may be normal in MH patients. Genetic testing is available, but the identified genetic abnormalities do not occur in all families. An increasing number of mutations are now recognized using modern techniques that increase the yield of detection [79].

Differential Diagnosis

The differential diagnosis of an attack of MH is limited. Attacks of myoglobinuria during anesthesia are considered to be caused by MH, but some individuals may develop rigidity without all the features of the typical syndrome, while others might not have the characteristically abnormal increased release of calcium by the SR, or a positive contracture test. As discussed previously, patients with myopathies, particularly those with muscular dystrophy, might become rigid during anesthesia and even develop myoglobinuria, but the pathogenesis appears to be different from the classic syndrome. This is called *hyperkalemic cardiac arrest* [2] and usually occurs during exposure to succinylcholine and is associated with severe hyperkalemia [2]. Some of these patients also might develop fever, although they do not have the mutations associated with MH, but some have a positive muscle contracture test. Despite the similar clinical presentation in these patients, there could also be muscle necrosis with excessive calcium accumulation. In the channelopathies, such as myotonias, rigidity during anesthesia is believed to be caused by increased myotonia from depolarizing drugs or low temperature.

Other acute changes observed in patients receiving anesthesia also should be considered, including arrhythmias from other causes, such as electrolyte imbalance, seizures, allergy to drugs, and shock [80]. These conditions should be easily recognized and do not have all the findings of MH. Because myoglobinuria in patients at risk of MH also may be induced by stress and exercise, metabolic myopathies that manifest with myoglobinuria during exercise should be considered in the differential diagnosis, including glycogen storage disorders, such as McArdle's disease, and other metabolic myopathies, such as carnitine palmitoyl transferase deficiency [24, 56, 81].

The differential diagnosis of an unexplained increase in end-tidal CO_2 during surgery includes hyperthermia secondary to sepsis, drug overdose, introgenic warming, and anesthesia machine malfunction [2]. Other differential diagnoses includes hyperthyroidism and pheochromocytoma.

The use of high ionic, water-soluble radiologic contrast agents intrathecally might result in fever and seizures as the contrast material enters the ventricles; these patients also might have acidosis and respond to dantrolene, but there does not seem to be a close correlation with MH, and those patients do not have the genetic mutations associated with MH.

Treatment

The most important treatment for MH is the discontinuation of anesthesia and the use of dantrolene, a muscle relaxant that decreases the release of calcium from the SR and therefore inhibits the contractures induced by halothane, reducing the cascade of metabolic events on muscle during attacks [20, 82]. Treatment of acute attacks also consist in hydration and cooling with correction of electrolyte imbalance and reversal of cardiac arrhythmia. The preoperative use of dantrolene and the early identification of at-risk individuals and prompt therapy have reduced mortality from 80 % in the past to the current 10 % [81, 83].

Table 54.5 Agents and their relationship to malignant hyperthermia

Triggering agents
Inhalational anesthetic
Halothane
Enflurane
Isoflurane
Desflurane
Sevoflurane
Depolarizing blockers
Succinylcholine
Decamethonium
Suxamethonium
Controversial agents
Calcium, potassium salts
Ketamine
Catecholamines
Phenothiazines, MAO inhibitors
Statins (?)
Safe agents
Nitrous oxide
Barbiturates
Local anesthetics
Narcotics
Nondepolarizing relaxants
Anitbiotics
Propranolol
Benzodiazepines
Thiopental

Source: Modified from [63], p. 233. With permission
MAO, monoamine oxidase

Patients identified as being at risk for MH should never receive any of the precipitating agents listed in Table 54.5 [24]. In addition, all equipment used in administering anesthesia must be appropriately cleaned and maintained to remove any traces of offensive agents that might trigger an attack. In at-risk patients, dantrolene can be administered orally for several days before surgery.

A list of recommended steps in the management of an acute attack of MH was developed by the Malignant Hyperthermia Association of the United States. [84] These steps are summarized as follows:

1. Discontinue the anesthetic and deliver 100 % O_2.
2. Use dantrolene intravenously in doses of 2–3 mg/kg every 5 min for a total of 10 mg/kg.
3. Administer sodium bicarbonate and iced intravenous saline infusions, avoiding Ringer's lactate.
4. Lavage the stomach, bladder, and rectum with iced saline and use cooling blankets, while closely monitoring body temperature.
5. Treat arrhythmias by reducing hyperkalemia and with antiarrhythmic drugs, but do not use calcium blockers.
6. Monitor end-tidal CO_2 and blood gases.
7. Treat hyperkalemia with hyperventilation, bicarbonate, glucose, and insulin, and when life threatening, use calcium chloride.
8. Assure urinary output of greater than 2 mL/kg per hour by hydration or mannitol and furosemide, or both.
9. Treat unexpected cardiac arrest in children by treating hyperkalemia first.
10. Continue monitoring in the recovery room and intensive care unit for a minimum of 24 h; monitor blood gases, potassium, and calcium; determine myoglobin in urine; and administer dantrolene 1 mg/kg intravenously every 6 h for 24–48 h, followed by oral dantrolene for another day.
11. Contact the MH Association hotline (800 – MH-Hyper) (8006449737).
12. Refer individual and family to a MH Diagnostic Center, for further diagnostic testing and counseling.

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Part VIII

Neuromuscular Disorders: Myopathies

Approach to Myopathies

55

Björn Oskarsson

Introduction

Muscle is the largest organ system in the human body. Severe disturbances of muscle function are life threatening, and more minor problems may cause marked disability.

This chapter will describe how to approach a myopathy for which the cause is not already established. A structured approach is the best for reaching a specific diagnosis in the majority of cases. Although a comprehensive knowledge of muscle diseases and other diseases that may cause weakness can be most helpful, eventually allowing for the recognition of the specific pattern of a myopathy in an increasing number of cases, a structured guide to the evaluation of weakness which does not demand such expert knowledge is provided here. As the clinician accumulates more knowledge, he/she will increasingly be able to rely on recognizing patterns specific to each myopathy; without such understanding, this approach is less often fruitful. However, even a novice may be able to recognize a pattern when a patient has a clear family history of a specific disease or an archetypical presentation of a common disease, and therefore, in these cases a more targeted approach will serve best. The pattern recognition strategy uses the specific if not pathognomonic aspects of myopathies such as in the rash in dermatomyositis, severe contractures in Emery-Dreifuss, or the pattern of extraocular and pharyngeal muscle involvement in oculopharyngeal muscular dystrophy.

A structured guide to evaluating myopathies is presented in this chapter combined with tables of common disease patterns are discussed, but more extensive text on this approach exists. Some 20 of the most useful patterns will be covered, but any pattern recognition system requires a certain amount of expertise. Otherwise the three basic steps in a myopathy workup are (1) a neurologic evaluation composed of history and examination, (2) electromyography (EMG) and creatine kinase (CK) testing, and (3) muscle histology (Fig. 55.1). After these have been performed, either a specific diagnosis will have been reached or a limited number of disease-specific tests will be indicated in the vast majority of cases.

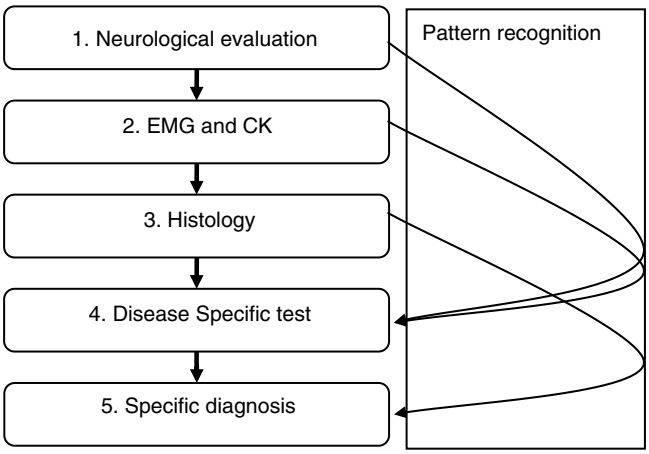

Fig. 55.1 Basic steps in myopathy evaluation

The pattern recognition approach will circumvent the need for EMG and histology in many patients. This book contains detailed chapters on the myopathies that can be discovered using this approach. Clinically, muscle problems most often present as weakness, but sometimes muscle pain, fatigue, or myotonia are the initial complaints. An ever increasing number of referrals are also seen in response to diagnostic abnormalities such as elevated creatine kinase values (CK), abnormal MRI imaging, or other tests.

History

When approaching a patient presenting for a myopathy evaluation, the first question to answer is whether or not a myopathy is present or not, and the starting point is to capture the history of the complaint. There are few absolute truths about

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Table 55.1 Weakness: Disease entities to consider in the differential

Systemic disorders (*many of these diseases may, in their extreme forms, cause muscle damage*)
Joint disease (causing pain and weakness)
Metabolic disturbances (hypo/hyperkalemia, hypernatremia, hypoglycemia)
Endocrinopathy (thyroid disease, adrenal insufficiency)
Anemia
Neurological disorders
Central nervous system disorders (parkinsonism, central pontine myelinolysis, myelopathy)
Motor neuron disease
Polyradiculopathy
Plexopathy
Neuropathy
Neuromuscular junction disorders

Table 55.2 Common acute myopathies

Toxic (statins, alcohol, and others)
Electrolyte disturbance (hypokalemia, other)
Inflammatory myopathies
Metabolic myopathies (McArdle's disease, carnitine palmitoyltransferase II deficiency)
Infectious (influenza, mycoplasma, other)
Rhabdomyolysis secondary to central nervous system activation (exercise, status epilepticus, neuroleptic malignant syndrome)

symptoms as they by definition are subjective events experienced by a person and then described to the physician. Some patients can describe symptoms in an accurate and concise manner that is easy to follow, but many have difficulty with articulating unfamiliar and disturbing experiences. The clinician's task is to discern whether a patient presenting with complaints of weakness is suffering from actual muscle weakness, because many other diseases can result in a feeling of weakness in a broad sense (Table 55.1).

Patients experiencing *muscle weakness* often will mention difficulties in performing specific tasks that are dependent on the strength of the affected muscle groups. If no task-specific problems are divulged spontaneously, then the patient should be prompted with a question such as "Give me an example of something that is hard to do due to the weakness." The by far most common myopathic pattern of weakness is the one involving proximal limb muscles, leading to complaints of standing out of chairs, walking up stairs, washing ones hair, or performing other tasks with the arms above the head. More distal weakness may be experienced as problems opening jars, turning keys when affecting the hands or stumbling, and tripping when affecting the legs. Quadriceps muscle weakness tends to lead to leg buckling. Leg buckling is also often reported in psychogenic weakness and presyncopal weakness.

On the list of diseases to consider that also cause more focal task-specific weakness, *joint diseases* are relatively common. Particularly hip weakness is not infrequently caused by hip arthropathy and history, and in rare cases clinical exam is not always conclusive in separating muscle weakness from joint pain, as they can cause similar functional limitations. The most distinguishing feature is pain which is normally present in joint problems, but rarely prominent in myopathies. Examination can normally identify a joint problem, and if not, then imaging, laboratory studies, and EMG should be able to distinguish joint from muscle disease. The conditions can coexist and the presence of one does not prove the absence of the other.

Fatigue is often described by patients as weakness, but fatigue is rarely due to muscle problem. Other words used to describe fatigue is tiredness and decreased stamina. Fatigue does not normally produce difficulties with specific tasks. Fatigue results in inability to engage in more general tasks such as shopping or cleaning or tasks that take longer periods of time compared to the specific tasks limited by muscle weakness. Fatigue is more commonly a symptom of systemic medical problems. However, fatigue can also be caused by myopathies. In particular, exercise-induced fatigue is commonly seen in the metabolic myopathies. Fatigue and weakness can also occur together from myopathies. This combination of symptoms can occur when a myopathy causes systemic symptoms due to inflammation. The myopathies that results in concomitant cardiomyopathy or respiratory muscle weakness will also frequently result in both fatigue and weakness. Fatiguing weakness is typical of neuromuscular junction disorders, and they need to be seriously considered in the differential when both appear to be present. Myasthenia gravis and several other less common neuromuscular junction disorders tend to markedly involve the bulbar region, which is unusual in myopathies. Others, such as the Lambert-Eaton myasthenic syndrome, may have a proximal leg distribution that is similar to most myopathies.

The temporal course of weakness can also provide clues as to the nature of the underlying myopathy. The periodic severe weakness often seen in the periodic paralyses is very specific, and no other myopathic conditions cause quite this pattern. There are relatively few myopathies that have an acute presentation with any frequency (Table 55.2).

Numbness is sometimes used by patients as a word to describe weakness, and clarification of what a person using the term is referring to is necessary. According to Collins English dictionary, numb can mean "unable to move; paralyzed," while in medicine the term tends to be used to relate to only a loss of sensation [1]. Using this correct definition, numbness can be a symptom of myopathy. Sensory loss and paresthesias should be queried in detail since they can suggest a peripheral or central nerve problem.

Table 55.3 Common conditions where myalgia commonly exceeds weakness

Fibromyalgia
Polymyalgia rheumatica
Toxic myopathy (statin, alcohol)
Hypothyroid myopathy
Infectious myopathy (influenza)
Metabolic myopathies (McArdle's disease, mitochondrial, myoadenylate deficiency, others)
Inflammatory myopathies (rarely polymyositis or dermatomyositis)

Pain can limit functional strength. If severe muscle pain i.e. myalgia exist, it may not be possible to discern whether there is any weakness by history alone. Most myopathies are painless, but some can be quite painful. When pain clearly exceeds weakness, then fibromyalgia and polymyalgia rheumatica might be considered. While these disorders are not considered to be myopathies in a strict sense, persons practicing myology need to have some familiarity with them, and they are covered in this book. Myalgia is one of the diagnostic features of influenza infection and is common in mycoplasma and several other systemic infectious diseases. In the vast majority of such infectious cases, symptoms are brief and the association with an obvious systemic infection precludes a referral to a myologist. Occasionally, patients for which the myalgia or weakness were dominating (or an underlying myopathy was unmasked) will be referred for further evaluation. Exercise-induced myalgia is common with statin use and several of the metabolic myopathies. Mild myalgia as a symptom does not narrow the differential of possible myopathies in a meaningful way, but when it is severe or when it is the dominating complaint, then it can help direct the workup (Table 55.3).

Past events of rhabdomyolysis should also be explored, with more fulminant events being easy to remember and of clear diagnostic value. A nonspecific milder episode of muscle pain and tenderness requires more careful consideration. Myoglobinuria should be asked about, and if brown or dark-colored urine has been noted, then try to discern if there is a pattern to it (e.g., it occurs after exercise).

Pattern Recognition and Rarely Involved Muscles

The pattern recognition approach to myopathies is particularly powerful when applied to the clinical pattern of muscle involvement. The myopathies that deviate from the proximal and symmetric distribution patterns that are characteristic of the majority of myopathies can often be identified clinically. When the differential diagnoses are few, genetic or other specific testing can often be done without the need for electrodiagnostic and histological evaluations.

Table 55.4 Myopathies with involvement of extraocular muscles

Oculopharyngeal muscular dystrophy (OPMD)
Mitochondrial myopathy
Thyroid orbitopathy

Muscles of eye movement are the only involved muscles and, more rarely, the most affected muscles in a minority of myopathies. This is a situation when the pattern recognition approach with reasonable certainty limits the number of possible myopathies to oculopharyngeal myopathy, thyroid orbitopathy, and several of the mitochondrial myopathies (Table 55.4). To exemplify eye movement weakness and marked ptosis, a patient with a large mitochondrial deletion is depicted in Fig. 55.2 a and b.

Likewise when *facial muscles* weakness is prominently reported, this suggests a short list of common myopathies (Table 55.5).

Shortness of breath, a weak cough, and orthopnea are symptoms attributable to weakness of *respiratory muscles*. Again a relatively short list of diseases is likely when respiratory muscles are involved early (Table 55.6).

A *cardiomyopathy* can cause some of the same symptoms and does in turn suggest another set of myopathies (Table 55.7).

Other symptoms that can markedly reduce the differential include skin changes, muscle cramps, muscle hyper- or hypotrophy, joint stiffness, or laxity. The majority of myopathies are quite symmetric, and if there is a striking left versus right difference, then this suggests one of the few myopathies which often are asymmetric (Table 55.8).

Most myopathies tend to affect proximal muscles more than distal muscles. However, if the history suggests mostly distal weakness with complaints of hand and foot weakness, then a distal myopathy should be considered. Neuropathies are certainly more common with this pattern of involvement, and a relatively large portion of the distal myopathies are made up of diseases that are rare (Table 55.9).

Family History

The family history may guide a workup in the direction of a certain disease if a typical inheritance pattern is described or if a specific ethnic origin or known consanguinity is apparent (Table 55.10).

The number or family members affected and unaffected often help clarify an inheritance pattern. A single affected individual – a "simplex case" – in a small family does not have quite the same implications as one in a larger family. Not only should a family history cover muscle problems, but autoimmune and rheumatologic conditions as well as other neurological conditions are of particular importance. There

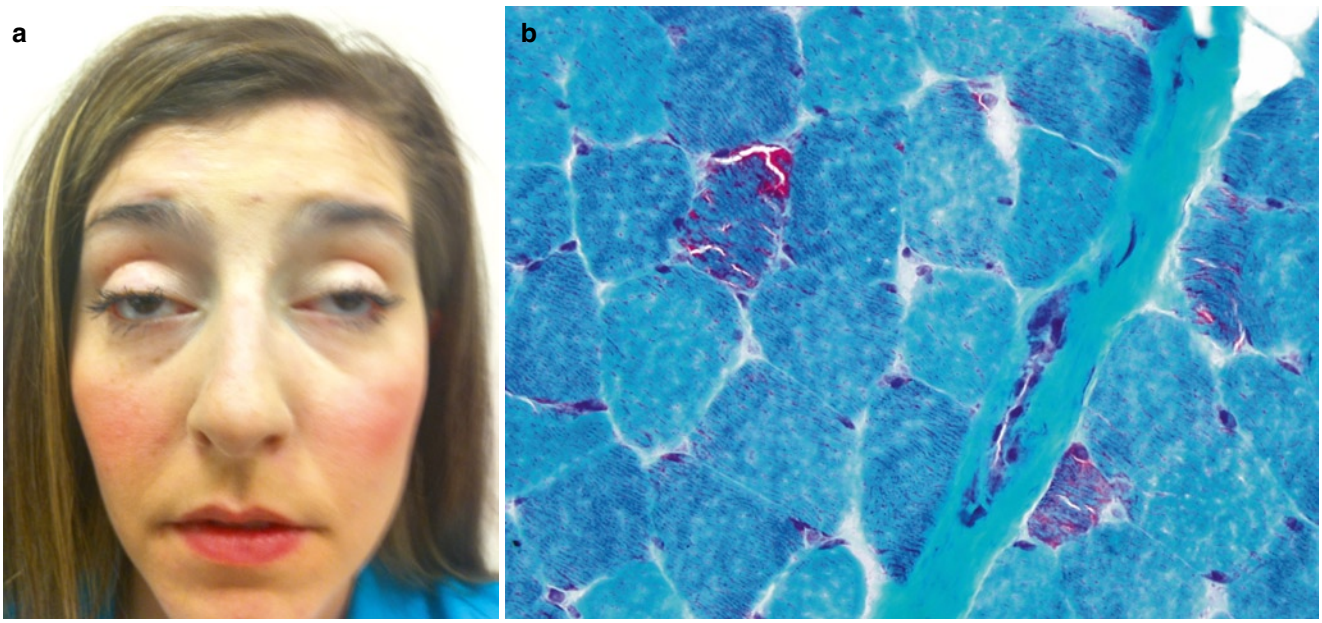

Fig. 55.2 (**a**) Patient whom is 60% heteroplasmic for a 2.4 Kb deletion within the major arc of mtDNA is pictured in primary gaze, with ptosis and subjective horizontal diplopia. (**b**) Modified trichrome ×200 magnification. Ragged red fibers due to increased mitochondrial content

Table 55.5 Myopathies affecting facial muscles

Facioscapulohumeral dystrophy (FSH)
Myotonic dystrophy I
Oculopharyngeal muscular dystrophy (OPMD)

Table 55.6 Myopathies with early respiratory muscle involvement

Pompe's disease
Myotonic dystrophy I

Table 55.7 Myopathies with cardiomyopathy

Dystrophinopathies (Duchenne, Becker, X-linked cardiomyopathy)
Emery-Dreifuss muscular dystrophy
Myotonic dystrophy I
Limb girdle muscular dystrophy (1B, 2 C-G)
Inflammatory myopathy (mild involvement uncommon and severe involvement rare)
Mitochondrial myopathy
Danon disease

are diseases such as mitochondrial problems where the symptoms of a common genetic defect may produce very different types of phenotypes including diabetes, deafness, and anemia. When different family members are affected in such disparate ways, a familial pattern is harder to perceive. There are also de novo mutations and cases of mistaken paternity that can confound a carefully crafted family tree.

Table 55.8 Asymmetric myopathies

Inclusion body myositis (IBM)
Facioscapulohumeral (FSH) dystrophy
Focal myositis

Table 55.9 Common distal myopathies

Myotonic dystrophy 1
Inclusion body myositis (IBM)
Dysferlinopathies (Miyoshi, limb girdle muscular dystrophy 2B)

Table 55.10 Family history in myopathies

Ethnic origin
OPMD in French Canadians or Hispanics from Southwestern United States [2]
Autosomal dominant
Limb girdle muscular dystrophy I
Myotonic dystrophy I and II
Oculopharyngeal muscular dystrophy
Facioscapulohumeral muscular dystrophy
Mitochondrial myopathies
Autosomal recessive
Limb girdle muscular dystrophy II
Metabolic myopathies (a majority of types)
Mitochondrial myopathies
Maternal transmission
Mitochondrial myopathies
X-linked
Duchenne and Becker muscular dystrophy
Emery-Dreifuss muscular dystrophy

Medical History

A detailed current and past medical history needs to be obtained. The purpose of the medical history is to allow the examiner to discern other diseases that associate with specific myopathies (Table 55.11).

Treatment History

Patients who have been treated with prednisone and other immunosuppressants before coming for evaluation and biopsy present special challenges. Corticosteroids appear to have an effect on creatine kinase (CK) that is independent of its effect on immune-mediated myotoxicity. CK can be lowered by corticosteroid administration in noninflammatory myopathies and in patients without a myopathy [3]. After corticosteroid treatment, an immune-mediated myositis may lose many of its histologically distinguishing features, and the clinical information may be more presentable. In dermatomyositis, a history of a rash normally is recalled, but sometimes skin changes such as mechanic's hands or an unrelated skin rash may not be remembered as a rash from dermatomyositis. Many patients with IBM will report some benefit from prednisone or other immunosuppressant medication treatment, but the positive effects are not generally apparent by examination, and the benefit does not last for any longer period [4].

Medications and toxins are relatively common causes of myopathy, and a detailed review of current and recent medications and exposures should be undertaken. Some toxic exposures can coast and continue to cause a myopathy for some time after the end of the exposure. A common example of this is the statin myopathies where symptoms often coast for a few months after discontinuation of the offending statin drug [5]. The emerging statin-induced myositis associated with antibodies to HMGCR does not only coast after the discontinuation of statin medication but may continue to worsen [6]. The use of some medications are not readily admitted such as ipecac use in an anorexic patient or illegal muscle building supplements and should be queried (Table 55.12).

Exacerbating factors are useful for understanding myopathies with impaired muscle relaxation (i.e., myotonia). Asking for situations in which an eye closed shut, or a hand grip or limb movement might have locked up, and any triggering events of the symptoms can help identify the illnesses (Table 55.13).

In conclusion, the history is a very important tool in discerning what type of muscle problem might be present or whether the problem experienced is due to another cause such as a systemic medical problem, central nervous system problem, neuromuscular junction issue, or a peripheral nerve problem (see Table 55.1).

Table 55.11 Common disease associations in myopathies

Violaceous rash → dermatomyositis
Interstitial lung disease → antisynthetase syndrome, other inflammatory myopathies
Cataracts → myotonic dystrophy
Mechanics hands → antisynthetase syndrome, other inflammatory myopathies
Malignancy → paraneoplastic inflammatory myopathy
Diabetes → mitochondrial myopathy
Cognitive impairment → congenital myopathy, muscular dystrophies (Duchenne, myotonic), mitochondrial disorders
Osteomalacia → vitamin D deficiency
Paget's disease → familial inclusion body myositis

Table 55.12 Common agents causing toxic myopathies

Statins
Corticosteroids
Alcohol
Colchicine
Ipecac
Amiodarone
Chloroquine
Hydroxychloroquine

Table 55.13 Common myotonic conditions and their exacerbating factors

Myotonia congenita, Thompsen type → none or mild effect of stress and cold
Myotonia congenita, Becker type → initial exercise
Myotonic dystrophy type I → cold, myotonia often mild
Myotonic dystrophy type II → warmth
Paramyotonia → increased by sustained exercise

General Physical Examination

The physical examination is the most important component of the diagnostic evaluation. It serves to confirm the diagnostic hypotheses that is suggested by the history and may raise new diagnostic possibilities. Furthermore, the examination is the most useful tool to use in order to follow the effect of a treatment on a myopathy. While surrogate biomarkers such as creatine kinase may be useful, strength as tested on bedside examination is normally more strongly associated with the functional limitations experienced by the affected individual. Bracing and therapy needs are also best judged by examination and history.

The physical examination may of a patient with a suspect muscle problem should include *vital signs* such as blood pressure, pulse, respiration, and temperature. In more acute disease processes, they may be useful to illustrate the severity

of the disease. Height and weight are also notable and can be of importance. The general exam should include an assessment of the body habitus. Short stature is associated with some mitochondrial myopathies and others myopathies such as Schwartz-Jampel syndrome.

Examination of the *eye, ear, nose*, *and throat* should include looking for dysmorphic features such as high arched palate. Dysmorphic features are often features of the congenital myopathies. Eye examination may reveal retinal abnormalities such as a cherry red spot in mitochondrial myopathies, cataracts in myotonic dystrophy type I, and Coats' disease in facioscapulohumeral muscular dystrophy.

Examination of the *skin* may be useful in both acquired and inborn muscle diseases. Dermatomyositis has a rash that often is pathognomonic for the condition. The rash is reddish-purplish in color and sometimes slightly raised; it has a preference for the hairline, eyelids, neck, and limb extensor surfaces. Not all patients have a striking rash, and with treatment the changes may be difficult to definitively identify. Calcification of the skin and underlying fascia can also occur and will normally linger. Gottron's papules are violaceous papules and plaques over the knees or extensor surfaces, the hands, and other joints. Inflammatory myopathies, particularly the antisynthetase syndromes, frequently also cause skin changes in the hands. This pattern of skin thickening and callusing with small cracks has been referred to as mechanics hands. Collagen VI disorders may show keloid formation and abnormal scars. Corticosteroid myopathy often exhibit striae and stretch marks.

Lungs should be auscultated with attention to crackles from interstitial lung disease and to how much air is moved to give a quick bedside impression of respiratory muscle strength. A weakened forced cough may suggest a thoracic muscle weakness. Pulmonary function testing (PFT) is relatively simple and many muscle clinics routinely perform basic spirometry on patients. If PFT is not available in clinic, a less accurate option is to have the patient take a deep breath and count out loud. A person who cannot count to more than 20 probably does have significantly impaired vital capacity.

Cardiac examination should be performed with attention to both arrhythmias and signs of a cardiomyopathy. The cardiac examination may suggest the need for further studies such as EKG and echocardiograms even in muscle diseases where cardiac involvement is rare. Detected abnormalities can increase the urgency which further studies are done in diseases where cardiac involvement is frequent.

Joints are important to consider as many myopathies can lead to different types of changes. Contractures may be seen in many myopathies, but they are often severe in Emery-Dreifuss dystrophy. The pattern of limited finger extension due to contractures is typical of the collagen VI disorders. Arthritis is seen in many rheumatologic conditions and the overlap syndromes where a myopathy occurs with one of the rheumatologic conditions. With arthritis there is typically pain on passive joint movement, which is rare in a pure myopathy.

Neurological Examination

The neurological examination should start with a cognitive evaluation, recognizing that cognitive impairment is a feature of many inborn myopathies. Cognitive impairments can be seen in the dystrophinopathies, myotonic dystrophy, several other dystrophies, and many congenital and mitochondrial myopathies (Table 55.14).

The *cranial nerve examination* can reveal extraocular muscle weakness which is a relatively rare feature in myopathies and therefore very helpful in narrowing the differential (see Table 55.4). The eye movements should be checked in the six cardinal directions and any ptosis should be noted. A fatiguing ptosis would be more typical of a neuromuscular junction disorder, whereas a fixed ptosis would be more likely in a myopathy. Similarly, facial muscle weakness may help reduce the number of possible myopathies (see Table 55.5). The muscles of mastication which are supplied from cranial nerve V should be included. Temporalis muscle atrophy is particularly striking in myotonic dystrophy type I. Facial-innervated muscles including the frontalis, orbicularis oculi, orbicularis oris, and the zygomatic and other muscles of smiling should be tested. A transverse smile is common in FSH. Normally forceful eye closure results in an upward and outward eye movement, but an absence of the phenomenon may be normal or caused by many types of neurological problems. Eyelid myotonia is observed by having the patient quickly open the eyes after a forceful contraction (see Table 55.13). Pharyngeal muscles should also be observed, and a gag reflex can be provoked to visualize pharyngeal muscle function. Accessory muscles should be observed and tested. Myotonic dystrophy I often causes striking atrophy of the sternocleidomastoid muscles. The size of the tongue should also be considered; amyloidosis

Table 55.14 Cognitive impairment and myopathy

Congenital myopathies
Mitochondrial myopathy
Duchenne dystrophy
Myotonic dystrophy (type I > type II)
Facioscapulohumeral muscular dystrophy (severe phenotype)
Inclusion body myositis-frontotemporal dementia

Table 55.15 Typical patterns of atrophy in myopathies

Inclusion body myopathy → forearm flexor muscles and quadriceps muscles
Facioscapulohumeral muscular dystrophy → facial, shoulder, and abdominal muscles
Myotonic dystrophy I → temporalis, sternocleidomastoid, distal muscle

Table 55.16 Modified MRC grade

5	Normal power
5–	Possible weakness
4+	Slight weakness
4	Moderate weakness
4–	Severe weakness
3+	Active movement through full range against gravity with transient resistance and collapse
3–	Active movement through full range against gravity with no resistance
2	Active movement when gravity eliminated
1	Flicker or trace of contraction
0	No contraction or movement

and Duchenne dystrophy are among the diseases causing tongue enlargement.

Motor examination is certainly the most telling part of the examination, and the patient should undress appropriately to allow inspection of the muscle bulk.

In order to complete an accurate neuromuscular examination, the patient should expose their limbs and trunk muscles; this can be done sequentially with respect to the patient's modesty. Relative muscle group involvement is easier to appreciate on a completely undressed individual. The use of examination shorts and other ways to keep the patient comfortable while allowing for a thorough inspection is useful.

Physical exam can be painful for patients with tender muscles. Explaining the importance of the physical examination as the single most important test in establishing the diagnosis of myopathy helps many patients comply with the examination and gives good effort. If the patient is encouraged to provide good effort, the examination is thereby more rapid and results in less discomfort for the patient. The physical examination also establishes physical contact between the examiner and the patient, and this helps in building the therapeutic relationship.

Any pattern of atrophy or hypertrophy should be carefully documented to enable the recognition of a pattern of involvement. Palpation of the muscle for size, consistency, and tenderness can be useful particularly when there is fat overlying the muscle. Large muscles are often seen in myotonia congenita, myotonic dystrophy type II, and rippling muscle disease (LGMD 1c). Enlargement of calf muscles is common in the dystrophinopathies and a few other limb girdle dystrophies. Generally, small muscles are seen throughout the body in patients with congenital myopathies or some mitochondrial myopathies. Some degree of muscle atrophy is common in most myopathies, and the pattern of atrophy can help distinguish which myopathy is present. The phenotypic expression from a genotype may vary significantly, and there is also significant overlap between different conditions (Table 55.15).

Increased firmness of muscles may be due to fibrosis in chronic myopathies and amyloid deposits. Tenderness is most often seen in the inflammatory myopathies but also in some metabolic myopathies and any condition where rhabdomyolysis has recently occurred. Adventitious muscle activity such as myotonia (see Table 55.13), rippling, or cramps should be noted. To provoke myotonia the patient should be instructed to squeeze two fingers with maximal force for 15 s and then quickly release the grip. In myotonia the relaxation will be slowed and a characteristic writhing movement is often employed by the patient when disengaging the hand.

Muscles should be percussed with a reflex hammer to view if this causes a persistent muscle contraction. The thenar muscles are good targets for percussion. Percussion should normally result in thumb abduction/opposition as the muscles contract, and the contraction due to direct percussion should be immediate, but then quickly relax. The quadriceps and deltoid muscles are other good targets where a clear dimpling of the muscle can often be observed after percussion. Percussing the muscles where the patient notes symptoms increases the chance of finding an abnormality. Another abnormality that can be observed after muscle percussion is myoedema which is a swelling lasting a few seconds that can be seen with hypothyroidism and cachexia. Muscle tone should also be examined but, outside of contractures, it is generally not affected by muscle disease. The muscle strength should be rated and the modified Medical Research Council (MRC) rating which grades muscles on a scale of 0 to 5 is the almost universally used scale [7] (Table 55.16).

Muscle groups to examine include the neck extensors and flexors, shoulder abduction, internal and external rotation, elbow flexion and extension, wrist flexion and extension, finger extensors and flexors. Often additional muscle groups such as forearm pronators and specific hand muscles can be useful to assess if there is any weakness in those regions. The hip extensors should be examined as well as the flexors. The hip adductors and abductors should be included as well as the knee flexors and extensors, and the foot plantar and

dorsiflexors. Other distal foot muscles can sometimes provide additional information.

Muscle stretch reflexes are often mildly reduced in amplitude due to muscle weakness, but even though the amplitude of muscle contraction may be diminished, the force of the reflex hammer needed to exert the response will still be normal. The sensory exam is normal in the majority of myopathic conditions were no concomitant neuropathy exists.

Coordination is not normally affected by muscle disease, and thus, it is a less important aspect of the motor examination when evaluating myopathies. A patient's stance can reveal hyperlordosis in the limb girdle dystrophies, and toe standing is particularly common in the dystrophinopathies.

Gait and station examination demonstrates leg weakness and both distal and proximal patterns can be discerned. Other functional tests to perform include standing from a seated position with and without the use of arms. If standing out of a chair presents little or no difficulty, then rising out of a squatting position should be attempted. Standing on heels and toes can reveal more distal weakness. A patient's stance can reveal hyperlordosis in the limb girdle dystrophies, and toe walking is particularly common in the dystrophinopathies.

Laboratory Testing

Electromyography

After the history and physical examination have been completed, a differential diagnosis should be constructed. This is discussed in detail in Chap. 7. When a myopathy is considered in the differential, this normally should be confirmed by an electromyogram (EMG). Occasionally, the differential diagnosis includes only one or two myopathies; then, confirmatory laboratory testing may be more appropriate. However, in the majority of cases, further differentiating or supporting information should be sought starting with an EMG. Most importantly, the EMG serves to confirm the presence of a myopathy and exclude mimicking conditions such as motor neuron disease. The nerve conduction studies also provide information regarding polyneuropathies and repetitive nerve stimulations regarding neuromuscular junction disorders. The sensitivity of needle EMG varies depending on the myopathic process. For example, hypokalemic periodic paralysis is not normally apparent on routine EMG and corticosteroid myopathy has to be severe before it is apparent on needle EMG. The early recruitment of brief, small amplitude, and polyphasic motor unit action potentials is the most typical appearance of a myopathy. In chronic myopathies, particularly inclusion body myositis, there are additional large, long, and polyphasic motor unit action potentials, which can be recruiting in a reduced pattern. This EMG pattern can be misinterpreted as representing a pure neurogenic condition. Additional information regarding the myopathy such as the presence of myotonia can be revealed by EMG. Electrical myotonia is not always associated with clinical myotonia, and disorders associated with electrical myotonia only by EMG are listed (Table 55.17).

Table 55.17 Myopathies with Myotonia by needle EMG only

Pompe's disease
Toxic myopathies (statin and others)
Hyperkalemic periodic paralysis

Table 55.18 Persistently elevated CK over 5,000 IU/L

Dystrophinopathies
LGMD II (most types)
Necrotizing myopathies (paraneoplastic, antisynthetase syndrome, HMG-Co R)
Pompe's disease

Many myopathies also exhibit fibrillations and positive sharp waves by EMG. The origin of these discharges may be from myocytes or parts of myocytes that are no longer functionally connected to a neuromuscular junction due to injury [8]. Fibrillations and positive sharp waves can occur in most myopathies, and their discriminatory value is limited, except that it reduces the likelihood of a pure corticosteroid myopathy. The EMG should also be used to guide a subsequent muscle biopsy because it can confirm active myopathic involvement of a specific muscle.

Creatine Kinase

Another basic laboratory test that often is indicated in myopathies is creatine kinase (CK). This is discussed in detail in Chap. 3. Creatine kinase is increased in many myopathic conditions, but persistently very high values do suggest a narrower list of diseases (Table 55.18).

Muscle Histology

In most myopathies, muscle histology provides important diagnostic information. In cases in which the histology

Table 55.19 Myopathies with inflammation on biopsy

Polymyositis
Dermatomyositis
Inclusion body myositis
Granulomatous myositis
Dystrophinopathies
Calpainopathies (limb girdle muscular dystrophy 2A)[a]
Dysferlinopathies (limb girdle muscular dystrophy 2B)
Facioscapulohumeral muscular dystrophy

[a]Predominantly eosinophils

Table 55.20 Necrotizing immune myopathies

Paraneoplastic necrotizing myopathy
Anti SRP myopathy
Antisynthetase syndrome
Anti-HMG-R myopathy

Table 55.21 Serum markers associated but not specific of inflammatory myositis

Antinuclear antibody → SLE, other conditions (unclear pathological value if < 1:340)
Anti-PM-Scl → scleroderma
Anti-RNP → mixed connective tissue disease
Human immunodeficiency virus → inflammatory myopathy
Angiotensin-converting enzyme → sarcoidosis
Erythrocyte sedimentation rate → nonspecific marker of inflammation
C-reactive protein → acute phase reactant, nonspecific marker of inflammation

does not in itself provide a final diagnose, it can inform and direct additional specific diagnostic testing. The main types of myopathies tend to be distinguishable by biopsy, and the more common histological patterns include inflammatory myopathies, necrotic myopathies, and dystrophic myopathies. This is discussed in Chap. 12. Many other distinct types of myopathies can be seen including glycogen storage, lipid storage, and mitochondrial myopathies. Although some cases are hard to identify, when an inflammatory myopathy is seen on routine histochemistry, it is often straightforward to discern between polymyositis, dermatomyositis, inclusion body myositis by routine histochemical, and immunostains. Clinical information most often convincingly will identify which one of the inflammatory myopathies is present, but some dystro-phies also can have striking inflammation on biopsy (Table 55.19).

The necrotizing myopathies may occur due to autoimmune mechanisms, but myonecrosis can also be noted in many toxic myopathies. In the absence of inflammatory cells, MHC-1 and enzyme stains such as alkaline phosphatase, acid phosphatase, and esterase does not exclude an immune-mediated cause (Table 55.20) [9].

Other Specific Testing

After the basic muscle histology has been performed, confirmatory diagnostic testing is often indicated. For an inflammatory myopathy where poly- or dermatomyositis is considered, further diagnostic tests such as the antisynthetase antibodies may be informative. When present they certainly strengthen the inflammatory myopathy diagnosis, as they have a high degree of specificity, but they are often not present and have low sensitivity for inflammatory myopathies as a group. The antisynthetase antibodies also suggest a higher risk for interstitial lung disease (ILD). ILD may occur without antisynthetase antibodies, and clinical consideration of this severe condition is always warranted in poly- and dermatomyositis. Other markers of inflammation and autoimmunity that can be considered for testing are listed (Table 55.21).

Genetic Testing

When a muscular dystrophy is suspected, the phenotype should guide further testing. For dystrophies with a specific phenotype (such as OPMD, DM1, or FSH), genetic testing for the disease can be ordered, often before EMG or muscle biopsy is performed. If genetic testing does not confirm a reasonably suspected diagnosis, then performing an EMG and biopsy would be indicated. The limb girdle syndromes are numerous, sometimes not due to dystrophies, and often difficult to reduce to a few diagnostic entities by phenotypical features alone. Today, immunostaining of the proteins affected by the dystrophies helps identify the condition. The recessively inherited conditions (LGMD2) currently are better covered by immunostains, and genetic testing covers more of the dominantly inherited conditions. Often a generic limb girdle muscular dystrophy presentation will require multiple tests to be performed because of marked phenotypic overlap between conditions. The mitochondrial myopathies can be approached by specific genetic testing when they have other associated features and/or an inheritance pattern. The investigation of an otherwise featureless mitochondrial myopathy can be started with respiratory complex testing to provide further details to direct the next step of testing. Testing muscle for coenzyme Q10 deficiency is worth special consideration as some patients are helped a great deal by replacement [10].

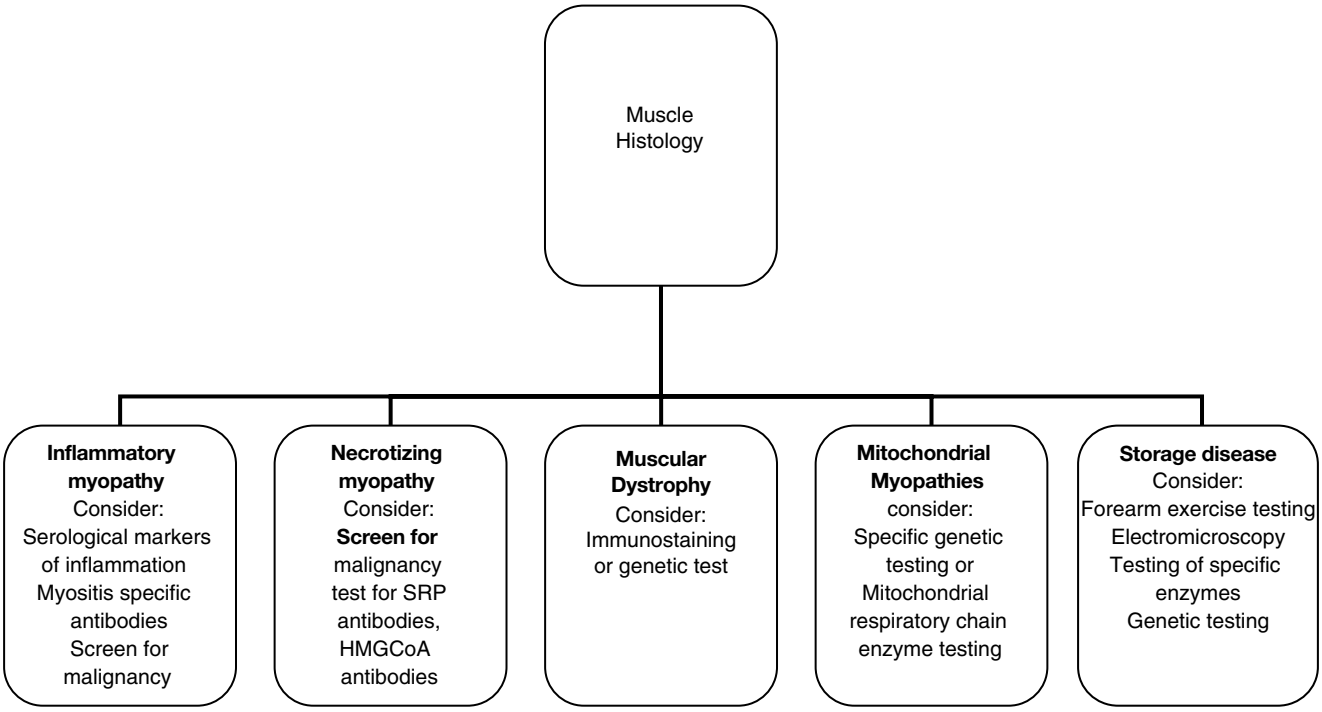

Fig. 55.3 Summary of common myopathies and their recommended workup

Figure 55.3 summarizes the common myopathies and their recommended investigations.

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Dystrophinopathies

56

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Introduction

The dystrophinopathies include a spectrum of muscle diseases caused by mutations in dystrophin gene (*DMD*) at Xp21 which encodes the protein dystrophin. The mild end of the spectrum includes the phenotypes of asymptomatic increase in serum concentration of creatine kinase (CK) and muscle cramps with myoglobinuria and isolated quadriceps myopathy. Variable phenotypic expression in dystrophinopathies relates mainly to the type of mutation and its effect on the amount of functional dystrophin production. Duchene muscular dystrophy (DMD) is in the most severe end of the spectrum and is typically associated with <5 % of normal levels of dystrophin in skeletal muscle. The diagnosis is made in most patients at approximately 5 years of age when their physical ability lacks behind their peers. In the milder allelic form Becker muscular dystrophy (BMD), dystrophin mutations do not disrupt the open reading frame; a shortened but functional dystrophin protein is produced, enabling most patients to remain ambulatory until the age of 15. Clinical phenotypes of other patients, so-called intermediate or outliers that do not fit the typical DMD or BMD, also exist. In general, manifesting carriers are in the milder end of the spectrum. Some dystrophin mutations cause an isolated cardiac phenotype resulting in *DMD*-associated dilated cardiomyopathy (DCM) when the heart is primarily affected.

DMD is the most common form of childhood muscular dystrophy with an estimated birth prevalence of about 1 in 3,500 (2.9 per 10,000) live male births [1]. A recent two-tier system of analysis for newborn screening for DMD that included a large cohort in the United States reports a lower incidence rate, 1 in 6,000 [2]. The disease carries the name of the French neurologist, Duchenne, who published his first description of DMD in 1861 with a more comprehensive account in 1868, establishing diagnostic criteria and accurately describing muscle biopsy features. British neurologist Gowers, in 1886, illustrated the characteristic features of calf muscle hypertrophy and described the way in which an affected child rises from the floor to reach the standing posture [3]; this sign was subsequently named after him. A milder form of the disease with later onset was recognized by Becker and Kiener in 1955 [4]. In the second half of the twentieth century, the histopathological characterization became more precise and the associated marked increases in CK were recognized in affected males and in carrier females to a lesser degree.

Advances in molecular genetics led to mapping of the gene responsible for DMD to band p21 of the short arm of the X chromosome [5–8] and then to the cloning of its DNA sequence in 1987 [9]. Subsequently, Kunkel's group was able to identify the muscle protein dystrophin encoded by the cloned gene [10], localized dystrophin in the sarcolemma of muscle fibers, and demonstrated its almost complete absence in DMD and its decrease in BMD. These advances permit unequivocal diagnosis of DMD and related phenotypes and allow accurate genetic counseling, reliable prenatal testing, and newborn screening.

Etiology and Pathogenesis

All dystrophinopathies are allelic conditions, resulting from different mutations of the dystrophin gene.

Dystrophin

Dystrophin is a scaffolding protein in muscle encoded by the DMD gene. The gene is the largest identified to date in humans, spanning approximately 2.4 megabases on the short

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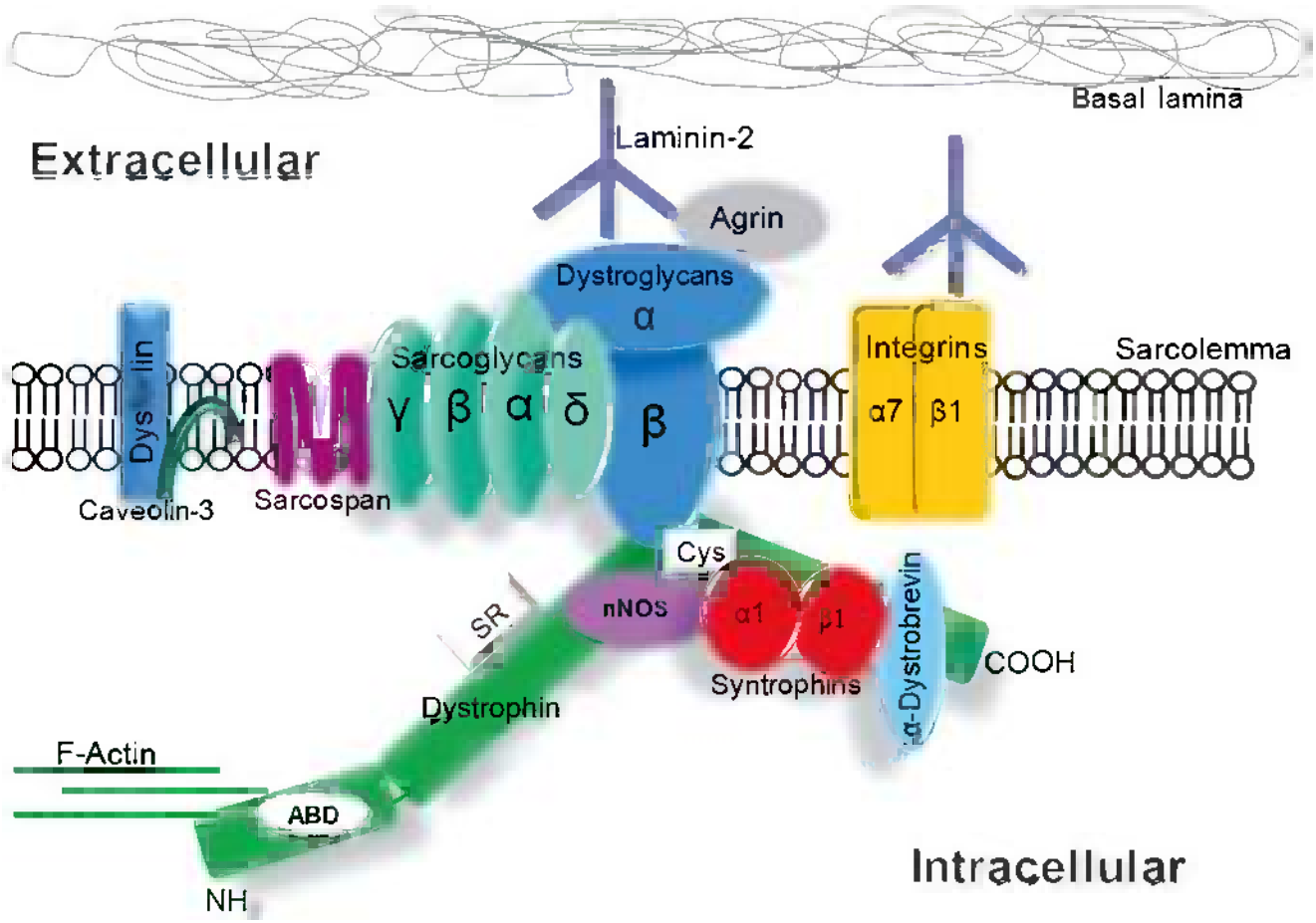

Fig. 56.1 The dystrophin-associated protein complex. The DAP is a large protein network that spans the sarcolemmal membrane comprised of dystrophin and interacting proteins to stabilize muscle fibers during contraction and relaxation. *NH_2* amino-terminal domain, *COOH* carboxy-terminal domain, *ABD* actin-binding domain, *SR* spectrin repeats, *CYS* cysteine-rich domain, *F-actin* filamentous actin, *nNOS* neuronal nitric oxide synthase

arm of the X chromosome (Xp21). The DMD gene contains 79 exons encoding for a 3685 amino acid, 427 kDa protein [9]. Dystrophin has four primary functional domains which together link the actin cytoskeleton to the extracellular matrix to provide stability and strength to muscle fibers (Fig. 56.1). These include (1) the amino-terminal actin-binding domain; (2) the central rod domain comprised of 24 triple helical spectrin-like repeats interspersed by 4 putative hinge domains imparting flexibility [11]; (3) the cysteine-rich domain containing two EF hands [12], a WW domain [13], and ZZ domain [14] important for signaling and binding β-dystroglycan, the link to the extracellular matrix; and (4) the carboxy-terminal domain which binds critical structural and signaling molecules the syntrophins and α-dystrobrevin [15].

The dystrophin gene can generate several tissue-specific isoforms of different molecular weight, each driven by a distinct promoter (Table 56.1) [16–18]. There are four full-length, large molecular weight (427 kDa) dystrophins: M-dystrophin (Dp427m) present in skeletal and smooth muscle [9], C-dystrophin (Dp427c) in the cerebral cortex and hippocampus [19], P-dystrophin (Dp427p) in Purkinje cells [20], and L-dystrophin (Dp427l) in lymphocytes [21]. Alternative promoters drive expression of five nonmuscle truncated isoforms including Dp260 found in the retina [22], Dp140 expressed in the central nervous system and kidney [23], Dp116 in Schwann cells [24], and two ubiquitously expressed forms, Dp71 and Dp40 [25, 26]. Dp71 is the most abundant isoform in the brain [17] and mutations that affect its expression correlate with the severity of mental retardation in DMD and BMD patients [27].

The Dystrophin-Associated Protein Complex

Dystrophin is part of a large, tightly associated glycoprotein complex containing structural and signaling proteins (Fig. 56.1), referred to as the dystrophin-associated protein (DAP) complex. The DAP is a large protein network that spans the sarcolemmal membrane stabilizing it during contraction and relaxation [28, 29]. This complex system,

Table 56.1 Dystrophin isoforms

Isoform	Name	Protein weight (kDa)	Amino acid length	Transcript length (bp)	Promoter location	Tissue expressed	References
Dp427m	Muscle dystrophin	427	3,685	13,993	5′ end of gene	Muscle	[9]
Dp427c	Cortical dystrophin	427	3,677	14,069	5′ Dp427m	Brain	[19]
Dp427p	Purkinje dystrophin	427	3,681	14,000	3′ Dp427m	Purkinje cells	[20]
Dp427l	Lymphocyte dystrophin	427	3,562	13,764	5′ Dp427c	Lymphoid	[21, 216]
Dp260	Retinal dystrophin	260	2,344	9,773	Intron 29	Retina	[22]
Dp140		140	1,225	7,410	Intron 44	CNS Kidney	[23]
Dp116	Apo-dystrophin 2	116	956	5,623	Intron 55	Schwann cells	[24]
Dp71	Apo-dystrophin 1	71	617	4,623	Intron 62	Ubiquitous	[25]
Dp40	Apo-dystrophin 3	40	340	2,200	Intron 62	Ubiquitous	[26]

Source: Modified from Leiden Muscular Dystrophy Pages

comprised of three subcomplexes, links the intracellular cytoskeletal actin to the basal lamina, through the extracellular matrix (ECM). The ECM is situated between the sarcolemma and the extracellular basal lamina composed mainly of laminin, collagen, fibronectin, and proteoglycans. Several forms of muscular dystrophy are caused by defects in the function and assembly of the DAP complex [28, 30]. As a central molecular scaffold of the DAP, dystrophin is critical to the structural integrity of the sarcolemma. Severing this link from the subsarcolemmal actin cytoskeleton to the ECM results in secondary deficiencies in other components of the DGC [28, 31]. The DAP can be classified into three domains: extracellular including laminin and α-dystroglycan, transmembrane (sarcoglycans and β-dystroglycan), and subsarcolemmal (dystrophin, syntrophins, dystrobrevins).

Skeletal muscle laminin is a heterotrimer made up of β1-, γ1-, and α2-laminin subunits which binds dystroglycan to the surface of muscle cells [32]. Mutations in laminin-α2 (also designated as merosin) have been described in a subset of patients with congenital muscular dystrophy [33]. In addition to dystroglycan, α7β1 integrin has been identified as a receptor for laminin [34]. Dystroglycan is composed of two subunits generated from a common precursor and cleaved to form α-dystroglycan, which binds to laminin-α2, and β-dystroglycan [35], which spans the membrane and binds to the cysteine-rich domain of dystrophin on the subsarcolemmal side [36].

The sarcoglycan group, comprised of four sarcolemmal transmembrane proteins (α-, β-, γ-, δ-sarcoglycans) along with the stabilizing protein sarcospan [37], demonstrates side-association linkage with dystroglycan [38]. Although the exact role of the sarcoglycans in the molecular organization of the DAP is not well defined, it is clear that it plays both structural and signal transduction roles [39]. Deficiency of the sarcoglycan complex proteins is responsible for several limb-girdle muscular dystrophies, known as sarcoglycanopathies, and secondary deficiencies of the sarcoglycans in DMD patients likely contribute to the dystrophic phenotype [39]. Dystrophin itself resides in the subsarcolemmal domain binding actin through its N-terminal domain and intracellular signaling molecules, the syntrophins [40], dystrobrevins [41], and neuronal nitric oxide synthase (nNOS) [42] via its C-terminal domain. The quantity of dystrobrevin is reduced in both DMD and patients with sarcoglycanopathies [41].

Dystrophin Gene Mutations

Accurate dystrophin mutation analysis is critical not only for diagnostic purposes but also for considering potential treatments due to mutation specificity. Dystrophin gene mutation analysis reveals a predominance of deletions of one or more exons in 60–70 % of DMD/BMD cases primarily clustering in two hotspots of the gene, proximal (exons 2–20) and distal (exons 45–55) [43, 44]. Duplications resulting in in-frame or out-of-frame transcripts account for 6 % of mutations in DMD and for about 10 % in BMD [44]. Point mutations (which can include small deletions or insertions, single base changes, and splice-site mutations) account for ~25–35 % of mutations in DMD but are less common in BMD, comprising about 10–20 % of cases [44–46]. Nonsense mutations occur more commonly in DMD, in approximately 20–25 % of cases as compared to <5 % in BMD [44, 46]. Splice-site mutations and small insertions or deletions account for a considerable proportion of sequence changes found in both DMD and BMD while missense mutations are rare. *DMD*-associated dilated cardiomyopathy (DCM) is caused by mutations in *DMD* that affect the muscle promoter (P_M) and the first exon (E1), resulting in no dystrophin transcripts being produced in cardiac muscle; however, two alternative promoters that are normally only active in the brain (P_B) and Purkinje cells (P_P) are active in the skeletal muscle, resulting in dystrophin expression sufficient to prevent manifestation of skeletal muscle symptoms [47–49]. *DMD*-associated DCM may also be caused by alteration of epitopes in a region

of the protein of particular functional importance to cardiac muscle [50] or possibly by mutations in hypothetic cardiac-specific exons [51].

Germline Mosaicism

Dystrophinopathies are familial diseases; however, sporadic cases do occur resulting from a spontaneous mutation in a single germ cell of the mother or perhaps in the proband's dystrophin gene early in postzygotic embryo development. If the mother is not a somatic carrier but has more than one affected offspring, that may be related to the phenomenon of germline mosaicism [52, 53]; the latter accounts for about 20 % of new DMD mutations [54, 55]. This phenomenon may be due to a mutation at a mitotic stage of germ cell lineage development. If this type of mutation occurs in a female, there is a substantial risk for more than one affected male offspring. If the germline mutation occurs in a male, his female offspring are at significant risk for becoming carriers [53]. Because of the possibility of germline mosaicism, if the mother of an affected male is not a carrier by deletion analysis of her lymphocyte DNA, her risk of having another affected son could be at least 7–10 % [56].

Dystrophinopathies in Females

During early embryonic development, random inactivation of one of the two X chromosomes occurs (lyonization), leaving active 50 % of the maternally derived chromosomes and 50 % of the paternally derived ones [57]. Thus, if the maternal X chromosome carries a mutated dystrophin gene, 50 % of the remaining nuclei have an active normal dystrophin gene and thus will produce enough dystrophin to prevent muscle necrosis [58]. In the case of nonrandom X chromosome inactivation, less than 50 % of the nuclei may have the normal dystrophin gene in an active state, thus resulting in dystrophin deficiency and clinical manifestations in females [59]. This happens most commonly in cases of twin pregnancies [59]. Cases of X-autosomal translocations with breakpoints at Xp21 resulting in preferential inactivation of the normal chromosome have also been described [5, 8]. In Turner syndrome (karyotype XO) or Turner mosaic (XO/XX or XO/XX/XXX) syndrome, if the X chromosome carries a mutated dystrophin gene, the female child will be clinically affected also.

Pathogenesis

More than a decade prior to the cloning of dystrophin, ultrastructural observations were made in DMD muscle biopsies which alluded to the pathogenesis of the disease. In 1975, Mokri and Engel noted focal plasma membrane defects in nonnecrotic fibers in DMD muscle [60]. These regions, referred to as delta lesions, were accompanied by nearby cytoplasmic defects where myofibrils were usually contracted. Histopathological findings and experiments in the *mdx* mouse model of DMD support the conclusion that reduced or absent dystrophin results in a mechanically weakened plasma membrane [61, 62], which is prone to focal tears during contractile activity [63]. This allows a massive influx of extracellular calcium, which activates proteolytic enzymes and leads to gradual necrosis of muscle fibers explaining why dystrophinopathies are progressive diseases [64]. A second aspect of DMD pathology is functional ischemia which was proposed as a pathogenic mechanism of muscle fiber damage in DMD over 30 years ago based on experimental findings reproducing the histopathological pattern of muscle necrosis and regeneration [65]. Recent studies reinforce the potential role of ischemia through molecular-based findings demonstrating deficiency of nitric oxide synthase (NOS) in DMD muscle as a contributory factor in muscle damage [66]. As a result, therapeutic strategies helping to circumvent ischemia by modulation of the NOS pathway are emerging (see section "Emerging Therapies").

Clinical Presentation

There is a great heterogeneity in the clinical presentation and course of the various dystrophinopathies, creating a spectrum ranging from very severe to very mild presentations.

Duchenne Muscular Dystrophy

In children with DMD, although there is histologic and laboratory evidence (elevated serum CK ≥ 2,000 [2]) of myopathy at birth, clinical manifestations are usually absent at this age. During the first 2 years of life, some affected boys exhibit mildly delayed gross motor development presenting primarily as delayed walking. The mean age of walking is approximately 18 months (range 12–24 months). Weakness is usually noted between 2 and 3 years of age; in some cases, however, it may be delayed and become apparent after the age of 3 years (Table 56.2). The first symptoms are usually difficulty with running, jumping, and going up the stairs, related to weakness that selectively affects proximal limb muscles before distal and the lower extremities before the upper ones. Between 3 and 6 years of age, a broad-based waddling gait, exaggerated lumbar lordosis, and calf enlargement are usually observed. Early on, toddlers may complain of leg pains. In arising from a supine position on the floor, affected boys turn their face to the floor, spread their legs,

Table 56.2 Genetic, clinical, and laboratory features of the dystrophinopathies

Type	Clinical features	Laboratory features	Mutations
Duchenne	Onset before age 5, progressive weakness of girdle muscles, Calf hypertrophy	Striking CK elevation 50–100× of NL up to age 3; ~20 % drop per year	Deletions (60–70 %)
	Wheelchair confinement by age 12, scoliosis, respiratory failure in second or third decade	Dystrophin <5 % on WB	Duplications (6 %)
	Cardiac involvement	Absent dystrophin by IHC; revertant fibers may occur	Point mutations[a] (20–25 %)
	Rapid decline		Nonsense (<15–25 %)
Intermediate	Intermediate severity	Decreased or altered dystrophin 5–20 %	Spectrum unknown
	Ability to walk after age 12 but not age 15		
Becker	Onset after age 5, progressive weakness of girdle muscles, Calf hypertrophy	CK > 20–75 % of NL	Deletions (60–70 %)
	Ability to walk after age 15	Decreased or altered dystrophin >20–40 % on BW	Duplications (10 %)
	Cardiac involvement	Variable staining intensity for dystrophin by IHC	Point mutations (10–20 %)
	Variability in clinical severity		Nonsense (<5 %)

CK creatine kinase, *WB* Western blot, *IHC* immunohistochemistry
[a]Includes small deletions or insertions, single base changes, and splice-site mutations

Fig. 56.2 A boy with Duchenne muscular dystrophy demonstrating Gowers' sign. To rise from the floor, he is faced to the floor, his legs are spread, and his buttock is raised; subsequently he will use his hands to climb up his thighs (Courtesy of Dr. John Kissel, The Ohio State University, Columbus, OH)

and use their hands to climb up their thighs to an upright position (Gowers' sign) (Fig. 56.2). Neck flexor weakness often goes unnoticed but it does occur at all stages of the disease; when lying on his back, a child with DMD is unable to lift his head against gravity [67]. This sign is helpful in distinguishing boys with DMD from patients with milder phenotypes, such as "outliers" and BMD.

Physical examination shows firm enlargement of the calf muscles and, in some instances, of the quadriceps, gluteal, deltoid, and rarely masseter muscles. Increased muscle bulk, early in the course of the disease, is the result of true hypertrophy, however later on is related to replacement of the muscle fibers by fat and connective tissue (pseudohypertrophy) [68]. The ankle plantar flexors and invertors remain very strong throughout the course of the disease, while the tibialis anterior muscles become weak gradually, resulting in heel cord contractures and toe walking; eventually, this imbalance in muscle strength will lead to bilateral equinovarus foot deformities.

Between 3 and 6 years of age, there may be some improvement; this is related to normal motor development of the child which outpaces disease evolution, to be followed gradually by relentless deterioration. Between 6 and 11 years, muscle strength decreases linearly and the ability to climb stairs, rise from a supine position, climb stairs with rails, and walk a short distance declines rapidly in the mentioned order [54, 68]. As the disease progresses, muscle stretch reflexes diminish or cannot be elicited; before the age of 10 years, the triceps, biceps, and knee reflexes become hard to elicit in approximately 50 % of patients. The brachioradialis stretch reflex remains active longer with the ankle reflex being elicited in one-third of patients even during the last phase of the disease [69]. Cranial and sphincter muscles are spared [70].

The development of joint contractures is another almost constant clinical feature of DMD. By age 6 years, the majority of DMD patients have contractures of the heel cords, iliotibial bands, and hip joints, causing toe walking and limitation of hip flexion. By age 8 years, knee, wrist extensor, and elbow contractures appear and correlate with decreasing ambulation [68]. Shoulder contractures occur only late in the disease course. At around age 10 years in most patients, the weakness leads to dependency on long leg braces for ambulation [68] and wheelchair confinement by approximately the age of 12 years [71]. The use of steroids prolongs ambulation 1 to 2 years. Scoliosis rarely occurs prior to age 11 while they are still ambulatory; severe curvatures usually evolve after wheelchair confinement requiring medical intervention [72]. Increasing scoliosis and gradual

deterioration of pulmonary function related to the weakening of respiratory muscles are leading cause of respiratory failure. Patient's age at respiratory failure correlates well with the degree of thoracic kyphoscoliosis [73].

Historically the patients, usually around age 20, succumbed to restrictive lung disease or complications but also died from cardiac failure secondary to progressive cardiomyopathy [74], but now improved care, including antibiotics, vaccines, and other ancillary methods, protects the cardiorespiratory system and prolongs life.

Involvement of Other Organ Systems

Heart, brain, and smooth muscle are also involved in the disease process, resulting from the lack of dystrophin expression in these organs.

Cardiac involvement is inevitable in DMD and the incidence of *cardiomyopathy* increases steadily in the teenage years. Approximately one-third of patients are affected by age 14 years, one-half by age 18 years, and all after age 18 years [75]. The majority of patients, however, remain free of cardiovascular symptomatology until late in the disease, probably due to their inability to exercise, which may mask the cardiac symptoms [54]. In the late stages of the disease, congestive heart failure and arrhythmias may develop, especially during infections. In very rare cases, congestive heart failure dominates the picture and can be the immediate cause of death without marked compromise of respiratory function [68].

At the time when boys with DMD are wheelchair dependent, the dystrophin-deficient myocardium may or may not demonstrate measurable changes by echocardiography [76]. In contrast, electrocardiographic (ECG) abnormalities can be detected from a young age (<6 years of age), identified in about 76 % of patients. The most common ECG abnormality noted in very young boys is related to left ventricular pathology, manifesting most commonly by a Q wave >98th percentile in lead III or V6 [77]. Prominent Q waves in leads II, aVF, and V_5 were also reported [78]. The characteristic changes in older boys include short PR interval, right ventricular hypertrophy, and deep Q waves in leads I, aVL, and V_5 [71, 72]. Intra-atrial conduction disturbances, sinus tachycardia, or other sinus arrhythmias are more frequent than atrioventricular conduction defects and infranodal/ventricular abnormalities. ECG changes are similar in patients with DMD regardless of presence of dilated cardiomyopathy (diagnosed by an ejection fraction <55 %) suggesting that ECG may not be predictive of disease course [78].

Autopsy studies of the heart in patients with DMD show the initial site of myocardial fibrosis and fatty infiltration to be in the posterobasal epicardium, progressing to involve the epicardial half of the left ventricular free wall, then occasionally involving septal segments as the fibrosis becomes more severe and more transmural [76, 79]. The right ventricle and the atria seldom are involved. Fibrosis and fatty infiltration can also involve the conduction system, the sinoatrial and the atrioventricular nodes [80, 81]. As in autopsy studies, cardiovascular magnetic resonance studies find that scar predominantly involves left ventricular segments and that septal segments are involved less frequently and only in patients with significant left ventricular free wall involvement [82]. Ultimately the fibrosis leads to dysfunction and dilation, to a severe generalized cardiomyopathy. In some instances, the left ventricle dilatation cannot occur if the wall is severely fibrotic, creating a restrictive myopathy. With dilation, patients can develop mitral regurgitation and, occasionally, aortic regurgitation. With left ventricular failure, there can be secondary pulmonary hypertension and right ventricular failure associated with pulmonary and tricuspid regurgitation [83].

Most patients with DMD exhibit nonprogressive *impairment of intellectual function*, initially described as a general leftward shift in the spectrum of IQ scores [84], reduced approximately one standard deviation from the normal population. In some cases, an occasional child with DMD may have average or above-average intelligence.

Although the neuropsychological profile of DMD has not yet been fully characterized, studies show significantly lower performances in verbal IQ, verbal short-term memory, and phonological abilities, as well as in praxis and executive functioning domains [85]. These deficits in executive function are often confused with attention deficit/hyperactivity disorder warranting appropriate neuropsychological testing for correct diagnosis. A neuropathologic abnormality underlying the cognitive deficit in DMD has not been found [68]. Loss of Dp71, the major DMD gene product in brain, is thought to contribute to the severity of cognitive impairment [27]. Studies in animal models suggest a role for Dp71 in excitatory synapse organization and function [86].

Degeneration of gastrointestinal tract smooth muscle resulting from dystrophin deficiency may lead to an important and even life-threatening complication, intestinal hypomotility, also known as *intestinal pseudo-obstruction*. It may present with acute gastric dilatation, vomiting, abdominal pain, and distension [68, 87]. Degeneration of the outer, longitudinal, smooth muscle wall of the stomach has been documented pathologically.

Osteoporosis in boys with DMD begins to develop early, while they are still ambulating; it is more severe in the lower extremities and may lead to frequent fractures that, sometimes in older children, hasten the loss of ambulation [88]. Corticosteroids further increase the risk of vertebral compression fractures.

Becker Muscular Dystrophy

BMD has been estimated to occur approximately one-tenth as frequently as DMD with an incidence of 1 individual per

30,000 male births (Table 56.2). Compared to fairly stereotypical clinical features of DMD, BMD comprises a more heterogeneous group, which can vary from mildly symptomatic forms to more significant muscular and cardiac involvement. In BMD, the age of onset of symptoms is later than DMD, usually between the ages of 5 and 15 years, sometimes even in the third or fourth decade or later [89]. Most patients with BMD remain ambulatory until 15 years of age and older, although this is an arbitrary cutoff, since these disorders represent a continuous spectrum related to the quantity and quality of dystrophin. In most cases dystrophin is reduced in amount and size [90, 91]. The pattern of muscle wasting is similar to DMD. Pelvic girdle and thigh muscles are involved first and calf muscle pseudohypertrophy occurs early in most patients. Tibialis anterior and peroneal muscle groups are less affected. Shoulder girdle weakness develops later after the onset of proximal lower extremity weakness. One exception is the relative preservation of neck flexor muscle strength, a helpful distinguishing feature of the BMD from DMD; neck flexors become weak later in the disease. Contractures are less likely to develop, and scoliosis is also less common, but becomes evident after the patient is confined to a wheelchair. Muscle pain can be very prominent in some patients with BMD and myoglobinuria occurs infrequently [92]. Serum CK levels can be very high, falling into the same range as the patients with DMD (usually >20 to 75 times normal).

Mental retardation is not as common or severe as in DMD, and gastrointestinal symptoms are essentially absent. Cardiac involvement is that of a dilated cardiomyopathy, sometimes starting with right ventricular dilation and progressing to a generalized dilated cardiomyopathy [93, 94]. Recent cardiac magnetic resonance imaging studies in BMD patients show many of the same findings seen in DMD, including fibrosis, and are more sensitive in detecting abnormalities of ejection fraction than echocardiogram [95]. The ECG findings in patients with BMD are also similar to those in patients with DMD with prominent Q waves in I, aVL, and V6, or in II, III, and aVF; tall R waves in V1; and increased QT dispersion [96]. Rarely, cardiac symptoms can be severe in patients with only mild skeletal muscle weakness [97–102] or can precede muscle weakness by several years [103]. The mean age at cardiomyopathy diagnosis is around 14 years, similar to that in DMD [104]. Despite the milder skeletal muscle involvement, heart failure from DCM is a common cause of morbidity and the most common cause of death [105]. Patients usually survive beyond the age of 30 years [68], with death from dilated cardiomyopathy/cor pulmonale or respiratory insufficiency occurring between 30 and 60 years [105].

Earlier studies have reported the presence of cardiac involvement with BMD is associated with deletions in two regions of the *DMD* (5′ end and exons 47 through 49) [93]. An extensive analysis of genotype–phenotype correlation in BMD patients shows that early-onset cardiomyopathy is associated with mutations in the amino-terminal domain; in contrast deletions removing portions of the rod domain along with the hinge 3 domain have a later onset, likely due to preservation of the spectrin-repeat structure of the protein [51].

Late-onset dystrophinopathy could in rare instances present with a myopathy involving predominantly, but not exclusively, the quadriceps [106–108]. Some of these patients may have cardiac involvement. In earlier reports of four patients, dystrophin deficiency, proved by immunoblot analysis, was demonstrated to be the cause of the myopathy which was considered "atypical form" of BMD [106]. Several other cases of isolated quadriceps myopathy have been reported since then and proven to be due to mutations in the dystrophin gene [107–109], thus demonstrating that quadriceps myopathy can sometimes be the only manifestation of dystrophin deficiency.

X-linked exercise-induced myalgias and cramps without skeletal muscle weakness, starting in childhood, especially in a family with cardiomyopathy, can be caused by mutations in the dystrophin gene [110, 111]. However, a longer follow-up period is necessary to definitely rule out late-onset skeletal muscle weakness, which could classify these cases as BMD [103, 110]. Two molecular regions on the dystrophin gene have been linked to the phenotype of cramps and myalgias: exons 10–44 [109, 110] and exons 45–52 [103, 111]. Some of the patients in these studies also had fixed weakness [109].

Dystrophin Gene-Associated Dilated Cardiomyopathy

X-linked *DMD*-associated DCM is a progressive and fatal type of heart disease that presents in the second or third decade of life with congestive heart failure in patients with minimal skeletal muscle symptoms [47, 112–114]. It should be noted that four separate genetic disorders with cardiac and skeletal myopathies are X-linked. DMD and BMD already have been discussed. Those with no or minimal abnormalities in skeletal muscle dystrophin but showing abnormal dystrophin in heart muscle are classified here as *DMD*-associated DCM. The other X-linked cardiomyopathies include Emery-Dreifuss muscular dystrophy, resulting from abnormalities in LINK components at nuclear envelope [115, 116], and Danon disease [117], also known as X-linked vacuolar cardiomyopathy and myopathy, which is caused by a mutation in the gene encoding lysosome-associated membrane protein-2 (LAMP2). Another disorder of this group is Barth syndrome [118] a mitochondrial disease caused by a mutation of the tafazzin gene associated with decreased amounts and altered structure of cardiolipin, the main phospholipid of the inner mitochondrial membrane.

Boys with *DMD*-associated DCM complain of exercise intolerance, muscle fatigue, pain, and cramping but do not manifest the weakness seen in patients with BMD and DMD [119]. Calf hypertrophy and elevated serum CK levels can be present [94]. Symptoms of congestive cardiomyopathy usually develop in late teen years to early adulthood that usually progresses to death within 2 years of the onset of the myopathy diagnosis. Arrhythmias and atrioventricular block can occur with much greater frequency than that seen in patients with either DMD or BMD. Female carriers develop mild dilated cardiomyopathy later in life with slow progression and often fatal outcome [47, 105].

Different mutations in the dystrophin gene cause selective absence of dystrophin in heart muscle [47, 54]. A review of families with *DMD*-associated DCM points out that mutations involving the 5′ end of the gene result in more severe cardiomyopathy than mutations in the spectrin-like region (centered around exons 48–49) [120]. With mutations involving the 5′ end of the dystrophin gene, the exclusive cardiac involvement seems to be related to a difference in RNA splicing regulation between heart and skeletal muscle. The skeletal muscle maintains dystrophin production by using exon skipping or alternative splicing, while the heart muscle is apparently unable to employ such mechanisms. Studies demonstrated that in individuals with the most severe cardiac phenotype the cardiac muscle is usually unable to produce functional dystrophin in the heart, while in skeletal muscle reduced levels of virtually normal dystrophin transcript and protein are present [121, 122]. Classification of *DMD*-associated DCM as a separate entity in dystrophinopathy spectrum is somewhat controversial. *DMD*-associated DCM may be the presenting finding in individuals with BMD who have little or no clinical evidence of skeletal muscle disease. Some investigators classify such individuals as having subclinical or benign BMD, whereas others may classify them having DCM with increased serum CK concentration [123].

Manifesting DMD/BMD Carrier Females

Carriers are usually free of symptoms but may have mildly increased serum CK and usually mild calf hypertrophy. In approximately 8 % of the cases they can, however, present with mild myopathy of the limb-girdle type or even typical DMD/BMD [124–128]. Cardiac involvement is usually subclinical, although few investigators have evaluated DNA-proven DMD and BMD female carriers. Earlier studies demonstrated that 8 % of DMD carriers have dilated cardiomyopathy versus none in BMD carriers. Only 38 % of the studied carrier population had a completely normal heart investigation. The remaining had subclinical EKG or echocardiographic abnormalities [129]. Severe cardiac symptoms can occur in some carriers [130].

A more recent study shows DMD carriers (mothers) can have significant left ventricular systolic dysfunction, which is unmasked by exercise, [131] implying the need for evaluation of proven female carriers, even if they are asymptomatic.

Differential Diagnosis

The process of making an accurate diagnosis in suspected DMD/BMD patients depends on the mode of presentation, in particular the pattern of muscle involvement, and additional clinical features, the serum CK level, and any informative family history. If there is clear evidence for autosomal dominant transmission, a dystrophinopathy can easily be excluded. If not, a diagnostic workup may include a muscle biopsy. Immunohistochemistry with antibodies against dystrophin epitopes, α-, β-, γ-, and δ-sarcoglycans, α- and β-dystroglycans, and merosin (laminin-alpha 2) may offer a specific biopsy diagnosis. Western blot analysis is useful for quantitation of dystrophin, calpain, or other proteins. However, DNA mutation analysis should ultimately be done to confirm the results from these biochemical studies.

Salient features of the following disorders that can be considered in the differential diagnosis of the DMD and BMB are discussed below.

Limb-girdle muscular dystrophy (LGMD) encompasses a heterogeneous group of muscle disorders characterized by a predominantly proximal distribution of weakness with the age of onset of symptoms varying from early childhood to late adulthood. Typically, the onset is not congenital. Pathogenic genes reported so far include those that encode integral components of DGC as well as other structural proteins, and even enzymes such as calpain 3. In certain types of LGMD there may be clinical clues, but there is substantial overlap in different forms. Recessive forms are far more common than autosomal dominant forms that have more heterogeneous clinical presentation with some families showing syndromic features.

LGMD2A or calpain 3 deficiencies, the most common recessive form, represent about 10 % of LGMD population and can present within the first decade with very high serum CK levels with a pelvifemoral pattern of weakness. Early contractures and absence of cardiac involvement are helpful clinical features. Presentation of calpainopathy with high serum CK can also occur, usually observed in children or young individuals, in which symptomatic individuals have only high serum CK concentrations. Clinical findings include the tendency to walk on tiptoes, difficulty in running, scapular winging, waddling gait, and slight hyperlordosis.

Other well-characterized LGMD subtypes are sarcoglycanopathies (α-sarcoglycanopathy, LGMD2D; β-sarcoglycanopathy, LGMD2E; γ-sarcoglycanopathy, LGMD2C;

δ-sarcoglycanopathy, LGMD2F). Clinical features range from early childhood onset with severe progression similar to DMD to later onset with milder progression as seen in BMD (see Table 56.2). Calf hypertrophy is commonly observed but scapular winging is more prominent than DMD/BMD. Heart involvement is variable, but typically less severe than in the dystrophinopathies. Overall, about 30 % of individuals have evidence of cardiomyopathy by ECG and echocardiogram; cardiomyopathy is common in β-, γ-, and δ-sarcoglycanopathy, but rare in α-sarcoglycanopathy [132, 133].

Most individuals with severe, childhood-onset LGMD are suspected to have sarcoglycanopathy [134]. Thus, a boy with a clinical presentation and progression similar to DMD but with normal dystrophin immunostaining in muscle is likely to have a primary sarcoglycanopathy. In contrast, only about 10 % of individuals with LGMD with milder disease (onset in adolescence or adulthood) have a sarcoglycanopathy.

LGMD2I is an important type of LGMD associated with abnormal α-dystroglycan labeling on the muscle biopsy and caused by mutations in genes encoding proteins involved in the glycosylation of dystroglycan such as *FKRP*, the gene encoding fukutin-related protein [135]. The phenotype ranges from severe to mild with no clinically apparent skeletal muscle involvement [136–140]. Cardiomyopathy without skeletal muscle involvement has been reported. In severe cases loss of ambulation occurs in the beginning of the second decade. The milder end of the spectrum more closely resembles BMD, with ambulation continuing into the third decade. Cardiac involvement occurs in 10–55 % of affected individuals.

Emery-Dreifuss muscular dystrophy (EDMD) in early childhood typically presents with prominent contractures involving ankles, elbows, and spine together with a slowly progressive muscle weakness and wasting initially in a humeroperoneal distribution and later extending to the scapular and pelvic girdle muscles. In some patients contractures may be less prominent and muscle weakness is more proximal with a slowly progressive course. The cardiac involvement is an important part of the clinical feature that may include palpitations, presyncope and syncope, poor exercise tolerance, and congestive heart failure. A pure cardiac presentation is seen in some families. The X-linked form is caused by mutations in EMD, the gene encoding emerin; the dominant/recessive forms are caused by mutations in LMNA, the gene encoding lamin A/C.

If symptoms of limb-girdle dystrophy are found in a girl, one should always consider the rare possibility of DMD or BMD occurring in a female with an abnormal karyotype (e.g., 45 XO) or nonrandom X chromosome inactivation.

Acid maltase deficiency (AMD) and spinal muscular atrophy (SMA) type III may be considered in the differential diagnosis with proximal muscle weakness and sometimes calf muscle hypertrophy; however, the serum CK, electrodiagnostic studies, and muscle biopsy features (i.e., glycogen storage in AMD, neurogenic changes in SMA) will easily permit the distinction from these disorders [54].

In rare instances, dystrophinopathies may present similarly to congenital muscular dystrophies [3, 141] with neonatal weakness, hypotonia, and subsequent developmental delay. The differential diagnosis can be made clinically by the modestly increased CK level and the frequent facial and eye muscle involvement and contractures in congenital muscular dystrophies. Muscle biopsy immunostaining for dystrophin may also be helpful in differentiating the two entities.

Dermatomyositis before the onset of the rash in rare instances can be mistaken for a dystrophinopathy, but the acute onset of symptoms permits easy distinction from DMD or BMD.

An unexplained persistent elevation of liver enzymes should always alert the clinician to the possibility of an underlying muscular dystrophy including females, who could prove to be symptomatic females, asymptomatic carriers of DMD/BMD, asymptomatic males with DMD/BMD, or patients with other muscular dystrophies [142]. In these instances, measurement of serum CK, which is a more specific muscle enzyme, should always be made to prove the myogenic origin of the elevated liver enzymes. Finally, a dystrophinopathy should be considered in all cases of dilated cardiomyopathy.

Laboratory Features and Diagnosis

The new era of advanced molecular diagnostic tools provides an accurate and prompt diagnosis of DMD/BMD, allowing initiation of appropriate measures, continuing support and education, and avoiding a potentially pervasive diagnostic process. Suspicion of clinical diagnosis for DMD or BMD should be considered irrespective of family history on the basis of the clinical presentation and level of serum CK. Reduced motor skills, particularly the inability of run and jump in a boy between ages 3 and 5 years, bring the possibility of DMD to attention. Older boys with later age of onset for similar pattern of weakness involving pelvic girdle and thigh muscles followed by proximal upper extremity weakness are suspect for BMD diagnosis. In both situations, testing for serum CK is indicated. The next step in the diagnostic strategy should be confirming the clinical diagnosis of DMD/BMD using available new tools for identifying precise genetic defect. Extensive mutation analysis is a necessity, not to satisfy academic interest but because evolving treatment paradigms depend on the full characterization of the deletion/duplication endpoints and the identification and position of point mutations.

Serum Muscle Enzymes

CK is the most important serum enzyme in the diagnosis of DMD. Striking CK elevation may be present even in the first years of life, preceding clinical manifestations of obvious motor impairment. Before the age of 5 years, the serum CK levels are usually 50–100 times of normal in DMD and can be markedly increased to 20–100 times of normal in BMD [68, 143] and, therefore, cannot be used as a way of differentiating between the two types of dystrophy. The concentration of CK, however, tends to decline with age, at a rate of about 20 % per year. In about 70 % of carriers, CK levels are elevated, but decrease with age.

Serum aminotransferases, AST and ALT, both produced by muscle as well as liver cells are also usually elevated in DMD and BMD. Their increased levels are thought to be related to leakage through muscle membranes [142]. Therefore, diagnosis of DMD should be considered before liver biopsy in a male child particularly with unintended discovery of increased transaminases.

Electromyography

Patients with classic features of DMD or BMD do not need electrodiagnostic studies for diagnostic purposes, but in sporadic cases of BMD or carrier females with modest serum CK elevation (less than 1,000 IU/L) and proximal muscle weakness, electromyography may have to be considered to exclude a neuropathic process (e.g., SMA) and before undergoing genetic testing for confirming the diagnosis. Nerve conduction studies including compound muscle action potentials (CMAPs) are normal in the early phases of the disease. Needle EMG in DMD/BMD shows myopathic changes, usually short-duration, low-amplitude polyphasic early-recruited motor unit action potentials (MUAPs), particularly in proximal muscles. It may also show increased insertional activity with fibrillation potentials. With disease progression, the CMAPs decrease in amplitude, the insertional activity diminishes, MUAPs become very small with decreased recruitment, and the fibrillation potentials disappear. At the advanced stages of DMD/BMD, the muscle may become electrically silent.

Molecular Genetic Testing

Until recently, multiplex PCR and Southern blotting were utilized for dystrophin gene deletion/duplication analysis. New tools for mutation detection have been introduced including multiplex ligation-dependent probe amplification (MLPA) and multiplex amplifiable probe hybridization (MAPH) providing relatively rapid and inexpensive exon screening [144]. When MLPA or MAPH are negative, DNA sequencing is required to detect subexonic rearrangements or point mutations [43] (see Dystrophin Gene Mutations).

Muscle Biopsy

Muscle biopsies derived from DMD/BMD patients are processed for examination of histopathological features, immunohistochemistry for detection of dystrophin in muscle membrane, and Western blot analysis for quantitation of dystrophin protein.

Histopathological Findings

Overall the muscle biopsy features of DMD include fiber size variability with atrophy and hypertrophy, an alteration in fiber type resulting in type I fiber predominance, muscle fiber degeneration, regeneration, isolated "opaque" hypertrophic fibers, and significant replacement of muscle by fat and connective tissue. The degenerating necrotic fibers are recognized on H&E and trichrome staining by their lighter-stained glassy or homogenous cytoplasm (Fig. 56.3a). Small groups of basophilic regenerating and necrotic fibers are an important feature of DMD biopsies. Hypercontracted large opaque and darkly stained fibers are seen commonly. Their origin is unclear but thought to be due to segmental hypercontraction resulting from plasma membrane defects that allow the influx of calcium-rich extracellular fluid [145]. Fiber splitting and central nuclei are less often, present in 2–4 % of the fibers compared to other dystrophies.

Inflammatory cells are seen in the perimysium, endomysium, and perivascular spaces. They consist mostly of T lymphocytes and macrophages. Most T cells are CD8+ and occasional nonnecrotic muscle fibers are focally surrounded and invaded by CD8+ cells [68]. A striking increase in the endomysial and perimysial fibrosis occurs with disease progression. The differences in the microscopic appearance of muscle between DMD and BMD correlate well with the severity of the disease, with fewer necrotic, hypercontracted, and regenerating fibers seen in milder phenotypes and the frequency of hypertrophic fibers and internal nuclei increase with age (Fig. 56.4a).

Dystrophin Immunostaining

In muscle biopsies derived from DMD patients, there is no detectable staining of the sarcolemma using commercially available anti-dystrophin antibodies against amino-terminal (dys3), carboxy-terminal (dys2), and rod domains (dys1) of the protein. However, in about greater than 50 % of DMD patients, antibodies against different epitopes show membrane staining for dystrophin in about 1 % of fibers in small clusters, which are called "revertant" fibers [146] (Fig. 56.3b–d). They arise from a somatic mutation

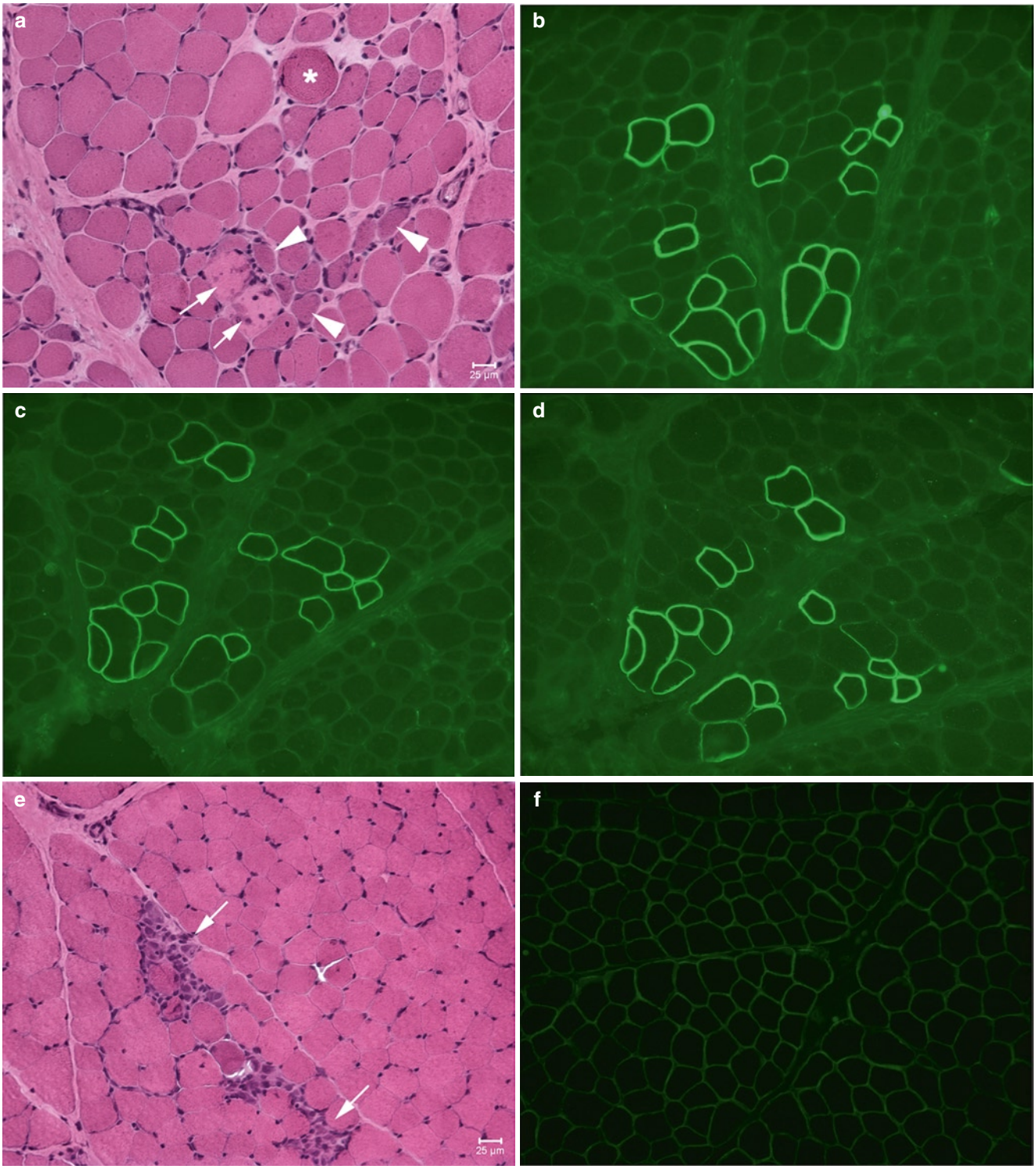

Fig. 56.3 H&E and immunofluorescence staining of frozen sections of skeletal muscle biopsies with anti-dystrophin antibodies. (**a**–**d**) From a 5-year-old boy who has DMD with a duplication of exons 55 through 63 in the dystrophin gene. H&E stained section (**a**) shows a small group of basophilic regenerating muscle fibers (between *arrowheads*) and necrotic fibers (*arrows*) among fibers with increased variability in size; *asterisk marks* a hypercontracted fiber. Membrane staining for dystrophin using specific antibodies to amino-terminal Dys3 (**b**), rod domain Dys1 (**c**), and carboxy-terminal Dys2 (**d**) is absent with the exception of small clusters of revertant fibers. H&E stained section (**e**) from a 5-year-old boy who has BMD with a duplication of exons 19 through 29 in the dystrophin gene, presented with history of exercise-induced myalgias and CK elevation at 2,000–11,000 IU/L range and no muscle weakness on examination. A small focal area of inflammation is present (*arrows*). Membrane staining for Dys3 is severely reduced (**f**), while membrane staining for Dys1 (**g**) and Dys2 (**h**) is present, compatible with an in-frame duplication mutation

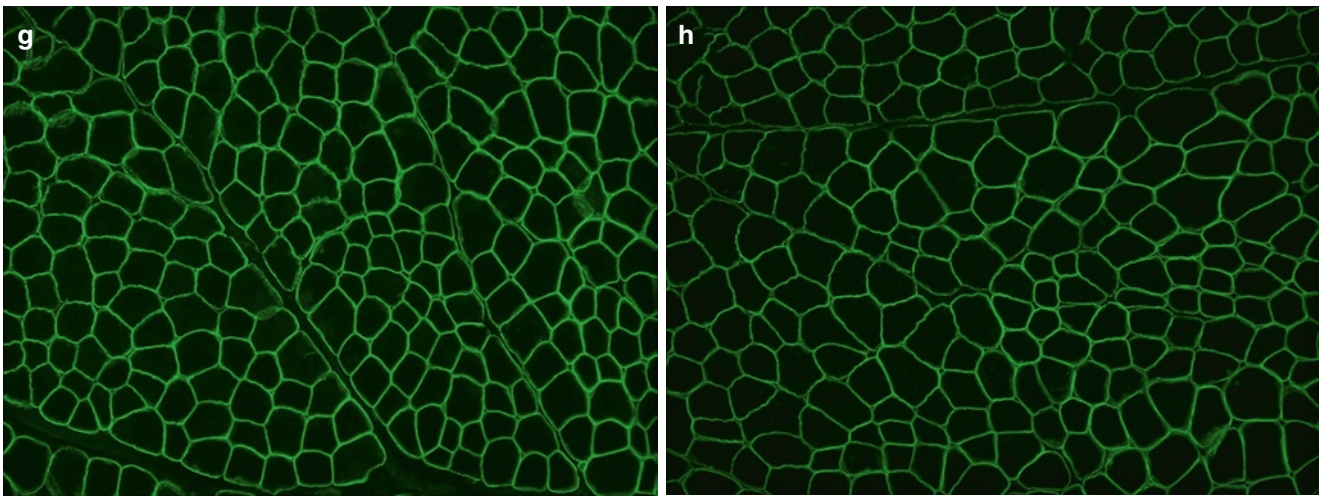

Fig. 56.3 (continued)

at a second site of the gene that corrects the original frame shifting mutation and restores the reading frame [147, 148]. In BMD patients, either normal or partial staining of the sarcolemma is observed (Figs. 56.3f–h and 56.4b). Immunohistochemistry for dystrophin is useful in identifying sporadic cases of symptomatic or asymptomatic female DMD carriers with high serum CK levels in families without a male proband, or in families with no detectable deletion/duplication results. Thus, symptomatic and asymptomatic DMD carriers with elevated CK values may exhibit a characteristic mosaic pattern of dystrophin immunostaining.

Immunostaining of muscles, from DMD patients or the mdx mouse model of the disease, shows that loss of dystrophin leads to a selective reduction or absence in the staining of the DAPs such as α-, β-, γ-, and δ-sarcoglycans and α- and β-dystroglycans [149]. However, another dystrophin-related protein, utrophin, which has homology to dystrophin shows diffuse membrane staining outside of neuromuscular junctional folds resulting from a compensatory upregulation in dystrophin-deficient muscle [150] (Fig. 56.4c).

Western Blot Analysis

Western blot for dystrophin quantitation accurately predicts the severity of the muscular dystrophy phenotype (Table 56.2), especially in cases with no family history (Fig. 56.4). Because of the exceptions to the reading frame rule, the type of the deletion (in-frame versus out-of-frame) is not always a reliable predictor of the severity of the disease. The Western blot assesses not only the amount of dystrophin but also the molecular size of the dystrophin molecule, which is often decreased (80 %) (Fig. 56.4d) and rarely increased (5 %) in BMD patients (in deletion and duplication cases, respectively). Antibodies against carboxy and rod domains should be utilized in the Western blot assay in order to avoid false-negative results. Given the qualitative nature of dystrophin immunostaining and the possibility of normal appearance in patients with BMD, Western blot has become the gold standard for dystrophin analysis.

Algorithm for Diagnosis of DMD/BMD

Familial or Sporadic Cases with Clear Phenotype

If the diagnosis of DMD/BMD has been made clinically in other family members but has not been confirmed previously by molecular diagnosis, the first step is DNA testing for detection of a dystrophin gene deletion/duplication mutation, by MLPA or MAPH (Fig. 56.5). If testing for deletion/duplication is negative, the next step is DNA sequencing to detect subexonic rearrangements or point mutations [43]. The mutation detected in the dystrophin gene may then be used as a marker for testing other at-risk family members, for carrier detection, and also for prenatal diagnosis, by means of amniocentesis or chorionic villus biopsy.

In sporadic cases (i.e., family history negative for DMD/BMD), the same diagnostic approach, outlined for familial cases, is recommended if the clinical presentation is clear and highly suggestive of DMD or BMD.

Sporadic Cases with Unclear Phenotype

In sporadic cases with unclear phenotype (outliers), if a deletion or duplication is found by MLPA or MAPH, its reading frame status will allow in most instances prediction of the phenotype (DMD or BMD). Because of the rare occurrence of exceptions to the "in-frame/out-of-frame" rule, some clinicians justify the option of a muscle biopsy for Western blot analysis to predict the severity of the disease, although this information has no clinically useful application since these cases represent the spectrum of dystrophinopathy.

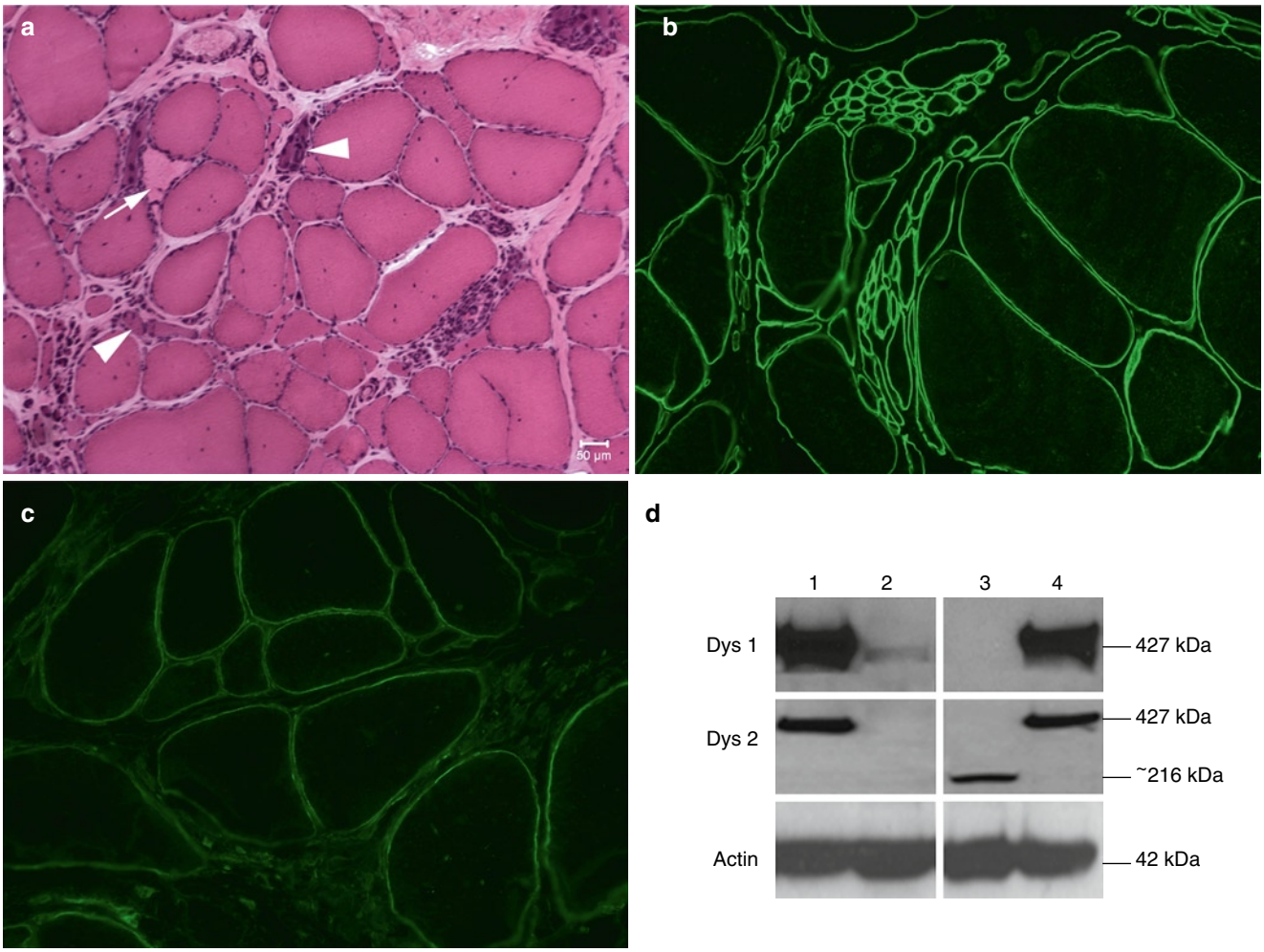

Fig. 56.4 H&E stained section (**a**) from a 12-year-old boy with BMD who has exons 10 through 44 and promoters Dp260 and Dp140 in-frame deletion. He is ambulatory and has CK levels over 14,000 IU/L. Marked variability in muscle fiber size (<10 to over 150 µm in diameter), an increase of internal nuclei, and rare necrotic (*arrow*) or regenerating fibers are seen. Immunofluorescence staining for Dys2 shows normal membrane staining (**b**); membrane staining for Dys1 and Dys3 is absent (not shown). Membrane staining for utrophin is present suggesting compensatory upregulation (**c**). Western blot analysis shows a truncated protein reduced in size with Dys2 antibody; dystrophin band is absent with Dys1 antibody (**d**, lane 2). Lane 3 shows severely reduced dystrophin with Dys1 and Dys2 from a DMD muscle

If DNA analysis fails to detect a dystrophin deletion/duplication, a muscle biopsy for dystrophin assay will need to be considered, particularly in (1) clinically atypical cases, (2) families without a clear-cut X-linked pattern of inheritance, and (3) families with affected male and female siblings, suggesting an autosomal recessive form of muscular dystrophy. If the Western blot demonstrates dystrophin deficiency, the symptoms may be due to a point mutation or subexonic rearrangements. If dystrophin immunostaining and Western blot analysis are normal, another muscular dystrophy (e.g., sarcoglycanopathy) must be considered.

Females with Dystrophinopathy

Female patients can have an early-onset, progressive muscular dystrophy if they have the following: (1) 45X0, 46XY, or Turner mosaic karyotypes; (2) an apparently balanced X/autosome translocation with breakpoints in Xp21, within the dystrophin gene, and preferential inactivation of the normal X; and (3) a normal karyotype but nonrandom (skewed) X chromosome inactivation leading to diminished expression of the normal dystrophin allele. Therefore, following the exclusion of other neuromuscular diseases (e.g., polymyositis, spinal muscular atrophy) by EMG and muscle biopsy, chromosomal analysis should be considered in all symptomatic females, especially those with highly elevated serum CK levels. Further study with a DNA deletion test may be diagnostic in a symptomatic female, especially in cases with 45XO, 46XY, or Turner mosaic karyotypes. About 2.5 to 10 % of manifesting carriers may have clinically apparent muscle weakness. Almost all symptomatic female carriers of mutant dystrophin genes show skewed X-inactivation, which can be detected by a PCR-based androgen receptor assay.

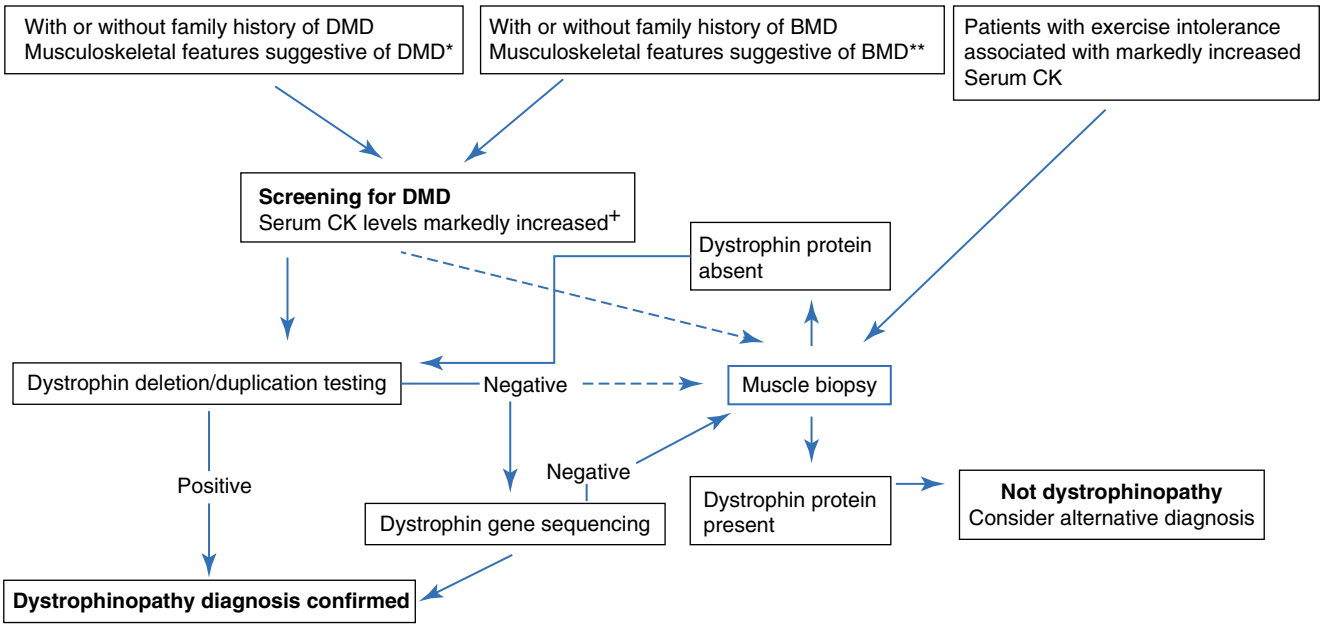

Fig. 56.5 Algorithm to guide diagnostic workup in suspected DMD/BMD patients for confirmation of dystrophinopathy diagnosis. For patients diagnosed by muscle biopsy, dystrophin genetic testing is also necessary. For patients diagnosed by genetic testing, muscle biopsy is not necessary, and if at all possible, defer muscle biopsy until patient participates in a later clinical trial. *DMD* Duchenne muscular dystrophy, *BMD* Becker muscular dystrophy, *CK* creatine kinase (*, ** see Table 56.2 for musculoskeletal features; + see Table 56.2 for serum CK levels)

Immunohistochemical stains in muscle biopsies from manifesting carriers with significant elevation of CK levels generally show high proportions of dystrophin-negative fibers, creating a mosaic pattern of dystrophin immunofluorescence. In asymptomatic carriers with increased CK, there may be dystrophin-negative fibers by IF; however, if the CK levels are normal, dystrophin-negative fibers are difficult to detect.

Genetic Counseling

With clear X-linked transmission, genetic counseling is similar to that for all X-linked recessive diseases. However, mothers of children with DMD or BMD should be made aware of the rare risk of mild skeletal muscle weakness or dilated cardiomyopathy in carriers, for the purpose of an adequate follow-up evaluation of themselves and their daughters.

In sporadic cases, with a negative mutation analysis in the mother of the proband, the parents should understand that germline mosaicism cannot be excluded; because of its relatively high incidence (20 %), there will be at least a 7–10 % statistical risk (may be higher in individual cases) of recurrence of DMD/BMD in subsequent male offspring. Again, because of possible germline mosaicism, sisters of a sporadic case should be tested for carrier status also, even if the mother of the sporadic proband is DNA deletion negative.

Treatment and Management

Supportive Treatment

The main goal in the management of DMD/BMD is to maintain ambulation for as long as possible and manage the associated complications, such as joint complications, scoliosis, cardiomyopathy, respiratory insufficiency, and weight gain. Therefore, therapeutic interventions in DMD/BMD patients require a multidisciplinary approach, aimed at maintaining function, management of pulmonary and cardiac complications, improving quality of life, and providing psychological support.

Contractures begin early; daily passive *stretching exercises* to minimize and delay contractures of iliotibial bands, Achilles tendons, and hip flexors are the mainstays of physical therapy. Lightweight plastic ankle-foot orthoses (AFOs) can be applied during sleep to prevent equinus contractures. Contractures of shoulders and elbows are usually not a major functional problem because of the patient's inability to abduct the arms or fully extend the elbows at advanced stages of the disease. Contractures of wrists and fingers should be treated by passive mobilization and by wearing wrist orthoses at night [71]. Exercise during physical therapy should be limited, especially if it induces muscle pain.

By the age of 9 years, standing and walking can be maintained by using lightweight plastic ankle-foot *orthoses* or long leg braces (knee–ankle–foot orthoses, KAFOs), the latter usually in conjunction with a walker to help maintain

balance [151]. The fitting and use of KAFOs may involve and orthopedic surgical intervention (Achilles tendon release) and intense physical therapy. The use of a standing frame should be introduced before the child is no longer able to walk. A standing frame used for a few hours a day, even with minimal weight bearing, can be important in preventing and reducing the severity of contractures, decubitus ulcers, and scoliosis and also improves bone density and gastrointestinal and respiratory functions.

Surgical release of contractures of the hip flexors, iliotibial bands, and Achilles tendons combined with the use of braces has been demonstrated to prolong the ability to walk by 1–3.5 years [72, 151–158]. Although this is a relatively short period of time, it can be functionally and psychologically very important for the patient and his family [159]. Furthermore, it appears that prolongation of ambulation, or even standing, delays the onset of scoliosis [158]. Several combined or isolated surgical procedures and techniques, such as release of tensor fasciae latae, tenotomy of the Achilles tendon, and posterior tibial tendon transfer, are used to obtain these results. However, timing of the surgical procedures, the type of operation, and the need for postoperative bracing are the subject of considerable debate in the literature [159]. Controversy has focused on the potential benefit of hip abduction contractures, which provide a more stable broad-based gait, and the need to correct them [159]. The current approach in many centers is strictly individualized and some patients elect not to have surgery. Markedly weak hip and quadriceps muscles are often deterring factors from surgery since reambulation can be difficult even if the knees and feet are straight. It is preferable to operate on patients while they are still ambulatory, because recuperation is easier and there is less need for postoperative bracing. Patients still ambulating with isolated equinus contractures often benefit from heel cord lengthening with posterior tibial tendon transfer [151, 159].

Scoliosis inevitably happens with wheelchair confinement. In order to avoid asymmetric positioning, the wheelchair should be properly fitted with a reclining back and neck extender and lateral chest wall supports, which may retard the development of scoliosis. During the ambulatory phase a spinal radiography is warranted if scoliosis is observed clinically and is indicated as a baseline for all patients around the time that wheelchair dependency becomes evident. Monitoring with an anteroposterior spinal radiography is recommended yearly for curves less than 15°–20° and every 6 months for curves more than 20° irrespective of steroid treatment up to skeletal maturity [160]. *Surgical correction of scoliosis* should be considered when the spine is at Cobb angle between 20° and 40° and should be planned before respiratory and cardiac functions decline significantly. To decrease the operative risk, it is optimally performed when FVC is still >30 % [160, 161]. The main reason for anterior spinal fusion is to prevent further progression of spinal deformity. Long-term objectives of the surgery are to achieve a good sitting posture, comfort, and quality of life by avoiding the complications of progressive scoliosis [160]. Cardiac and pulmonary evaluations should always precede surgery. Adverse anesthetic reactions during surgery can be minimized by the use of appropriate agents [162]. Boys who have been treated with daily corticosteroids have a greatly decreased risk of scoliosis [163]. Thoracic-lumbar-sacral orthoses are not very helpful in the prevention or arrest of evolving scoliosis [157, 164–169].

Weight control is important and should be monitored carefully. As mobility declines, weight gain is common and contributes to the loss of ambulation. Dietary consultations are recommended in patients who are receiving prednisone therapy to ensure an adequate intake of vitamin D and calcium, provide guidance regarding weight control, plan a healthy diet, and monitor calorie and sodium intake.

Symptomatic involvement of gastrointestinal smooth muscle is more common in older patients and may lead to constipation, impaction, and even acute gastric dilatation. Care givers should be encouraged to promote a diet rich in fiber and adequate hydration of patients. Vaccinations against influenza and pneumococcal infections should be performed regularly and can be administered to patients treated with corticosteroids.

After the age of 6 years or older, pulmonary function studies should be performed yearly. In nonambulatory patients, respiratory assessment may become necessary during clinical visits at least every 6 months. During nonambulatory stage, overnight monitoring of oxygen saturation with pulse oximetry allows the detection of early nocturnal hypoventilation and is recommended at least once every 6 months [170]. Nocturnal hypoventilation responds well to initiation of *noninvasive intermittent positive pressure* ventilation. Daytime lung function parameters predict sleep hypoventilation [171] and may prove to be useful in appropriate scheduling of polysomnography and noninvasive ventilation during sleep. Respiratory assistance may be used during periods of respiratory infections.

Baseline assessment of cardiac function is recommended at the diagnosis or by the age of 6 years and the care team should include a cardiologist who should be involved in diagnosis and management of cardiomyopathy. A minimum cardiac assessment to include EKG and echocardiogram is recommended once every 2 years until the age of 10 [170]. Annual cardiac assessments could begin at the age of 10 or at an earlier age if abnormalities are detected. *Cardiac transplantation* is a therapeutic option that can be lifesaving for patients with Becker MD assuming that they have first had a careful trial of medical therapy and, in some, implantable cardiac defibrillators [102, 172, 173].

Anesthesia must be approached with caution in patients who have dystrophinopathies [174]. Patients with DMD and

BMD can have severe complications from anesthesia, including cardiac arrest. Most complications seem to be related to use of succinylcholine, a muscular relaxant that may trigger hyperkalemia [174]. Others have been attributed to use of volatile anesthetic agents. Patients also can have a reaction similar to malignant hyperthermia [174], develop rhabdomyolysis, and have masseter muscle spasm.

Pharmacologic Treatment

Corticosteroids are the best treatment option currently available. Randomized control trials have shown that oral prednisone produces a significant increase in muscle strength, pulmonary function, and overall functional ability in DMD [175, 176]. The mechanism of improvement seen in individuals with DMD treated with prednisone is not well understood but thought to be through an anti-inflammatory effect related to reduction in total T cells and cytotoxic–suppressor T cells [175]. This improvement is most effective with a single daily dose of 0.75 mg/kg regimen, begins within 10 days, and reaches a plateau after three months. Observed side effects include weight gain, hypertension, behavioral changes, growth retardation, and cataracts [175, 176]. There is also an increased frequency of vertebral and long bone fractures with prolonged corticosteroid use [163]. Deflazacort, a synthetic derivative of prednisolone (0.9 mg/kg/day), appears to be equally effective but is not available in the United States [177]. Daily corticosteroids improve muscle strength and function, significantly slow the progression of weakness, prolong ambulation to the mid teens or later, and delay the onset of respiratory and cardiac dysfunction [178, 179]. Asymptomatic cataracts are more common with deflazacort, and weight gain is more prominent with prednisone. If adverse effects require a reduction in prednisone dosage, doses as low as 0.3 mg/kg/day produce improvement that is less prominent but still significant. High-dose weekly prednisone, 5 mg/kg, given each Friday and Saturday, can be considered as an alternative to daily treatment in males on a daily regimen with excessive weight gain and behavioral issues [180].

Data regarding the optimal age to begin treatment with corticosteroids or the optimal duration of such treatment are insufficient. Thus, at this point corticosteroid therapy remains the treatment of choice for affected individuals between ages 5 and 15 years. It is recommended that boys with DMD who are older than age 5 years should be offered treatment with prednisone (0.75/mg/kg/day, maximum daily dose: 40 mg) as soon as plateauing or decline in motor skills is noted. Prior to the initiation of therapy, the potential benefits and risks of corticosteroid treatment should be carefully discussed with parents and caregivers individually.

Information about the efficacy of prednisone in treating individuals with BMD is limited. Many clinicians advocate continuing treatment with glucocorticoids after loss of ambulation for the purpose of maintaining upper limb strength, delaying the progressive decline of respiratory and cardiac function, and decreasing the risk of scoliosis. Retrospective data suggest that long-term daily corticosteroid treatment may reduce the progression of scoliosis; however, an increased risk for vertebral and lower limb fractures has been documented [163].

Emerging Therapies

Although there is no curative treatment for DMD, there are many areas of therapeutic intervention under investigation. Three major treatment strategies have emerged to repair the DMD gene defect which include viral-mediated gene replacement, exon skipping, and mutation suppression. Additional strategies include but are not limited to utrophin upregulation, muscle enhancement, fibrosis reduction, and nNOS modulation which will be discussed in brief.

Gene Replacement

Adeno-associated virus (AAV) delivery remains the most promising strategy for replacement of the dystrophin gene. It is nonpathogenic and remains stable in nonreplicating cells (i.e., muscle), and multiple serotypes exhibit tropism for muscle. One caveat for AAV delivery as a treatment for DMD is the large size of the dystrophin gene which exceeds the packaging capacity of AAV (<5kb). Fortunately, the modular structure of dystrophin allows some flexibility; deletions of nonessential coding regions allow dystrophin to retain significant function if the reading frame is intact. This conclusion was initially based on a clinical observation in a BMD patient with a large in-frame deletion of exons 17–48 removing a significant portion of the rod domain [181]. The patient remained ambulatory until age 61 despite the absence of 46 % of the dystrophin gene. This led to the design of mini- and micro-dystrophin transgenes that were able to fit into AAV. Numerous proof-of-principle studies using AAV delivery of miniature dystrophin genes have shown reversal of the dystrophic phenotype in the *mdx* mouse model for DMD. The first trial of AAV-mediated delivery of mini-dystrophin defined potential hurdles to consider for future trials that restore dystrophin regardless of approach [182]. These lessons include the potential for an immune response generated against novel epitopes presented by exogenous dystrophin in patients with large endogenous deletions as well as immunity primed by revertant fibers. Revertant fibers result from spontaneous second-site mutations which restore the reading frame of dystrophin. Once thought to be tolerizing, the AAV mini-dystrophin trial revealed that revertant fibers

could be immunogenic and accelerate responses following gene transfer.

Upregulation or replacement of utrophin is another therapeutic strategy for DMD that has shown promise. Utrophin shares 80 % sequence homology with dystrophin and has been shown to partially restore function as a dystrophin surrogate in preclinical transgenic mice [183] or gene replacement studies [184]. Utrophin expression is limited to the neuromuscular and myotendinous junctions in normal muscle. However, in both dystrophic mice and DMD patients, it is overexpressed in the sarcolemma of all muscle fibers, partially compensating for the mechanical role of dystrophin in the membrane. Upregulation of utrophin holds particular advantage because of the unlikely occurrence of an immune response as seen following mini-dystrophin gene replacement [182]. Alternative strategies have also emerged to upregulate utrophin at the sarcolemma including several small molecules which demonstrate transcriptional upregulation through the utrophin-A promoter [185–187] or by the use of DAP-stabilizing molecules such as biglycan (rhBGN) [188].

Exon Skipping

Exon skipping is a second molecular treatment approach which is targeted at the messenger RNA (mRNA) level allowing one or more exons to be omitted to restore the dystrophin reading frame. This is accomplished with antisense oligonucleotides (AONs) that are artificially synthesized to hybridize in a complementary fashion to mRNA to modify splicing. Preclinical efficacy has been demonstrated in the mdx mouse, dystrophin/utrophin knockout mouse, and CXMD dog [189–191]. It has been predicted that through targeted skipping of particular exons, as many as 60–80 % of DMD mutations could be corrected. Two phase I safety trials were conducted in DMD patients targeting exon 51 using AONs with two different chemical backbones, 2-*O*-methyl AON-PRO051 and phosphorodiamidate morpholino oligomer (PMO) – AVI-4658 [192, 193]. Safety was demonstrated in both studies which were limited to an intramuscular injection of the AON in a single muscle. Phase I/II extension studies were performed with both AONs to assess efficacy and tolerability following systemic delivery. In the PRO051 trial, dose-related efficacy was achieved with evidence of new dystrophin expression in approximately 60–100 % of muscle fibers in 10 of 12 patients and modest improvement in the 6-min walk test [194]. In the AVI UK phase II open-label study with AVI-4658 (Eteplirsen), 7 of 19 patients saw a modest response with a mean increase of sarcolemmal dystrophin from 8.9 % to 16.4 % [195]. Additional phase II randomized, double-blind, placebo-controlled trials are under way to assess multiple-dose efficacy.

Mutation Suppression

A second molecular approach involves suppression of stop codon mutations of the *DMD* gene that comprise approximately 15 % of DMD cases. Two pharmacologic tactics have shown preclinical efficacy and have also been tested clinically. In mdx mice, in vivo mutation suppression was shown with the aminoglycoside antibiotic, gentamicin [196]. In the most definitive trial, DMD patients ($n = 16$) with stop codons, treated weekly or twice weekly for 6 months (7.5 mg kg IV), showed a significant increase in dystrophin levels with the highest levels reaching 13 % and 15 % of normal. Muscle strength was stabilized and a modest increase in forced vital capacity was achieved. Although this study demonstrates the therapeutic potential of gentamicin, higher doses might be necessary to improve functional outcomes. The known renal toxicity of aminoglycoside antibiotics and the nuisance of intravenous administration have pushed the field to identify an orally administered agent.

Ataluren, formerly referred to as PTC124 (PTC therapeutics), demonstrated promise as an orally administered pharmacologic read-through agent for stop codon mutations [197]. Preclinical studies in the *mdx* mouse revealed dystrophin expression in skeletal, cardiac, and diaphragm muscle and protected skeletal muscle from eccentric contraction-induced injury. A phase I study in healthy volunteers established safety and tolerability at doses exceeding what was required for preclinical efficacy [198]. Dystrophin appeared to increase posttreatment in a phase IIa proof-of-concept 28-day study in DMD/BMD patients. Following these results, a randomized, double-blind, placebo-controlled phase IIb trial was conducted evaluating safety and efficacy over a 48-week treatment period. PTC, Inc., released preliminary results indicating a very strong safety profile; however, the primary endpoint of the 6-min walk test did not reach statistical significance [199]. Ataluren is under continued development for the treatment of cystic fibrosis [200] and hemophilia (clinicaltrials.gov NCT00947193); positive results from these studies may provide evidence for further pursuit as a treatment option for DMD.

Muscle Growth Products

Increasing muscle fiber size and strength is another treatment strategy for DMD under intense investigation. Inhibition of the myostatin pathway shows promise for clinical application. Myostatin is a member of the transforming growth factor beta (TGF-β) family and is a potent regulator of muscle growth. Accordingly, myostatin knockout mice demonstrate dramatic muscle hypertrophy and hyperplasia [201]. The role of myostatin as a negative regulator of muscle mass is highly conserved across species including humans, as shown by the

identification of a myostatin splice-site mutation leading to the loss of myostatin protein in a hypermuscular family [202]. As a disease characterized by progressive muscle loss, DMD is a natural therapeutic target for myostatin blockade. In one approach, a recombinant human antibody (MYO-029) that binds with a high affinity to myostatin and inhibits its activity [203] was shown to increase muscle mass in immunodeficient mice by approximately 30 % over 3 months, similar to the biological response demonstrated for other myostatin-neutralizing antibodies [204]. MYO-029 was subsequently studied in a double-blind randomized clinical trial in Becker, limb-girdle muscular dystrophy (including multiple types), and facioscapulohumeral muscular dystrophy where safety but not clear efficacy was established [203]. Based on this principle, a potentially more potent agent is follistatin, a myostatin inhibitor that has been demonstrated to lead to muscle growth in vivo. Delivery of the follistatin gene by adeno-associated virus (AAV) in mice or nonhuman primates shows dramatic increases in muscle size and strength, and this approach is poised for gene therapy [205, 206].

Apart from myostatin inhibition, insulin growth factor-1 (IGF-1) treatment is another strategy to increase muscle mass and strength under investigation for DMD. IGF-1 is a growth factor and key mediator of anabolic pathways in muscle which stimulates whole body protein metabolism [207]. It is involved in muscle repair and regeneration by stimulating the proliferation and differentiation of skeletal muscle cells [208–210]. Preclinical studies found that transgenic overexpression of IGF-1 in DMD mice increased skeletal and diaphragm muscle mass, increased force generation, and reduced fibrosis and myonecrosis [211, 212]. IGF-1 is already FDA approved for severe primary IGF deficiency. A prospective, randomized, open-label, controlled phase II clinical trial of recombinant IGF-1 (INCRELEX™) has been initiated in glucocorticoid (GC)-treated DMD patients to test its ability to preserve muscle function.

Several other therapeutic strategies are also on the horizon for DMD in either proof-of-principle animal studies or in clinical trial. Fibrosis is a confounding factor for any treatment for DMD. Proliferation of endomysial connective tissue limits muscle regeneration, contributing to progressive muscle weakness. Strategies to prevent or reduce fibrosis alone or in combination with other therapies are under exploration including TGF-β blockade and altering expression of micro-RNAs [213, 214]. Another therapeutic target is neuronal nitric oxide synthase (nNOS). Two variants of nNOS contribute to normal muscle metabolism by attenuating vasoconstriction and helping maintain the ability of contracting muscle to generate force following exercise. nNOS is either downregulated or mislocalized in dystrophic tissue [215] and contributes to overall disease pathology; therefore, reversal of ischemic-induced pathology by upregulating nNOS expression has potential as a treatment strategy. To summarize, multiple therapeutic strategies are on the horizon for treating dystrophinopathies with the goal of replacing the missing dystrophin gene or reversing resultant pathology. This multifaceted disease may not be curable by any one therapy as demonstrated by various treatments under investigation presented here.

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Limb-Girdle Muscular Dystrophies

57

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Introduction

The limb-girdle muscular dystrophies (LGMD) are a heterogeneous group of hereditary neuromuscular disorders with predominant or selective weakness in proximal limb and axial muscles, having an estimated incidence of 1:100,000. While they are congenital in nature, most of them manifest in adulthood with a range of presentation from early childhood to late adulthood, even into 70s and 80s. LGMD has onset of weakness of pelvic and shoulder girdle muscles although specific disorders may initially manifest more prominently in the pelvic or the shoulder girdle. During the progressive course, weakness may spread outside of the pelvic and the shoulder girdle. Depending on the type of LGMD, the lungs and heart may be involved. Creatine kinase (CK) levels may be normal, mildly elevated, or highly elevated. Usually extraocular muscles are spared. Cranial muscles are spared as well, except, in some special cases, facial muscles may be involved. A large number of LGMDs have been described – both clinically and molecularly.

The current classification system of LGMD bases nomenclature on inheritance pattern. Dominant forms of the LGMD are classified as type 1 (LGMD 1), and the recessive forms are classified as type 2 (LGMD 2), with a progressive alphabetical letter indicating the order of gene mapping/identification [1]. The X-linked LGMDs are not numbered or alphabetized. These are listed as a separate group in this chapter. About one third of LGMD patients defined clinically are without genetic identification, and they are classified according to disease mechanism [2].

Historical Perspective

Since the 1800s children with "muscular dystrophies" were found with variable inheritance patterns – X-linked recessive, autosomal recessive, and autosomal dominant. Most such patients presented with proximal weakness, specifically weakness of the muscles of the limb and pelvic girdle. In 1910, Batten classified muscular dystrophies into seven specific categories, based on pattern of presentation, clinical progression, and age of onset [3]. The muscular dystrophy class termed "juvenile type of Erb" comprises the current-day limb-girdle muscular dystrophies (LGMD). The term LGMD was coined by Stevenson in 1953 [4] and was further expanded by Walton and Nattrass in 1954 [5]. Walton and Nattrass described sporadic manifestations of a Duchenne muscular dystrophy (DMD)-like phenotype in three women [5] and suggested that LGMD must be a form of muscular dystrophy. After evaluating several LGMD patients, Walton summarized the clinical manifestations of this heterogeneous disorder that included the following criteria: (1) manifestation in both sexes; (2) common manifestation in the second or third decade (but occasionally later in mid-life); (3) sporadic, autosomal recessive, or autosomal dominant inheritance patterns; (4) primary involvement of shoulder and pelvic girdle muscles, with variable presentation and progression; (5) pseudohypertrophy of the calves (Fig. 57.1); (6) abortive cases which are uncommon; (7) variability in severity and rate of progression but usually severe disability in 20 years after onset; (8) severe disability by mid-life; and (9) later occurrence of contractures and skeletal deformities. The heterogeneity in the LGMD patient population was soon recognized in the late 1980s leading to consideration that LGMD had various pathological mechanisms [6, 7]. The

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subtle overlap (and differences) between previously described conditions was beginning to be noticed (e.g., facioscapulohumeral muscular dystrophy). Since the dawn of molecular genetics in the 1990s, several individual LGMD entities have been defined based on clinical and molecular criteria.

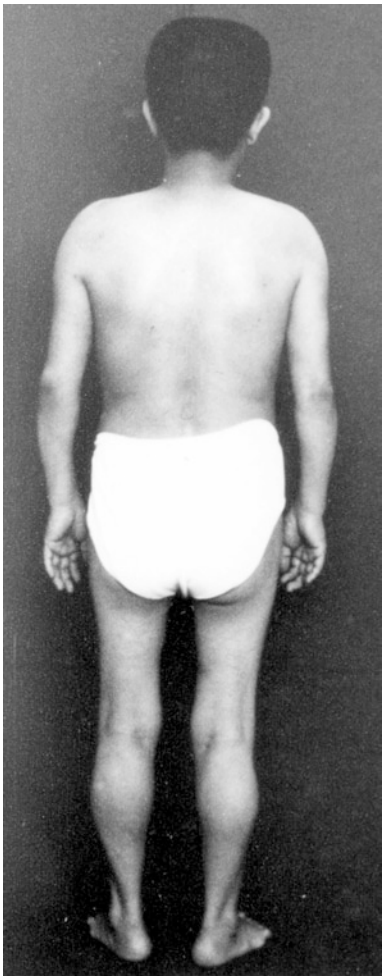

Fig. 57.1 A male patient with calpainopathy with very mild calf hypertrophy

LGMD 1 (Dominant Forms of LGMD)

Eight LGMD 1 loci with dominant inheritance patterns have so far been described based on clinical criteria, but the heterogeneity of the dominant forms of LGMD is expected to expand. Sporadic forms of the disease are often not appreciated, since de novo dominant mutations can present with the disease phenotype but with an obvious lack of family history of the disease. The LGMD 1 forms are usually of an adult-onset pattern and are mild. Affected patients are usually in good health at reproductive age. Thus far, mutations in five genes have been identified to underlie forms of LGMD 1. The LGMD 1 subtypes, characteristic features, clinical features, and limited gene information are provided in Table 57.1. Individual LGMD 1 subtypes are described below.

LGMD 1A (Myofibrillar Myopathy 3, Myotilinopathy)

Over 15 families have been described with women equally as affected as men. The gene responsible for this syndrome is located on chromosome 5q31.2 and identified to be myotilin. Most of the mutations are missense mutations (Lys36Glu, Ser55Phe, Thr57Ile, Ser60Cys, Ser60Ile, Gln74Lys, Ser95Ile, Ala115Thr) and are localized in the serine-rich area of myotilin (see below). The mode of inheritance may be dominant, or sporadic. The onset of the disease is between 42 and 77 years of age except in Virginia family (Thr57Ile), in which the onset was at 27 years of age.

Table 57.1 Listing of subtypes of LGMD 1 and their characteristics

	Clinical phenotype			Gene information		
	Typical onset	Progression	CK increase	Allelism	Gene/locus	Protein
LGMD 1A	Adulthood	Slow	1–15 X	Myofibrillar myopathy, spheroid body myopathy	TTID	Myotilin
LGMD 1B	Variable; childhood to adults	Slow	1–6 X	Several, EDMD2, CMD1A	LMNA	Lamin A/C
LGMD 1C	Childhood	Slow to moderate	10–15 X	Rippling muscle disease	CAV3	Caveolin
LGMD 1D	Adulthood	Slow	1–3 X	None noted	DNAJB6	HSP40
LGMD 1E	Adulthood	Slow	2–4 X	Myofibrillar myopathy	DES	Desmin
LGMD 1 F	Variable; infancy to adults	Rapid	Variable; normal to 6 X	None noted	7q32	To be identified
LGMD 1 G	Adulthood	Slow	Variable; normal to 9 X	None noted	4q21	To be identified
LGMD 1H	Variable; childhood to adults	Slow	Variable; normal to 10 X	None noted	3p23	To be identified

EDMD Emery–Dreifuss muscular dystrophy, *CMD* congenital muscular dystrophy

Weakness is symmetric and starts in the lower extremities and then progresses to the upper extremities. Distal weakness is observed with further progression. Many patients initially present with foot drop. When the upper extremities are involved, the weakness is noticed in the wrist extensors and finger extensors and in the deltoid muscle. Facial and neck extensor muscle weakness may occur. Some patients develop dysarthria (palatal weakness) [8], myalgias, and joint contractures mainly of the ankles. Cardiomyopathy is present in half of patients with onset between the sixth and seventh decade.

Tendon reflexes are absent at the knees and the ankles, but loss of tendon reflexes may be diffused. Progression of the weakness is slow with loss of ambulation 10 years after onset. Serum CK can be normal to 15-fold elevated. Needle electromyography reveals myopathic changes, and in addition fibrillations or myotonic discharges are seen in some patients.

Muscle biopsy reveals a myopathic pattern: significant size variability, rounded fibers, rimmed or autophagic vacuoles, and hyaline inclusions. Abnormal internal architecture can be observed. ATPase stains may reveal spheroid bodies. On immunocytochemistry, myotilin stain is normal, but in abnormal fibers, patches of increased staining may be seen. Increased immunoreactivity of other proteins such as desmin, plectin, gelsolin, and ubiquitin is frequent.

Myotilin, a 498 amino acid protein, is associated with the Z disc and is expressed in skeletal and, to a lesser extent, cardiac muscle. The exact function of the protein is unknown. However, the protein binds to α-actinin and filamin C, cross-links actin filaments, controls sarcomere assembly, and is probably important in stabilizing and anchoring thin filaments to the Z disc during myofibrillogenesis. Defects in the myotilin gene have been associated with the LGMD 1A phenotype [9] and, in a variant syndrome, spheroid body myopathy.

LGMD 1B (Emery–Dreifuss Muscular Dystrophy 2, Laminopathy)

Manifestations of the disease usually begin before the age of 20 years. The most common presentation is symmetrical weakness affecting the proximal lower extremities. A variant of this syndrome (Arg377His mutation of the lamin A/C gene; see below) affects mainly the quadriceps. The progression is slow. The upper extremities are usually involved in the third or fourth decade. Cardiomyopathy is present in about 60 % of patients and is typified by atrioventricular conduction block, bradycardia, and sudden cardiac death [10]. Dilated cardiomyopathy is present before onset of the weakness with Arg377His mutation [11]. Serum CK is normal to mildly elevated. Muscle biopsy shows myopathic changes, and mutated lamin is mislocalized and aggregated in the nucleus and the cytoplasm.

Mutations in the lamin A/C gene are responsible for the LGMD 1B phenotype. Patients with EDMD2 also harbor mutation in the lamin A/C gene, but the clinical manifestations differ. These include contractures of the posterior cervical muscles, the elbows, and the ankles, cardiac involvement, slowly progressive weakness involving the humeral and peroneal muscles with some pelvic girdle involvement, tendon areflexia, and slight elevation in CK levels. The clinical manifestation is similar to the classic X-linked Emery–Dreifuss muscular dystrophy, but the mode of inheritance of EDMD2 is autosomal dominant.

Lamins A and C are members of the intermediate filament family and are present in terminally differentiated cells. The lamin gene is located on chromosome 1. Together, they form part of the nuclear lamina, a fibrous layer on the nucleoplasmic side of the inner nuclear membrane thought to provide a framework for the nuclear envelope. Lamins form dimers through their rod domain and interact with chromatin and integral proteins of the inner nuclear membrane through binding sites located in their rod domains and their carboxy-terminal globular tail. Lamins are structural protein components of the nuclear lamina, a protein network underlying the inner nuclear membrane that determines nuclear shape and size.

LGMD 1C (Rippling Muscle Disease, Caveolinopathy)

In LGMD 1C the onset of symptoms is between 5 years of age and adulthood. Manifestations are moderate and start with proximal weakness in the lower extremities, with difficulty walking and a positive Gowers' maneuver. Multiple reports support the clinical variability of LGMD 1C in presentation and age of onset [12, 13]. For example, a 4-year-old girl with myalgias in the lower limbs but no muscle weakness; a 4-year-old girl with myalgias and a dystrophic pattern in the skeletal muscle biopsy; an 11-year-old girl with a history of floppiness at birth, marginally delayed motor milestones, progressive proximal muscle weakness, and exercise-induced myalgias; a 71-year-old woman, without any previous neuromuscular symptoms, who has mild proximal muscle weakness, scapular winging, slight calf hypertrophy, and a positive Gowers' sign, and two boys (3 and 6 years old) who have muscle pain, calf hypertrophy, increased CK levels, but no muscle weakness; a 57-year-old woman with mild proximal weakness of the lower limbs, calf pseudohypertrophy, and high CK levels; and a 58-year-old woman with myalgias, proximal weakness, calf pseudohypertrophy, and dilated cardiomyopathy were all shown to have LGMD 1C based on molecular genetic analyses. Cramps after exercise may be a complaint. Variable clinical manifestations may occur in single family. The disorder is

characterized by a generally benign clinical course. There is no evidence of respiratory impairment and life expectancy is not reduced.

In LGMD 1C patients, electromyographic results range from a normal to a myopathic pattern, whereas muscle biopsy analysis can show variably sized, degenerating/regenerating muscle fibers, with an increased number of central nuclei, and a mild substitution of connective tissue. Mutations in caveolin-3 (*CAV3*) gene were shown to be responsible for the LGMD 1C phenotype. As might be expected, the expression of CAV3 is reduced invariably both by immunohistochemistry and immunoblot analysis of muscle fibers.

Patients with mutations in *CAV3* may present with a rippling muscle disease (RMD) phenotype. RMD is characterized by signs of increased muscle irritability such as percussion-induced rapid contraction and percussion-induced muscle mounding. Clinically, mechanical stimulation of the muscle leads to electrically silent muscle contractions that spread to neighboring fibers that cause visible ripples to move over the muscle. RMD is usually inherited as an autosomal dominant trait, but autosomal recessive inheritance is also noted. Age of onset of disease varies between 3 and 36 years of age. Muscle hypertrophy is also frequent. At times, a parent may be a benign carrier with muscle hypertrophy but no other signs or symptoms. The presenting manifestations are usually fatigue, tiptoe walking difficulty, and myalgias. The patients usually experience muscle cramps, pain, and stiffness, particularly with exercise. Balling of muscle occurs after percussion, and a characteristic lateral rolling movement of the muscle occurs after contraction followed by stretching. Serum CK levels are usually more than ten times normal. Electromyography reveals myopathic activity. Histological assessment reveals fiber diameter variability and hypertrophy of type 2 fibers. Immunohistochemical evaluation for caveolin is often abnormal.

The gene mutation underlying the LGMD 1C phenotype has been associated with mutations in caveolin-3 gene (*CAV3*). Caveolins are proteins that are localized in the ultrastructural components of the plasma membrane called caveoles. Caveoles were initially described by electron microscopy and described as flask-shaped invaginations of the plasma membrane [14]. Caveolar architecture is thought to be orchestrated by caveolins, a family of proteins composed of the three isoforms, caveolin-1, caveolin-2, and caveolin-3. CAV3 protein is 151 amino acids long and is divided in separate functional domains including N-terminal, scaffolding, transmembrane, and C-terminal domains. In adult myofibers, CAV3 is present throughout the T-tubule system where it assists in the electrical transmission of the contractile impulse. The CAV3 is also present within the sarcolemma where it provides a link between the cytoskeleton and the extracellular matrix and therefore is essential to confer stability to the muscle cell membrane. Most of the caveolinopathies are inherited by autosomal dominant inheritance pattern. Only six autosomal recessive CAV3 mutations have been described.

The critical role of CAV3 in muscle cell physiology was shown by in vitro and in vivo studies and was confirmed by the findings that mutations in caveolin-3 gene lead to distinct neuromuscular and cardiac disorders such as LGMD 1C, idiopathic elevation of serum CK, rippling muscle disease, distal myopathy, and familial hypertrophic cardiomyopathy. Mutations in the *CAV3* gene have been found in patients with the arrhythmogenic long QT syndrome and in sudden infant death syndrome as well.

LGMD 1D (Myofibrillar Myopathy Type 1, HSP40-Opathy)

LGMD 1D is characterized by proximal muscle weakness beginning in the hip girdle region, resulting in waddling gait, and then usually progressing to the shoulder girdle; however, not all patients develop arm weakness. The age of onset is between 20 and 60 years of age, although most patients recall being slow and clumsy as children. The progression is gradual with need for wheelchair 20–30 years or later after disease diagnosis. Most patients have walking difficulties by the eighth decade, and dysphagia occurs in one of five patients. Dysarthria may occur. Mild calf hypertrophy may be present. Cardiac or respiratory involvement has not been observed with LGMD 1D. Most patients have elevated serum CK (up to five times normal). Electromyography shows myopathic changes. Skeletal muscle biopsy reveals dystrophic changes, including variation in fiber size, rounded fibers, endomysial fibrosis, rimmed vacuoles, and eosinophilic cytoplasmic bodies.

The gene mutation underlying the LGMD 1D phenotype has been localized to mutations in the *DNAJB6* gene [15]. The protein product belongs to the heat shock protein 40/DNAJ group which regulates molecular chaperone activity by stimulating ATPase activity. While the exact function of this protein is unknown, it may protect other proteins from undergoing irreversible aggregation. HSP40 is expressed in muscle and other tissues and interacts with proteins implicated in causing myofibrillar myopathies.

LGMD 1E (Familial Cardiomyopathy with Conduction Deficit, Desminopathy)

LGMD 1E is characterized by dilated cardiomyopathy, cardiac conduction-system disease, and adult-onset myopathy [16]. Cardiac manifestations include arrhythmia which becomes manifest in age of 20–25 years and congestive heart failure with 4-chamber enlargement with onset between the

third and fifth decade. Sudden cardiac death without prior cardiac symptoms has been reported.

Muscle pathology reveals variation in fiber size, increased connective tissue, and eosinophilic inclusions and cytoplasmic bodies.

The mutation underlying this phenotype was found in the Desmin gene. The most common mutation was the intron splice donor site mutation (IVS3+3A>G). Desmin is an intermediate filament protein, present abundantly in both skeletal and the cardiac muscles.

LGMD 1F

LGMD 1F was first described in a Spanish family with 32 affected members, spanning five generations. The patients developed proximal muscle weakness with variable age of onset ranging from less than 1 year to 58 years. Genetic anticipation was suggested by the age of onset of the third through fifth generations being significantly less than the preceding generations. Two groups of patients were identified based on the age at onset and clinical progression: a juvenile group (66 %) with manifestations prior to age 15 years and rapid progression and an adult group (28 %) with slow progression and disease onset in the third or fourth decade. All affected patients showed characteristic pelvic and shoulder girdle proximal weakness. Pelvic girdle impairment was more severe and occurred earlier than shoulder girdle weakness, and distal weakness often occurred later. Respiratory muscles were clinically affected in four patients with juvenile onset.

Symptoms of pelvic girdle muscular weakness were noted at onset in 80 % of patients. Commonly affected muscles were the iliopsoas (nearly all), gluteal, hip adductors, deltoid, biceps brachii, paraspinal, and neck flexors. Pelvic girdle impairment was more severe and occurred earlier than in the shoulder girdle. Proximal muscle weakness ranged from MRC grade 0 to 4+, with symmetric distribution. Distal weakness appeared late in the disease course or accompanied initial presentation in severely affected juvenile-onset patients, frequently affecting the extensor digitorum, tibialis anterior, and toe extensor muscles. Scapular winging was reported, and mild facial weakness was seen in juvenile-onset disease. Early-onset patients had generalized muscular wasting, predominantly involving the quadriceps, gluteus, deltoid, biceps, infraspinatus, and supraspinatus muscles. Late in the disease course, contractures are seen at the Achilles tendon, and respiratory muscles might be affected in juvenile onset [17].

Serum CK was normal in 40 % of patients and varied between normal and highs close to 3,000. Electromyography demonstrated myopathic changes with short duration, polyphasia, and low-amplitude potentials, which were more pronounced in the proximal muscles. Sensory and motor nerve conduction velocities were normal.

Muscle histology revealed abnormal fiber size and shape variation, increased endo- and perimysial connective tissue, and scattered degenerative fibers with myophagia. Rimmed vacuoles and central nuclei were reported. Desmin was overexpressed in some fibers, but was not abundant enough for consideration as a significantly abnormal desmin accumulation. LGMD 1F has been linked to chromosome 7q32.1-32 [18]. The causative gene is unknown.

LGMD 1G

LGMD 1G was described in twelve members of a Brazilian-Caucasian family who had mild late-onset proximal weakness associated with progressive finger and toe flexion limitation with an age at onset from 30 to 47 years. The initial symptoms were proximal lower limb involvement in eight patients and muscular cramps followed by lower limbs weakness in one individual and by upper limbs weakness in another. The disability progressed slowly over years. With exception of the youngest patient in the family, all others showed progressive and permanent finger and toe flexion limitation, with reduced movement range in interphalangeal joints. However, intrinsic hand muscles were not amyotrophic and had normal strength. Serum CK was normal or slightly increased (up to 10-fold).

Muscle biopsy revealed fiber size variation with very discrete perimyseal fibrosis and several necrotic fibers with rimmed vacuoles. Scattered groups of small atrophic angulated fibers were also observed. Some of the vacuoles were clearly labeled with antibodies for sarcolemmal proteins, such as dystrophin and α-sarcoglycan, confirming the presence of sarcolemmal membrane in the vacuoles [19]. The gene mutation underlying this LGMD phenotype is yet to be discovered.

LGMD 1H

LGMD 1H was described in 11 members of a large family from Southern Italy. The disease was segregating in four generations with incomplete penetrance with the variable expressivity observed in age at onset and muscular manifestations. With few exceptions, the disease was characterized by slowly progressive proximal muscle weakness in upper and lower limbs, with onset during the fifth decade of life and a relatively benign course. Hypotrophy of both upper and lower limb-girdle muscles, reduced deep tendon reflexes, and calf hypertrophy were present. Cranial nerve innervated and cardiac muscle involvement was not found, and early joint contractures were not observed. Serum CK levels were elevated ranging from 997 to 2,300 U/L.

Table 57.2 The subtypes of LGMD 2

	Clinical phenotype			Gene information		
	Typical onset	Progression	CK	Allelism	Gene/locus	Protein
LGMD 2A	12–30 years	Slow	Mildly elevated	None	CAP3	Calpain-3
LGMD 2B	Adolescence	Slow	10 X	Miyoshi distal myopathy	DYSF	Dysferlin
LGMD 2C	Early childhood	Moderate to rapid	20 to 30 X	SCARMD	SGCG	γ-Sarcoglycan
LGMD 2D	Variable	Rapid	20 X	None	SGCA	α-Sarcoglycan
LGMD 2E	Early childhood	Moderate to rapid	20 X	None	SGCB	β-Sarcoglycan
LGMD 2 F	Early childhood	Rapid	10 to 50 X	None	SGCD	δ-Sarcoglycan
LGMD 2 G	Childhood, adolescence	Moderate	3 to 30 X	DCM 1 N CMD	TCAP	Telethonin
LGMD 2H	Adolescence, adult	Slow	1 to 20 X	Manitoba Hutterite dystrophy, sarcotubular myopathy	TRIM32	E3 ubiquitin ligase
LGMD 2I	Early childhood	Rapid to slow	5 to 40 X	MDC 1C, myopathy with abnormal merosin, Walker–Warburg syndrome	FKRP	Fukutin-related protein
LGMD 2 J	Childhood, adult	Slow	10 to 15 X	Finnish distal myopathy	TTN	Titin
LGMD 2 K	Childhood	Slow	10 to 40 X	MDDGC 1	POMT1	O-Mannosyl transferase 1
LGMD 2 L	Adult	Slow	1 to 100 X	Miyoshi-like myopathy 3	ANO5	Anoctamin 5
LGMD 2 M	Early infancy	Slow	50 to 100 X	MDDGC 4	FKTN	Fukutin
LGMD 2 N	Prenatal to infancy	Rapid	6 to 12 X	Walker–Warburg syndrome, MDDGC 2	POMT2	O-Mannosyl transferase 2

SCARMD severe childhood autosomal recessive muscular dystrophy, *DCM* dilated cardiomyopathy, *CMD* congenital muscular dystrophy, *MDC* muscular dystrophy, congenital, *MDDGC* muscular dystrophy–dystroglycanopathy

Myopathic changes without evidence of denervation were identified by electromyography. Muscle histology showed abnormal fiber size and shape variation and increased presence of endo- and perimysial connective tissues on hematoxylin–eosin staining. Central nuclei were occasionally present. Ragged red fibers were observed in one patient, and subsarcolemmal accumulation of mitochondria on succinate dehydrogenase staining and fibers negative for cytochrome *c* oxidase staining were seen in two patients, suggesting a defect in oxidative phosphorylation and mitochondrial dysfunction. Mitochondrial DNA deletions were reported in two patients, but the significance of this observation is unclear.

The LGMD 1H mutation has been linked to region on chromosome 3p23–p25.1 [20].The transmission model of the disease is consistent with an autosomal dominant inheritance pattern with variable expressivity and incomplete penetrance.

LGMD 2 (Recessive Forms of LGMD)

Fourteen distinct LGMD 2 loci with dominant inheritance patterns have thus far been described based on clinical criteria. There appear to be a heterogeneity in presentation, and the number of recessive forms of LGMD is expected to be greater than what has thus far been described. CK is normal in most patients, even those with significant disability. The LGMD 2 forms are usually of an early childhood onset and can be debilitating. Adult-onset forms have been described. A variable, progressive course is typical. Mutations in 15 genes have been shown to underlie LGMD 2. The LGMD 2 subtypes, characteristic features, clinical features, and limited gene information are provided in Table 57.2. Individual LGMD 2 subtypes are described below.

LGMD 2A (Calpainopathy)

Although LGMD 2I is the most common form of all LGMDs in northern Europe, LGMD 2A is the most prevalent in many European countries, Turkey, Brazil, Japan, Russia, and Australia, with variable frequencies that differ depending on ethnic clusters and geographic origin. Estimates based on molecular data indicate that LGMD 2A frequency ranges from about 10 % of LGMD cases in the United States to 80 % in the Basque Country of Spain and Russia.

LGMD 2A is characterized primarily by a symmetric, selective atrophic involvement of limb-girdle and trunk muscles [21]. Muscle weakness usually begins in the pelvic girdle, with problems running, climbing stairs, or rising from a chair. The lower limb-girdle muscles are the most severely affected, even in the few patients in whom the disease began in the shoulder girdle or both simultaneously. Hip adductors and gluteus maximus are the earliest clinically affected muscles, and to a lesser degree, the hip flexor hamstring muscles are also involved. Hip abductors are relatively better preserved as well as distal muscles in the lower limbs. Clinical complaints about shoulder girdle and upper limb weakness

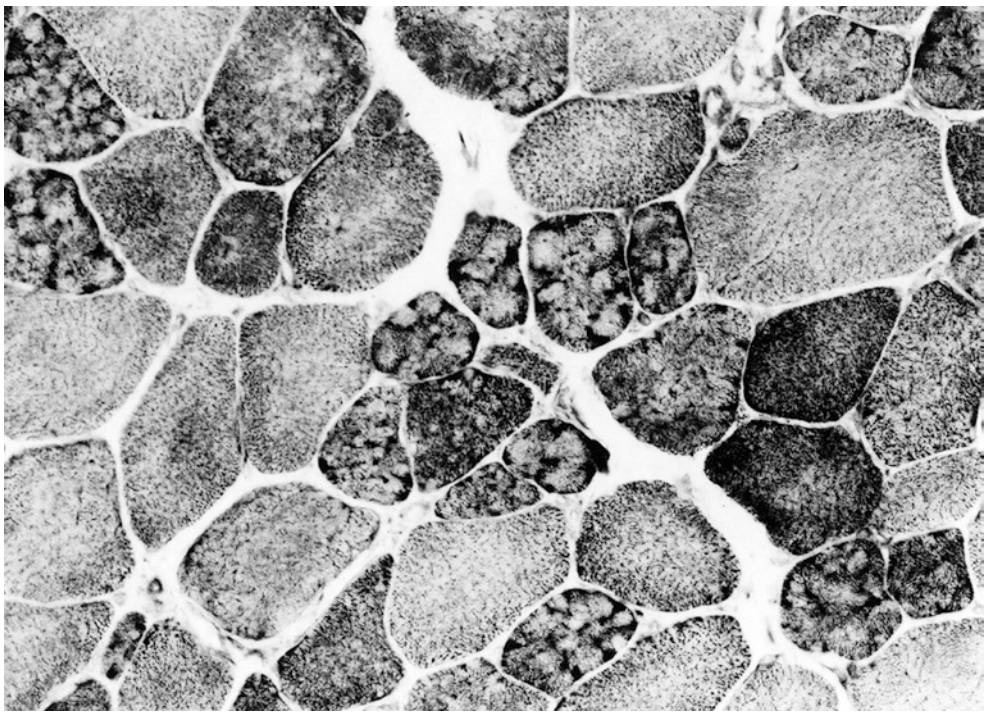

Fig. 57.2 NADH–TR-stained muscle from a 27-year-old man with a calpain gene mutation. Note the disorganized intermyofibrillar network showing "lobulated" appearance in darkly stained small type 1 fibers. ×350

appear later in the disease course. However, the neurological examination shows early muscle involvement in the scapular girdle muscles, including predominantly the latissimus dorsi, rhomboids, serratus magnus, and pectoralis causing scapular winging. To lesser degrees, the trapezius, deltoid, biceps brachii, brachialis, and brachioradialis are involved. As disease progresses, weakness and atrophy also involve the quadriceps and the tibialis anterior in the lower extremities, the triceps brachii, and the forearm muscles. Abdominal muscles become weak. Facial, extraocular, and pharyngeal muscles are usually spared. Muscle hypertrophy is unusual but observed in three quarters of patients in the Brazilian population. Contractures are common at the early stages of the disease in the calves with toe walking as a presenting sign and at wrists, elbows, and fingers. Later in the disease, contractures can involve the spine. No primary cardiac involvement has been observed, but with increasing respiratory insufficiency, cardiac complications may develop. Atypical clinical presentations can include the Leyden–Mobius variant with onset between 13 and 29 years of age with weakness of the pelvic and thigh muscles as well as a late-onset variant, which begins in the fourth decade of life with pelvic girdle weakness.

LGMD 2A is characterized by a wide variability in clinical features and rates of progression. The mean age at onset is at about age 14 years but a considerable variation between 2 and 40 years. The average age that inability to walk occurs is around 17 years but again with a wide range from 5 to 39 years but may occur earlier with infantile onset. However, the age of onset is not an exact predictor of progression or use of wheelchair. No sex difference is evident in age at onset or disease progression. Patients with two null mutations usually have a rapid course, but in the remaining cases (two missense mutations or compound heterozygote mutations), prognosis is uncertain. Serum CK varies from normal to the high tens of thousands. Serum CK is markedly raised in the first stages of the disease and gradually decreases as the muscular atrophy and weakness progresses and the muscles become more atrophic. CK levels are not as high as in other common muscular dystrophies such as Duchenne muscular dystrophy, dysferlinopathies, or LGMD 2I.

Electromyography shows increased insertional activity and spontaneous activity in the form of fibrillation potentials and positive sharp waves. Muscle histology shows (1) variability of fiber size and interstitial fibrosis. Necrotic and regenerating fibers are seen. (2) ATPase staining shows type 1 predominance in severely affected patients. (3) Lobulation of type 1 fibers is seen later in the disease (Fig. 57.2). (4) Inflammation is seen in perivascular or endomysial areas [22]. Eosinophilic infiltrates are fairly characteristic. Computed tomography of the thighs has shown marked atrophy of the hamstrings and hip adductors and moderate atrophy in quadriceps with sparing of the sartorius. MRI has shown involvement of the posterior thigh muscle. With progression of the disease, other thigh muscles are also affected depending on clinical severity: the adductors and semimembranosus muscles are involved in young patients with minimal functional motor impairment. In patients with restricted ambulation, a diffuse involvement of the posterolateral muscles of the thigh and of the vastus intermedius is found, with

relative sparing of the vastus lateralis, sartorius, and gracilis. MRI of the legs reveals involvement of the soleus muscle and the medial head of the gastrocnemius with relative sparing of the lateral head.

LGMD 2A is caused by mutations in the *CAPN3* gene mapped to 15q15.1–q21.1 encoding for a muscle-specific proteolytic enzyme called calpain-3 that is involved in the complex process of sarcomere remodeling. The calpains, or calcium-activated neutral proteases, are nonlysosomal intracellular cysteine proteases. CAPN3 plays a role in the dysferlin protein complex and that disruption of CAPN3 function may affect muscle membrane repair and remodeling. More than 300 CAPN3 mutations have been identified with a distribution that varies according to specific regions or ethnic groups.

Western blot analysis of muscle biopsy shows reduced level of calpain-3 although this has also been observed in other forms of LGMD such as dysferlinopathy and tibial muscular dystrophy. In about a fifth of patients with LGMD, normal levels of calpain-3 are observed by Western blot indicating protein expression levels are normal, but the mutation suppresses autocatalytic function of the enzyme, either by affecting inter-domain protein interaction or by lowering calcium sensitivity. About a third of patients with mutations in the CAPN3 gene show normal proteolytic activity, suggesting that other functions of the protein must be impaired. These results suggest that Western blot can be an initial screening test for LGMD 2A, but a normal calpain-3 level does not rule a calpainopathy, and therefore, mutational analysis of CAPN3 gene must be performed for definitive diagnosis.

LGMD 2B (Dysferlinopathy)

The LGMD 2B has a wide range of presentations including being found to be allelic to Miyoshi muscular dystrophy type 1 and distal myopathy with anterior tibial onset (Fig. 57.3). Symptom onset of LGMD 2B ranges between 10 and 39 years of age, with intra- and interfamilial heterogeneity. Muscle weakness in LGMD 2B starts in the proximal pelvic girdle and presents as difficulty with running and climbing stairs. Early inability to walk with involvement of distal posterior muscles, especially gastrocnemius, is often observed. The upper extremities (mainly biceps) are involved approximately 10 years after the lower extremities [23]. The progression is slow and loss of ambulation is seen after 30 years of age. Some patients may still be able to walk into the sixth decade. Hypertrophy of the deltoids with biceps atrophy and calves hypertrophy at the earlier stage of the disease is observed in some patients. Typically at the time of symptom onset, the medial gastrocnemius shows atrophy. Cramps and muscle discomfort are reported.

When the disease manifests as Miyoshi distal myopathy (also known as distal anterior dysferlinopathy), the onset is usually in the early adulthood, presenting mainly with foot drop and steppage gait. The upper limbs and proximal muscles become involved later. Serum CK levels are considerably increased. Muscle imaging confirms a selective involvement of the soleus and gastrocnemius and early muscle edema. Miyoshi and LGMD phenotypes can be present in the same family.

The serum CK is usually high (10–70 X the normal value). In presymptomatic patients, levels up to 3,000 may be seen [24]. Electromyography shows typical myopathic changes. Muscle pathology shows necrosis and degeneration of muscle fibers, fiber size variability, fiber splitting, and inflammation. Increase in endomysial connective tissue is seen in more involved muscles. Amyloid deposition at the surface of the muscle fiber, in the endomysial connective tissue and perivascular area, is present in muscles of some patients [25]. Some mutations are associated with T-cell infiltrates in the perimysial and perivascular spaces. In patients with LGMD 2B, the dysferlin tissue staining is absent or reduced. However, the absence of staining is more specific for LGMD 2B than reduced staining. However, there is no correlation between level of staining and clinical severity. Western blot may identify the presence, absence, or reduced levels of dysferlin.

LGMD 2B is caused by mutations in the gene encoding the skeletal muscle protein dysferlin on chromosome 2p13.2 [26]. More than 300 mutations have been described. Eighteen percent of patients with dysferlin deficiency have only 1 (heterozygous) mutation on 1 allele. Certain mutations have geographical distributions: 1624delG is common in Libyan Jews; G3370T, G3510A, 3746delG, and 4870delT are common in Japan; and Arg1905X is common in Spain.

Dysferlin is a ubiquitously expressed 230 kDa molecule that is localized to the periphery of muscle fibers, T-tubule, and cytoplasmic vesicles. Dysferlin is composed of a short C-terminal hydrophobic transmembrane domain and a longer cytoplasmic-oriented hydrophilic region that harbors six C2 domains. C2 domains can bind calcium and thus mediate calcium-dependent signaling events. C2 domains can also bind phospholipids, inositol polyphosphates, and intracellular proteins; interact with cellular membranes; and mediate molecular trafficking, vesicle transport, lipid modifications, and protein phosphorylation. Dysferlin interacts with multiple proteins, including annexins A1 and A2, caveolin-3, calpain-3 (CAPN3), affixin (ß-parvin), and the dihydropyridine receptor (DHPR). Dysferlin also interacts with AHNAK, a protein implicated in cell membrane differentiation, repair, and signal transduction.

Dysferlin is one of the sarcolemmal proteins located at the plasma membrane or within the basal lamina, whose reduced expression cause inherited degenerative myopathies. Proteins in this group include dystrophin; α-, β-, γ-, and δ-sarcoglycan; the laminin a2 chain of merosin; the integrin

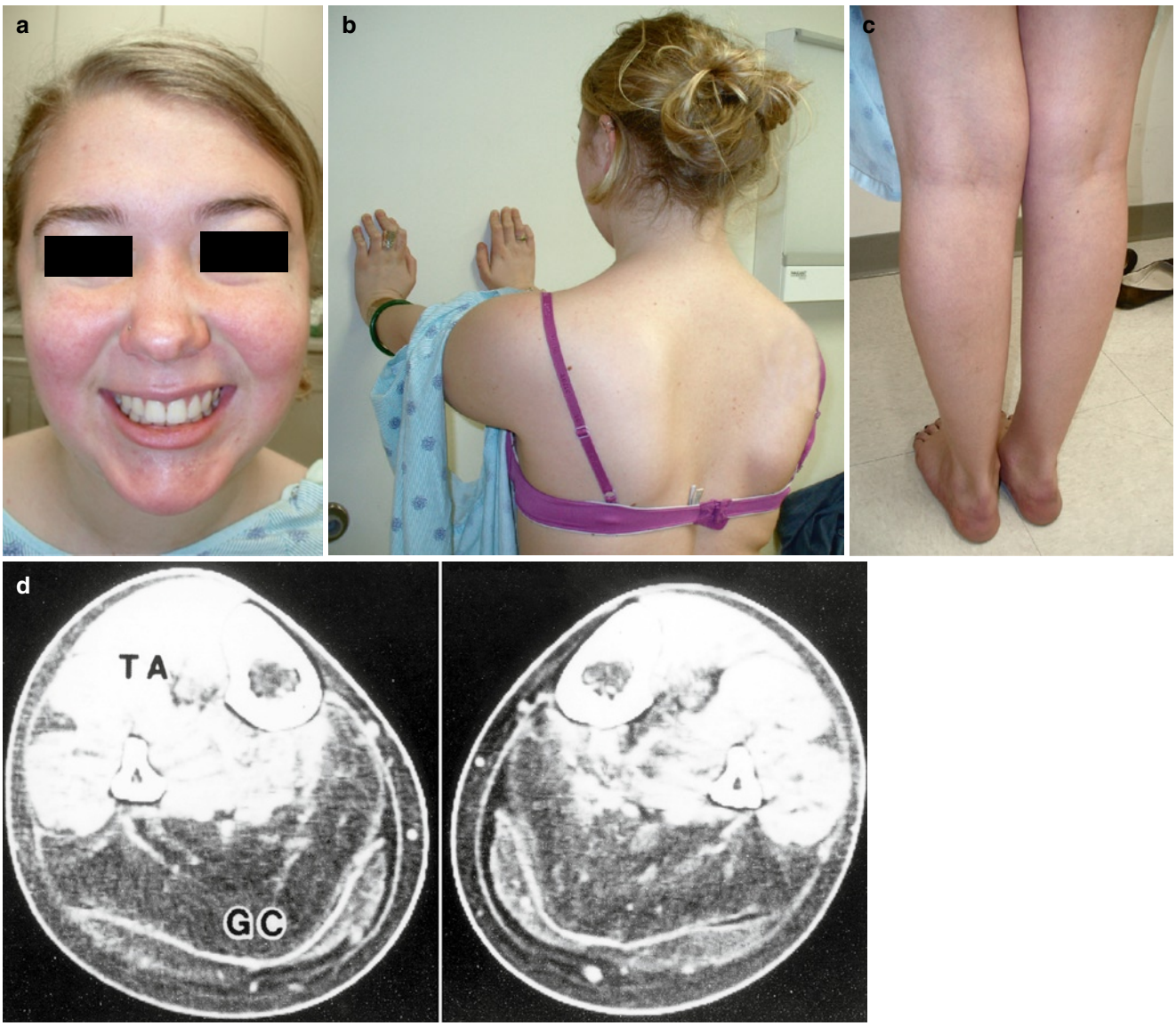

Fig. 57.3 Clinical features of limb-girdle muscular dystrophy 2B (dysferlinopathy). (**a**) No facial weakness or atrophy or asymmetry is noticed. (**b**) Scapular winging. (**c**) Selective atrophy of the medial gastrocnemius muscle is observed in early course of the disease. Note the fairly preserved lateral gastrocnemius muscle. (**d**) Muscle CT in dysferlinopathy. In later course of the disease, the gastrocnemius muscle (both heads) is largely replaced by fat tissue, while the tibialis anterior (*TA*) and the anterior compartment of the leg are spared

a7 chain; and caveolin 3. The function of some or all of these proteins may be structural, whereby the loss of protein leads to muscle fiber degeneration. Given the homology of dysferlin to a nematode spermatogenesis factor (Fer-1) that is required for successful membrane fusion, the lack of dysferlin may cause faulty myotube fusion and thereby impair muscle regeneration.

LGMD 2C (Gamma-Sarcoglycanopathy)

The sarcoglycans, which are deranged in the pathology of LGMD 2C, 2D, 2E, and 2 F, appear to play a structural role in maintaining muscle membrane integrity. Defects in sarcoglycans cause a similar type of LGMD. The plasma membrane cytoskeleton of muscle fibers is composed of several protein components. Dystrophin, a large rod-like protein present on the intracellular surface of the myofiber plasma membrane, is a principal component. Additional protein components of the myofiber plasma membrane cytoskeleton, known collectively as dystrophin-associated proteins, classified into the dystroglycan, sarcoglycan, and syntrophin subcomplexes were identified as important proteins to maintain the integrity of myofiber plasma membrane. Localized within the myofiber plasma membrane, the sarcoglycan complex consists of at least four transmembrane proteins: α-, β-, γ-, and

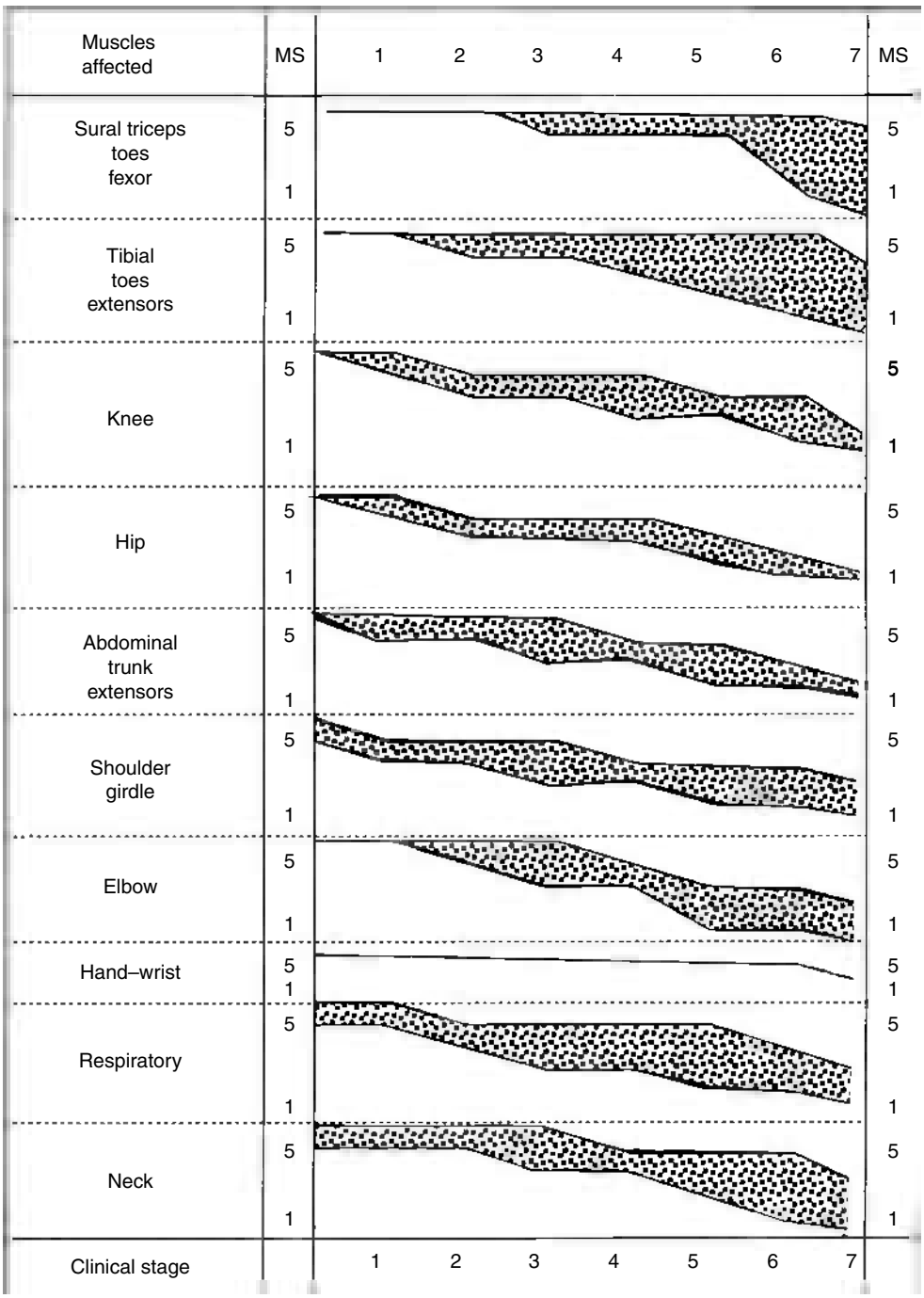

Fig. 57.4 The chronology of involvement of the different muscle groups in SCARMD [3, 62] . The dotted area corresponds to the limits of scores in different stages. Stage 1. Unable to run. Stand without using the arms. Stage 2. Waddling gait. Climbs stairs without using the banister. Stage 3. Climbs stairs only with the banister. Stage 4. Unable to climb stairs. Stage 5. Unable to rise from a chair without assistance. Stage 6. Walks only with assistance. Frequent falls. Stage 7. Unable to walk or stand erect. Confined to bed. Requires help for all activities. *MS* muscular strength

δ-sarcoglycan [27]. The sarcoglycan complex is thought to associate with dystrophin and the dystroglycan complex; however, the exact binding sites have not been identified. Like dystrophin and the other dystrophin-associated proteins, the sarcoglycan complex may impart structural integrity to the myofiber plasma membrane and prevent contraction-induced damage through maintenance of the sarcolemma (basal lamina, plasma membrane, cytoskeleton complex) [28]. The individual LGMDs will be described below.

The age of onset and clinical pictures of LGMD 2C have a wide inter- and intra-familial heterogeneity (Fig. 57.4). The clinical presentation can vary from a Duchenne-like course to intermediate to a mild Becker-like phenotype in a given family (Fig. 57.5). The onset of the disease is approximately 5 or 6 years of age with involvement mainly of proximal muscles, although distal involvement may occur. Inability to walk may occur anywhere between 10 and 37 years of age. The glutei, adductors, paraspinal, abdominal, subscapular, and soleus muscles are affected whereas quadriceps is spared in some patients [29]. Patients may develop calf and tongue hypertrophy (specifically with the C283Y mutation) and

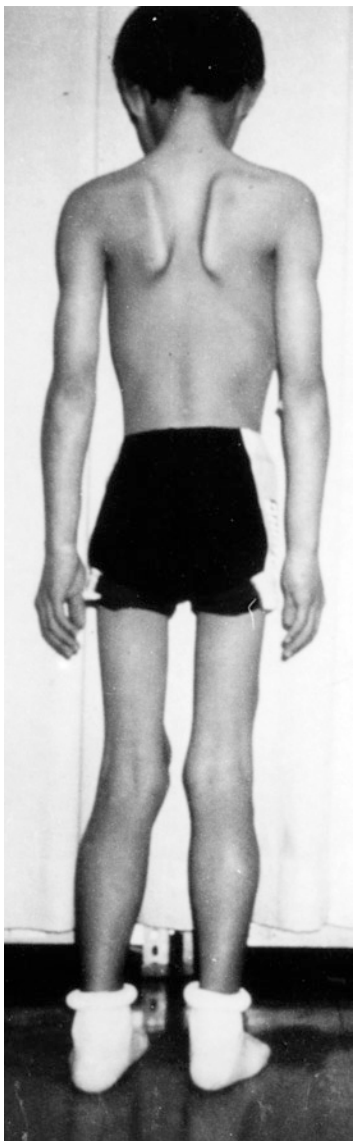

Fig. 57.5 Boy with SCARMD. Note proximal atrophy, calf hypertrophy, and winged scapulae

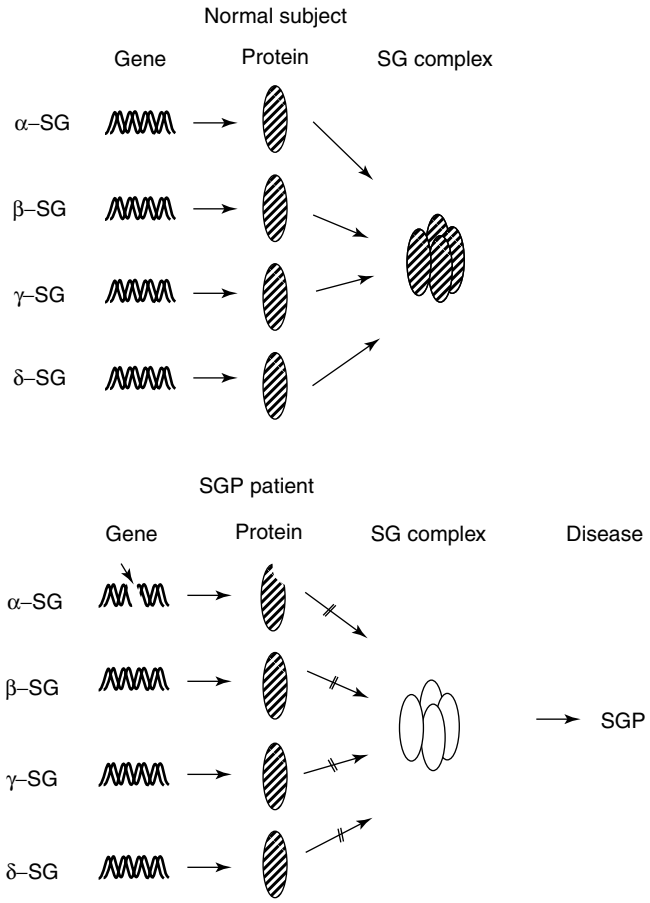

Fig. 57.6 Mutation of a single SG gene results in the defect of the single sarcoglycan, affecting localization of multiple sarcoglycans. Loss of a subunit of SG complex results in the absence or great reduction of all subunits of SG complex

deafness. Respiratory failure occurs in the third decade of life. The C283Y mutation has been associated with lumbar hyperlordosis, scapular winging and subclinical electrocardiographic abnormalities, diastolic dysfunction, and right ventricular hypertrophy.

The serum CK is usually extremely high and electromyography shows myopathic changes. Muscle histology shows a myopathic or dystrophic pattern. Inflammatory infiltrates can be present. γ-Sarcoglycan immunoreactivity is reduced or absent. The other sarcoglycans are usually reduced, but there is no correlation with the phenotype. Dystrophin may be normal or reduced.

LGMD 2C is caused by mutation in the γ-sarcoglycan gene located on chromosome 13q12.12 [30]. It is most commonly seen in patients from Maghreb, Tunisia [31], and India. Del521-T mutation is most commonly reported in Tunisia and North Africa and C283Y in the gypsies.

LGMD 2D (Alpha-Sarcoglycanopathy)

In patients with LGMD 2D, the onset of the disease symptoms is usually between 2 and 15 years (Figs. 57.6 and 57.7). The manifestations can vary from a mild to severe phenotype [32]. Early-onset disease has more rapidly progressive weakness, which is associated with absence of α-sarcoglycan. Patients with late-onset symptoms have reduced α-sarcoglycan levels and have a slower course of the disease. The weakness is symmetric and proximal. In the severe phenotype, quadriceps and scapular weakness occurs. Some patients will present with calf hypertrophy and rarely cardiomyopathy.

The serum CK is high (often more than 5,000 IU/L). Muscle pathology shows fiber size variability, increase in endomysial connective tissue, and evidence of degeneration and regeneration of muscle fibers. On sarcoglycan

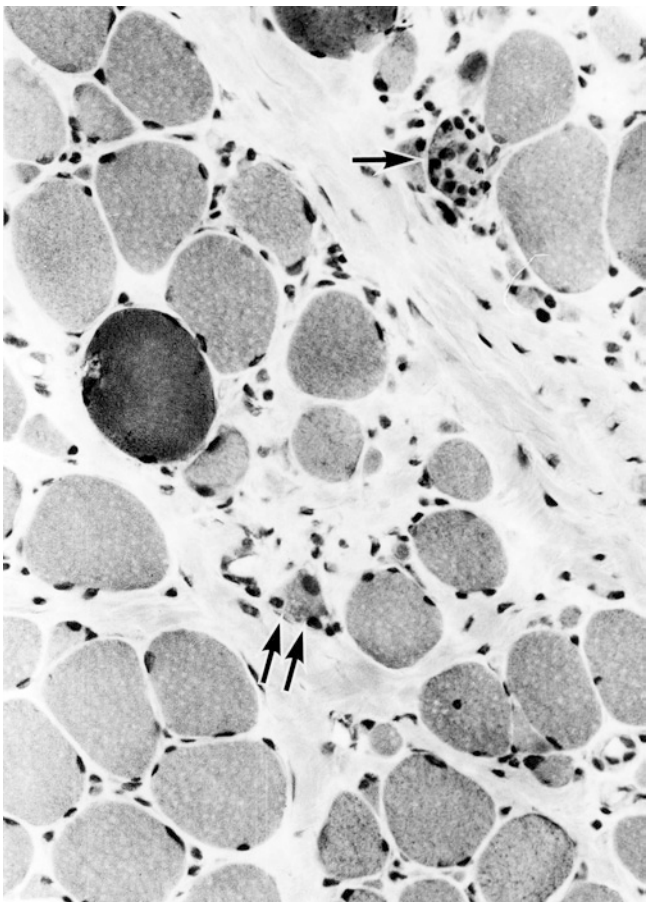

Fig. 57.7 Muscle biopsy from a 7-year-old girl with α-sarcoglycan deficiency. In addition to marked variation in fiber size with notable interstitial fibrosis, there are necrotic (a *single arrow*) and regenerating (*double arrows*) fibers, showing active necrotic and regenerating processes. Notice the hyper-contracted fiber (dark-staining fiber on the *left*). The overall findings are similar to those seen in Duchenne muscular dystrophy. Hematoxylin and eosin, ×300

immunostaining, there is absence of α-sarcoglycan and reduction or absence of other sarcoglycans.

This disease is caused by mutation in the alpha-sarcoglycan gene which encodes adhalin, located on chromosome17q21.33 [32, 33]. Missense and nonsense mutations have been described. In cases of null mutations, the α-sarcoglycan is usually absent, whereas it is only reduced in cases of missense mutations. Some patients who are heterozygous for Ile124Thr missense mutation may report myalgias. Scapular winging is seen in 60 % of patients, calf hypertrophy in 15 %.

LGMD 2E (Beta-Sarcoglycanopathy)

LGMD 2E is usually a severe disease, with onset in early childhood and adolescence (between 3 and 17 years) and shows significant intra-familial variability. Patients are wheelchair bound at the age of 10–25 years. The weakness is usually proximal at the limb girdles (pelvic worse than the shoulder girdle). Tongue hypertrophy and scapular winging can be present. Cardiomyopathy can be seen in occasional patients. At least 4 of the described mutations cause a Duchenne-like phenotype. The serum CK is very high (7 to 80X). Muscle histology shows myopathic changes. All sarcoglycans are usually absent or markedly reduced.

LGMD 2E is caused by mutation in the gene encoding beta-sarcoglycan on chromosome 4q12 [34, 35]. This disease is common in northern and southern Indiana in Amish population [36] and in Bern, Switzerland.

LGMD 2F (Delta-Sarcoglycanopathy)

LGMD 2F is associated with severe weakness with most mutations producing myopathy. The disease starts early, between 2 and 10 years of age, with loss of the ability to walk anywhere between 9 and 16 years and death between 9 and 19 years of age. The weakness initially involves the proximal muscles bilaterally and symmetrically. In some patients, calf hypertrophy and cramps occur. Dilated cardiomyopathy may develop without skeletal myopathy. Milder phenotypes have been described.

The serum CK levels are elevated 10–50 times normal. Muscle pathology shows degeneration and regeneration of muscle fibers. Immunostaining shows absence of δ-sarcoglycan. α- and β-sarcoglycans are absent; γ-sarcoglycan is reduced or absent.

LGMD 2F is secondary to mutations in the delta-sarcoglycan gene on chromosome 5q33.3 [37]. Frameshift mutation (premature truncation of protein: del656C) has been reported in African-Brazilian ancestry. Other mutations include missense (Glu262Lys) and nonsense mutations (premature truncation of protein: E93Ter, Arg165Ter, Trp30Ter).

LGMD 2G (Telethoninopathy, Dilated Cardiomyopathy 1N)

Patients with LGMD 2G have a mean age of 12.5 years at symptom onset. Patients present with difficulty walking, running, and climbing stairs. Walking on heels is usually more difficult to perform than walking on toes, suggesting greater involvement of tibialis anterior and sparing of gastrocnemius, in contrast with LGMD 2B or Miyoshi myopathy. As a result, the patients are unable to perform ankle dorsiflexion, and foot drop is a characteristic feature. In the upper limbs, proximal muscle atrophy is marked, whereas, in the lower limbs, proximal and distal muscle atrophy is evident. Approximately 40 % of patients usually become non-ambulatory by third or fourth decade. Calf atrophy or hypertrophy as a manifesting sign has been reported in approximately half of patients. The

neck muscles are mildly or not affected, and extraocular and facial muscles are spared in all patients. Cardiac involvement is observed in about half of patients.

The serum CK is increased 3- to 30-fold normal. Muscle histology reveals marked variation in fiber size. Necrotic and regenerating fibers are found with an increase in central nuclei. Rimmed vacuoles are seen in great proportions of the muscle fibers. There is no predominance of type 1 or type 2 and no fiber-type grouping. In Western blot analysis, telethonin is absent in LGMD 2G patient muscle biopsies.

LGMD 2G is caused by mutations in the gene encoding telethonin, located on chromosome 17q12 [38, 39]. Mutations are point mutations or small deletions that produce stop codons. It has been reported in Brazilian patients with Italian ancestry and in Europe. Other variant telethonin syndromes include dilated cardiomyopathy 1N and congenital muscular dystrophy.

Telethonin is a sarcomeric protein of 19 kDa found exclusively in striated and cardiac muscle. In adult skeletal muscle, it is localized to the Z-disc. Telethonin interacts with titin, which acts as a molecular "ruler" for the assembly of the sarcomere by providing spatially defined binding sites for other sarcomeric proteins. After activation by phosphorylation and calcium/calmodulin binding, titin phosphorylates the carboxy-terminal domain of telethonin in early-differentiating myocytes. The mutations in the telethonin gene cause the disruption of a functionally important domain of telethonin, the carboxy-terminal region, which appears to alter in sarcomeric structure [40].

LGMD 2H (Manitoba Hutterite Dystrophy, Sarcotubular Myopathy)

LGMD 2H is a mild form of autosomal recessive muscular dystrophy, with a variable clinical presentation. The onset of disease symptoms is usually within the second or third decade of life, and progression is slow. Most patients continue to walk into their sixth decade. Quadriceps and pelvic girdle musculature are primarily involved. The patients show a waddling gait and difficulty rising from the squatting position. Cardiac and facial involvement does not occur.

The serum CK is high (between 250 and 4,500 IU/L). Electromyography shows myopathic changes. Muscle histology reveals mild dystrophic changes including fiber size variability, endomysial fibrosis, and muscle fiber degeneration and regeneration. Fiber splitting and internal nuclei are observed. To date, the disorder has been described only in the Hutterite population of North America [41].

Sarcotubular myopathy, another variant of LGMD 2H, presents with exercise-induced fatigue and myalgias. Proximal limb-girdle weakness and neck flexor weakness is present in all patients. Winged scapula, hypertrophied calf muscles, and Gowers' sign are present. Muscle atrophy is proportional to muscle weakness. Mild facial weakness may be observed. Achilles tendon contractures occur. Tendon reflexes are normal or reduced. The serum CK levels are increased up to 5- to 20-fold greater than normal. Muscle histology shows varied fiber size. Small rounded vacuoles (less than 4 μm) are observed in 20–30 % of the type 2 fibers and less than 4 % of the type 1 fibers. Segments of many muscle fibers harbor a myriad of small abnormal spaces. Electron microscopy reveals that the small spaces arise from focal dilations of sarcoplasmic reticulum. Small foci of Z-disc streaming are seen.

The gene mutations underlying LGMD 2H are mutations in the gene encoding tripartite motif-containing protein-32 (TRIM32) on chromosome 9q33.1. The specific mutation at codon 487 of TRIM32 gene, with an amino acid change from aspartate to asparagine (D487N), is described, both in Hutterite dystrophy and in sarcotubular myopathy. A subset of Hutterite patients with LGMD have LGMD 2I, which is caused by L276I mutation in the FKRP gene on chromosome 19q13. Hutterite LGMD 2I patients have an earlier age at diagnosis, a more severe course, and higher serum CK than LGMD 2H patients. In addition, some of the LGMD 2I patients show calf hypertrophy, cardiac symptoms, and severe reactions to general anesthesia; none of these features occur among LGMD 2H patients.

TRIM32 is a member of a growing family of TRIM, or RING–B-box coiled-coil, proteins [42]. The RING-finger domain indicates that it may have intrinsic ubiquitin-ligase activity, and all RING-finger proteins may be E3-ubiquitin ligases. The ubiquitin–proteasome pathway is a specialized mechanism for the posttranslational regulation of protein levels. The initial step in the ubiquitin–proteasome pathway is the activation of ubiquitin by an E1-ubiquitin-activating enzyme. The activated ubiquitin is transferred to the E2-ubiquitin-conjugating enzyme. The E3 ligase interacts with E2-ubiquitin complex and recruits a protein to be targeted to the 26S proteasome. The E3 ligase catalyzes the transfer of ubiquitin to the target protein. The ubiquitinated protein is released from the complex and is recognized by factors associated with the 26S proteasome. The 26S proteasome digests the ubiquitinated protein into small peptides.

The E3 enzymes are responsible for the selection of proteins for ubiquitination by this pathway. The RING-finger domain of an E3 ligase mediates interaction with the E2-ubiquitin-conjugating enzyme and is the source of the ligase activity. Therefore, recognition of target proteins by E3 ligases occurs through protein–protein interactions with areas of the protein other than the RING-finger domain. In the case of TRIM32, this function may be fulfilled by a series of NHL domains. Mutations in the NHL domain abolish an interaction with another protein, thereby leading accumulation of protein in tissue, in this case muscle, with a toxic effect.

LGMD 2I (Fukutin-Related Proteinopathy)

LGMD 2I is characterized by limb-girdle weakness, dilated cardiomyopathy, and respiratory insufficiency [43]. The age of onset is between 5 months and 40 years of age. The patients with early onset of symptoms present in the first 2 years of life with hypotonia and delayed motor milestones followed by muscle hypertrophy, primarily of the legs but at times involving the tongue. Patients never acquire the ability to run or hop and followed a Duchenne-like disease course, with loss of independent walking in the early teens, followed by development of cardiomyopathy [44]. The patients with later onset of symptoms have milder disease and a relatively benign course. Calf muscle and, to a lesser extent, thigh muscle, brachioradialis, and tongue hypertrophy is present in most patients. Muscle cramps following exercise are also relatively common. Myoglobinuria may occur. Intelligence and brain MRI are normal [45]. Serum CK is elevated between 10 and 30 times normal.

LGMD 2I is caused by mutation in Fukutin-related protein gene (FKRP) on chromosome 19q13.32 [46]. This disease is mostly common in Denmark and parts of England. The most common genetic finding in northern Europe is the homozygous mutation (C826A) in FKRP. FKRP encodes a putative Golgi-based glycosyltransferase and is involved in posttranslational glycosylation of α-dystroglycan. Mutations in FKRP lead to α-glycosylation defect and subsequently downregulation of α-dystroglycan which constitutes an essential component of the proteoglycan–dystrophin complex [47].

LGMD 2J (Titinopathy)

The onset of symptoms in LGMD 2J occurs between childhood and the third decade. Weakness is more proximal than distal and is worse than that observed in the allelic form "distal myopathy." Muscle wasting is seen in anterior tibialis muscle. Patients are unable to walk within 20 years of symptom onset [48]. No associated cardiomyopathy is usually seen. The serum CK is up to 20 times normal. Muscle histology shows myopathic changes and secondary reduction in calpain-3 [49].

Mutations in the titin gene (located on chromosome 2q31.2) are responsible for LGMD 2J. Common mutations are missense mutations Leu293,356Pro in French (both leucine amino acids changed to proline) and 11-base-pair deletion at last exon (exon 363) in the Finnish patients. Titin protein is an enormous protein that spans the entire sarcomere from the M line to the Z-disc. Titin may assist in assembly of contractile elements, provide elasticity to the sarcomere, regulate the size of the Z-disc, and be involved in cell signaling [50].

LGMD 2K (Muscular Dystrophy–Dystroglycanopathy (Limb-Girdle) Type C1)

LGMD 2K was first reported in Turkish families with disease onset ranging from 1 to 6 years of age with difficulty in walking and climbing stairs. LGMD 2K is characterized by slow progression, proximal muscle weakness, mild pseudohypertrophy, microcephaly, and mild mental retardation with IQ ranging from 50 to 76. Joint contractures occur in about half of patients [51]. The serum CK is 40 times normal. Muscle histology shows fiber size variability and reduced α-dystroglycan. Brain MRI is typically normal.

Mutations in the POMT1 gene were shown to underlie the LGMD 2K phenotype [52]. POMT1 and POMT2 are mannosyl transferase enzymes. In humans, impaired protein O-mannosylation results in congenital muscular dystrophies that are referred to as secondary α-dystroglycanopathies since a common pathologic feature is the hypoglycosylation of α-dystroglycan. The most severe disorder is Walker–Warburg syndrome characterized by congenital muscular dystrophy associated with severe brain malformations and ocular abnormalities. Patients often die within the first year of life. In contrast, the mildest disorders may not present until adulthood, such as LGMD without brain or ocular involvement. The proteins O-mannosyl transferases POMT1 and POMT2 initiate the biosynthesis of O-mannosyl glycans in the endoplasmic reticulum.

LGMD 2L (Miyoshi Muscular Dystrophy 3, Anoctaminopathy)

LGMD 2L is characterized by late-onset proximal scapular and pelvic girdle muscle weakness with a range of onset from 20 to 55 years. Prominent asymmetrical atrophy of quadriceps femoris and biceps brachii occurs. Though calf hypertrophy may be observed at presentation, calf atrophy, often asymmetric, occurs later in the disease, unassociated with weakness. Distal weakness of the upper extremities does not occur. The patients usually maintain the ability to walk, despite difficulties with climbing stairs because of proximal weakness. Facial weakness may be observed in some patients. Muscle pain, with or without exercise, is a major complaint in approximately the great majority of patients.

The serum CK ranges between normal and 80 times normal. Electromyography reveals myopathic alterations and spontaneous activity has been reported. Muscle histology shows dystrophic changes, increased connective tissue, and fiber splitting. Inflammation is observed in patients with more severe disease. One patient was found to have amyloid deposition in perivascular spaces and muscle fibers. A variant syndrome of LGMD 2L is termed Miyoshi

myopathy 3, in which significant calf hypertrophy is a common feature.

Mutations in the Anoctamin 5 (ANO5) gene on chromosome 11p14 underlie the LGMD 2L phenotype, in French-Canadian families [53]. The human Anoctamins include a family of at least ten proteins all exhibiting eight transmembrane domains. These proteins are capable of functioning as calcium-activated chloride channels. Mutations in ANO5 gene may cause defective membrane repair. Mutations in ANO5 gene were also identified in patients with Miyoshi muscular dystrophy 3 [54].

LGMD 2M (Muscular Dystrophy–Dystroglycanopathy (Limb-Girdle) Type C 4, Fukutinopathy)

This disease was named first LGMD 2L by Godfrey et al., and then renamed as LGMD 2M, and now designated as muscular dystrophy–dystroglycanopathy type C4 [55, 56]. LGMD 2M was described in Israeli Jewish, Indian, Portuguese, Turkish, and French families. The onset is usually at 6 months of age, with hypotonia and motor developmental delay and normal intellectual development. An acute and dramatic deterioration in functional ability is seen after a febrile illness, with back-to-baseline functioning level after recovery. Weakness is usually diffuse, progressive, more proximal than distal, and affecting lower limbs more than upper and extensors more than flexors. The weakness improves with steroid therapy, and worsening of weakness occurs with steroid reductions. Muscle hypertrophy is seen in the posterior leg and, in some patients, the tongue. Spinal rigidity, joint contractures, and cardiomyopathy may occur [55, 56].

The serum CK is usually extremely high. Muscle biopsy shows dystrophic changes with muscle fiber necrosis, increase in endomysial connective tissue, macrophages infiltration around necrotic fibers and in the endomysium without eosinophils, and nearly absent glycosylated α-dystroglycan. Laminin-α2, laminin-β1, and laminin-γ1 are mildly reduced. Brain MRI is normal although vermis hypoplasia and polymicrogyria have been reported.

LGMD 2M is secondary to defective glycosylation of α-dystroglycan, collectively known as "dystroglycanopathies" (Figs. 57.8 and 57.9), secondary to mutations in the Fukutin gene on chromosome 9q31.2.

LGMD X-Linked

The X-linked LGMDs are summarized in Table 57.3. Brief descriptions of selected X-linked LGMDs are provided below.

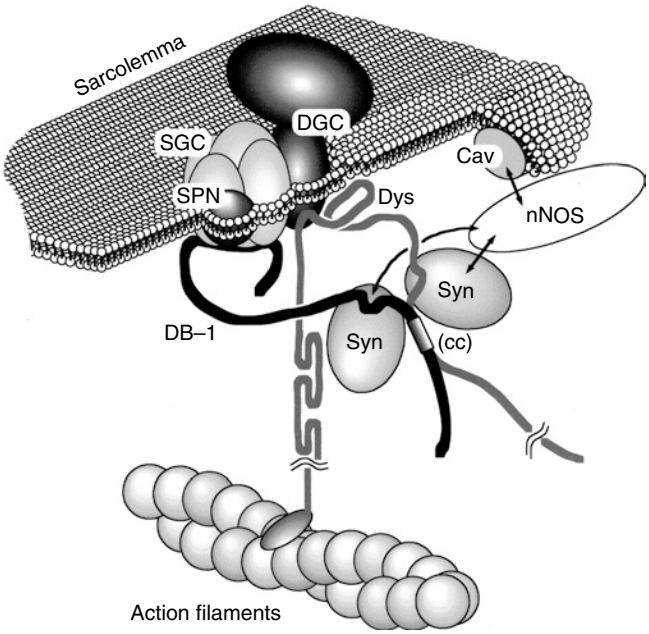

Fig. 57.8 Dystrophin and dystrophin-associated proteins. Basal lamina including laminin which binds to α-DG is removed from this scheme. Note that N-terminal dystrobrevin associates with sarcoglycan complex at protoplasmic sites. *Dys* dystrophin, *DGC* dystroglycan complex, *SGC* sarcoglycan complex, *SPN* sarcospan, *DBN* dystrobrevin, *SYN* syntrophin, *nNOS* neuronal nitric oxide synthase, *Cav* caveolin-3

Barth Syndrome (X-Linked Dilated Cardiomyopathy)

This syndrome is characterized by cardioskeletal myopathy and neutropenia [57]. The clinical course may be severe with lethal cardiac disease and recurrent infections during infancy and early childhood but relative improvement in later childhood. The initial presentation varies from congenital dilated cardiomyopathy to infantile congestive heart failure to isolated neutropenia without clinical evidence of heart disease. The myopathy is mild and nonprogressive. Early in the course, patients may have hypotonia. Later, weakness may be more prominent proximally than distally; Gowers' sign is usually present. The patient often maintains ambulation, and there has been no report of respiratory failure.

Lab evaluation demonstrates a normal CK, neutropenia, and increased level of 3-methylglutaconic acid. Increased urine levels of some branched-chain organic acids may be appreciated. Mitochondrial function is impaired with 3-methylglutaconic aciduria. The genetic loci map to Xq28. The gene, designated G4.5, is highly expressed in cardiac and skeletal muscle and encodes Tafazzin which is involved in phospholipids synthesis [58].

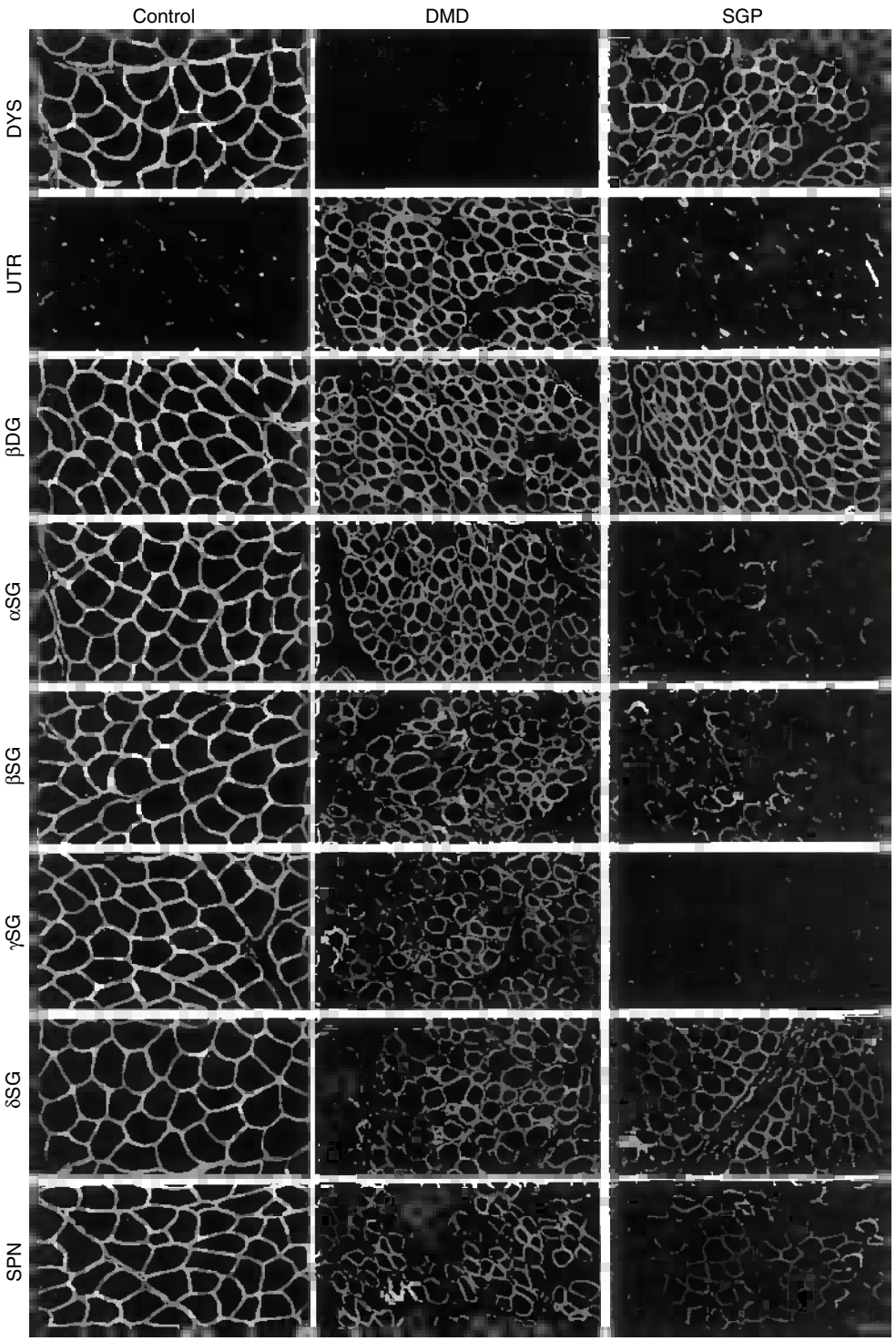

Fig. 57.9 Immunohistochemistry of dystrophin, DAPs, and related proteins. *DMD* Duchenne muscular dystrophy, *SGP* sarcoglycanopathy, *DYS* dystrophin, *UTR* utrophin, *DG* dystroglycan, *SG* sarcoglycan, *SPN* sarcospan

Emery–Dreifuss Muscular Dystrophy 1

Clinically, the patients have difficulty climbing stairs initially, and later symmetric humeroperoneal weakness evolves, involving biceps and triceps. Deltoid is usually spared. Early contractures are very common. Cardiac involvement is manifested by conduction disorders, syncope, sudden death, and bradycardia which is an indication for pacemaker placement in certain cases.

Serum CK is mildly to moderately elevated. Muscle biopsy shows myopathic changes, endomysial fibrosis, type 1 fiber atrophy, and breakdown of nuclear membrane. Immunostaining with antibodies to emerin shows no immunoreactivity. It is a recessive disorder linked to Xq28,

Table 57.3 The X-linked LGMDs

	Clinical phenotype			Gene information		
	Typical onset	Progression	CK	Allelism	Gene/loci	Protein
Duchenne muscular dystrophy	Early childhood	Slow to moderate	10 to 20 X	Becker muscular dystrophy	DYS	Dystrophin
Becker muscular dystrophy	Late childhood	Slow	10 to 15 X	Duchenne muscular dystrophy	DYS	Dystrophin
Barth syndrome	Infancy	Moderate	Normal	X-linked dilated cardiomyopathy	TAZ	Tafazzin
Emery–Dreifuss muscular dystrophy 1	Variable; teen age	Slow	2 to 10 X	X-linked sinus node dysfunction	EMD	Emerin
Emery–Dreifuss muscular dystrophy 6	Adult	Slow	2 to 10 X	Hyaline body myopathy, X-linked myopathy with postural muscle atrophy	FHL1	Four-and-a-half-LIM protein 1
Danon's disease	Early childhood	Moderate	4 to 35 X	X-linked vacuolar cardiomyopathy and myopathy	LAMP-2	Lysosome-associated membrane protein 2

affecting Emerin gene which encodes for Emerin protein, a membrane protein that interacts with lamins or chromatin. The exact function of the emerin protein still remains unknown.

Emery–Dreifuss Muscular Dystrophy 6

Emery–Dreifuss muscular dystrophy type 6 is characterized by weakness in the shoulder girdle and peroneal muscles, with a myopathic form of scapuloperoneal syndrome [59]. The age of onset was between 20 and 58 years of age, and clinically, patients have an early foot drop. Arms are affected proximally before the hand weakens distally, and scapular winging is present. Other features include weakness in neck extensors muscle, hearing loss, skeletal contractures, and cardiac disorders. Death occurs from respiratory or cardiac failure. Serum CK is 1.5–10 times normal. On muscle histopathology, hyaline body inclusions seen as eosinophilic bodies on H&E staining are localized at the central or subsarcolemmal areas, mostly in type 1 fibers. These inclusions are formed by desmin, four-and-a-half-LIM protein 1 (FHL1), and dystrophin.

FHL1 gene mutations are responsible for this dominant disorder and are localized to the X chromosome, Xq26.3, with 60–80 % penetrance and the succeeding generation of same sex being more affected [60]. Mutations include missense (Trp122Ser) and in-frame insertion. However, FHL1 protein mutations are involved in multiple diseases including X-linked myopathy with postural muscle atrophy, Emery–Dreifuss muscular dystrophy 6, and X-linked reducing body myopathy.

Danon's Disease

Danon's disease is characterized by weakness in scapuloperoneal distribution, hypertrophic cardiomyopathy, and mental retardation. The onset of the disease is between 5 and 25 years of age, with death occurring by the third decade. Serum CK is elevated three to eight times normal. Skeletal muscle biopsy shows no fibrosis or inflammation. Fiber size is normal. A slight increase in internal nuclei and few centrally located pale vacuoles may be appreciated. Immunohistochemistry demonstrates absence of lysosome-associated membrane protein-2 (LAMP-2).

Mutations in LAMP-2 gene (at chromosome Xq24) underlie Danon's disease. Women that are carriers of LAMP-2 have cardiomyopathy [61]. LAMP-2 is thought to protect the lysosomal membrane from proteolytic digestion and to act as a receptor for proteins imported into lysosomes.

Prognosis of LGMD

The LGMD syndromes cause progressive weakness, although the rates of progression vary considerably among the LGMD. Certain LGMD syndromes have cardiac involvement, and patients are prone to cardiac conduction-system deficits, which may lead to sudden death. Rarely, respiratory insufficiency may occur but usually in late stages of the diseases. In general, the later the disease onset, the better the prognosis.

Treatment of LGMD

The LGMDs cause progressive weakness. Physical therapy and occupational therapy should be provided to the patient to prevent formation of contractures and to maximize the use of the limbs. Serial electrocardiograms and echocardiograms may be helpful in monitoring the heart. Cardiological follow-up with placement of pacemaker/defibrillator may be necessary if abnormalities are appreciated. Although significant respiratory involvement in most LGMDs has not

been observed, pulmonary function tests may be helpful in identification of respiratory weakness. Whether noninvasive or invasive methods of ventilation are helpful in the clinical setting is not clear. Steroids have been helpful in maintaining muscle function, as in the case of Duchenne muscular dystrophy and fukutinopathy. Some patients complain of cramps in the muscles and symptomatic treatment may be provided with either baclofen or tizanidine. Genetic counseling may be helpful for the affected families and the patients.

Currently there is no specific treatment of LGMD. At least in a subset of patients with heart involvement, screening and early diagnosis may prevent premature cardiac death. Exon-skipping treatment strategies are being attempted in both Duchenne muscular dystrophy and dysferlinopathies.

LGMDs are a heterogeneous group of disorders. As the name suggests, the disease manifests as weakness in the shoulder girdle and the pelvic girdle muscles. Both dominant and recessive forms of LGMDs have been described, and the current classification system of LGMDs utilizes the notation type 1 and type 2, respectively. With the advancement of sequencing technologies, the list of LGMD will grow. Understanding of gene functions and mutation pathology will help shed insights into the disease process and possible therapy in the future.

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Facioscapulohumeral Muscular Dystrophy

58

Rabi Tawil

Introduction

Facioscapulohumeral muscular dystrophy (FSHD) is an indolent inherited myopathy characterized by an initially restricted, distinctive regional distribution of muscle weakness. It is the third most common muscular dystrophy after myotonic dystrophy and Duchenne dystrophy with a prevalence of 1:20,000 [1, 2]. It is a dominantly inherited dystrophy but up to a third of the cases are sporadic resulting from de novo mutations. The spectrum of clinical severity is wide, from minimally symptomatic to wheelchair-bound individuals. There are as yet no effective treatments for FSHD. However, recent research has identified the likely causal genetic mechanism in FSHD opening the way for targeted treatment of this disorder.

Etiology and Pathogenesis

Since 1992, the causal genetic defect in >95 % of patients with FSHD was known and consists of deletion of an integral number of large repetitive DNA elements, each 3.3 kb in size, known as D4Z4 on chromosome 4q35 [3, 4]. Whereas healthy individuals have 11–100 D4Z4 repeats, most individuals with FSHD carry one array of 1–10 units. How this deletion results in FSHD remained unclear until recently. A series of observations over the past 15 years have lead to the discovery of a unifying mechanism for FSHD [5]. This mechanism postulates that FSHD results from a sequence of events leading to the aberrant expression of the *DUX4*, a gene contained within each D4Z4 repeat [6]. First, contraction of the number of D4Z4 repeats to between 1 and 10 repeats changes the chromatin structure from a closed (heterochromatic) to an open (euchromatic) configuration allowing gene expression [7, 8]. Each repeat, containing a copy of the *DUX4* gene sequence, starts transcribing the *DUX4* gene. The resultant mRNA, however, is unstable as the *DUX4* gene sequence within each repeat lacks a polyadenylation (polyA) signal which is essential in stabilizing mRNA (Fig. 58.1). Only the most distal *DUX4* copy can potentially produce a stable mRNA as it can splice on a polyA sequence just distal to the last repeat that is present in only one of two variants (A variant) of the 4q35 subtelomere. Consequently, a contraction of the repeats occurring on the appropriate A variant background allows the expression of stable *DUX4* mRNA and consequently DUX4 protein from the last D4Z4 unit [5, 9]. DUX4 is normally expressed only in germline cells. The consequences of its ectopic expression in muscle are not clear. In vitro expression of DUX4 was shown to cause apoptosis, increase susceptibility to oxidative stress, and interfere with myogenesis [10–12].

Whereas greater than 95 % of patients with FSHD present with the characteristic contraction in the D4Z4 repeat (FSHD1), less than 5 % of patients with a typical FSHD clinical phenotype show no contraction of the D4Z4 repeats (Fig. 58.1) [13]. Such patients, now known as FSHD2, have permissive chromatin changes at the D4Z4 repeat similar to that observed in patients with FSHD1 [14–16]. In addition, just as in FSHD1, FSHD2 requires that at least one 4q35 allele have a permissive A distal genetic variant. Thus, although FSHD1 and FSHD2 are distinct genetically, the ultimate causal gene abnormality, the aberrant reactivation of DUX4 expression, is likely to be the same for both conditions [17].

Clinical Presentation

Most patients with FSHD come to medical attention by the second decade of life. However, in a comprehensive survey of familial FSHD in Holland, Padberg found that as many as 30 % of affected individuals remain asymptomatic [2].

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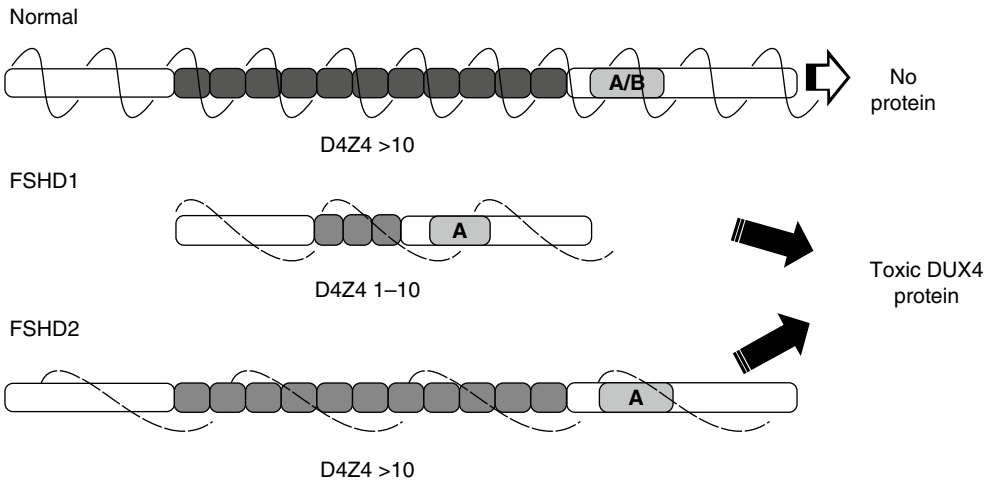

Fig. 58.1 Molecular mechanisms of FSHD. *Top:* normal 4q35 with greater than 10 D4Z4 repeats and nonpermissive chromatin structure. *Middle:* in FSHD1, there is a loss of a critical number of D4Z4 repeats leaving 1–10 repeats leading to chromatin relaxation and in the presence of the poly A containing **A** distal variant results in inappropriate expression of DUX4 protein in somatic cells. *Bottom:* in FSHD2, there is a primary relaxation of chromatin without loss of D4Z4 repeats and in the presence of distal **A** variant allows the inappropriate expression of DUX4 protein

The most common presenting symptom relates to weakness of shoulder fixators. Although FSHD is generally thought of as starting rostrally and having a descending course of progression, a surprising number of patients present with difficulty walking from foot drop. Examination, however, almost invariably, reveals coexisting scapular fixator and facial weakness to which the patient may not be aware of. This fact reflects the indolent nature of this disorder and consequent unconscious adaptation of these patients to their functional limitations. Often, the complaint is unilateral and the presenting history is one of the subacute deterioration suggesting an acquired disorder. This is especially true of patients presenting with unilateral scapular winging and misdiagnosed as long thoracic nerve injury with associated serratus anterior muscle weakness. In such patients, careful examination will reveal the existence of weakness of several periscapular muscles in addition to pectoral muscle weakness. In patients presenting with what appears to be an acquired acute or subacute weakness, careful questioning usually elicits a long-standing history of weakness elsewhere. Long-standing facial weakness is confirmed by a patient's inability to whistle, blow up a balloon, or drink through a straw and the observation by family members that the patient sleeps with their eyes slightly open. Indications of long-standing scapular weakness are difficulty climbing rope or doing push-ups and long-standing winged appearance of the scapulae.

Typical FSHD is defined by a descending sequence of progression with initial involvement starting in the facial and shoulder girdle muscles followed by variable involvement of the peroneal and hip-girdle musculature. Although the severity of weakness of a given muscle group generally reflects this progression, it is not invariably so. Thus, patients whose initial involvement was clearly in the shoulder and face may show moderate weakness in these muscles but more profound foot dorsiflexor or hip-girdle weakness. Indeed, proximal lower extremity involvement in FSHD is more common than previously thought. A prospective natural history study demonstrated that, when compared to age- and gender-matched normals, patients with FSHD frequently have notable weakness of knee extensors and flexors even in the early stages of the disease [18]. On examination of the face, the palpebral fissures are widened and facial expression is diminished. The lips are pouty with dimples often evident at the corners of the mouth. Bifacial weakness is confirmed with a transverse smile, inability to purse lips, or inability to bury eyelashes (Fig. 58.2). As with all muscle involvement in FSHD, facial weakness is often asymmetric. Extraocular, eyelid, and bulbar muscles are spared. Neck flexor muscles are relatively spared compared to the neck extensors. The characteristic shoulder appearance includes straight clavicles as well as forward sloping and rounding of the shoulders. The pectoral muscles are atrophied resulting in the presence of axillary creases (Fig. 58.3). The scapulae are laterally displaced and winging is evident either at rest or with attempted forward arm flexion or abduction (Fig. 58.2). Preferential wasting of the lower trapezius muscles results in a characteristic upward jutting of the scapulae on attempted arm forward flexion (Fig. 58.2). The biceps and triceps muscles are also involved with sparing of the deltoid muscles. Except for wrist extensors, the forearm and hand muscles are spared (Fig. 58.3). Weakness of abdominal muscles results in a protuberant abdomen and exaggeration of lumbar lordosis. Preferential weakness of lower abdominal muscles results in upward movement of umbilicus on attempted neck flexion (Beevor's sign), a sign specific for FSHD (Fig. 58.2) [19]. In the lower extremities, foot dorsiflexor weakness sparing the calf muscles is evident. Proximal lower extremity

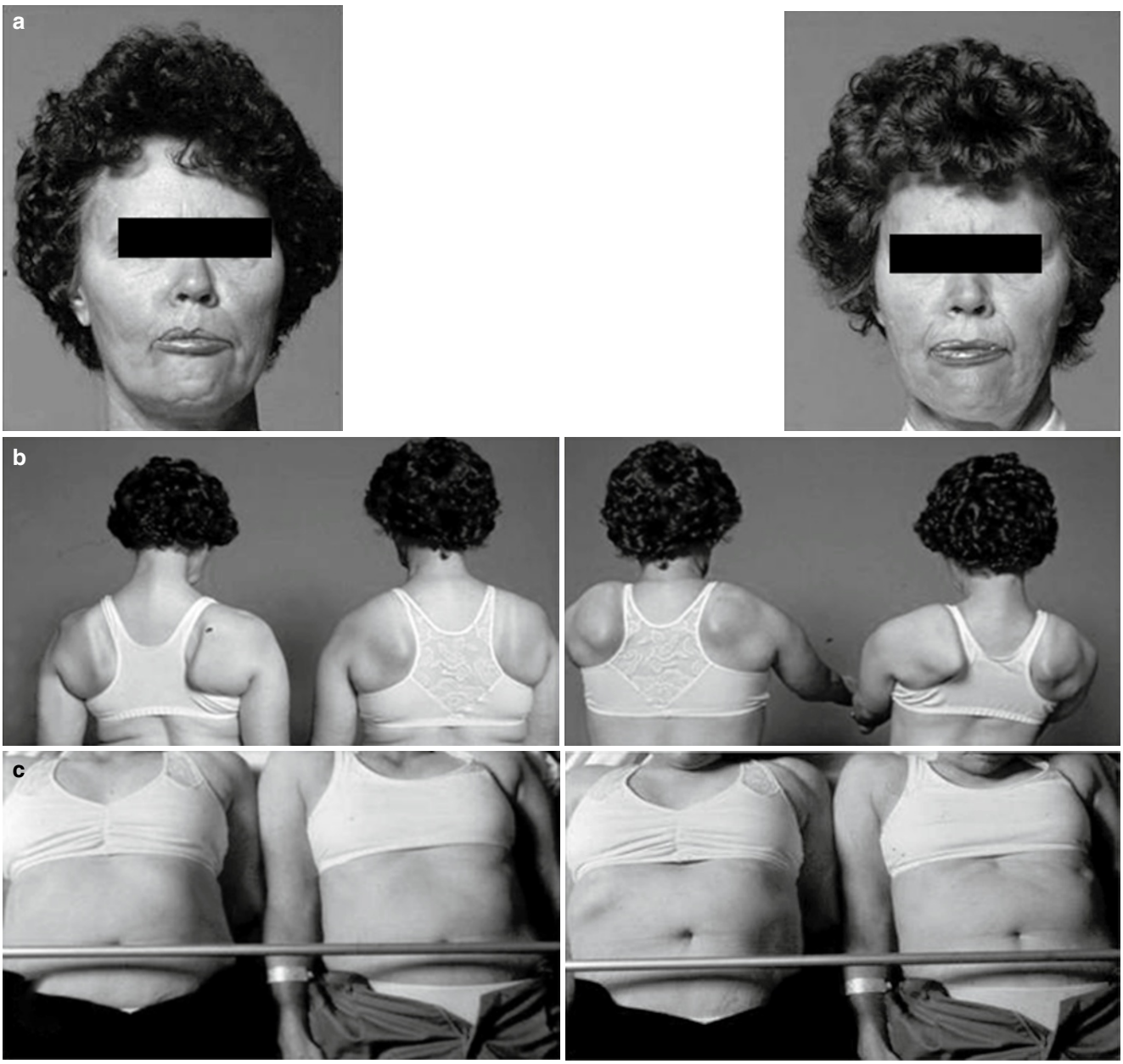

Fig. 58.2 Monozygotic twins with FSHD. (**a**) Asymmetric weakness of orbicularis oris muscles on attempted whistling. (**b**) Wide-set, winged scapulae at rest (*right*) and marked winging on attempted arm forward flexion. (**c**) Marked rostral movement of the umbilicus (*left*) with neck flexion in a supine position (Beevor's sign) (Reprinted from Griggs et al. [47]. With permission from John Wiley & Sons, Inc.)

is usually spared early on although early proximal lower extremity involvement is more common than previously thought [18]. Muscle stretch reflexes are often reduced in FSHD and sensory examination is normal.

Extramuscular Manifestations

Largely asymptomatic hearing loss and retinal telangiectasias occur in association with FSHD [20, 21]. Screening of FSHD families with audiograms also shows mild high-frequency hearing loss in the majority of affected individuals [20]. Rarely, especially in severely affected infantile-onset FSHD, hearing loss can be severe enough to require the use of a hearing aid. In the vast majority of patients with FSHD, the retinal vascular abnormalities are asymptomatic with subtle vascular changes seen at the periphery of the retina on fluorescein angiography [21]. These vascular malformations rarely result in an exudative retinal detachment or Coats' syndrome with resultant visual loss [22–25].

Symptomatic cardiac involvement in FSHD is rare. Atrial, AV-nodal, and infranodal abnormalities on surface ECG are evident in greater than 60 % of patients [24]. In addition, 10 of 12 patients studied electrophysiologically had inducible

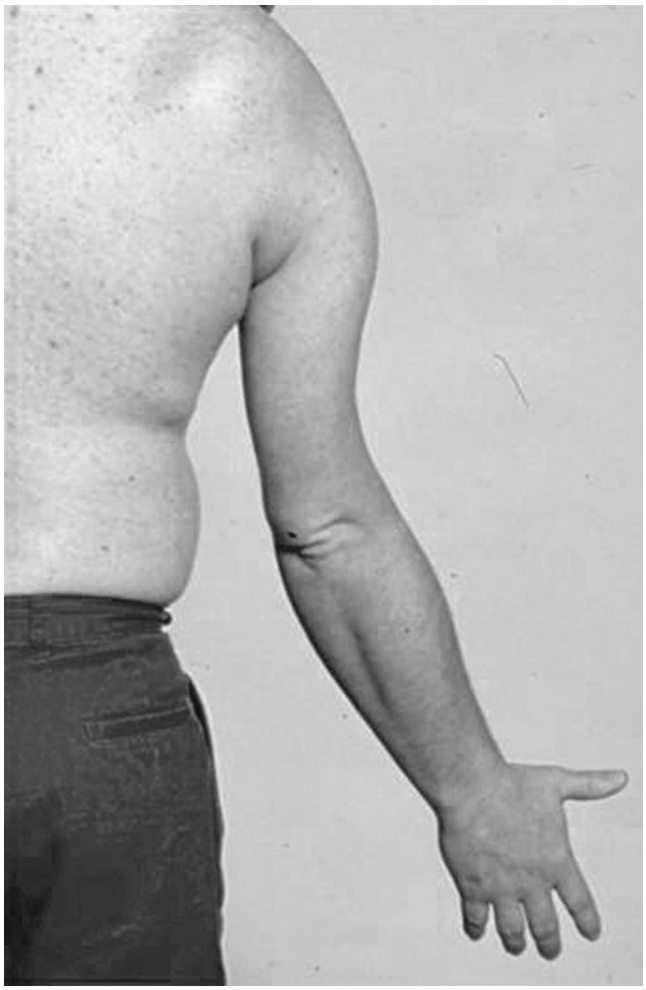

Fig. 58.3 Preservation of the forearm muscles with selective wasting of the biceps and triceps muscles giving the characteristic "Popeye" arm appearance. Prominent axillary crease resulting from pectoral muscle atrophy (Reprinted from Tawil and Griggs [48]. With permission from Butterworth-Heinemann)

atrial flutter or fibrillation [24]. In a large study of genetically confirmed cases of FSHD, 5 % were estimated to have cardiac involvement with conduction abnormalities and a predilection for supraventricular tachyarrhythmias [26].

Symptomatic restrictive respiratory insufficiency is rare in FSHD, with only 1 % of patients developing respiratory insufficiency that is severe enough to require intervention [27, 28]. Respiratory complications are typically seen in more severely affected individuals. Risk factors for respiratory insufficiency include the presence of severe pectus excavatum, significant limb-girdle weakness, kyphoscoliosis, and hyperlordosis and wheelchair-bound patients.

Central nervous system involvement does not, as a rule, occur in FSHD. However, a survey of Japanese patients with molecularly confirmed FSHD showed that, of 20 patients with severe, early onset FSHD, 8 were mentally retarded of whom 4 also suffered from seizures [29]. More recent case reports have extended this finding in other populations [29–31]. All these patients invariably have severe, often infantile-onset, FSHD with large deletions.

Table 58.1 Differential diagnosis

Limb-girdle dystrophy type 2A (calpainopathy)
Emery-Dreifuss syndrome
Polymyositis
Inclusion body myositis
Mitochondrial myopathy
Myofibrillar myopathies
Congenital centronuclear myopathy
Acid maltase deficiency

Differential Diagnosis

The differential diagnosis is fairly narrow when there is a confirmed autosomal dominant history as there are few dominantly inherited myopathies and most are easily distinguishable from FSHD based on clinical features. The differential diagnostic list is longer in sporadic cases as a number of myopathies can have some of the features of FSHD such as scapular winging and facial weakness. Table 58.1 includes conditions reported in the literature mimicking FSHD as well as conditions referred to our clinic initially misdiagnosed as FSHD. Most of these conditions can be differentiated from FSHD by careful attention to the pattern of clinical involvement, associated clinical features, the pattern of progression, and, in many, by their characteristic histopathological changes.

Evaluation and Diagnosis

Clinical Diagnosis

Individually patients with FSHD may differ greatly, but most fit in a clinically typical pattern of presentation. Table 58.2 includes previously published clinical inclusion and exclusion criteria [32]. Also included is a list of supportive features, characteristic of FSHD, that help bolster confidence in the clinical diagnosis. The presence of a dominantly inherited pattern is very helpful as it significantly narrows the differential diagnosis and allows confirmation of FSHD clinical features in other family members. Ancillary testing shows a serum CK level which can be normal but is most often mildly to moderately elevated (<10× upper limit of normal). Electromyographic findings in FSHD are nonspecific and help rule out the presence of a neurogenic condition. With the advent of specific and sensitive FSHD molecular diagnosis, muscle biopsy is no longer considered a routine procedure in the evaluation of a patient with suspected

Table 58.2 Clinical diagnostic criteria

Inclusion: Weakness of facial muscle, weakness of scapular stabilizers and ankle dorsiflexors
Exclusion: Autosomal recessive or x-linked inheritance, diffuse severe contractures, extraocular and bulbar weakness, sensory loss, neurogenic EMG, biopsy suggestive of alternative diagnosis, skin rash suggestive of dermatomyositis
Supportive features: Prominent asymmetry, descending sequence of involvement, sparing of deltoids, early involvement of abdominal muscles (Beevor's sign), selective involvement of lower trapezius, typical shoulder appearance, relative sparing of neck flexors, minimal if any contractures, high-frequency hearing loss, or retinal vasculopathy

FSHD. Muscle biopsy should be reserved to patients with suspected FSHD whose DNA testing is negative and where an alternative diagnosis is being considered.

Molecular Diagnosis

Molecular diagnosis of FSHD is currently limited to FSHD1 and is highly specific (95 %) and sensitive (>95 %) [33–35]. Molecular diagnosis is performed on DNA extracted from leukocytes, double digested with the restriction enzymes *Eco*RI and *Bln*1 followed by Southern blot or pulse field gel electropheresis and hybridization to probe p13E-11. The results measure the size of a DNA fragment that encompasses the repeats on 4q35. Normal individuals will have alleles between 50 and 300 kb in size. Individuals affected with FSHD have one allele containing a deletion of variable size resulting in a restriction fragment from 10 to 38 kb in size depending on how many residual repeats remain (i.e., the larger the deletion, the smaller the allele size). Interpretation of this test can be complicated by the presence of translocated 10q26 repeat elements on 4q35 [35]. In patients where the clinical presentation of FSHD is typical and genetic testing is done for confirmation, a simple determination of the presence of a contracted allele at 4q35 should suffice. However, if the clinical presentation is atypical, further testing is needed. The subtelomere of 4q35 distal to the repeats comes in two variants: 4qA or 4qB. As discussed above, only the 4qA variant is pathogenic. Thus, a false-positive test can result if the contraction occurs on a 4qB background. Most molecular diagnostic labs will test for the 4qA/B variants when requested.

Genetic confirmation of FSHD2 is currently not available in clinical diagnostic laboratories because of the complexity of the testing required. Prenatal diagnosis for FSHD1 is possible and offered by several diagnostic laboratories. Preimplantation genetic diagnosis (PGD) is more complicated and the outcome less certain. PGD for FSHD1 cannot be done directly on DNA from a single cell because FSHD genetic is not PCR based and requires more DNA than can be obtained from a single cell. Consequently, affected status is determined by linkage, an indirect method that is less certain and requires DNA from several family members to complete [32].

Management and Treatment

There are no effective treatments to arrest or reverse muscle weakness in FSHD. Nevertheless, supportive treatment and management of potential complications is important. A recent ENMC conference resulted in recommendations for the diagnosis and management of individuals with FSHD [32].

Individuals with FSHD often develop effective adaptive strategies to compensate for their disabilities without necessitating the use of assistive devices. Nevertheless, certain forms of bracing are often needed at various stages of the disease. Ankle-foot orthoses (AFO) are useful for foot drop early on but may become a hindrance to ambulation when quadriceps muscles become severely affected. When foot dorsiflexion weakness coexists with knee extension weakness, a lightweight, carbon fiber dynamic AFO is much more useful than a conventional posterior AFO. A frequent complaint among patients with FSHD is neck and shoulder pain as well as lower back pain. The shoulder and neck pain is due to traction on the musculoskeletal structures from the forward displacement of the shoulder. Some patients may even have associated symptoms and signs of traction on the brachial plexus. Various forms of shoulder bracing can be tried and may offer temporary relief but are usually too constrictive and uncomfortable to be worn for any length of time. Physical therapy and management of chronic pain are often needed for such patients.

Surgical scapular fixation is used successfully in FSHD patients to improve shoulder range of motion [36]. Before surgery is recommended, however, several factors should be considered. The first critical determination is how much gain in range of motion can be expected from scapular fixation. This can easily assessed at the bedside; by manually fixing the scapula to the chest wall, the patient can determine the degree of functional gain that can be expected. The other consideration is the functional state of the arm and shoulder muscles and the individual's rate of disease progression. Surgery is best done in patients with fairly preserved upper arm function and slowly progressive disease. Scapular fixation can also result in difficulty rolling the shoulders forward especially if done bilaterally. Scapular fixation is best done by shoulder surgeons experienced in the procedure. Several different surgical methods for scapular fixation are used but scapula-thoracic arthrodesis is the preferred method [36].

Respiratory insufficiency is infrequent in FSHD but clinicians should be vigilant to its occurrence in patients at risk. The risk factors include wheelchair-bound patients, presence of kyphoscoliosis, significant hip-girdle weakness,

and the presence of pectus excavatum [27]. Such patients should have yearly pulmonary function tests and should be regularly asked about symptoms of nighttime hypercapnea [32]. Measurement of forced vital capacity is also indicated in all FSHD patients prior to surgery.

In patients with infantile FSHD, special attention to hearing loss and retinal vascular abnormalities is critical as they are much more likely to be symptomatic than the rest of the FSHD population. Failure to detect significant hearing loss early in such patients may result in delayed language development. On the other hand, failure to detect and treat significant retinal vasculopathy could result in an exudative retinopathy and blindness (Coats' disease) [25]. In fact, given that an exudative retinopathy is potentially preventable in with laser treatment, it is recommended that all patients diagnosed with FSHD obtain a screening dilated ophthalmologic exam [32].

As in other neuromuscular diseases, about 25 % of women with FSHD experience worsening of their overall strength during pregnancy [37, 38]. Although no consistent adverse pregnancy outcome was noted, it is recommended that pregnant women with FSHD be followed by high-risk obstetricians [32]. Additionally, close monitoring of respiratory function is indicated, especially in more severely affected individuals and those with one or more of the risk factors listed above.

The utility of exercise in slowing progression or improving muscle function is a frequent concern and question of patients with different forms of muscular dystrophy. Short-term studies of moderate weights or resistance training have shown no adverse effects in FSHD [39]. Additionally, it was shown that regular aerobic exercise improves exercise performance in FSHD [40]. Based on these findings, interested patients should be referred to physical therapy to develop an exercise program emphasizing aerobic fitness that is individualized to a patient's particular physical limitations.

Therapeutic trials in FSHD to date have been limited to nonspecific interventions aimed at slowing disease progression, none of which proved effective. Pharmacologic interventions have included corticosteroids, beta agonists, diltiazem, and MYO-029, a myostatin inhibitor [39, 41–45]. Two small studies of a number of neuromuscular conditions, including FSHD, demonstrated improvement in overall strength following short-term supplementation with creatine monohydrate. There have been no subsequent confirmatory studies in FSHD. With the identification of the likely primary causal mechanism in FSHD, the inappropriate expression of the DUX4 gene, a more targeted approach to therapy in FSHD is now possible.

Prognosis

In general, the absence of significant bulbar, respiratory, and cardiac involvement predicts a normal life expectancy in FSHD. Nevertheless, 1 % of patients with respiratory insufficiency requiring intervention are likely to have a poorer prognosis and shorter life span. Progression is steady and slow but some patients report long periods of quiescence interrupted by relatively rapid deterioration in a particular muscle group [18]. About 20 % of patients above the age of 50 eventually become wheelchair bound [2].

One factor affecting prognosis is deletion size. There is no linear correlation between deletion size and severity; however, large deletions that result in 1–3 residual repeats, resulting contracted allele sizes of 10–15 kb, have earlier onset and more severe disease. Gender also plays a factor in prognosis. Female patients with FSHD, as a group, tend to do better than male patients [2, 46]. It is likely that other, unknown, genetic, epigenetic, or environmental factors also affect prognosis and could explain the marked intrafamilial variability that can be seen in FSHD.

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The Myotonic Dystrophies

59

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Introduction

The myotonic dystrophies are muscular dystrophies that are clinically and genetically complex disorders and are distinct from both the non-myotonic muscular dystrophies and the non-dystrophic myotonias. Myotonic dystrophies directly involve almost all organ systems in the body [1–3]. Although the name "myotonic dystrophy" does not indicate the multisystem nature of these disorders, it is a historically well-established designation and aptly identifies two prominent features of these disorders, i.e., myotonia and muscular dystrophy. In addition to myotonic dystrophy type 1 (dystrophia myotonica 1, DM1) which was described more than 100 years ago, recent clinical studies and genetic mapping revealed a second rather distinct form, myotonic dystrophy type 2 (DM2) which was originally referred to as proximal myotonic myopathy (PROMM). Repeat expansions are the mutations underlying both types: DM1 is caused by CTG repeat expansion in the 3′ untranslated region of the *dystrophia myotonica protein kinase* (*DMPK*) gene in chromosome 19q13.3, where DM2 is due to CCTG expansion in intron 1 of the *zinc finger protein 9* (*ZNF9*) gene in chromosome 3q21.3 [2].

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History

Myotonic Dystrophy Type 1 (Dystrophia Myotonica Type 1, DM1, Steinert's Disease)

Following Thomsen's seminal descriptions of familial myotonia congenita in 1876 [1], investigators began to notice differences in the disorders of affected families. In the early twentieth century, atypical families with myotonia were reported to not maintain the classic features of Thomsen's disease because their involved muscles ultimately became atrophic and weak. Following detailed descriptions by Steinert in 1909 [1], these families were eventually identified as having a distinct disorder that was referred to as Steinert's disease, myotonic dystrophy, or dystrophia myotonica. When involvement of the eye and heart was recognized, the multisystem nature of the disorder was appreciated, which further distinguished it from myotonia congenita.

The full description of the clinical features, inheritance, and epidemiology of myotonic dystrophy was accomplished during the twentieth century. Neurologists and medical geneticists identified non-Mendelian features of inheritance, including variable penetrance, anticipation, a maternal transmission bias for congenital forms, and preferential transmission of the pathogenic allele rather than the normal allele [4, 5]. Although the genetic locus of myotonic dystrophy was mapped to chromosome 19 in the late 1970s, the causative mutation was not identified until the recognition that trinucleotide repeats could expand to cause Fragile-X and bulbospinal muscular atrophy (Kennedy's syndrome). Following that lead, several laboratories reported the genetic cause of the most common form of myotonic dystrophy, i.e., DM1 in 1992 [6–10], identifying an expanded region of repeated cytosine, thymine, and guanine (CTG) residues in the 3′ untranslated region of the *DMPK* gene. This led to a genetic testing, and recognition of DM as the most common form of muscular dystrophy in adults. At the time of discovery, no clear pathogenesis could be deduced. However, there were

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several hypotheses, including theories of decreased DMPK protein from an abnormal gene (haploinsufficiency) and interaction with nearby genes, such as the upstream *DMWD* gene, which is expressed in the brain and testes, or the downstream *SIX5* gene, which is associated with cataracts. The last and most important hypothesis, initially described in 1995, is the concept of RNA toxic gain of function [11, 12]. This theory was later supported by the discovery of a tetranucleotide repeat expansion in the DM2 gene in 2001 [13], which led to a better explanation and understanding of DM (see below).

Myotonic Dystrophy Type 2 (Dystrophia Myotonica Type 2, DM2)

In 1995, several reports identified families with dominantly inherited multisystem myotonic disorders that were genetically distinct from the classical form of myotonic dystrophy, i.e., DM1 [14–16]. Ricker et al. most thoroughly evaluated this new disorder [16] and clearly demonstrated that the genetic cause in these families was distinct from the known causes of myotonia congenita, paramyotonia, and DM1, indicating the existence of a novel genetic locus. The authors furthermore noted that the pattern of weakness of affected family members differed from DM1 and referred to the disorder as proximal myotonic myopathy (PROMM) to emphasize the proximal distribution of weakness which contrasts the characteristic distal weakness of DM1. In 1998 and 1999, Day and Ranum reported a large Minnesota kindred with a second form of myotonic dystrophy (DM2) in which affected members had a phenotype that closely mimicked the phenotype of DM1 [17, 18]. They localized the disease gene to a 10cM locus on chromosome 3q. Subsequently, Ricker reported that the gene for PROMM also mapped to the DM2 locus for many families [19].

The International Myotonic Dystrophy Consortium and Online Mendelian Inheritance in Man (OMIM) both recognize that DM2 and proximal myotonic myopathy refer to the same condition. Most families with PROMM have now been shown to have the characteristic tetranucleotide repeat expansion in *ZNF9* observed in individuals with DM2. Currently, the diseases are collectively referred to as the myotonic dystrophies, and each individual genetic disorder is referred to by the same name as the locus name (DM1 or DM2). The term PROMM is sometimes used to refer to the clinical phenotype if the causative mutation is unknown. However, the International Myotonic Dystrophy Consortium and others have suggested that any new identified multisystem myotonic dystrophy should be sequentially named as forms of myotonic dystrophy. A single family which was initially labeled as DM3 was subsequently shown to have familial inclusion body myositis, Paget disease, and frontotemporal dementia caused by mutations in *valosin-containing protein* (*VCP*) gene [20, 21].

Epidemiology

DM is recognized as being the most common form of muscular dystrophy in adults and may prove to be overall the most common form of muscular dystrophy when the multiple genetic causes of DM are all known. In Germany and in Minnesota, many families with DM2 have been identified, suggesting that the disease is not uncommon, at least in populations of northern European ancestry [17–19]. Before the identification of the distinct genetic mutations of DM1 and DM2, the combined prevalence of the myotonic dystrophies was estimated at 1 in 8,000 (12.5/100,000) with a wide difference among populations. There are now reports of high prevalence in northern Sweden, the Quebec province of Canada, and the Basque region of Spain. DM1 is most common in populations of European descent, is less common in Japan, is rare in India and the Middle East, and is absent in Africa except for a kindred form of DM1 in sub-Saharan region. DM2 is most common in Finland and northeast Europe but single kindreds of Afghan and Japanese origin have been identified [2]. A higher prevalence of DM2 is observed in individuals of German and Polish ancestry [22].

Classification of Myotonic Dystrophies

Patients with DM1 have diverse presentations which could be often classified into 3 subgroups: an adult-onset DM1 is the most common myotonic dystrophy, while childhood-onset and congenital forms are more severe but less prevalent [23] (Table 59.1). In contrast, DM2 has no known distinct subgroups including no evidence of congenital or childhood forms [2].

Congenital Myotonic Dystrophy Type 1

This is the most severe form of DM1 with a common but poorly understood maternal transmission. It may present prenatally by signs of polyhydramnios, reduced fetal movements, and other deformities detected on ultrasound examination. At birth, hypotonia, respiratory failure, and feeding difficulties are the common presenting features. Mental retardation becomes soon evident. Affected infants have bilateral facial weakness and a characteristic inverted V-shaped upper lip (also termed tented or fish-shaped) which renders sucking and feeding difficult [3, 24]. Despite the high mortality rate, some infants survive and are intubated and may achieve independent walking [2].

Table 59.1 Types of DM1

Phenotype	Clinical signs	CTG repeat size	Age of onset
Congenital	Hypotonia, respiratory failure, mental retardation, cardiorespiratory complications	Usually >1,000	Birth
Childhood onset	Mild mental retardation, early cardiac conduction abnormalities, facial weakness, subtle neuromuscular problems	50–1,000	1–10 years
Classical adult onset	Distal muscle weakness, foot drop, ptosis, axonal peripheral neuropathy, and neck/finger/wrist flexors are involved; handgrip myotonia, multisystem involvement (cataract, heart, etc.)	50–1,000	10–30 years
Mild late onset	Cataract, late moderate muscle atrophy, mild myotonia	50–100	20–70 years

Childhood-Onset Myotonic Dystrophy Type 1

This relatively uncommon form of DM1 usually presents with mental retardation; children have no or minimal limb weakness or myotonia. In many cases, the diagnosis is made when a parent, also usually the mother, is diagnosed with adult-onset DM1 [2].

Adult-Onset Myotonic Dystrophy Type 1

This is the most common form of the myotonic dystrophies. It is a multisystem disease and often presents with the classical triad of myotonia, muscle weakness, and cataracts. The multisystem nature of the disease may result in varied symptoms in affected family members. In moderately or severely affected individuals, DM1 is easily recognizable on clinical grounds [1, 23]. Patients commonly come to medical attention due to weakness, myotonia, or myalgias, though the multisystem nature of the disorder may trigger the initial symptoms due to ocular, endocrine, cardiac, reproductive, gut, or skin abnormalities.

Myotonic Dystrophy Type 2

DM2 has a variable mode of presentation, which includes proximal muscle weakness, myalgia with no weakness, asymptomatic hyperCKemia, or cataracts. Early cardiac death and respiratory failure have been reported but are less common than in DM1. Also, the majority of patients become symptomatic later in life, usually after the age of 40 years, and congenital and childhood-onset forms have not been described in DM2 (Table 59.2).

Clinical Features

Muscle

Muscle weakness is the most common presenting complaint in DM [1, 18, 23, 25, 26]. In DM1, symptoms become evident between the second and fourth decade of life and slowly progress with time (except for the congenital form). Patients with DM1 and DM2 commonly complain of muscle pain that is distinct from, but related to, the coexistence of myotonia. The pain is a deep ache that can be confused with rheumatologic disorders and incompletely responds to various treatments (steroids, nonsteroidal anti-inflammatory drugs, quinine, phenytoin, mexiletine). While muscle atrophy usually distinguishes DM from the non-dystrophic myotonias, minimally affected individuals with either DM1 or DM2 may have normal bulk; rare DM1 patients and occasional DM2 patients actually have muscle hypertrophy, as is seen in myotonia congenita.

Distribution of Weakness

DM1 patients have a very characteristic distribution of weakness, with ptosis, and weakness of eye and mouth closure, neck flexion, long finger flexors, and ankle dorsiflexors [1, 18, 23, 25, 26]. A careful observation of minimally affected DM1 subjects reveals weakness of forearm, thumb, and deep finger flexors prior to involvement of finger extensors, with preferential involvement of the lateral fingers. This distribution is similar to that seen in inclusion body myositis, but is distinct from the pattern seen in facioscapulohumeral dystrophy wherein extensors are involved prior to flexors. DM1 patients may develop weakness of hip and shoulder girdle muscles at some time during the course of their disease, with most having preserved strength proximally despite profound distal weakness; some have more equal involvement of proximal and distal muscles.

DM2 patients have this same distribution of weakness (see Table 59.2), though the degree of weakness is typically mild until late in the course of the disease. As in DM1, DM2 patients have ptosis, facial weakness, weakness and atrophy of sternocleidomastoid muscles, and weakness of thumb and lateral finger flexors early in the course of their disease. Unlike DM1, weakness in DM2 only rarely becomes marked, with the most marked weakness involving neck flexors, long finger flexors, and hip girdle musculature. The distal finger flexor involvement early in the course of disease was identified in studies of DM2 families, often in subjects who had not

Table 59.2 The common and distinguishing features of DM1 and DM2

Feature	DM1	DM2
General features		
Congenital form	Common with maternal inheritance	Not reported
Anticipation	Common	Rare
Life expectancy	Reduced	Normal
Disability due to muscle weakness	30–50 years	60–85 years
Muscle symptoms		
Myotonia	Common	Variable and may be absent
Ptosis	Present	Mild
Eye and mouth closure weakness	Prominent	Variable
Neck flexor weakness	Common	Variable
Distal muscle weakness	Evident	Mild
Proximal muscle weakness	Late	Common and early
Calf hypertrophy	Not present	May be present
Myalgia	Rare	Common
Systemic symptoms		
Cardiac conduction block	Common	Variable
Cataracts	More common	Less common
Dysphagia	Prominent, late	Rare, mild
Respiratory failure	Late	Rare
Testicular failure	Common	Occasional
Hyperglycemia	Common	Occasional
Male frontal balding	Common	Variable
Hyperhidrosis	Rare	Common
Excessive daytime somnolence	Common	Absent
Central nervous system abnormalities		
Mental retardation	Variable, severe in congenital form	Rare and mild
Brain MRI abnormalities	Common	Subtle
Pathological findings		
Muscle fiber internal nuclei and atrophy	Mostly type I fibers	Mostly type II fibers
Nuclear clumps	Late	Early
Ring fibers	Frequent	Less frequent
Genetics		
Chromosome	19q13.3	3q21.3
Mutation gene	*DMPK*	*ZNF9*
Location	3′ untranslated region	Intron 1
Mutation type	CTG expansion	CCTG expansion

DMPK, *dystrophia myotonica protein kinase*; *ZNF9*, *zinc finger 9*

sought medical attention for any recognized weakness. In contrast, most DM2 individuals who seek medical attention for muscle weakness typically are most concerned about proximal lower extremity weakness, but do usually complain of weakness in other muscle groups. Winged scapulae have been reported in both DM1 and DM2 patients [27].

Deep tendon reflexes in DM2 patients are usually normal or brisk, in contrast to DM1 in which DTRs are hypoactive or absent [28], except in the few cases associated with upper thoracic myelopathy due to disk herniation triggered by neck extensor weakness [29].

Facial Features

Patients with DM have characteristic facies, which is, in the eyes of experienced observers, pathognomonic. The face is typically long and has a hatchet-like shape due to temporomandibular wasting, with slack eyes, ptosis, flat smile, and balding. The head may tilt slightly backwards (to compensate for the ptosis) revealing the significant atrophy of the sternocleidomastoid muscles. However, this typical appearance is extremely variable between families and within the same family of patients with DM1 or DM2 (Figs. 59.1 and 59.2).

Myotonia

Myotonia is demonstrable in almost all patients with DM1. The predominant myotonic symptom in DM1 is grip myotonia, due to the effects of the disease on finger flexor and extensor muscles of the forearms (Fig. 59.3). Compared to myotonia congenita, the myotonia associated with DM1 is typically much milder, is more likely distal and less diffuse, and usually does not require specific symptomatic treatment. The myotonia can be relieved by repeated muscle activation ("warm-up" phenomenon) [2]. Patients commonly mention cold-induced exacerbation of the myotonia, but DM1 is not associated with the cold-induced contractures that are typical of paramyotonia [1, 18, 23, 25]. Myotonia is often absent in infancy and becomes evident later in childhood. Though myotonic discharges are easily elicitable during needle EMG in the vast majority of DM1 individuals, occasional subjects have fibrillation potentials with rare true runs of electrical myotonia. The myotonic runs typically last for several seconds, with frequencies ranging from 30 to 100 Hz. The molecular basis for myotonia remains unclear, though in DM1 it is associated with markedly increased muscle fiber expression of a calcium-activated potassium channel (the apamin receptor). The means by which this increased potassium current results in repetitive muscle fiber activation remains unclear, but local injection of apamin was reported to stop myotonia in DM1 [30–36].

Myotonia is less prominent and more variable in DM2 than in DM1, both clinically and electromyographically [16, 18, 23, 25, 26]. In DM2, myotonia is clinically evident in 75 % of patients and electrically in 90 % of patients [28]. Patients may have intermittent grip myotonia which may also improve with quinine or mexiletine. Percussion myotonia may be demonstrable in the tongue, extensor forearm, and thenar muscles of DM2 patients. Clinical myotonia may be also absent in many patients. Electrical myotonia is,

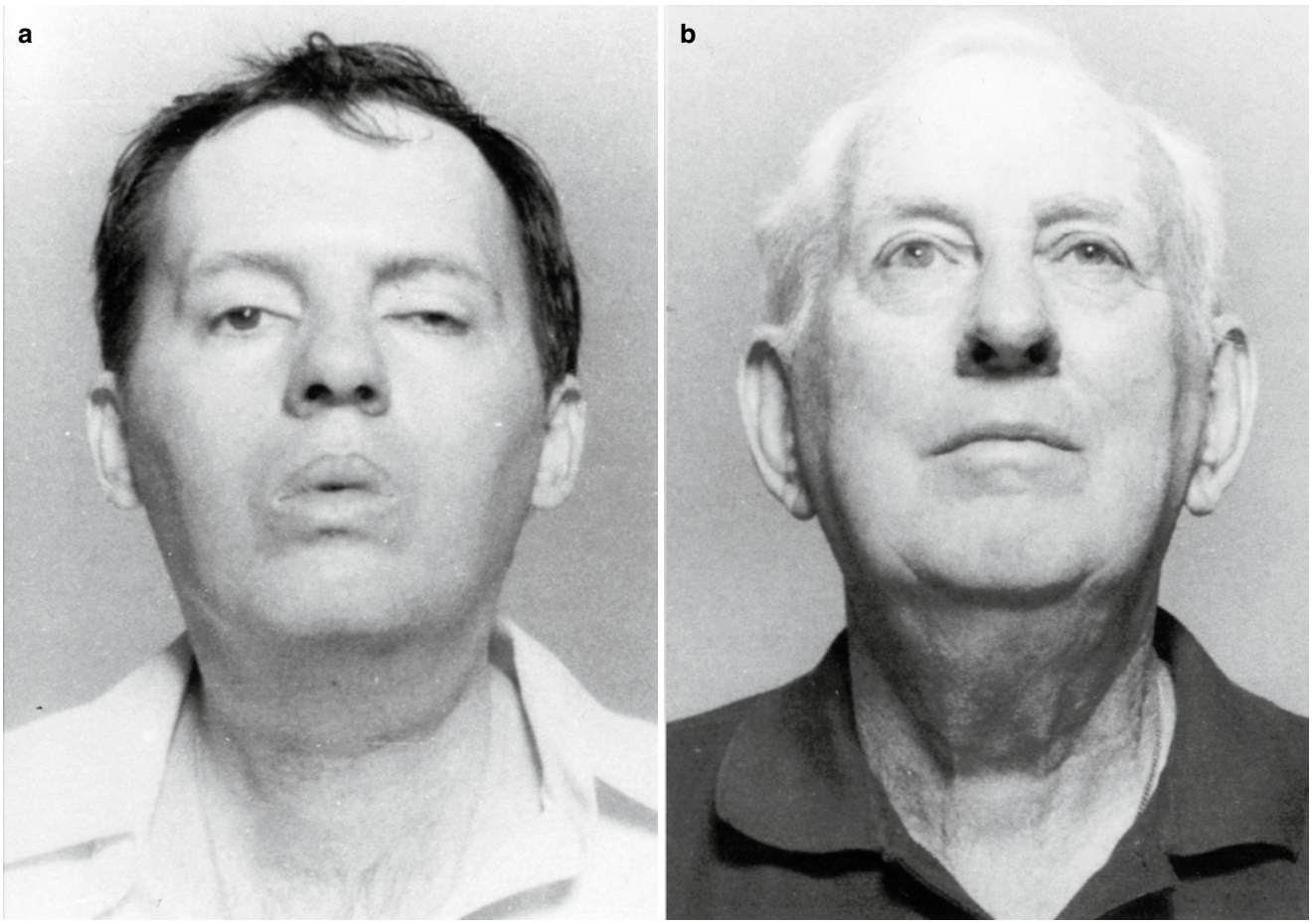

Fig. 59.1 Facial appearance in a 41-year-old son (**a**) and a 77-year-old father (**b**) with DM1. Note the ptosis, facial weakness, and masseter and temporalis wasting in the son and the minimal facial changes in the father (From Meola et al. [155]. With permission)

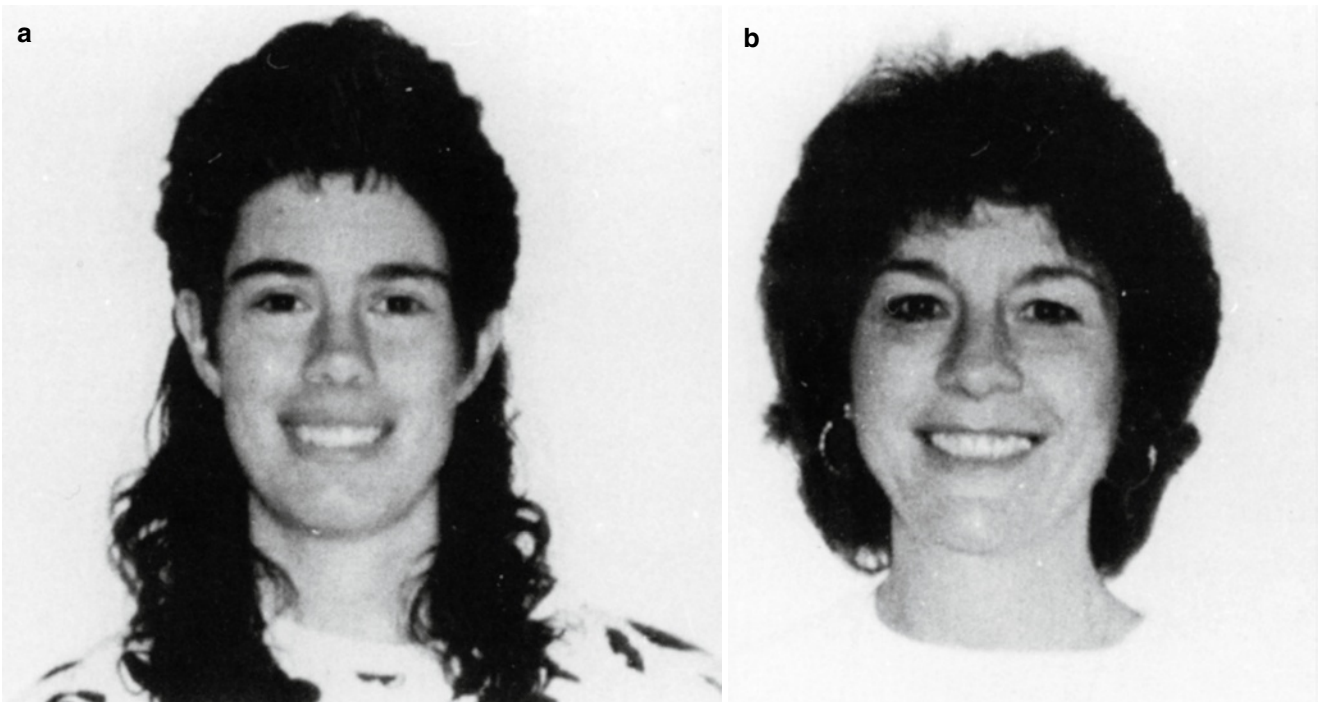

Fig. 59.2 Facial appearance in a 26-year-old daughter (**a**) and her 47-year-old mother (**b**) with DM2. Note the transverse smile, mild ptosis, and temporal wasting in the daughter. Contrast this family with the family in Fig. 59.1. The clinical features in both families suggest anticipation

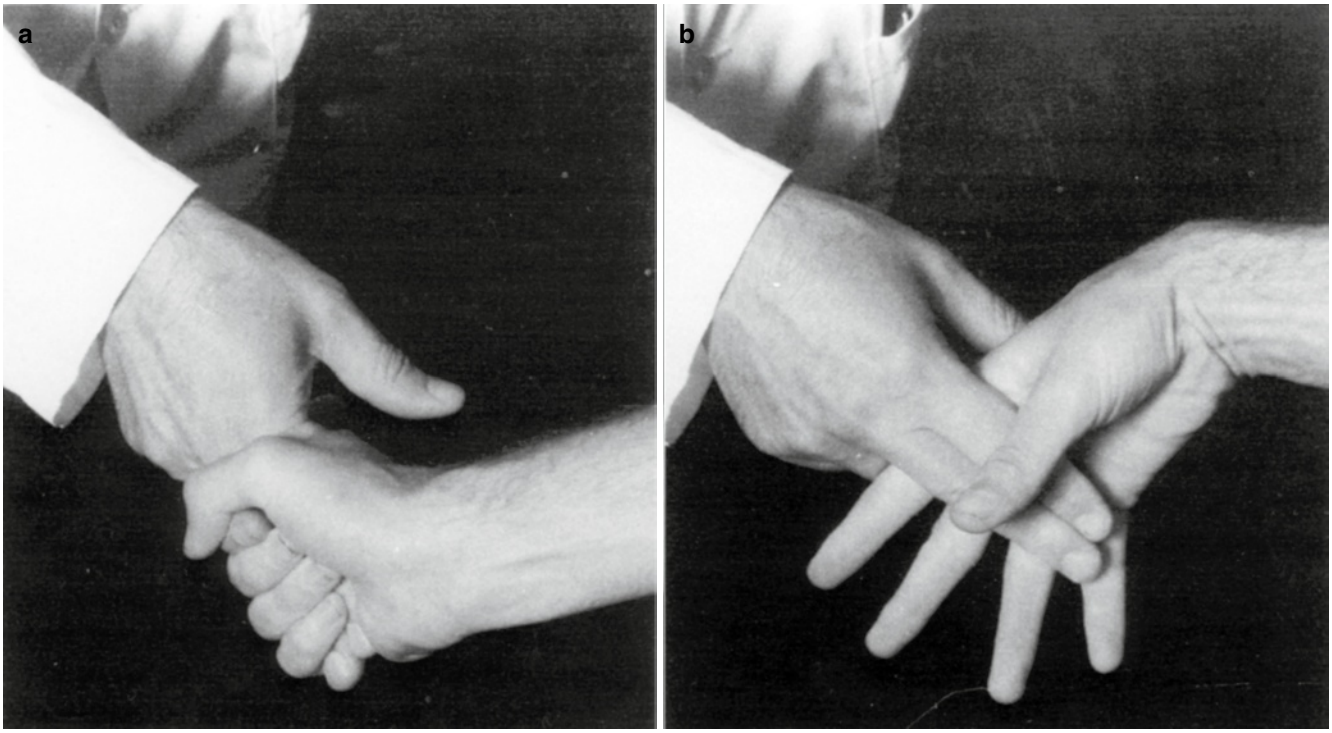

Fig. 59.3 Grip myotonia. Forceful grip (**a**), followed by delayed relaxation (**b**). Note that the thumb and fingers remain flexed at the metacarpophalangeal joints while the other joints are extended (**b**). This usually lasts about 5–10 s, but occasionally as long as a minute (From Meola et al. [155]. With permission)

however, a highly penetrant feature of DM2 patients, but often requires a detailed needle EMG examination which should include proximal and distal muscles as well as paraspinal muscles. Occasional patients with DM2 may have no evidence of electrical myotonia despite a thorough search [37, 38]. Sometimes, affected individuals have diffuse fibrillation potentials and occasional fasciculation potentials that obscure the myotonic runs, leading to misdiagnoses of diffuse neurogenic atrophy or motor neuron disease. Some have reported seeing occasional brief high-frequency (250–300 Hz) "pings" in DM2 and believe this finding might be specific to DM2 [16, 25, 26].

Eye

A reliable feature of the disease is the presence of iridescent posterior subcapsular ("Christmas tree") cataracts that are identifiable by slit lamp examination in almost all adults affected by DM1 or DM2. Many adults are completely asymptomatic despite the presence of such cataracts, while some DM1 and DM2 patients may require lens removal as early as the second decade of life to preserve visual acuity [1, 18]. "Christmas tree" cataracts are highly suggestive of DM, but whether they are truly pathognomonic of DM has been challenged [39]. In a prospective study, fewer than 2 % of normal individuals without a DM1 CTG expansion had characteristic cataracts. However, no other clinical or genetic assessment was apparently performed to see if these individuals had DM2. In addition to cataracts, DM1 has been associated with ptosis, slow saccades, and decreased intraocular pressure, with both central and peripheral mechanisms proposed for the eye movement abnormalities [40–42]. DM2 is occasionally associated with ptosis, but the other ocular features have not been described. Frank ophthalmoplegia is rare in DM1 and not observed in DM2.

Heart

The heart is commonly involved in DM1 which is associated with cardiac conduction defects and fatal arrhythmias [1, 18]. These cardiac defects are highly variable in DM2. Atrioventricular conduction defects are present in a high percentage of individuals with DM1, but are rare in DM2. Intraventricular conduction abnormalities occur in both disorders and may be more directly related to arrhythmias and sudden death, which also occur in both disorders [43–46] and do not correlate with disease severity or repeat length [47, 48]. Cardiomyopathy and heart failure are rare, but were reported in both DM1 and DM2 [49, 50]. Sudden death may occur in patients with DM1 as a consequence of myocardial

fibrosis and degeneration of the cardiac conduction system. Sudden death may result from asystole after atrioventricular block or from a ventricular tachyarrhythmia. Arrhythmias may occur including sinus node dysfunction; progressive heart block; atrial tachycardia, flutter, or fibrillation; and ventricular tachycardia or fibrillation. Atrial tachyarrhythmias predict sudden cardiac death [51]. Cardiac manifestations including severe cardiac arrhythmias may also be the first symptoms in young patients with DM1 [52]. Sudden cardiac death due to arrhythmogenic right ventricular cardiomyopathy attributed to cardiac DM1 has been also reported [53].

Cardiac involvement initially manifests as asymptomatic electrographic abnormalities, commonly prolongation of the PR interval and QRS duration. Therefore, it is recommended for patients to have annual EKG, and Holter monitoring and transesophageal echocardiogram every 2 years. Electrophysiological cardiac studies should be performed in patients who experience syncope, dizziness, or palpitations, or have documented arrhythmias or family history of sudden death or ventricular arrhythmias [54]. Cardiac pacemaker is recommended for patients with clinically significant cardiac conduction abnormality and implantable cardiac defibrillator in patients with cardiac tachyarrhythmia [51, 54].

Endocrine

Hyperinsulinemia, hyperglycemia, and insulin insensitivity are common features of both DM1 and DM2, with frank diabetes occurring occasionally in both disorders [1, 18]. Hypothyroidism is infrequent in both, but can be a remediable cause of worsening myopathy [55]. Hyperthyroidism was also reported in DM1 patients [56]. Testicular failure commonly results in hypotestosteronism and can also cause oligospermia in both DM1 and DM2, with serum testosterone levels commonly remaining in the low normal range despite the presence of markedly elevated follicle-stimulating hormone (FSH) levels [1, 18]. Adrenocortical regulation may also be affected in DM1, which could have secondary effects on multiple systems [57, 58] and on cytokine levels that further affect the function of many organ systems [59]. Serum levels of dehydroepiandrosterone are markedly reduced in DM 1 patients compared with age-matched healthy controls [60]. There are also reports of hyperparathyroidism due to pituitary adenoma, with multiple systemic effects that may result from the aberrant calcium regulation in DM1 patients [56, 61, 62].

Central Nervous System

DM1 results in personality changes, behavioral abnormalities, centrally mediated hypoventilation, mental retardation, dementia, and nonspecific cerebral white matter MRI T2 abnormalities [63–68], with seemingly early specific effects on memory [69].There is a growing evidence that cognitive impairment in the myotonic dystrophies is characterized by impairment in frontal lobe functions resulting in dysexecutive syndrome both in DM1 and DM2 which is not correlated to the degree of cortical atrophy or white matter hyperintense lesions on brain MRI but rather to a reduced cerebral perfusion in the frontal and temporal lobes by positron emission tomography (PET) scans. The cognitive impairment is usually frontal (attentional) and progressive, without extension to additional areas of cognition. The efficacy of a specific treatment, whose target is muscle strength improvement, may be underestimated by the coexistence of a dysexecutive syndrome [70]. Pathologically, neurons in the limbic system and/or brain stem of patients with DM1 and DM2 contain tau-associated neurofibrillary tangles, suggesting a common neuropathological process and a possible link with the central features of DM1 including apathy and sleepiness [3].

In addition to executive dysfunction, patients with DM1 and DM2 tend to have avoidant personality trait disorder [71]. Obsessive-compulsive personality and passive-aggressive personality features have also been reported in myotonic dystrophies [66]. In DM1, anxiety and depression are common and quality of life can be significantly impaired. Apathy in patients may be confused with depression [3].

Frontotemporal dementia has been reported in individuals with proximal muscle weakness at onset, clinical/electrical myotonia, and DM-type cataracts. The diagnosis was supported by brain single-photon emission computed tomography (SPECT) study that revealed marked frontotemporal hypoperfusion and by postmortem examination that showed frontotemporal spongiosis, neuronal loss, and rare neuronal and glial tau inclusions. There was cortical atrophy without white matter lesions on brain MRI [63–71].

Sleep and Respiratory System

Excessive daytime sleepiness (EDS) is a common complaint of DM1 patients, more particularly in those with higher degree of muscular impairment. In addition, DM1 patients sleep longer at night, and those with EDS more frequently reported hypnagogic hallucinations and feelings of weariness and pain in the legs upon morning awakening [72]. EDS in DM1 may be severe and may resemble the sleepiness of primary hypersomnias such as narcolepsy. Besides EDS, severe fatigue is present in up to 74 % of adult-onset DM1 patients [73]. Central and obstructive sleep apneas are yet other commonly reported sleep abnormalities in DM1. In addition, DM1 patients may exhibit sleep-onset rapid eye movement periods in the multiple sleep latency test such as those classically found in narcolepsy. Decreased hypocretin-1

levels in the cerebrospinal fluid of DM1 patients with EDS were recently observed, suggesting a dysfunction of the hypothalamic hypocretin system [72].

In DM2, EDS is usually absent, a clinical feature that helps differentiating it from DM1 (see Table 59.2). On the other hand, there is a decrease in the quality of sleep in patients with DM2, likely due to nocturnal awakenings caused by muscle pain and not explained by depression or other comorbidities. Pain management may improve sleep and quality of life in DM2 patients [73]. Fatigue is another commonly experienced symptom in DM2 and is not correlated with the use of beta blockers, thyroid dysfunction, or poor sleep quality.

In addition to EDS, respiratory involvement in patients with DM1 includes alveolar hypoventilation, which results from respiratory muscle weakness as well as dysfunction of the central control of respiration. Also, patients with DM1 are at higher risk of aspiration pneumonia due to weakness and myotonia of the pharyngeal and esophageal muscles. Acute postoperative respiratory failure is a reported complication in older patients with DM1 with advanced muscle weakness undergoing abdominal surgery. This was explained in part by the depressant effect in the respiratory system of certain anesthetic agents such as thiopentone, halothane, and suxamethonium [74]. In contrast to DM1, patients with DM2 have relative preservation of respiratory function which also reduces the risk of right heart failure which may occur in patients with DM1 [28].

Skin

In addition to early male balding [1, 18], hyperhidrosis is a unique complaint in patients with DM2, affecting the hands and trunk mostly [28]. Other dermatological manifestations include seborrheic dermatitis as well as pilomatrixomata and epitheliomas on the scalp which may be misdiagnosed as sebaceous cysts [3, 22, 75].

Immune System

In both DM1 and DM2, hypogammaglobulinemia is associated with low levels of IgG and IgM [1]. The frequency of autoimmune diseases and overall presence of autoantibodies (such as antinuclear antibody and rheumatoid factor) are increased in DM2 patients. This may be due to the effect of the DM2 mutation on the immune system through an RNA-mediated disease process or through a genetic linkage [76].

Gastrointestinal Tract

Gastrointestinal dysfunction is common in DM1 and is disabling in ¼ of the patients [2, 77]. Gastrointestinal complaints in DM1 range include dysphagia, diarrhea, constipation, and fecal incontinence. Dysphagia in DM1 may contribute to aspiration pneumonia. Reduced motility is common in DM1 patients and severe obstructive symptoms such as megacolon have been described. New evidence suggests that gastrointestinal problems are also common in DM2 patients [78]. Cholecystitis and gallbladder stones due to an increase tone of the gallbladder sphincter have been reported in DM1 patients with high postoperative complication after cholecystectomy [3].

Neoplasia

Patients with DM1 may have an increased risk of thyroid cancers and choroidal melanoma. An increased risk for malignancies of the testis, prostate, endometrium, ovary, colon, thymus, and brain has been also reported [75].

Other System Abnormalities

In addition to hormonal abnormalities mentioned above (testosterone, FSH, LH, thyroid studies), abnormal laboratory studies are very common in patients with DM1 and DM2. This includes low BUN and creatinine, low serum albumin, low calcium, and elevated cholesterol [79, 80]. Total white cell count, platelets, hemoglobin, and hematocrit are typically reduced in both patient populations. Total lymphocyte count and red cell mean corpuscular volume may be increased in DM1 patients. Liver dysfunction is frequently implicated as a cause for serum transaminase elevation in both disorders [81], with normal liver biopsies frequently and needlessly performed, since the source of the increased enzymes is often the skeletal muscle; minimal gamma-glutamyl transpeptidase (GGT) elevation may indicate some true, though apparently slight, hepatocellular injury [1, 16, 18, 26]. Mildly elevated GGT does not require specific liver investigation in these patients [82].

Genetic Mechanisms and Pathogenesis

Research into the genetics of myotonic dystrophy (DM) leads to advances in the areas of molecular pathogenesis and pathophysiology, both of which aid in understanding the clinical manifestations of this multisystem disease. In addition, this research will ultimately have implications for potential therapeutic options.

DM was initially described about 100 years ago. In the past 10 years, there have been a number of advances, particularly in the concept of genetics and molecular pathomechanisms. Here we describe the clinically relevant genetics of DM.

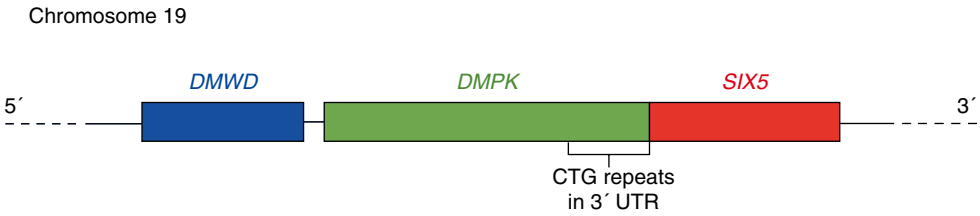

Fig. 59.4 The location of *DMWD*, *DMPK*, and *SIX5* genes on chromosome 19. Of note, diagram is not depicted in the actual ratio. UTR, untranslated region

Mutations

As compared to some other genetic diseases, the genetic mutations of DM1 and DM2 are not as complicated. Indeed, there is only one gene involved in each DM subtype, and the basic changes are trinucleotide and tetranucleotide repeat expansion in DM1 and DM2, respectively.

DM1 results from a CTG repeat (CUG in RNA) expansion in the *DMPK* gene, which is located in the 3′ untranslated region (UTR) of chromosome 19q13.3. This gene is immediately upstream to the promoter region of the *SIX5* gene (Fig. 59.4). In DM2, there is a CCTG (CCUG in RNA) repeat expansion in intron 1 of the *zinc finger 9* (*ZNF9*) gene on chromosome 3q21.3 (see Table 59.2). Both DM1 and DM2 have an autosomal dominant mode of inheritance. Most patients are heterozygous, but a minority is homozygous. Proximal myotonic myopathy (PROMM), which was described clinically before the discovery of DM2 gene, was found to have the same genetic mutation as DM2 [25]. Therefore, PROMM is, in fact, the same entity as DM2. There were case reports of possible myotonic dystrophy type 3 (DM3) when the patients had clinical phenotypes similar to DM, particularly DM2, but genetic testing for DM1 and DM2 was negative [22, 83, 84]. However, one family was proven later to be inclusion body myopathy with Paget disease of bone and frontotemporal dementia associated with *valosin-containing protein* (*VCP*) gene mutation [20, 21]. Diagnosis of DM3 needs to be cautious since two standard genetic techniques including standard PCR and Southern blot can detect only approximately 80 % of DM2 patients [85]. It is also possible that reported DM3 cases may in fact have DM2 or other undiagnosed neuromuscular diseases.

There are two important concepts in nucleotide repeat expansion disorders which deserves a detailed discussion. These are: (1) anticipation and (2) the relationship between the number of repeats and disease severity.

Anticipation

In 1918, DM1 was the first disorder in which anticipation was described [86]. Anticipation is an increase in the number of repeats when the gene is passed to future generations that lead to an earlier disease onset and an increase in disease severity. Instability of repeat sequences may be caused by slippage of replication machinery during DNA synthesis [87]. In normal circumstances, slippage can occur and mismatch repair processes will then take place. Mismatch repair defects, in addition to slippage during DNA synthesis, can lead to unstable repeat expansions.

Short repeat sequences, known as "simple tandem repeats (STR)," are found in normal individuals. When the number of repeats within one particular gene expands, usually to the upper limit of the normal range, the repeats become unstable and are referred to as "unstable repeat expansions (UREs)." UREs are prone to further expansion.

It is worth mentioning that in DM, the reported number of repeats refers to the number of repeats as measured in leukocytes. "Somatic instability" refers to the fact that different cell types have different numbers of repeats [88, 89]. For example, muscle and brain cells have a significantly greater number of repeats as compared to leukocytes, but leukocytes are the cells used most often in genetic studies of DM. In addition to somatic instability, age is another factor that affects the number of repeats [90–92].

Gender also plays an important role in DM and there is a maternal transmission bias in transmitting congenital DM. Congenital DM1 usually occurs in infants born to mothers with DM1 or repeat sequences in the premutation range of DM1. In congenital DM1, the number of repeats is typically greater than 1,000. The maternal transmission observed may be related to UREs during oogenesis [93]. It is also proposed that sperms with a high number of repeats may not survive [94]. Sex and "meiotic drive," a preferential transmission of a particular allele during meiosis at a given locus, is another proposed theory but this remains controversial and debating data is discussed elsewhere.

Disease Severity and the Number of Repeat Expansions

In general, the patients have earlier onset and greater severity of disease when the number of repeats is higher [95, 96]. However, there is no clear correlation between the number of repeats and disease severity; In other words, we can neither predict the exact number of repeats based on disease severity nor predict the severity of the disease from the number of repeats. We can only infer the possible range of repeats. It is very difficult to predict disease severity, especially when the number of repeats is high. However, as mentioned above, normal individuals have a low number of repeats. As the number of repeats approaches the premutation range, sequences are more unstable. When the number of repeats is in mutation

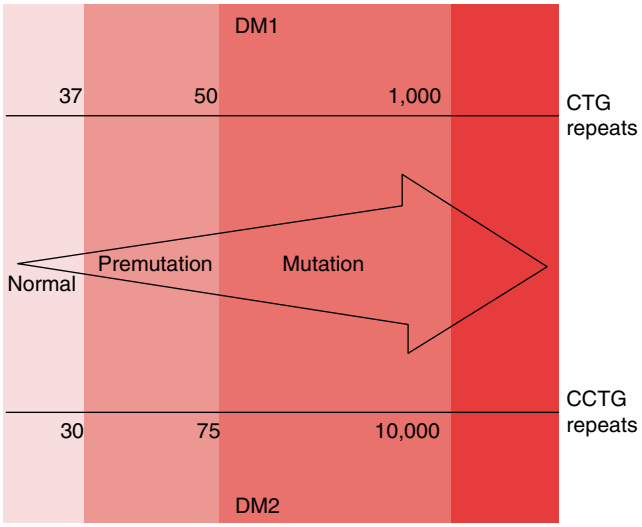

Fig. 59.5 Correlation between severity of diseases and the number of repeats in DM1 and DM2

range, the patient will have earlier onset and more severe disease if the number of repeats is higher. When the number of CTG repeats is greater than 1,000, the patient typically has congenital DM1 [97] (Fig. 59.5).

DM1 manifests clinically when the patient has a repeat number greater than 50. In the 50–100 range, patients will have a mild form of the disease, with such symptoms as skin abnormalities and frontal balding but without cognitive impairment. If the number of repeats is greater than 1,000, the patients often have severe clinical manifestations at birth or even in utero, i.e., congenital DM1 [96, 98].

Even though clinical phenotypes of DM1 and DM2 share some similar features, the number of repeats in the two diseases is different. Interestingly, in DM2, the number of repeats overall is much higher than in DM1 and can be in the 11,000 range (with an average around 5,000) despite milder clinical phenotype [85]. Although the nucleotide repeat expansion concept is similar between DM1 and DM2, there are several issues not yet fully explained. As opposed to DM1 and despite the high number of repeats, DM2 does not usually result in a congenital phenotype [99].

Molecular Pathogenesis

Knowing the genetic basis of DM1 and DM2 as nucleotide repeat expansion disorders provides the opportunity to explain the pathogenesis of these diseases. It is interesting why a mutation in one gene leads to multisystem disease, including myotonia, weakness, cataract, insulin resistance, and cognitive impairment.

We will use DM1 as a model herein. Prior to 2001, there were several proposed mechanisms, including haploinsufficiency, interaction between neighboring genes, and

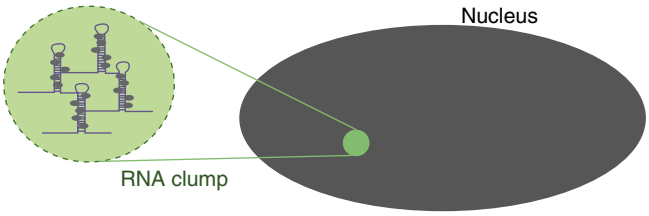

Fig. 59.6 RNA clump ("toxic RNA") within nucleus of myocyte demonstrated by fluorescence in situ hybridization (FISH) technique. This clump comprises pre-mRNA with hairpin loop formation and RNA-binding proteins sequestered in hairpin loops

RNA toxic gain of function. The discovery of CCTG repeat expansion in DM2 and several subsequent studies support the latter theory, which is believed to be the main and the most important mechanism at present.

RNA Toxic Gain of Function

This mechanism has been proposed since 1995 [11, 12]. With regard to genetic dogma, DNA is transcribed to pre-mRNA in nucleus, which then will have posttranscriptional modification and alternative splicing into mRNA. mRNA will then be translated into protein in the cytoplasm.

When pre-mRNA is transcribed from unstable repeat sequences in DNA, it forms multiple hairpin loops. Protein sequestration then occurs when RNA-binding proteins in the nucleus bind to these hairpin loops [100]. RNA then becomes "toxic." This mechanism is confirmed by demonstrating nuclear foci of RNA clumps, rather than dispersion throughout the nucleus, on fluorescence in situ hybridization (FISH) technique (Fig. 59.6). One of the important RNA-binding proteins is CUG-binding protein 1 (CUGBP1) (Fig. 59.7). This protein was thought to be sequestered in hairpin loops; hence the name "binding protein" was initially assigned. However, CUGBP1 failed to co-localize with the RNA clumps in the nucleus on FISH, possibly due to weak affinity for expanded CUG repeats. In fact, CUGBP1 level is increased within the cell [101–103]. The mechanism with regard to increased CUGBP1 level remains unclear. Also, importantly, protein kinase C, which has an increased activity in DM1, will phosphorylate CUGBP1 and lead to multisystem problems as mentioned below [104]. The trigger of protein kinase C activation also remains unclear. Although CUGBP1 has a role in DM1 pathogenesis, it has no role in DM2 [105]. A protein that co-localizes nuclear foci of toxic RNA clumps was found later. It is the muscleblind-like protein (MBNL) [102, 103, 106, 107]. This protein is a homolog of *Drosophila* muscleblind protein and can lead to muscle and eye problems, as the name implies [108]. There are three subtypes of MBNL, MBNL1, 2, and 3 [109]. All subtypes co-localize toxic RNA clumps within the nucleus. This is the second protein that is sequestered within hairpin loops and is also important in the toxic RNA pathomechanism [110, 111].

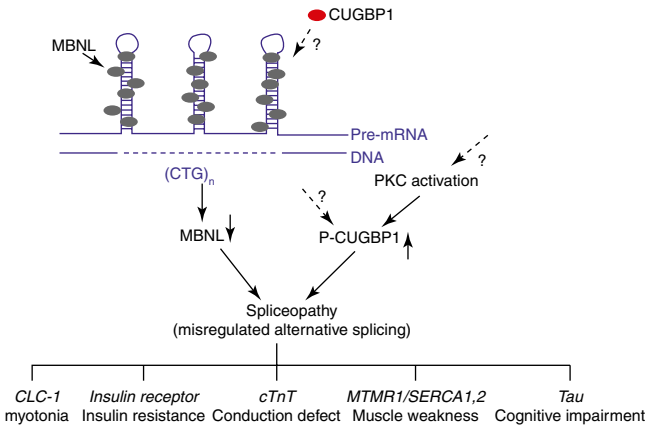

Fig. 59.7 RNA toxic gain-of-function pathomechanism. MBNL, muscleblind-like protein; P-CUGBP1, phosphorylated CUG-binding protein 1; $(CTG)_n$, CTG repeat expansion; PKC, protein kinase C; *CLC-1*, *chloride channel-1* gene; *cTnT*, cardiac troponin T gene; *MTMR1*, *myotubularin-related 1* gene; *SERCA1, 2*, *sarcoendoplasmic reticulum* Ca^{2+} *ATPase 1, 2* gene; ?, unclear mechanism. Of note, spliceopathy is a misregulated alternative splicing of mRNA products of these genes, not the genes

Unlike CUGBP1, MBNL level is decreased within the cell due to sequestration [112].

Increased phosphorylated CUGBP1 and decreased MBNL can explain multisystem phenotypes of DM1 by leading to misregulated alternative splicing of mRNA [113, 114]. This is also called "spliceopathy." Normally, alternative splicing of mRNA can produce different combinations of exons resulting in the synthesis of different proteins with different functions [115]. This spliceopathy may lead to misregulated alternative splicing of mRNA products including those from chloride channel gene leading to myotonia [116–118], from the insulin receptor gene leading to insulin sensitivity [119], from the *tau* gene leading to cognitive impairment [120, 121], from the cardiac troponin T gene leading to cardiac conduction defect [122, 123], and from *myotubularin-related 1* (*MTMR1*) and *sarcoendoplasmic reticulum* Ca^{2+} *ATPase 1, 2* (*SERCA1, 2*) genes leading to muscle weakness [123, 124].

This mechanism also applies in DM2. There is evidence of nuclear foci of CCUG repeats in DM2, similar to that seen in DM1. Co-localization of MBNL proteins and these nuclear foci is also found [112, 125]. These findings make this theory more convincing for shared pathogenesis between DM1 and DM2. However, data on DM2 is limited as compared to DM1 and needs to be further investigated.

Haploinsufficiency

This mechanism was proposed even prior to the RNA toxic gain-of-function mechanism. However, there is some compelling evidence that will be discussed below. It was previously thought that CTG repeat expansion in *DMPK* gene would cause reduced expression of one allele. However, this might not be true. Although the DMPK protein level is decreased in cytoplasm, pre-mRNA level from the *DMPK* gene is, in fact, not decreased in the nucleus [11]. Heterozygous *DMPK* knockout mice, which were comparable to heterozygous mutations in humans, did not show evidence of myopathy or multisystem phenotypes, whereas homozygous *DMPK* knockout mice had cardiac conduction defects and skeletal muscle abnormalities, but not typical DM1 histology [126, 127]. Not all systemic features can be explained by the *DMPK* knockout mouse model. In addition, haploinsuffiency of *SIX5* gene which is immediately downstream to *DMPK* gene has been proposed in DM1. *SIX5* knockout mice showed abnormal cardiac and muscle development [128]. Heterozygous *SIX5* knockout mice had QRS prolongation that was apparent only under general anesthesia [129]. Therefore, *SIX5* haploinsufficiency cannot explain all DM1 clinical features. In DM2, *ZNF9* knockout mice had abnormal forebrain development and craniofacial abnormalities, but did not show classic phenotypes of DM2 [130].

Gene Interaction

The promoter region of the *SIX5* gene is immediately downstream to the *DMPK* gene [131, 132] (see Fig. 59.4). The *SIX5* gene is related to eye and distal limb muscle development in the fruit fly and mouse, respectively. Cataracts and distal limb weakness are common features in DM1. Therefore, it was thought that there might be an interaction between the *DMPK* and *SIX5* genes. However, this theory cannot explain all systemic features [133]. In addition, despite the similarity of phenotypes between DM1 and DM2, DM2 cannot be explained by the interaction between these genes as they do not exist on chromosome 3.

Genotype-Phenotype Correlation

As mentioned previously, the number of repeats correlates with the onset and the severity of disease in both DM1 and DM2. However, phenotype cannot be accurately predicted based solely on the number of repeats. This is especially true when the number of repeats is beyond 600 in DM1. A CTG repeat count greater than 1,000 in the *DMPK* gene is associated with congenital DM1 [96, 98].

Diagnosis and Evaluation

In moderately or severely affected individuals, myotonic dystrophy is easily recognizable on clinical grounds [1, 23, 24]. Even in minimally affected individuals, the clinical phenotype is highly suggestive of the diagnosis. Patients commonly come to medical attention due to weakness, myotonia, or myalgias, though the multisystem nature of the disorder may result in initial presentations due to ocular, endocrine, cognitive, cardiac, reproductive, sleep, gut, or skin

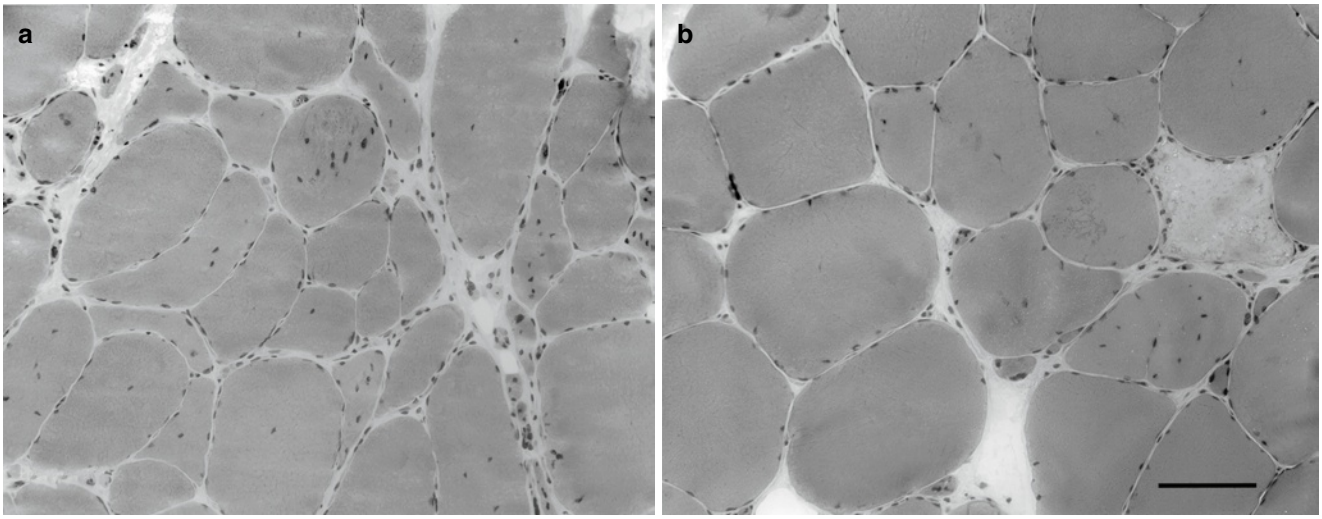

Fig. 59.8 Histology of DM1 and DM2. The figure shows hematoxylin- and eosin-stained sections of myotonic dystrophy type 1 (**a**) and myotonic dystrophy type 2 (**b**). In each section fiber size variation is greater than normal, with diameters ranging from 10 to more than 200 μm. There are many severely atrophic fibers. There is a marked increase in the number of fibers with centrally located nuclei. Fiber splitting is evident in both sections. A necrotic fiber is evident in the DM2 muscle. There is endomysial and perimysial fibrosis. Calibration 100 μm

abnormalities. The presence of typical facies, clinical and electrical myotonia, characteristic pattern of weakness, modestly elevated serum CK, the typical histological pattern on muscle biopsy (see below), iridescent posterior subcapsular cataracts, insulin insensitivity, hypogammaglobulinemia, male balding, and testicular failure, all inherited as a dominant disorder, provides a compelling clinical diagnosis of DM1 [18]. DM2 is slightly more difficult to diagnose clinically because of the variability of symptoms and lack of typical facial features and subtle myotonia. Genetic testing reliably identifies affected DM1 and DM2 patients, obviating invasive diagnostic testing in this disorder.

Muscle Biopsy

The histological features of muscle biopsies in DM1 and DM2 are distinct, though not pathognomonic (Fig. 59.8). Characteristic findings to both types include prominent central nuclear migration, muscle fiber atrophy, bags of myonuclei, and ring and split fibers. In DM1, type I muscle fibers are predominantly affected, while DM2 shows preferential involvement of type II muscle fibers. Fibrosis and adipose deposition does occur late and parallels disease severity [1, 18, 23]. Despite this, DM1 and DM2 specimens cannot be reliably differentiated histologically. The severely atrophic fibers seen in DM1 and DM2 are curiosities since they are typically seen in neurogenic atrophy, though definite features of muscle denervation or reinnervation have not been identified in either DM1 or DM2 [1, 18]. The fiber necrosis, fibrosis, and adipose deposition in DM1 and DM2 validate the categorization of the disease as a muscular dystrophy.

Genetic Testing

Genetic diagnosis remains the gold standard test for DM1 and DM2. It is not infrequent that the clinical manifestations, including characteristic facies, myotonia, cataracts, and apathy, provide a convincing evidence for the diagnosis of DM1. In DM1, polymerase chain reaction (PCR) is used as a first step. The principle is that PCR cannot detect very large repeats. It can detect only small repeats. In normal individuals, there should be two bands if the numbers of repeats in each allele on chromosome 19 are different. However, a single band can occur if numbers of repeats in each allele are equal or very close. In DM1 patients, there is also only one band, as the pathogenic allele which contains large repeats cannot be detected by PCR. Therefore, if there are two bands shown on PCR, the disease can be excluded. However, if there is only one band, this could be a normal individual with an equal number of repeats in two alleles or a DM1 patient. Further Southern blot testing is necessary to confirm the diagnosis [134, 135].

In DM2, similar techniques are used but a third test – the repeat-primed PCR-based assay – may also be required to increase the detection rate to 99 %. The first two tests may detect only 80 % of DM2 [22, 85, 136]. The threshold for genetic testing in DM2 should be low since myotonia and cataract may be absent and the clinical presentation may be late, mild, or predominantly myalgic in type. Also, findings that are fairly typical for DM2 on muscle biopsy are sometimes another indication for genetic testing [82].

Prenatal genetic diagnosis using chorionic villous sampling and amniocentesis can be done with some risks of miscarriage. In vitro fertilization is also used in preimplantation genetic diagnosis. Sperm and egg are fertilized in vitro and

Table 59.3 Disorders associated with clinical and/or electrical myotonias

Muscular dystrophies
Myotonic dystrophy type 1
Myotonic dystrophy type 2
Limb-girdle muscular dystrophy 2A (calpainopathy)
Channelopathies
Myotonia congenita type 1 (Thomsen disease)
Myotonia congenita type 2 (Becker disease)
Hyperkalemic periodic paralysis
Paramyotonia congenita
Congenital myopathies
Myotubular myopathy
Metabolic myopathies
Acid maltase deficiency (Pompe's disease)
Drugs/toxins
Colchicine
Statins

the embryonic cell is then genetically tested and selected. A normal cell is selected and implanted into the uterus [137, 138].

Recommended Additional Tests

Once the diagnosis of DM1 or DM2 is made, several evaluations need to be obtained to assess and monitor systemic disorders. These include measurement of blood count, electrolytes, lipid panel, TSH, FSH, LH, testosterone, IgM/IgG levels, and 2-h glucose tolerance test. Patients should have an initial and an annual EKG [54]. Holter and echocardiography are recommended by others every 2 years [54]. Patients with syncope, dizziness, palpitation, documented arrhythmias, or family history of sudden death or ventricular arrhythmias should undergo cardiology consultation and undergo electrophysiological cardiac studies [54]. Annual ophthalmologic examination to detect cataract and choroid melanoma and annual thyroid examination to detect early thyroid cancer should be done [75]. Sleep studies should be considered for patients with suspected EDS.

Differential Diagnosis

Patients with severe or advanced form of DM1 are relatively easy to diagnose. In contrast, patients with mild DM1 or DM2 are more elusive and may be misdiagnosed for years. These mild disorders may be difficult sometimes to distinguish from the non-dystrophic myotonias including myotonia congenita. Other inherited and acquired disorders with electrical or clinical myotonia need to be included in the differential diagnoses (Table 59.3). DM2 may be mistaken for limb-girdle muscular dystrophies since they both exhibit proximal limb weakness and for inclusion body myositis because of the late onset. Congenital DM1 may be difficult to diagnose accurately due to the lack of myotonia during infancy and may be mistaken for congenital myopathy or muscular dystrophy.

Treatment and Management

There is currently no known curative therapy for DM1 or DM2. Appropriate clinical management of patients with DM includes symptomatic treatment of muscle pain and myotonia and prevention and management of complications and other organ involvements.

There is a strong recommendation (class I evidence) regarding the use of mexiletine as an antimyotonia treatment in patients with DM1. Mexiletine given at a dosage of 150–200 mg three times daily is well tolerated, safe, and effective in reducing grip myotonia with no associated serious adverse events or prolongation of PR, QTc intervals, or QRS duration [139]. Flecainide at a dose of 50–100 mg twice a day or propafenone at a dose of 150–300 mg twice a day may be considered as an alternative treatment of myotonia [82]. Quinine, phenytoin, and dihydroepiandrosterone are also of value in patients with DM1 or DM2, though drugs with effects on cardiac function or conduction need to be used cautiously due to the intrinsic effects of DM on the heart.

Excessive daytime sleepiness is significantly reduced with a single 20-mg daily dose of methylphenidate in patients with DM1 [140]. Hypothyroidism and gonadal failure are treated with hormonal replacement therapy [82]. Constipation is treated with dietary and pharmacologic adjustments like osmotic laxatives, along with supplementary fibers. The use of tramadol and other opiates should be avoided because of the potential negative side effects on gastrointestinal motility or precipitating megacolon [78].

Therapeutic implications of the genetic discoveries in DM1 and DM2 are still evolving. RNA toxic gain-of-function theory leads to several important therapeutic implications. For example, antisense oligonucleotides (ASOs) can be used to bind mRNA, thereby preventing hairpin loop formation and subsequent protein sequestration [141–147]. Reducing protein kinase C activity [148], increasing MBNL activity [149–152], or reducing CUGBP1 activity [105] can lead to a decrease in misregulated alternative splicing. There are also other targets of which the studies are under way.

Prognosis

Most patients with DM1 and DM2 remain ambulatory till later in life. DM1 and DM2 typically remain stable during childhood, but lead to progressive loss of function and motor

skills during adulthood. However, life expectancy in DM1 is significantly reduced due to the increased risk of fatal arrhythmias, ventilatory failure, neoplasia, and coronary artery disease [46, 153, 154]. In DM1, death can occur as early as the 2nd or 3rd decade [47]. DM2 has rarely been associated with fatal arrhythmias as early as the 3rd decade of life and is unlikely to cause severe ventilatory insufficiency even in later life.

Congenital DM1 is characterized by hypotonia, poor feeding, and respiratory compromise, with the potential for neonatal fatality due to ventilatory collapse. Myotonia may be absent in infancy, and most children have mild or moderate mental retardation.

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Oculopharyngeal Muscular Dystrophy

60

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Introduction

In 1915, Taylor from Boston, Massachusetts, reported the familial association of eyelid ptosis and dysphagia in a family of French-Canadian (FC) descent [1]. However, it was not until 1962 that oculopharyngeal muscular dystrophy (OPMD) was recognized as a distinct muscular dystrophy [2]. OPMD manifests primarily as an autosomal dominant disorder usually after the age of 50, with late-onset selective progressive ptosis and dysphagia. A recessive form has also been reported [3]. In 1980, Tomé and Fardeau identified by electron microscopy a specific histological marker, unique filamentous intranuclear inclusions, in the deltoid muscle of three unrelated OPMD patients [4, 5]. In 1998, the gene defect of OPMD was found to be a $(GCG)_n$ repeat expansion in the first exon of the polyadenylate-binding protein nuclear 1 (*PABPN1*) gene, known as PABP2 [6]. OPMD was thus the first disease to be caused by a short $(GCG)_n$ expansion coding for polyalanine residues.

OPMD has a worldwide distribution with patients described in, or originating from, 30 countries (Fig. 60.1). OPMD is particularly prevalent in the FC population (1:1,000) and in Bukhara Jews living in Israel (1:600) [7, 8]. Most North American cases of OPMD descend from three French sisters who arrived in Québec in 1648 [6, 9]. Numerous other historically distinct OPMD mutations have also been introduced or have appeared in North America in Louisiana Cajuns, Hispanic Americans from the Southwestern United States, Jews of Eastern European origin, Italians, Mennonites, and descendants of British immigrants [6, 10–14]. In France, a prior estimate of OPMD prevalence identified one case per 200,000 [15], but the identification of many new families over the past decade suggests that OPMD has at least twice this prevalence [16]. The Western European prevalence, based on the large number of families tested for the mutation since 1998, may also be in the range of 1:100,000–200,000. The predicted prevalence of the recessive form is about 1:10,000 in Québec, France, and Japan [6].

Etiology and Pathogenesis

Pathologically, the OPMD intranuclear inclusions (INI) consist of tubular filaments often arranged in palisades or tangles [4]. The filaments are 0.25 μm in length and have an 8.5 nm external diameter and a 3 nm internal diameter (Fig. 60.2). In deltoid muscles, 4–5 % of the nuclei seen in every ultrathin section contain these filaments [4]. Other nonspecific pathological findings in OPMD include rimmed vacuoles and small angulated muscle fibers [5]. One group reported that 8 % of nuclei in the more affected cricothyroid pharyngeal muscle bear INI compared to half that percentage in the deltoid muscle. In homozygous OPMD patients, twice as many muscle nuclei show INI than is usually observed in heterozygous patients [17–19]. Tubular filaments described in OPMD muscles are also found in inclusion body myositis [20, 21].

Using three large FC families, the dominant OPMD locus was mapped to chromosome 14q11.2-q13 [7]. Linkage to the same haplotype was documented for families of other ethnic backgrounds suggesting that dominant OPMD is a genetically

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Fig. 60.1 Countries of origin of OPMD cases reported in the literature ($n = 30$). The size of the *circles* indicates a relative prevalence

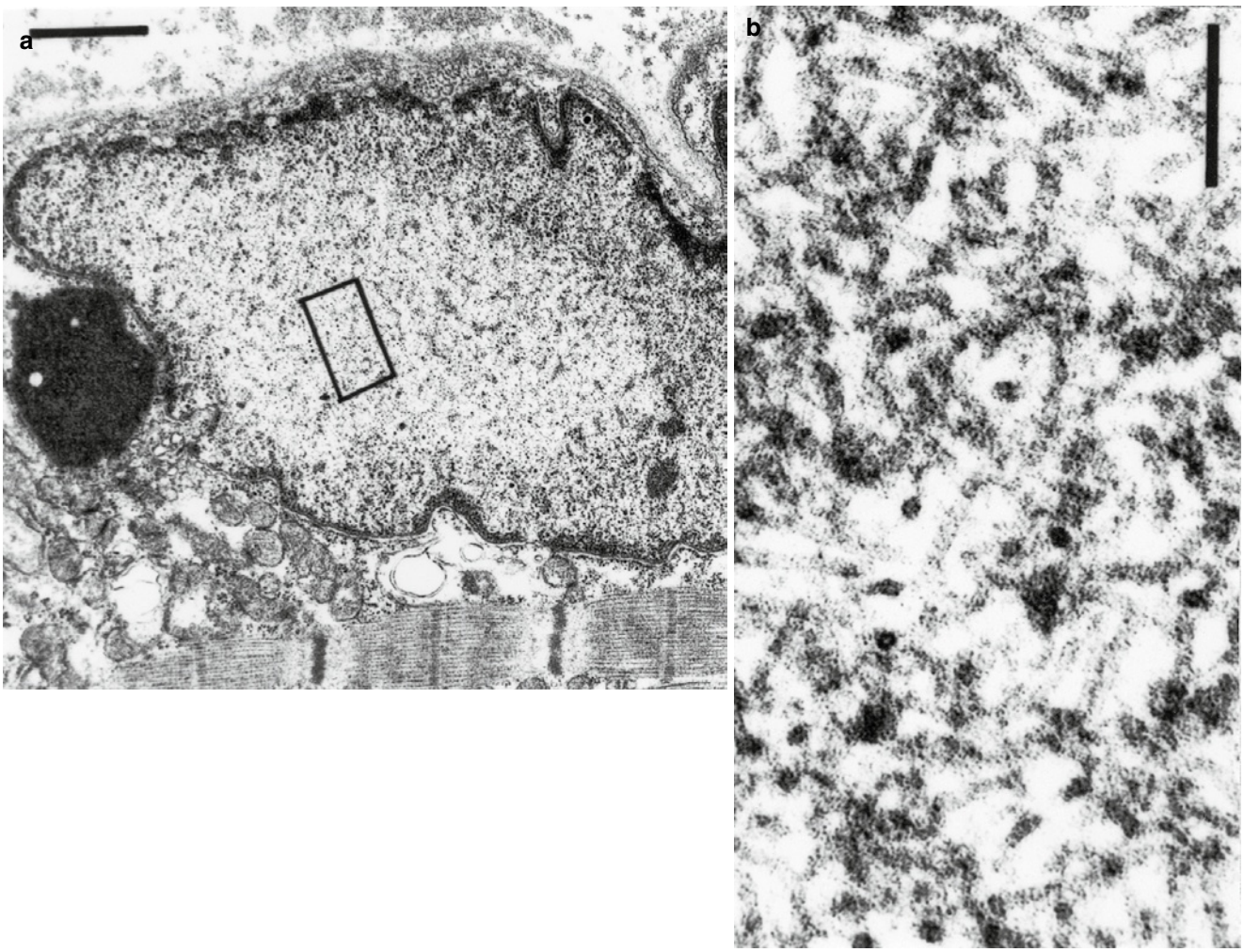

Fig. 60.2 (**a**) Electron micrograph of deltoid muscle showing the classical Tomé OPMD intranuclear tubular filaments (% 11,500, bar = 1 mm). (**b**) The INI at higher magnification (% 110,000; bar = 0.1 mm)

Table 60.1 Genomic OPMD *PABPN1* dominant mutation and polyalanine expansions of the homopolymeric polyalanine domain of the PABPN1 protein in OPMD

PABPN1 OPMD $(GCN)_{12–17}$ dominant mutations
ATG GCG GCG GCG GCG GCG GCG $(GCN)_{2–7}$ GCA GCA GCA GCG
Or a point mutation# changing a (GGG) into a (GCG)
ATG GCG GCG GCG GCG GCG GCG GCA GCA GCA GCG GC#G GCT GCG
OPMD dominant expansions in the PABPN1 N-terminus of the polyalanine domain
$M(A)_{12–17}$ GAAGGRG or M(A)13GGRG

homogeneous condition [10, 13, 22, 23]. A positional cloning strategy led to the identification of short $(GCN)_{8–13}$ expansions in the *PABPN1* gene in all dominant OPMD patients (Table 60.1) [6]. The mutations consist of mitotically and meiotically stable insertions of GCN triplets in the first exon of the gene [24]. All GCN trinucleotide codons code for alanine. Thus, the normal allele is characterized by 10 GCN repeats $(GCN)_{10}$, and dominant mutations consist of the addition of 12–17 (GCN) repeats of the normal $(GCN)_{10}$ stretch (formerly referred to as the $[GCG]_6$ normal allele) [6]. In a study of 81 non-FC families originating from 17 countries, six different mutation sizes were found. The percentage of families sharing the mutations were 5 % $(GCN)_{12}$, 40 % $(GCN)_{13}$, 26 % $(GCN)_{14}$, 21 % $(GCN)_{15}$, 7 % $(GCN)_{16}$, and 1 % $(GCN)_{17}$ [6]. In FC, OPMD is caused by a founder $(GCN)_{13}$ mutation [6, 19]. Recessive inheritance characterized by homozygous $(GCN)_{11}$ has only been observed in few individuals [3, 6, 19, 25]. A gene dosage effect seems clearly to affect the phenotype as demonstrated in an observational study homozygous OPMD cases of four FC and three Bukhara Jews. They demonstrated an earlier age of onset (18 years earlier), more severe muscle involvement, and significantly reduced life span as well as cognitive decline [3, 19, 25].

PABPN1 is a nuclear protein of 306 amino acids which is involved in the polyadenylation of all messenger RNAs [26–30]. PABPN1 has four distinct domains: polyalanine, RNA binding, dimerization, and nuclear localization signaling. The biphasic polyadenylation process depends on poly(A) polymerase, cleavage and polyadenylation specificity factor (CPSF), and cleavage stimulation factor (CstF), while the rapid final elongation of the poly(A) tails is dependent on adjoining PABPN1to the polyadenylation complex [26]. PABPN1 is expressed in all tissues but more highly in skeletal muscle [6].

At the protein level, the OPMD mutations cause the lengthening of the predicted N-terminus polyalanine domain (see Table 60.1). A polyalanine nuclear toxicity gain of function is proposed as a pathogenic mechanism [6, 31, 32]. In this model, PABPN1 is suggested to carry a expanded polyalanine domain to the nucleus. This is reminiscent of carrier models proposed in CAG repeat diseases [33]. The polyalanine oligomers could form degradation-resistant macromolecules. Polyalanine oligomers are known to be resistant to protease digestion or chemical degradation such as KCL extraction [34, 35]. They form β-sheet structures in vitro [34, 36]. Furthermore, polyalanine oligomers containing more than eight alanines in a row form spontaneous fibrils [37]. It is proposed that beyond ten alanines, the normal number of alanines in PABPN1, polyalanine domains polymerize to form stable β-sheets that are insoluble and resistant to nuclear proteosomal degradation. The mutated PABPN1 is an integral part of the muscle OPMD inclusions [4, 35, 38]. The misfolded and resistant PABPN1 protein induces aggregation of ubiquitin-related proteins such as HSP-40, HSP-70, and ubiquitin itself, thus avoiding degradation by the intranuclear proteasome system [39]. Also, poly(A) RNA were found inside the misfolded protein, and mPABPN1 is known to interact with hnRNP proteins interfering with mRNA export from the nucleoplasm [35, 39]. Although PABPN1 is expressed ubiquitously, muscles are particularly involved in OPMD. This could be explained by mPABPN1 protein interference with co-transcription factor SKIP (SKI-interacting protein), preventing the expression of muscle-specific genes [39, 40]. When a significant part of the nucleus is occupied by the inclusions, normal nuclear function would be altered leading to cell death either by trapping of other proteins or of mRNA. The phenomenon would lead to gradual muscle cell death, thereby giving rise to the OPMD phenotype.

Clinical Presentation

The following diagnostic criteria for dominant OPMD have been proposed: (1) a positive family history of OPMD, (2) ptosis with at least one palpebral fissure at rest smaller than 8 mm (or previous corrective surgery), and (3) dysphagia with a swallowing time greater than 7 s when asked to drink 80 ml of ice-cold water [7]. The decade-specific penetrance for carriers of a dominant $(GCN)_{13}$ mutation are 1 % (<40), 6 % (40–49), 31 % (50–59), 63 % (60–69), and 99 % (>69) [41]. Therefore, dominant $(GCN)_{13}$ OPMD is fully penetrant past 70 years old. Other signs observed in affected individuals are proximal arm weakness (38 %), facial muscle weakness (43 %), limitation of upgaze (61 %), dysphonia (67 %), proximal leg weakness (71 %), and tongue weakness/atrophy (82 %) [42]. Some patients also develop mild to severe ophthalmoparesis, and of these, some complain of diplopia. Rarely, distal weakness occurs [43–45]. The recessive OPMD phenotype appears to be similar, though possibly milder with an older age of onset [46]. One recessive OPMD patient was also found to have coincidental hereditary neuropathy with liability to pressure palsies [47].

The severity of the dominant OPMD phenotype is variable [42]. Severe cases have onset of ptosis and dysphagia before age 45, followed prior to age 60 incapacitating

proximal leg weakness with ultimate wheelchair dependence. In the FC cohort, patients are identified as severe OPMD if symptomatic proximal leg weakness begins before age 60. These represent 5–10 % of patients. Twenty percent of the more severe patients inherit, beside a dominant mutation, a polymorphism in the other copy of the *PABPN1* gene, which causes the insertion of one extra (GCG) triplet (i.e., a $(GCG)_7$ mutation) [6]. This polymorphism has a 1–2 % prevalence in North America, Europe, and Japan. Severe cases tend to cluster in families, suggesting that other genetic factors modulate severity. However, patients with more severe phenotypes do not appear more likely to transmit their phenotype variability than patients affected with the classical form.

The molecular basis of autosomal recessive OPMD appears to be at least in some cases the double inheritance of the $(GCG)_7$ polymorphism [6]. Therefore, these patients may be underdiagnosed because of a milder phenotype and the absence of a clear family history. Recently, Semmler described the first two recessive $(GCG)_7$ OPMD cases in Europe that showed a more severe phenotype than the two cases reported previously in FC cases [19]. Thus, the $(GCG)_7$ allele is an example of a polymorphism which may act either as a modifier of a dominant phenotype or as a recessive mutation.

The most severe OPMD phenotype occurs in individuals homozygous for the dominant OPMD mutation [6, 18, 19]. A study of four FC and three Bukhara Jewish OPMD homozygotes identified an average age of onset of 18 years earlier than in $(GCN)_{13}$ heterozygotes. These patients have twice as many muscle nuclei containing intranuclear inclusions than heterozygotes (9.4 % vs. 4.9 %). Interestingly, in the same cohort, after a follow-up of many years, most homozygotes showed mental changes such as paranoid behavior or other psychiatric disorders, as well as subcortical dementia. They also demonstrated a reduce life span with death in their 50s. Thus a large burden of mutated PABPN1 could affect the central nervous system [25]. In addition, the more severe phenotypes observed in homozygotes and compound heterozygotes for a dominant and a recessive mutation suggest a gene dosage effect [6, 19, 31].

Differential Diagnosis

A diagnosis of dominant OPMD should be considered in the face of cardinal features of a slowly progressive late-onset ptosis accompanied with dysphagia, dysarthria, proximal limb weakness, and a family history. Other diagnoses that may be entertained include myotonic muscular dystrophy, myasthenia gravis, or mitochondrial myopathy with or without progressive external ophthalmoplegia. The presence of fluctuating symptoms suggests myasthenia gravis or congenital myasthenic syndrome. Lambert-Eaton myasthenic syndrome can be more difficult to differentiate because it presents with ptosis, dysphagia, and proximal limb weakness. In chronic progressive external ophthalmoplegia, ptosis and ophthalmoparesis predominate, while dysphagia is a late manifestation. Inflammatory myopathies and progressive bulbar palsy are usually excluded by the absence of ptosis. Late-onset isolated familial ptosis is distinguished from OPMD by the lack of dysphagia. Inclusion body myositis presents with typical features of late-onset proximal weakness (particularly involving the quadriceps) often with swallowing difficulties. Finally, proximal myopathic myopathy, some late-onset limb-girdle muscular dystrophies, and oculopharyngodistal myopathy are other diagnostic considerations [48–50]. Most of these disorders may be distinguished from OPMD on clinical grounds alone. If in doubt, repetitive nerve stimulation, serum acetylcholine receptor antibody, or voltage-gated P/Q-type Ca^{2+} antibody assessment may be performed to identify myasthenic syndromes. Needle electromyography may point towards an inflammatory muscle condition or myotonic muscular dystrophy. Mitochondrial disorders may require a muscle biopsy and genetic testing for confirmation. The clinical diagnosis of recessive OPMD may be more problematic. Late-onset ptosis and dysphagia without a clear family history should raise this diagnostic possibility and lead to genetic testing for OPMD [25].

Evaluation and Diagnosis

Until the identification of the OPMD *PABPN1* mutations, definitive diagnosis relied on the observation of OPMD INI on electron microscopic evaluation of muscle biopsy specimens [51]. Genetic testing has now replaced muscle biopsy [6]. Since autosomal dominant and recessive OPMD are allelic, the molecular diagnosis of both conditions is straightforward. A single polymerase chain reaction (PCR) is required to establish the carrier status of an individual [6]. The test, which is offered commercially and in numerous academic laboratories worldwide, has more than 99 % sensitivity and 100 % specificity. The major indications for DNA testing of symptomatic individuals are (1) confirmation of the diagnosis in a family where no individual has been tested previously, (2) a clinical picture presenting a diagnostic dilemma, (3) a patient with a severe early onset form, and (4) a patient with possible recessive OPMD. Testing of asymptomatic individuals in an OPMD family should not be offered routinely, since there is no known medical therapy to slow disease progression, and it is unclear that such individuals would benefit from testing. Therefore, presymptomatic testing should thus be performed with prior genetic counseling and psychological support.

Needle electromyography shows, as in other dystrophies, myopathic changes with small polyphasic motor unit

potentials [31]. Neuropathic changes on nerve conductions are not found in OPMD [31, 52–54]. Serum CK may be normal or mildly elevated [31]. Muscle MRI utilization is growing and may be useful to identify dystrophic muscle groups such as the adductor, the harmsting, soleus, and gastrocnemius. MRI has been used as a prognostic indicator [55, 56].

Management

There is no specific medical treatment for OPMD, but therapies exist to moderate symptoms. Surgical treatments are used to correct ptosis and improve swallowing in moderately to severely affected individuals. Resection of the levator palpebrae aponeurosis and frontal suspension of the eyelids are used to correct the ptosis [57]. Resection of aponeurosis is easily done but usually needs to be repeated once or twice [58]. Frontal suspension of the eyelids consists of using a thread of skeletal muscle fascia or special wires as a sling that is inserted in the tarsal plate of the upper eyelid and attached at its ends to the frontalis muscle, which is relatively preserved in OPMD [57]. Its major advantage is that it is a permanent solution. Surgery is recommended when ptosis interferes with vision or when cervical pain appears secondary to compensatory extension of the neck, since this position may also aggravate swallowing problems [59]. Contraindications to blepharoplasty are marked ophthalmoplegia, a dry-eye syndrome, or a poor orbicularis oculi function.

The first step in the treatment of dysphagia generally consists in the optimization of the swallowing process such as improved head positioning and food consistency. A high-protein diet is strongly recommended to avoid weight loss and starvation [40, 60, 61]. Surgical evaluation for symptomatic dysphagia is prompted by marked weight loss, choking (which may rarely be a cause of death), or recurrent pneumonia [62]. Cricopharyngeal myotomy will alleviate symptoms in most patients. In usual circumstances, this surgery requires an overnight hospitalization and a 1-week convalescence. Unfortunately, dysphagia will reappear slowly over years in many patients. Severe dysphonia and lower esophageal sphincter incompetence are contraindications to surgery [63]. Repetitive dilatations of the upper-esophageal sphincter with bougies are still at an investigational stage [64]. In patients with advanced manifestations, percutaneous gastrostomy should be considered [60].

Some experts recommend evaluation for obstructive sleep apnea syndrome since OPMD is a dystrophy particularly affecting the pharyngeal muscles [65]. Despite numerous searches for experimental therapies in animal and cell models of OPMD, no clinical trial have been launched because of unacceptable side effects of the candidate substances [66–69].

Prognosis

Except for homozygous cases [25], life expectancy is close to normal for most OPMD patients. However, quality of life is diminished. The impact of this disease depends on individual severity and the familial experience with the condition. OPMD severity is likely influenced by other genetic and environmental factors. Molecular diagnosis may in some patients confirm that the disease will progress to significantly affect mobility, such as when patients are compound heterozygotes for a dominant $(GCN)_{12–17}$ *PABPN1* mutation and a recessive $(GCG)_7$ mutation. The major clinical predictor of severity is the appearance of symptomatic proximal leg weakness before the age of 60. Though the definitive answer is still to come, the larger the size of the mutation likely also influences phenotypic severity. Early surgical treatment for ptosis and dysphagia is encouraged and appears to significantly improve quality of life. Local and general anesthesia seems safe in patients with OPMD [70]. The usual recommendation of a high-protein diet, as for all dystrophic patients, applies also in OPMD. Mild exercise is suggested mostly to maintain cardiovascular health. Since aspiration pneumonia is a frequent cause of death, patients should be advised to consult early if they develop productive cough accompanied by fever. Social withdrawal is one of the most devastating consequences of this condition, and its possibility should be discussed with patients. Patients are strongly encouraged not to avoid social gatherings simply because they are often accompanied by meals. Rather, patients should eat prior to or after these events. Lastly, the hope of finding a medical treatment that stops disease progression now that the mutations are known allows clinicians to present a more optimistic future to patients and their descendants.

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Emery-Dreifuss Muscular Dystrophy

61

Luciano Merlini and Nadir Mario Maraldi

Etiology and Pathogenesis

EDMD can be inherited in an X-linked, autosomal dominant (AD), or autosomal recessive (AR) fashion and is caused by mutations in proteins of the nuclear membrane. Mutations in the *EMD* gene, which encodes emerin, a transmembrane protein found at the inner nuclear membrane, are responsible for the X-linked form (EDMD1) [1, 2]. Mutations of the *LMNA* gene, that encodes the intermediate filament protein lamins A and C, cause autosomal dominant [3] and recessive [4, 5] EDMD (EDMD2 and EDMD3, respectively). Mutations in additional genes encoding nuclear membrane proteins have been implicated in few families, such as *SYNE1* in EDMD4 [6], *SYNE2* in EDMD5 [6], *FHL1* in EDMD6 [7], and *TMEM43* in EDMD7 [8].

The finding that emerin and lamin A/C mutations cause similar disorders indicates that nuclear membrane components play a crucial role in skeletal and cardiac muscle function, and that *loss of integrity of the nuclear component is an underlying cause of the muscular dystrophy*. The nuclear envelope comprises the outer and inner nuclear membranes, separated by a lumen, and the nuclear lamina. The nuclear lamina, a meshwork of intermediate filaments (IF) called lamins, is localized between the inner nuclear membrane and chromatin. Lamins interact with several integral proteins of the inner nuclear membrane including, the lamina-associated proteins LAP1 and LAP2, emerin, the lamin B receptor (LBR), MAN1, small nesprin 1 isoforms, and SUNs. SUNs interact with large nesprin isoforms, integral proteins of the outer nuclear membrane, which also interact with actin, linking the nuclear lamina to the cytoskeleton. Emerin is a type II integral nuclear membrane protein that extends into the nucleoplasm from a hydrophobic C-terminal tail anchored to the inner nuclear membrane [9]. LAPs 1A and 1B specifically bind to both lamins A and C and lamin B1 [10]. LAP 2 has a key role in the initial events of nuclear envelope reassembly, and both LAP 2 and LAP 1 may be involved in attaching lamins to the nuclear envelope [10].

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Pathogenesis

The use of integrated approaches that combine mouse models of nuclear envelopathies with cell-based and biochemical assays has been instrumental in beginning to determine the molecular mechanisms underlying how nuclear envelope proteins function in a variety of integral cellular processes, including chromatin dynamics, nuclear architecture, and transcription regulation.

The working hypotheses attempting to explain how mutations in ubiquitously expressed proteins of the inner nuclear membrane specifically affect cardiac muscle and certain skeletal muscles and tendons include and combine nuclear envelope fragility, signaling defects in response to mechanical stress and altered gene expression caused by a disorganized lamina [11, 12].

The "mechanical stress hypothesis" is based upon the fact that cells with lamins mutations present characteristic deformation of the nuclear profile and nuclear fragility upon stress, predicting that disease-causing mutations interfere with the atomic structure, assembly, and stability of lamins [13–16]. The nuclear fragility model may be particularly effective in tissues which undergo mechanically induced strain such as skeletal and cardiac muscles, vascular smooth muscles, or fibroblasts of some connective tissues. Many of the mutations causing the muscular laminopathies alter the lamin incorporation in the nuclear lamina [17], as well as the localization of emerin and nesprin-3 [18], which could result in

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increased levels of apoptosis following mechanically induced strain [19].

The "gene expression hypothesis" proposes that proper expression of lamins and associated integral proteins of the nuclear envelope inner membrane play an essential role in chromatin scaffolding and mutations in the nuclear membrane proteins will alter chromatin organization and gene expression [12, 20]. EDMD-linked lamin point mutation, when expressed in *C. elegans*, causes abnormal retention at the nuclear envelope of a gene array bearing muscle-specific promoter and an altered expression of a number of muscle-specific genes; moreover adult animals carrying the same mutation have perturbed body muscle ultrastructure and reduced muscle function [21]. Positioning of the nucleus is an active mechanism essential to the formation of functionally polarized cells, cell division, cell migration, and formation of multinucleated syncytia. Cytoskeleton-nuclear interactions are mediated by the LINC complex (*LI*nker of *N*ucleoskeleton and *C*ytoskeleton), which spans the nuclear envelope via nesprin proteins in the outer nuclear membrane and SUN proteins in the inner nuclear membrane [22]. Multiple LINC complexes assemble into transmembrane actin-associated nuclear (TAN) lines that attach nuclei to actin filaments during nuclear movements in migrating cells [23]. This mechanism is altered in EDMD4 patients carrying heterozygous mutations in *SYNE-1* and *SYNE-2* genes [6]. Because nesprins bind emerin, it has been suggested that disrupting the interaction with emerin could impair the coupling of the nucleus and the cytoskeleton, leading to the progression of EDMD4 [24]. This has been further confirmed by the demonstration that disruption of nesprin-1 causes an EDMD-like phenotype in mice and cardiomyopathy [12, 25].

A further mechanism by which accumulation of SUN1 could be pathogenic in laminopathies has been recently reported. In $Lmna^{-/-}$ mice, which represent the animal model of dominant EDMD, Sun1 over accumulation in the Golgi is cytotoxic and causes a reduction of cell viability of cultured cells. Accordingly, loss of the *Sun1* gene in $Lmna^{-/-}$ mice extensively rescues cellular, tissue, organ, and life-span abnormalities [26].

The "cell differentiation/proliferation hypothesis" proposes an impairment of tissue homeostasis and regeneration in patients. Some data suggest that abnormal control of cell differentiation or proliferation is responsible for the striated muscle abnormalities in EDMD. Expression of lamin A encoded by an *LMNA* mutant that causes autosomal dominant EDMD in cultured myoblasts inhibits differentiation into myotubes [27]. Similarly, myoblasts lacking or with reduced levels of A-type lamins or emerin exhibit impaired differentiation kinetics, reduced differentiation potential, and decreased levels of proteins important for muscle differentiation [28]. Regenerating muscles from emerin-deficient mice have abnormalities in cell-cycle parameters and delayed myogenic differentiation, which is associated with perturbations to transcriptional pathways, regulated by the retinoblastoma and *MyoD* genes [29]. Emerin has also been reported to regulate beta-catenin activity by restricting its accumulation in the nucleus, and the aberrant cellular localization of beta-catenin in emerin-deficient cells may lead to abnormalities in proliferation [30]. Hence, abnormalities in muscle satellite cell proliferation or differentiation may underlie the pathophysiology of skeletal muscle disease in EDMD by impairing the replacement of fibers.

Clinical Presentation

EDMD presents in one of three ways: muscle weakness (1) or contractures (2), which precede cardiac signs or, a less frequent but more dangerous cardiac onset (3) with sudden death [1, 31, 32].

Myopathy and Contractures

Onset is commonly in childhood with toe walking, frequent falls and difficulty running. At this early stage, muscle wasting may be difficult to notice or only present in calf muscles. A careful search for contractures may reveal early limitation of elbow extension, neck flexion, and ankle dorsiflexion. An earlier presentation with predominantly proximal weakness and mild equinovarus deformity has been reported in a 2 1/2-year-old boy with EDMD1 [33]. Initial manifestation in childhood with muscular weakness in the upper arms has also been noted [34]. The other usual presentation is with flexion contractures at the age of 4–6 years, with no significant muscle weakness [35].

Neck extension and elbow and ankle flexion contractures are present in all patients with muscle involvement. Progression of contractures is noticeable during the growth spurt leading to the typical phenotype (Figs. 61.1 and 61.2). In EDMD, contractures are in the direction of the weakest joint-moving muscle. This is in favor of a passive mechanism within the weakest muscle, i.e., loss of elasticity (substitution of elastic-contractile tissue by fat-connective tissue) with muscle shortening, limiting the movement of the joint in the opposite direction. The biceps is weaker than the triceps and shorten, causing flexion of the elbow and impeding its full extension; gastrocnemius is weaker than tibialis anterior and the shortened posterior leg muscles cause equinus deformity of the feet; wrist and finger extensors are weaker than flexors and shorten resulting in limitation of wrist and fingers flexion. Contractures of the neck extensors cause limitation of neck flexion and contractures of the weak lower

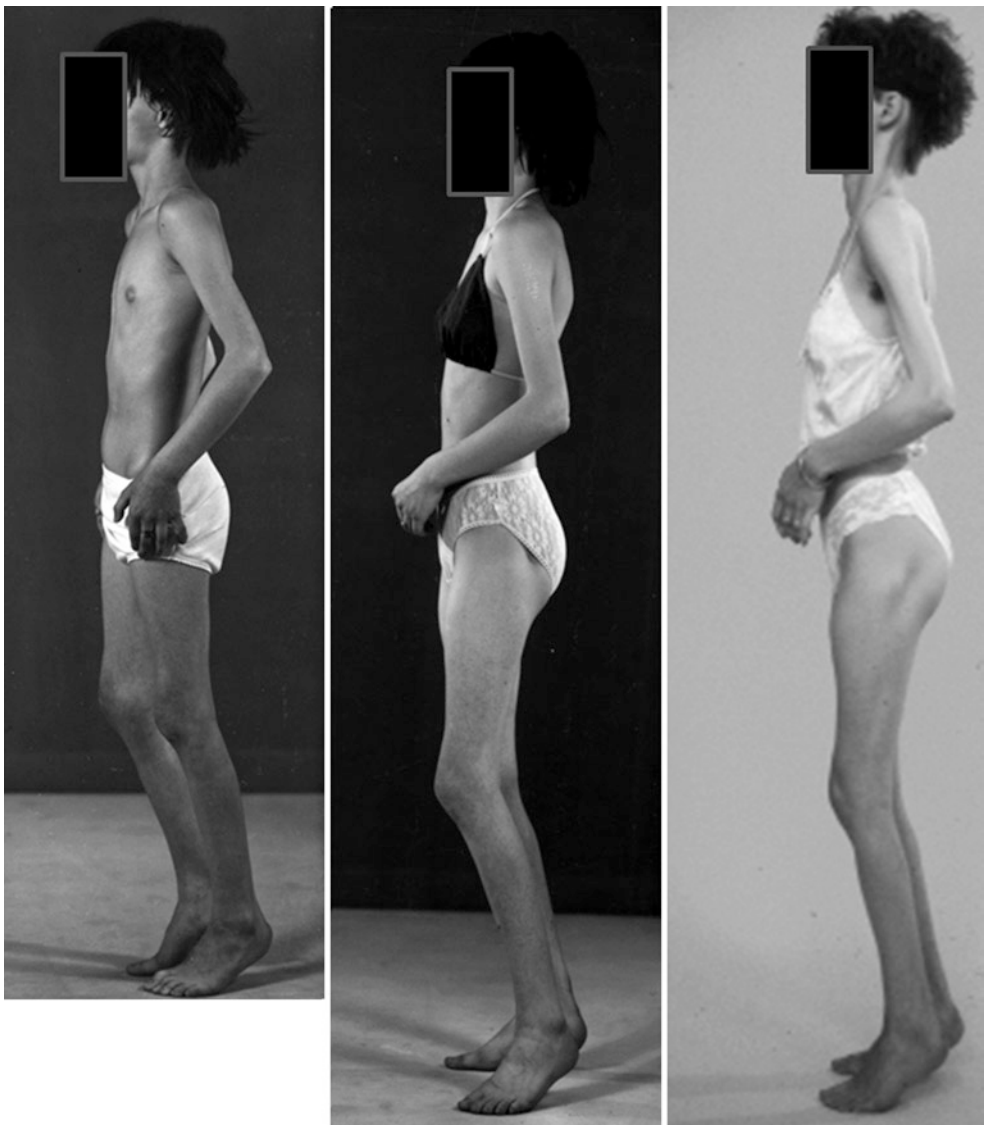

Fig. 61.1 Woman with EDMD2 shown at ages 10, 15, and 22. Spine, elbow, and ankle contractures were first noticed at the age of 8 years and were then increased in severity with time. Cardiac involvement was documented at age 10 years with conduction block and arrhythmia. Later on she developed dilatative cardiomyopathy, atrial fibrillation and flutter, and ventricular ectopic beats. Sudden death occurred at age 27

back muscles cause rigid spine. Knee flexion contractures are rarer [36]. In early adulthood, functional impairment is more dependent on the limited range of motion of the spine, elbows, and ankles than on muscle weakness. An exception is elbow flexion, which can be particularly weak, owing to the early and progressive degeneration of the biceps [32–34].

Muscle wasting is particularly evident in the posterior leg compartment and in the biceps brachii (Figs. 61.1 and 61.2) [32]. Some patients demonstrate a striking hypertrophy of the extensor digitorum brevis muscle despite prominent posterior leg muscle wasting [35, 37]. Clinical examination of muscle strength shows selective weakness of elbow flexion and finger extension compared to scapular and hip girdle strength, which are relatively spared. Strength of lower leg muscles may be difficult to test reliably owing to the fixed deformity of the ankle. Slight weakness of the intrinsic hand muscles is not exceptional [38, 39]. Slight symmetrical weakness of the orbicularis oris and oculi has been described [1, 36, 38]. Progression of weakness is very slow and patients rarely lose the ability to walk. It should be stressed that both in EDMD the severity of muscle involvement may be extremely variable, even within families [11, 12, 32, 40–42]. Occasionally patients exhibit a severe phenotype with inability to walk in adolescence [43, 44] or even earlier [38, 45]. Carriers of EDMD1 usually do not manifest musculoskeletal symptoms, but occasionally skewed inactivation may produce a typical phenotype in women [46].

Scoliosis is usually neither frequent nor severe in EDMD1 [1, 32, 47]. Mild scoliosis occurred in three patients but stabilized without treatment [47] and thoracic deformity was documented in eight of ten patients [48] but not the extent of the deformity. Occasionally marked hyperextension of the neck and thoracic lordoscoliosis may cause postural

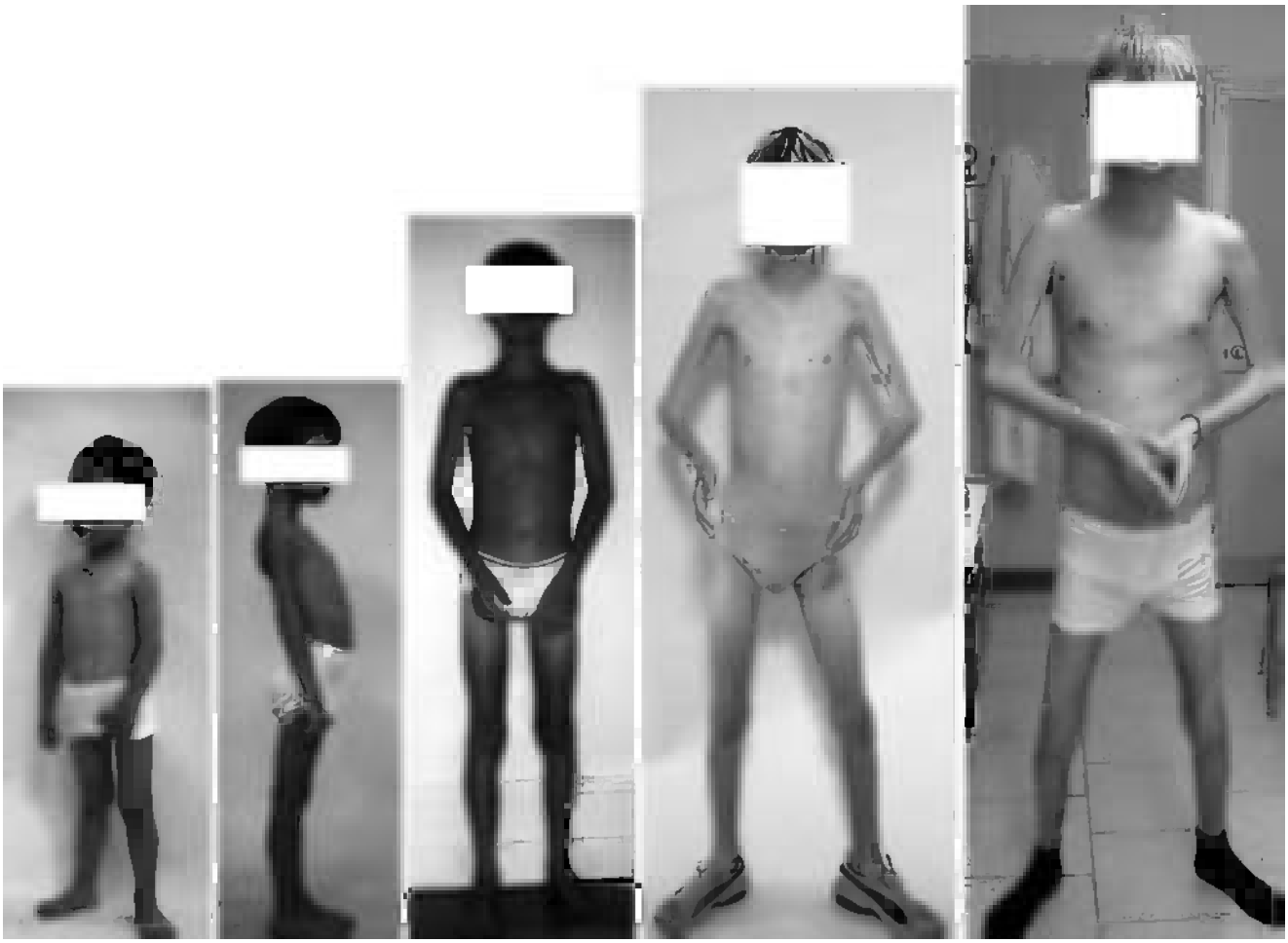

Fig. 61.2 A patient with EDMD2 shown at ages 3, 5, 8, 14, and 24. First steps at 13 months, he was never able to run. At age 3 years positive Gowers maneuver and CK three times normal. Lumbar hyperlordosis at age 8 years and limitation of neck flexion and elbow flexion. Rigid spine, increase in elbow flexion contracture, limitation of finger flexion, and lipodystrophy at age 14. He then developed dilatative cardiomyopathy and severe cardiac conduction defects. He had heart transplantation at age 20

imbalance and severe discomfort [49]. Borderline [39] or reduced [35, 48] intelligence is found in some patients.

Cardiac Manifestations

EDMD may manifest with cardiac symptoms consisting of arrhythmias causing syncope, cerebral emboli, or sudden death [50, 51]. Cardiac involvement invariably presents between the early second to fourth decades in EDMD1 and between the third to fourth decades in EDMD2. Two major types of cardiac involvement are recognized: atrial paralysis and dilated cardiomyopathy. Atrial paralysis is the hallmark of EDMD1, while both complications may be present in EDMD2. Permanent atrial paralysis is a rare condition and in 33 % of 109 of well-documented cases it was found to be associated with Emery-Dreifuss muscular dystrophy [52].

In six families with definite X-linked inheritance (EDMD1), 30 of 73 patients died suddenly between 25 and 59 years of age [32]. Among the 36 patients who underwent cardiac examination only 4 [1, 48] were normal, and all were under 16 years of age. Of the 32 patients with cardiac abnormalities [32], only four had minor subjective symptoms such as dizziness or syncopal episodes, while the remainder were symptom-free. Risk of sudden death is thus extremely high and unpredictable [32]. Women carriers of EDMD1 have a substantial cardiac risk which increases significantly with age [38, 48, 53, 54]. In one family with a novel deletion of the last three exons of the emerin gene, a carrier had a cardiomyopathy and very low emerin levels due to skewed X-inactivation [46]. Cardiac transplantation has successfully been performed in EDMD [55–58].

In autosomal dominant EDMD according to a meta-analysis involving 299 patients [59], cardiac dysrhythmias have an early onset (in 18 % before age 10 years) and occur in 92 % of patients after the age of 30 years. Cardiomyopathy with heart failure manifests later and is found in 10 % of patients by age 30 years and in 64 % after the age of 50.

Sudden death was the most frequently reported mode of death (46 %) in both the cardiac and the neuromuscular phenotype. Carriers of lamin A/C gene mutations often received a pacemaker (28 %). However, this intervention did not alter the rate of sudden death.

Both X-linked and autosomal dominant EDMD patients risk not only bradyarrhythmia (requiring pacemaker implant) but also atrial fibrillation/flutter, which often anticipates atrial standstill and can cause disabling embolic stroke at a relatively young age [55].

Cardiomyopathy in EDMD1 affects the atria with predominant right heart involvement. The reason for this is unknown but may relate to the smaller muscle mass of the right heart [60]. The normal myocardium is replaced by adipose and fibrous tissue resulting in loss of atrial contractility (atrial paralysis) and marked atrial dilatation [34, 35, 56, 61]. The conduction system, atrioventricular node or bundle of His, show no significant abnormalities [61]. In the later stages of the disease, the ventricles may become involved with fibrous replacement of the myocardium and, ultimately, ventricular failure occurs. Macroscopic and microscopic examination of the explanted heart in a patient with EDMD2 showed a dilated cardiomyopathy with hypertrophy and dilatation of the atria and ventricles, fiber size variability, and a predominately focal interstitial fibrosis [62].

EDMD1 vs. EDMD2

There is wide clinical variability in EDMD1. However, patients almost invariably have a combination of early musculoskeletal signs and late cardiac conduction disorders; isolated cardiac involvement is exceptional; walking is usually preserved. In EDMD2 there is significant intra and interfamilial variability. Individuals carrying a heterozygote mutation may be asymptomatic. De novo mutations are quite frequent, isolated cardiac involvement is not exceptional, ventricular fibrillation and dilated cardiomyopathy are more common, and there are some patients with loss of ambulation by 8–13 years.

Differential Diagnosis

Clinical overlap exists with rigid spine syndrome, mild congenital myopathies including Bethlem myopathy, and some muscular dystrophies. However, the presence of early flexion contractures at the elbows, ankles and neck, characteristic distribution of weakness, and cardiac involvement are helpful in differentiating among these disorders. Some patients with a clinical diagnosis of rigid spine syndrome [63] have been subsequently recognized to have EDMD1 [39] or EDMD2 [4]. Any muscle biopsy of a patient with elevation of CK up to ten times normal and possible muscular dystrophy should probably be tested for the presence of emerin.

Evaluation and Diagnosis

Patients are examined clinically for the distribution of muscular wasting and weakness, contractures, and cardiac involvement.

Laboratory Studies

In young patients creatine kinase (CK) may be elevated to ten times normal [31, 32, 64]. Detailed electromyography study of the limb and paraspinal muscles, including automated analysis of the interference pattern and single fiber electromyography, shows myopathic changes, but no definite neurogenic involvement of the muscles. Nerve conduction studies are normal [65].

Muscle Imaging

Muscle CT or MRI scans may complement the clinical evaluation (Fig. 61.3). They may reveal more extensive fatty muscle degeneration than suggested by clinical findings particularly in the posterior leg and paravertebral muscles [67]. Patients with EDMD1 and EDMD2 have an early involvement of the gastrocnemius particularly of the medial head, while the lateral head is relatively spared at the beginning [66, 68]. At the thigh level, vastii muscles, hamstrings, and abductors are all involved to varying degrees, while irrespective of the age and severity of the disease a clear sparing of the rectus femoris is evident [66].

Muscle biopsy commonly shows a myopathic picture with variation of fiber size, endomysial fibrosis, and type I fiber atrophy or predominance [32, 53]. Emerin is absent in nuclei in more than 95 % of EDMD1 patients; [69] residual or normal emerin is detectable in the rare missense or promoter mutations [70]. In contrast, the perinuclear localization of lamin A/C and emerin is preserved in patients with EDMD2 [37].

Nuclear changes ranging from marked condensation of chromatin to complete damage are noted in skeletal muscle and skin cultured cells at the ultrastructural level [71, 72], indicating anomalous nuclear lamina organization in the absence of emerin [72].

In younger patients with initial cardiac involvement, EKG shows low amplitude P waves with prolongation of the P-R interval. Subsequently conduction disturbance may progress to atrial fibrillation or flutter. The characteristic EKG pattern is that of a junctional escape rhythm at 40–50 beats/min

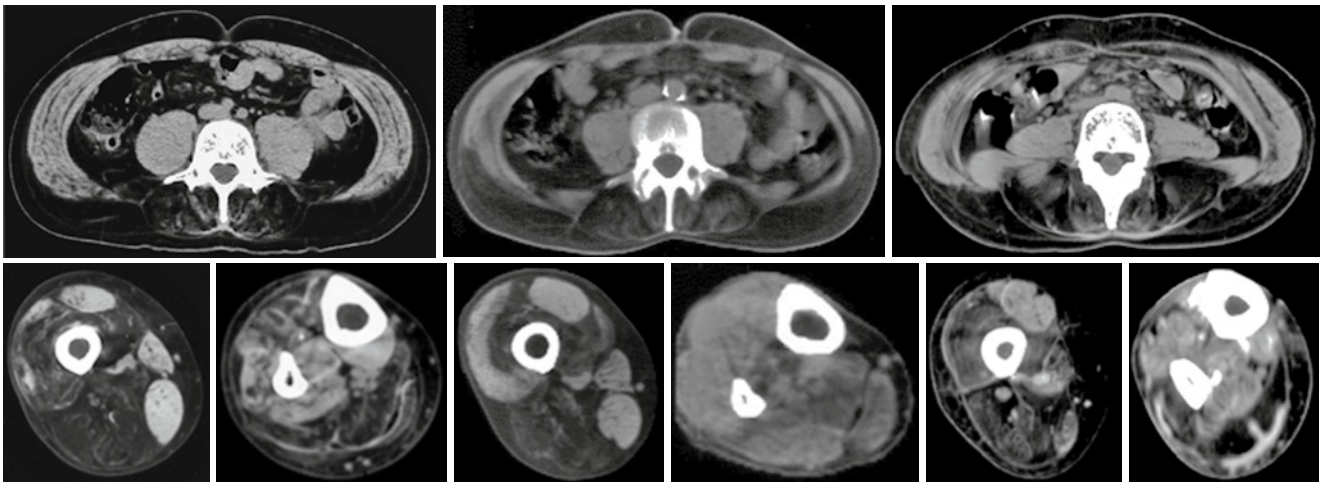

Fig. 61.3 *Left panel.* Muscle CT of a 55-year-old man with EDMD1 with a del 29 bp frameshift mutation in the emerin gene causing a codon 22>stop [2, 32]. Note complete hypodensity of the lumbar paravertebral muscles, early involvement of the abdominal muscles with patchy spots of low-density and normal psoas muscles (*top left*). The mid-thigh level (*bottom left*) shows complete substitution of muscle with low-density fat and connective tissue of the posterior compartment (adductors and hamstrings) and of the vastii, with preservation of rectus femoris [66], sartorius, and gracilis muscles. The mid-calf level shows marked hypodensity of the soleus and gastrocnemius and some involvement of the anterior compartment (tibialis anterior, extensor digitorum and peroneal muscles). *Middle panel.* Muscle CT of a 47-year-old man with EDMD2 caused by a R527P mutation of the LMNA gene [4]. Muscle CT shows a nearly identical pattern of selective involvement/preservation of muscles as in the patient with EDMD1. Note in particular the similar severe involvement of the lumbar paravertebral muscles (*top middle*), of the vastii and ischiocruralis with selective sparing of the rectus femoris. At the mid-calf there is a clear involvement of the sural and medial gastrocnemius muscle. *Right panel.* Muscle CT of a 38-year-old woman with EDMD2 with progressive muscle weakness and who lost the ability to walk unaided at age 36. Note the severe involvement of the lumbar paravertebral muscles (*top right*), of the vastii and ischiocruralis with selective sparing of the rectus femoris. At the mid-calf there is a severe involvement of the medial and lateral heads of the gastrocnemius muscle

without an obvious P wave because of the atrial standstill. The diagnosis is confirmed by lack of all electrical and mechanical activity of the atria and the inability to pace the atria. This last feature demonstrates that EDMD affects the atrial myocardium and is not confined to impulse formation or transmission [44].

A positive diagnosis of EDMD1 is made by emerin analysis. Western blot and immunohistochemistry show an absence of emerin in muscle [73], skin tissue [70], and buccal smears [74] in male patients with X-linked EDMD (EDMD1), and a reduction of the protein content with a mosaic expression pattern in female carriers. Evaluation of emerin expression on skin biopsy and in the exfoliating epithelial cells of oral mucosa are a less invasive though sensitive and more convenient means for diagnosing X-linked EDMD (EDMD1). In particular, these methods can be used to distinguish X-linked EDMD (EDMD1) from the autosomal forms [74]. In the autosomal dominant (EDMD2) and autosomal recessive forms, emerin is normal and genetic analysis is necessary for diagnosis.

Genetics

Most emerin mutations are nonsense, frameshift, or putative splice mutations resulting from base substitutions, small deletions, or insertions [75]. These mutations result in absence of the protein as shown by immunoblotting or immunohistochemistry studies in any tissue studied [70]. However, a few in-frame deletions and missense mutations have been associated with residual or normal expression of the mutant protein [70, 75]. The phenotype in two families with in-frame deletions was similar to that of families with null mutations. In the family with the missense mutation P183, the musculoskeletal phenotype was milder and of later onset, but there was no difference in the age of onset of cardiac involvement [53].

The majority of mutations in EDMD-AD are missense, although nonsense mutations, small deletions, and splice site mutations are reported [76, 77]. Mutations are found throughout the gene and for this phenotype there is, as yet, no apparent correlation with genotype.

Treatment and Management

Achilles tenotomy is recommended for patients with foot deformities in order to allow a wider and more stable stance. No correction for the limited elbow extension is advisable since elbow flexion allows the hand to be closer to the mouth and may compensate for the severe paralysis of the flexor muscles. Neck hyperextension is rarely a problem in EDMD compared to the RSS, where this more often compromises function. A procedure for surgical correction of neck

hyperextension was devised in RSS [78, 79] and applied in one EDMD1 patient [49].

Scoliosis in EDMD patients is usually not so severe to require surgical correction and stabilization. In the exceptional event of severe scoliosis, the benefits of surgery should still be balanced against the peculiar problem its correction poses in EDMD. First, scoliosis in patients with rigid spine is a fixed deformity with limited correction even with surgery. Second, if correction requires lumbosacral fixation, this may precipitate loss of ambulation. Finally, scoliosis surgery stresses cardiac function to its limits, which is a risk in EDMD patients.

Although no complications are reported in EDMD patients receiving general anesthesia, it is advisable to use all the well-established rules for patients with neuromuscular disorders who require general anesthesia [80, 81]. In addition, prophylactic cardiac pacing should be considered before surgery, and facilities for emergency cardiac pacing should be on hand at all times [82].

Arrhythmias are usually more severe during sleep, indicating that continuous 24-h EKG monitoring in the evaluation of patients with EDMD is advisable [32, 54]. A yearly Holter monitor is indicated in all EDMD patients when arrhythmias are detected on routine EKG or after age 17 years. Early recognition of heart involvement is of utmost importance as placement of a pacemaker and/or implantable cardioverter-defibrillator (ICD) may be lifesaving [83–85]. A survey of ICD utilization in 19 subjects with *LMNA* mutations followed over 3 years indicates that about 40 % of these patients had an ICD discharge during the period of observation [86]. The results of this study validate the use of ICDs as prevention for sudden death and indicate that cardiac conduction system disease can precede the development of overt cardiac dilation and arrhythmias. However the treatment of the conduction defect does not prevent intra-atrial thrombus formation and cerebral embolization. Increased awareness of this sequel should lead to successful prophylaxis with anticoagulants [55]. If there is significant ventricular involvement, diuretic therapy and ACE inhibitors may be indicated. Cardiac transplantation should be considered in EDMD patients in whom the dilated cardiomyopathy is not otherwise treatable [55–58, 87–90]. Women carriers of EDMD1 are at risk for cardiac arrhythmias, particularly after age 40, and should be monitored on a yearly basis with EKG or Holter monitoring.

Two inhibitors of ERK and JNK signaling, PD98059 and SP600125, respectively, have been demonstrated to inhibit the expression of RNAs encoding natriuretic peptide precursors and protein involved in sarcomere architecture in $Lmna^{H222P/H222P}$ mice, preventing left ventricular and systolic dilatation [91]. In a near future, drugs that have been entered phase II clinical trials for patients with cancers may be used to treat patients with cardiomyopathy caused by *LMNA* mutations.

Prognosis

Musculoskeletal involvement in EDMD is usually mild and non- or slowly progressive. Loss of ambulation is exceptional. The course of cardiac involvement is the major determinant of the prognosis *quoad vitam*. Initially, the disease was defined as "benign" [1]. However, subsequent surveys suggest that this is not the case, given the high incidence of sudden death [32, 92, 93]. Early recognition of heart involvement, placement of a pacemaker and/or implantable cardioverter-defibrillator [83–85], prophylaxis with anticoagulants [55], diuretic therapy and ACE inhibitors, and cardiac transplantation in patients with nonmedically responsive-dilated cardiomyopathy have changed the cardiac prognosis of EDMD. Hopefully, in the near future EDMD will again be regarded as a benign condition. Furthermore, the heart may be a more reasonable initial target for gene therapy than the skeletal muscles.

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Congenital Myopathies

62

John B. Bodensteiner

Introduction

The congenital myopathies are a diverse group of skeletal muscle disorders which are genetic in origin, frequently apparent at birth, usually slowly or not progressive and have overlapping clinical features [1–4]. Until recently, the classification of congenital myopathies into distinct groups was most frequently based on the histopathological features of the muscle [5]. Increasingly, however, the molecular genetic basis of these diseases is being delineated and in the future, the identification of distinct types of congenital myopathies will require the demonstration of the gene abnormality in addition to, or in concert with, the clinical features and the histopathology of the muscle.

The congenital muscular dystrophies are subgroup of the congenital myopathies in which histologic examination of the muscle reveals "dystrophic features." The congenital muscular dystrophies historically were further divided into those conditions with and those without brain involvement, and those which are merosin negative or merosin positive [4, 6]. The delineation of the genetic basis of most of the congenital muscular dystrophies has put the classification schemata in flux and there is currently no universally accepted classification for this uncommon but interesting group of diseases [7].

Most infants affected with a congenital myopathy will have a slowly progressive course. Some infants, however, are severely affected at birth leading to early respiratory failure and death. Occasionally a rapidly progressive course is seen in some patients with congenital myopathy, and rare patients may improve with time [8, 9]. Some individuals with a genetically determined congenital myopathy will not become symptomatic until later in childhood or as an adult.

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Nearly four dozen congenital myopathies have been described. The majority of these disorders is rare and considered to be nosologically questionable entities [3]. Because of the limited number of pathological alterations possible in skeletal muscle any classification based on morphologic features will have limitations. Central core disease, nemaline myopathy and centronuclear myopathy are the three most prominent clinical entities, with advances in genetics that have altered our understanding of these diseases (Table 62.1). Less common diseases including multicore disease, congenital fiber-type disproportion, reducing body myopathy, fingerprint myopathy, and cytoplasmic or inclusion body myopathy are not as well delineated, but as the genes responsible for these conditions are identified, the classification is changing and now is perhaps best classified as reducing body myopathies (Table 62.2), myofibrillar myopathies (Table 62.3), and protein aggregate myopathies (Table 62.4) [7]. Also, application of molecular genetics to these conditions has allowed the identification of most of the congenital muscular dystrophies as distinct genetic entities, though the classification is not well-established currently (Table 62.5).

Etiology and Pathogenesis

The well-established congenital myopathies are all genetic in origin. The gene locus and the gene product are known for some for most but for some neither is known. Currently, there are over 20 known genes known to be related to the clinical picture of a congenital myopathy [7]. It is clear that in some of these conditions, the one gene one phenotype axiom is not valid as there are sometimes several genes, dysfunction of which can produce apparently identical clinical (phenotypic) entities. The characteristic histopathologic features of the three well-established conditions are the result of the absence of an intracellular protein necessary for the maintenance of the structural integrity or function of, or the maturation and differentiation of, the myofiber. The characteristic pathological feature of nemaline myopathy, for

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Table 62.1 The classical congenital myopathies

	Central core disease	Nemaline myopathy	Centronuclear (myotubular) myopathy
Presentation/severity			
Infantile	Severe	Severe	Severe
Childhood	Moderate	Moderate	Moderate
Adult	Mild	Mild	Mild
Muscle wasting	No	Yes	Yes
Somatic abnormalities	Yes	Yes (infantile)	Yes (dominant)
Ocular muscle weakness	No	Yes	Yes with ptosis
Pain/cramps	No	Yes (adult onset)	No
Malignant hyperthermia	Yes (characteristic)	No	No
Cardiomyopathy	Occasionally	Rare	No
Mental retardation	No	No	No
Genetic defect(s)	19q13.1 (RYR1 gene) Ryanodine receptor, (MYH7) Cardiac β-myosin heavy chain	NEM1: α-tropomyosin (TPM3)	*Myotubular myopathy*
		NEM2: Nebulin (NEB)	X-linked: myotubularin 1 (MTM1)
		NEM3: α-actin (ACTA1)	Myotubularin-related protein 14 (MTMR14)
		NEM4: β-tropomyosin (TPM2)	*Centronuclear myopathy*
		NEM5: slow troponin T (TNNT1)	Dynamin 2: (DNM2) (a-d)
		NEM6: Kelch repeat BTB [POZ] domain containing 13 = (KBTBD13)	Ryanodine receptor: (RYR1) [a-d]
		NEM7: Cofilin 2 (CFL2)	Amphiphysin (BIN1) [a-r]

Table 62.2 Less common congenital myopathies: reducing body myopathy and other FHL1*-related muscular disorders

Disease phenotype	Reducing body myopathy	X-linked myopathy with postural muscle atrophy	Emery-Dreifuss muscular dystrophy	X-linked scapuloperoneal myopathy	Rigid spine syndrome
Clinical presentations	Loss of ambulation in 1st decade	Pseudo-athletic neck rigidity early	Joint contractures weakness and wasting pelvic, peroneal, and scapular muscles	Early foot drop, scapular winging, proximal weakness of legs and arms	Rigid spine, scoliosis proximal weakness
Respiratory compromise	Frequent, and frequent cause of death	Progressive and life limiting	Occasional but not prominent compared to cardiac	Not usually	Not usually
Significant/ suggestive features	Atrophy of Post-med soleus sparing of glutei.	Scoliosis and Achilles contracture	Early contractures	Males worse than females	May have contractures with cardiomyopathies
	Rigid Spine	Scapulo-axial-peroneal syndrome later	Rigid spine, scapuloperoneal wasting	Most W/C bound	In males
			Late-onset cardiac involvement		
Cardiomyopathy	Not usually significant	Rhythm abnormalities not cardiomyopathy	Cardiomyopathy, arrhythmia, Conduction defects	Occasional	Occasional and occasionally severe
Genetic defect(s)	FHL1 gene	FHL1 gene in the fourth LIM domain (Schessl)	FHL1	Sarcomeric myosin heavy	LIM domain FHL1 gene
				Chain, Desmin gene, FHL1 mutations	

**FHL-1* gene = four and a half Lin-11, Lsl-1, Mac-3 (LIM) domain protein 1 gene

example, is the accumulation of disorganized Z disk material which may be seen on histochemical staining of frozen sections and which represents normal Z disk material which has not been held in its proper position in the lattice of the myofibril because of dysfunction of one of three proteins (α-actinin, tropomyosin-3, or nebulin) known to be abnormal in genetically distinct forms of the disease.

The etiology and pathogenesis of the clinical picture in the congenital myopathies is less well established. Hypotonia and weakness are the most common clinical findings. If the weakness is present in utero, the infant may have deformities or contractures as a result. The mechanisms involved in the production of hypotonia are somewhat obscure and may differ with each of the clinical

Table 62.3 Genes associated with myofibrillar myopathies

Myopathies with myofibril accumulation with known mutations
Desminopathy
αβ-Crystallinopathy
Myotilinopathy
Selenoproteinopathy
γ Filaminopathy
Valosin-containing proteinopathy
Laminin (A/C) opathy
ZASPopathy
Bag 3 myopathy
FHL1 myopathy
NEM6

Table 62.4 Congenital myopathies with protein aggregates

Congenital myopathy	Gene common to both conditions	Protein aggregate myopathy
Nemaline myopathy (NEM3)	ACTA1	Actin filament aggregate myopathy
Multiminicore disease	RYR1/SEPN1	Core myopathy
Reducing body myopathy With central cores	RYR1	Core myopathy
Reducing body myopathy (RBM)	FHL1	RBM
Granulofilamentous myopathy	DES/CRYAB	Desminopathy
		αβ-Crystallinopathy
Hyaline body myopathy	MYH7	Myosinopathy
Spheroid body myopathy	MYOT/TTID	Myotilinopathy
Cytoplasmic body myopathy	Several genes	Myofibrillar myopathies

entities, though more likely they share a common pathophysiology [10, 11].

Clinical Presentation

Floppy Infant: Evaluation and Diagnosis

The clinical presentation of the infant with a congenital myopathy is usually that of a "floppy infant" (see Chapter 77). The affected baby demonstrates decreased tone, weakness, decreased spontaneous movement, and later, delayed acquisition of motor milestones. Most commonly, the floppy infant with these clinical abnormalities will be found to have a non-neuromuscular problem (Table 62.6), and it is frequently worth the physician's effort to spend some time trying to localize the origin of the problem at the beginning of the evaluation [2, 12]. Although the distinction between hypotonia secondary to systemic disease and hypotonia plus/minus weakness due to primary neuromuscular disease would appear to be easy, in actual practice, the localization of the problem to the muscle and the determination of weakness in addition to hypotonia is difficult for most examiners.

In clinical practice, the measurement of muscle tone is subjective. Defined as the resistance to passive movement, tone in the young infant (first month of life) is, normally, dependent on the state of well being and the state of alertness of the infant and can be divided into postural or truncal tone and phasic or appendicular tone:

Postural tone: Postural tone is the tone of the back, hips, and neck muscles and is partially reflected by the posture of the infant at rest. Postural tone is assessed most reliably by four maneuvers (Fig. 62.1):

1. The traction response (pull to a sit)
2. The "scarf sign"
3. Shoulder suspension
4. Ventral suspension (the examiner lifts the prone infant with one hand under the abdomen)

Phasic tone: Phasic tone or axial tone is the tone in the arms shoulders and legs and is more difficult to quantify in the infant. Phasic tone is also very dependent on state of alertness and reflex activity, and for a variety of reasons it can be very difficult to assess strength in the presence of phasic hypotonia. One of the reliable signs of phasic or appendicular hypotonia is the scarf sign [the examiner grasps the hand and pulls the arm across the body to the opposite shoulder as far as the tone in the arm will reasonably allow, in the full-term infant, the elbow does not pass the midline of the thorax (Fig. 62.1b)] [12]. Remember that weak infants are hypotonic, but not all hypotonic infants are weak [2, 9, 10].

Although localizing the cause of the hypotonia is not as easy as it might appear, an attempt to localize the problem before launching into the evaluation may pay dividends in time and effort. Some of the clinical features which may be of help in this localization scheme are the following (Table 62.6):

1. Recent onset, if identifiable, would suggest a more acute systemic condition such as sepsis, meningitis, or congestive heart failure. In the newborn, these conditions should be considered before the evaluation for neuromuscular disease is undertaken.
2. Abnormal texture of the muscle on palpation may indicate the deposition of material in the muscle or an alteration of innervation of the muscle.
3. Absence of myotatic reflexes would suggest motor unit localization of the hypotonia.

Table 62.5 Congenital muscular dystrophies

Disease	Protein/gene	Clinical	Neuroimaging brain MRI	Biopsy feature
CMD with merosin deficiency	Laminin-α2 (LAMA2)	Severe = no merosin Milder = partial deficiency	Abnormal white matter T2 signal, otherwise usually normal	Absent Laminin-α2
CMD partial merosin deficiency	Locus 1q42	Variable	Mild white matter possible gray abnormalities	Variable staining
LARGE-related CMD (MDC1D)	LARGE (like-glycosylated transferase)	Mental retardation blend of MEB/WWS phenotypes	White and gray abn Hypoplastic cerebellum and brainstem	Variable staining…no specific stain
Fukuyama CMD	Fukutin (FKTN)	Frequent in Japanese, do not reach ambulation, MR, overlap with MEB	Lissencephaly type II/pachygyria Hypoplastic cerebellum +/− cysts	Variable staining…no specific stain
Muscle-eye-brain disease (MEB)	POMGnT1 FKRP	Ocular involvement, severe weakness, mental retardation	Lissencephaly II/pachygyria Hypoplastic cerebellum and brainstem	Variable staining…no specific stain
Walker-Warburg syndrome (WWS)	POMT1/POMT2/FKRP/FKTN	Often lethal in first few years, severe brain anomalies	Lissencephaly Lissencephaly II/pachygyria Hypoplastic cerebellum and brainstem Hydrocephalus	Variable staining…no specific stain
CDG1 α-dystroglycan glycosylation defect	Dolichol-phosphate-mannose synthetase 3 (DPM3)	Weakness plus cardiomyopathy, Stroke like episodes, MR	Cerebellar vermis hypoplasia Microcephaly	Reduced glycosylated aDG Variable Laminin-α2
CDG1 (DPM2)	Dolichol-phosphate-mannose synthetase 2 (DPM2)	As above with Severe myoclonus epilepsy	Cerebellar vermis hypoplasia Microcephaly	Reduced glycosylated aDG Variable Laminin-α2
CDG1e (DPM1)	Dolichol-phosphate-mannose synthetase 1 (DPM1)	Usually typical of CDG disease	Cerebellar vermis hypoplasia Microcephaly	Reduced glycosylated aDG Variable Laminin-α2
Collagen VI-related spectrum Ullrich/Bethlem (UCMD)	α1/2 and α3 collagen VI COL6a1, COL6a2 COL6a3	Distal hyperlaxity Proximal contractures Follicular hyperkeratosis Soft palms	None	Variable deficiency of collagen VI staining
Rigid spine muscular dystrophy	Selenoprotein N (SEPN1)	Delayed walking with axial weakness and stiff spine	None	Non-diagnostic
Lamin A/C-related CMD	Lamin A/C LMNA	Dropped head characteristic	None	Non-diagnostic

4. Presence of deformities suggesting weakness in utero such as high palate, club feet, pectus excavatum, long narrow facies with small mandible, and scoliosis would suggest motor unit involvement.
5. Presence of dysmorphic features not resulting from weakness in utero, such as abnormal ear placement, hypo/hypertelorism, abnormalities of nipple position, and anomalies of other systems (heart, genitourinary, gastrointestinal), particularly if the reflexes are present, would suggest a supraspinal localization for the hypotonia.

Table 62.6 Localization in the "floppy infant"

Type of hypotonia	Structural localization	Clinical pathological conditions
Supraspinal hypotonia (preserved DTR)	Brain	Systemic disease (sepsis, HIE, CHF)
	Brainstem	Syndromes (Down, Smith-Lemli-Opitz, Prader-Willi)
		Malformations
	Craniovertebral junction	Cord injury (birth and beyond)
Motor unit hypotonia (DTR decreased or absent)	Anterior horn cell	Spinal muscular atrophy
	Peripheral nerve	HMSN
	Neuromuscular junction	Myasthenia, myasthenic syndromes, botulism
	Muscle	Congenital myopathies, metabolic myopathies
		Neonatal presentation of muscular dystrophy

DTR deep tendon reflexes, *HIE* hypoxic-ischemic encephalopathy, *CHR* congestive heart failure, *HMSN* hereditary motor sensory neuropathy

The severity and distribution of involvement may be variable, and many authors have suggested that the pattern of involvement may be useful in making a diagnosis; however, there is sufficient overlap between the clinical features of the various diseases that specific conditions cannot generally be identified without histopathologic study of the muscle and/or genetic testing.

Routine laboratory investigations are of limited value in the evaluation of the floppy infant. If the examiner localizes the lesion to the supraspinal category and acute systemic disease is not a consideration, a large number of potential investigations become considerations including neuroimaging, genetic and metabolic screens and specific metabolic and genetic tests. Serum CK (creatine kinase) determination may be normal or elevated in any of the congenital myopathies. The CK value in the congenital muscular dystrophies may also be normal but is more likely elevated. On rare occasion, one of the dystrophinopathies will present in infancy as a hypotonic child and a CK 50–100 times normal may be a clue to that diagnosis [13–15]. Imaging of the muscle with ultrasound or magnetic resonance (MR) imaging has revealed a number of identifiable changes in the gross structure of the muscle and is becoming a useful tool in the diagnosis of the congenital myopathies [16, 17]. MR spectroscopy and positron emission tomography have been used to ascertain specific metabolic characteristics of muscle but have not been of use in the diagnostic process.

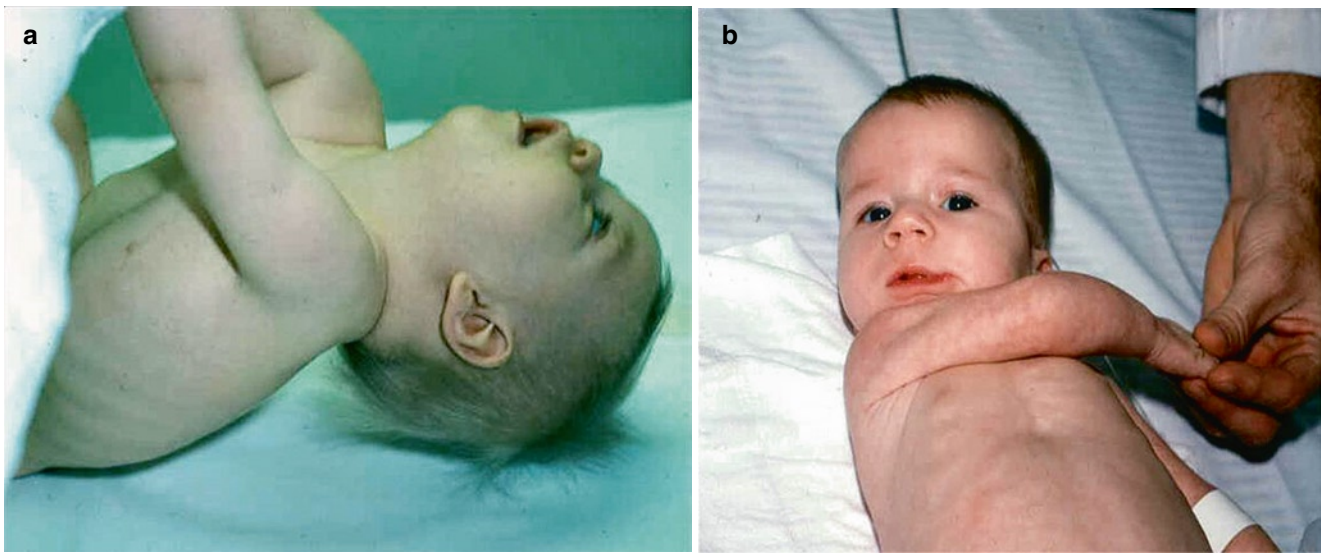

Fig. 62.1 Reliable clinical measures of tone (**a**) "Pull to sit" where the examiner gently pulls the baby from supine to a sitting position, measures axial tone of neck and back and appendicular tone of shoulders and arms. (**b**) "Scarf sign" where the examiner grasps the hand and pulls the arm across the face, normally the elbow will not pass the midline of the chin. This tests appendicular tone. (**c**) "Shoulder suspension" where the examiner picks up the infant under the arms measures appendicular tone unless head control is a problem, then axial tone is also assessed. (**d**) "Ventral suspension" where the examiner holds the infant with one hand placed under the abdomen and thorax measures axial tone mostly, but the arm position may give some information about appendicular tone (Figure from Bodensteiner [12]. With permission)

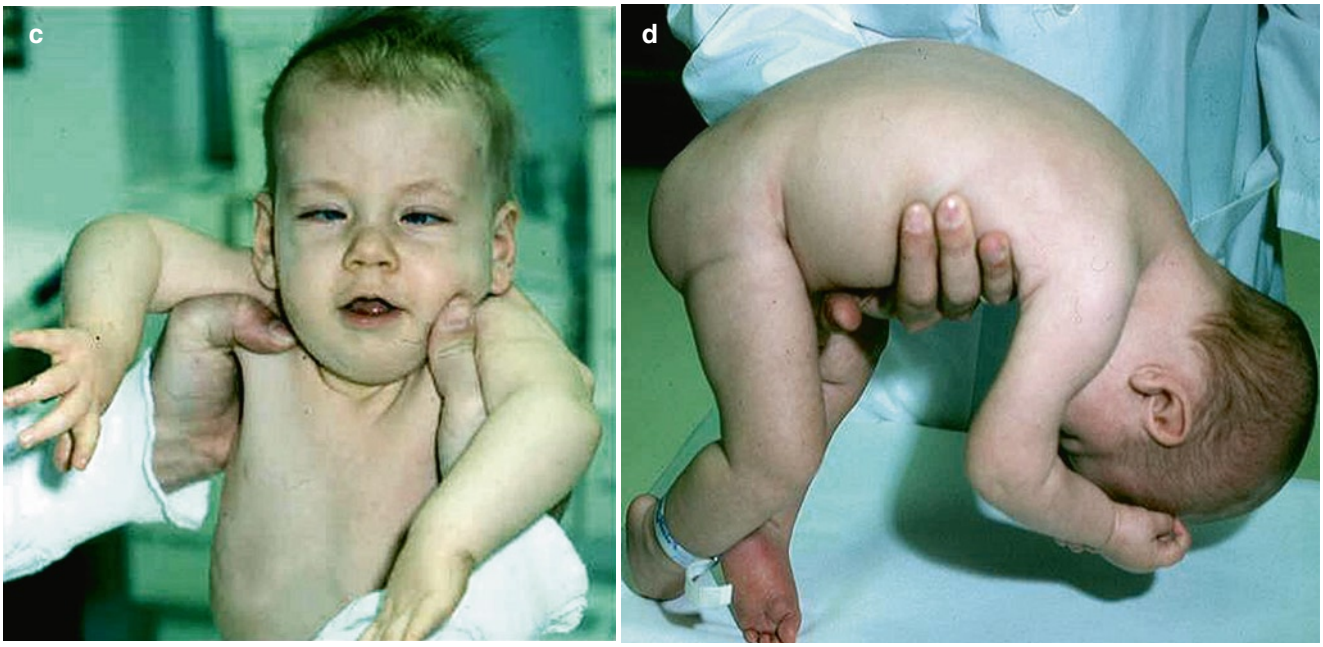

Fig. 62.1 (continued)

Needle electromyography (EMG) is still a useful tool in the diagnostic evaluation of the floppy infant. The finding of small amplitude, short duration, and polyphasic motor units is helpful in localizing the problem to the muscle and choosing an appropriate muscle for histological study. Performing an adequate EMG on a newborn infant, however, is difficult even in the hands of the most experienced examiners, and the findings are sometimes nonspecific. One would hope to be able to distinguish a primary myopathy from anterior horn cell disease by needle EMG, and in the later half of the first year, this is entirely possible and for most experienced electromyographers, this determination can be made in the younger infant. The distinction may not be so easy in the newborn. Thus, the finding of an abnormal EMG may help to localize the lesion and choose the biopsy site but is otherwise unlikely to provide reliable diagnostic information [18].

Because of the number of shared clinical characteristics, it is usually impossible to make a specific diagnosis on the basis of clinical features alone, although some congenital myopathies are more likely to display specific clinical features suggesting a possible diagnosis. The routine laboratory evaluation is equally nonspecific. If the clinical localization of the lesion is the motor unit and the EMG is clearly "myopathic," the next most useful step is muscle biopsy with histochemical study of the muscle and biochemical, electron microscopic and genetic studies available as determined by the biopsy. The needle EMG is also frequently useful in choosing a muscle with an appropriate degree of involvement for biopsy [14]. Open biopsy is preferred in infants in order to get an adequate tissue sample for diagnosis. If the EMG suggests motor unit localization and a "neurogenic" process, the current recommendation is to do the genetic testing for the deletion of the survival motor neuron gene (SMN-1) and copy number determination of SMN-2 for spinal muscular atrophy before undertaking a muscle biopsy. If the expected genetic abnormality is identified, it would obviate the need for direct examination of the muscle tissue.

Congenital Myopathies with Cores (Core Myopathies)

Clinical Features

The congenital myopathies characterized by the presence of "cores" are now generally grouped into the core myopathies which include central core disease and multicore disease, myopathy with minicores, and others, all characterized by focal reductions in oxidative enzyme activity on histochemical staining of frozen sections of muscle tissue. The most commonly used designation for this group of diseases with multiple core structures is now multiminicore disease (MmD) [19]. Mutations in the ryanodine receptor are the most common cause of core myopathies while mutations in the selenoprotein N (SEPN1) are less common [20].

Central core disease, the first congenital myopathy to be identified, is characterized by proximal muscle weakness, hypotonia absent reflexes, and delayed acquisition of motor milestones along with skeletal anomalies such as short stature, kyphoscoliosis, pes cavus, and dislocated hips [21]. Affected adults with central core disease may be nearly asymptomatic or may have muscle cramps and myalgias with varying degrees of proximal muscle weakness which is

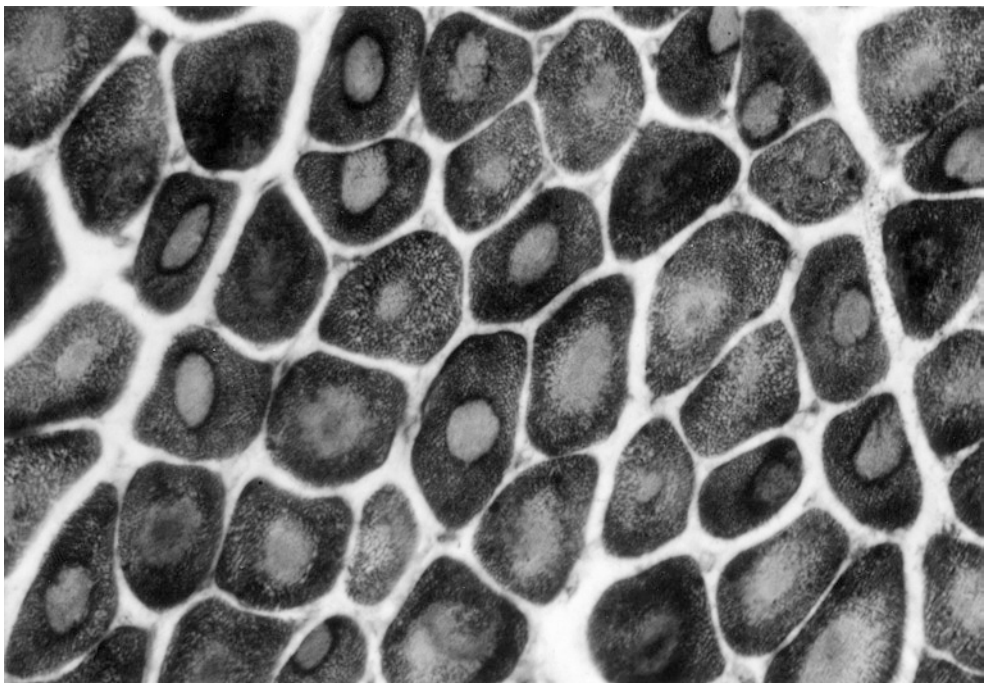

Fig. 62.2 Central core disease. Both this child and her mother had proximal muscle weakness that was more evident in the lower extremities. The central cores are well demarcated with the NADH-TR reaction and probably extend throughout the entire length of the myofibers. Note also the type 1 myofiber predominance. NADH-TR × 350 (original magnification)

typically more pronounced in the lower extremities. Many patients with central core disease have the potential to develop malignant hyperthermia (MHS) with the use of volatile anesthetics and/or muscle relaxants. Patients with truncating mutations in the SEPN1 gene may also be MHS. Magnetic resonance imaging of the muscle in the core myopathies may be useful as the pattern of involvement is one of the more characteristic patterns seen. The gluteus maximus is prominently involved in the pelvis. The thigh shows that the adductor magnus, vastus lateralis, vastus intermedius, semitendinosus, and sartorius muscles are all involved with sparing of the rectus femoris, adductor longus, gracilis, and biceps femoris. In the lower leg, the soleus and peroneal muscles are involved with preservation of the anterior tibial, posterior tibial, and gastrocnemius [17]. Patients with SEPN1 mutations show prominent involvement of the anterior thigh and many will also have rigid spines [22]. Although the precise epidemiological data does not yet exist, the core myopathies are more common than any other congenital myopathies, and RYR1 mutations are the most common identifiable cause with an incidence of 1:250,000 for central core disease in England and perhaps as high as 1:2,000 for the heterozygous state in Japan [23, 24]. The incidence of SEPN1 gene mutations in the population is not known at this time.

Pathological Features

The histology of the muscle from patients with central core disease is characterized by distinctive, well-circumscribed circular regions in the center of most type 1 fibers (Fig. 62.2). These more or less cylindrical structures are seen easily with many stains but are most clearly demonstrated with the NADH-TR technique with which the cores are unstained. The cores extend throughout the length of the myofiber. Most patients with central core disease show type 1 myofiber predominance, though the percentage of fibers containing cores varies considerably. Occasionally one finds nemaline rods in association with cores.

Etiology and Pathogenesis

The pathogenesis of core formation remains undefined [25, 26]. Central cores may result from fusion of myotubes at different stages of maturation during the 24th to 28th week of gestation. Alternatively, the similarity between target fibers and cores suggests possible aberrant innervation. However, targets do not extend throughout the full length of the affected muscle fiber. Studies have failed to show increased extrajunctional acetylcholine receptors in fibers with cores as would be expected with denervation. Structures resembling cores have been produced after tenotomy. Nevertheless, significant differences between experimentally induced lesions and naturally occurring cores and target fibers exist.

Genetics

Most patients with Central core disease inherit the disease as an autosomal dominant. Sporadic cases presumably represent new mutations. The gene for the most common form is located on chromosome 19q13.1, and the gene product is the ryanodine receptor (RYR1) [27, 28]. The ryanodine receptor is one of two genes responsible for malignant hyperthermia, the other being the skeletal muscle dihydropyridine-sensitive L-type voltage-dependent calcium channel gene (CACNA1S) [29–31]. A third gene coding for beta-myosin heavy chain

(MYH7) has been found in patients with a hypertrophic cardiomyopathy and central core like changes in the skeletal muscle [32]. Less frequently, SEPN1 gene mutations cause myopathy with cores/mini cores or multiple cores.

Sequencing of the RYR1 gene has only recently become available and genotype-phenotype correlations are still developing. The dominant RYR1 mutations disrupt excitation contraction coupling and/or disturb intracellular homeostasis, but the mechanisms of the recessive RYR1 mutations are less well understood [20]. The pathogenesis of SEPN1-related core disease (MmD) is not clearly delineated, but there is a close functional and spatial relationship between the ryanodine receptor and the selenoprotein N suggesting a role in calcium homeostasis for the latter [20].

In patients with core structures in the muscle and neither RYR1 or SEPN1 mutations other genetic diseases which may be associated with core structures should be considered. Clinical or pathological features not usually seen in RYR1- or SEPN1-related core myopathies may be helpful in making a diagnosis. For example, cardiomyopathy may be a feature of missense mutations in B-myosin heavy chain gene (MYH7), ACTA1 mutations, or lamin A/C mutations (LMNA gene), all of which may also have core structures [19].

Nemaline Myopathy

Clinical Features

Nemaline myopathy was originally described independently by Shy et al. and Conen et al. in 1963 as a nonprogressive myopathy with a distinctive morphologic abnormality designated myogranules [33] or rods of thread-like fibrous material [34]. The clinical spectrum of nemaline myopathy has expanded considerably since. Infants with nemaline myopathy can have severe weakness and hypotonia, with a rapidly progressive course leading to early death from respiratory failure [35, 36]. The childhood presentation is typically relatively benign with a nonprogressive course characterized by proximal weakness, hypotonia, and delayed motor development. Many afflicted children have a narrow face, high arched palate, kyphoscoliosis, and talipes varus deformity. Many patients also have strikingly diminished muscle bulk. The extraocular muscles tend to be spared in nemaline myopathy, despite the palatal and facial deformities which suggest intrauterine weakness [37].

Adult onset of nemaline myopathy has been reported [38–41]. Adult patients with nemaline myopathy show a wide spectrum of clinical severity; some are asymptomatic, others have mild nonprogressive weakness present since childhood or restricted weakness (such as head drop), and still others manifest progressive weakness [41]. Some adult patients with this condition have severe wasting of distal leg muscles. Fatal cardiomyopathy has been reported in adult patients with nemaline myopathy [42].

Nemaline myopathies are now recognized as a spectrum of disorders resulting from 1 of 7 known genes with the clinical presentation divided into six different categories including severe congenital, intermediate congenital, typical congenital, mild NM of childhood onset, adult onset, and other (unusual) forms [43]. The one feature which is common to the first 4 types at least is the particular involvement of the muscles of respiration. It should be noted that not only are defects in several genes able to produce similar histopathologies but defects in the same gene can result in more than one structural defect such that a single gene mutation may produce nemaline rods, cores, or central nuclear myopathy like changes making any single feature, short of gene identification, less than reliable for diagnosis. Furthermore, the clinical spectrum of nemaline myopathy even associated with a single gene is quite wide making genotype-phenotype correlations difficult [43].

Pathological Features

The diagnosis of nemaline myopathy is still based on the demonstration of the characteristic rods in skeletal muscle. Rods are best demonstrated in frozen sections stained with the modified trichrome technique with which they appear as reddish-purple granules measuring 2–7 μm in length. There commonly are collections of rods which are quite conspicuous and tend to aggregate under the sarcolemma (Fig. 62.3). Rods are found predominantly in type 1 myofibers. Affected fibers are often somewhat smaller than normal and there may be some degree of type 1 myofiber predominance. The number of rods and the number of fibers containing rods varies greatly from patient to patient and from muscle to muscle within patients. There is little correlation between the severity and the number of rods or the number of fibers with rods, but there is a correlation between the severity of the clinical manifestations and the alterations in size and proportion of type 1 myofibers. Type 1 myofiber predominance has been observed in asymptomatic relatives of patients with nemaline myopathy. In one study of patients who underwent repeat biopsy 5–18 years after the diagnosis was made, the second biopsies showed fewer type 2 fibers and increased myofiber size variation with more atrophic fibers [44]. Rods are sometimes found in the nuclei of the myofibers and in the diaphragm muscles in infantile cases with severe clinical manifestations or rapid progression of the clinical course [36, 45]. Nuclear rods, actin accumulation, and the appearance of Zebra bodies are the only histological features which are associated with a specific gene defect that being ACTA1 mutations [43]. Adults with relatively mild clinical manifestations of nemaline myopathy, however, have also been found to have intranuclear rods [38, 46]. Intranuclear rods are not specific to nemaline myopathies as they have been observed in patients with plectin deficiency and ZASP mutations [47, 48].

Ultrastructurally, nemaline rods are elongated osmiophilic structures that are similar in appearance to the Z disks. They

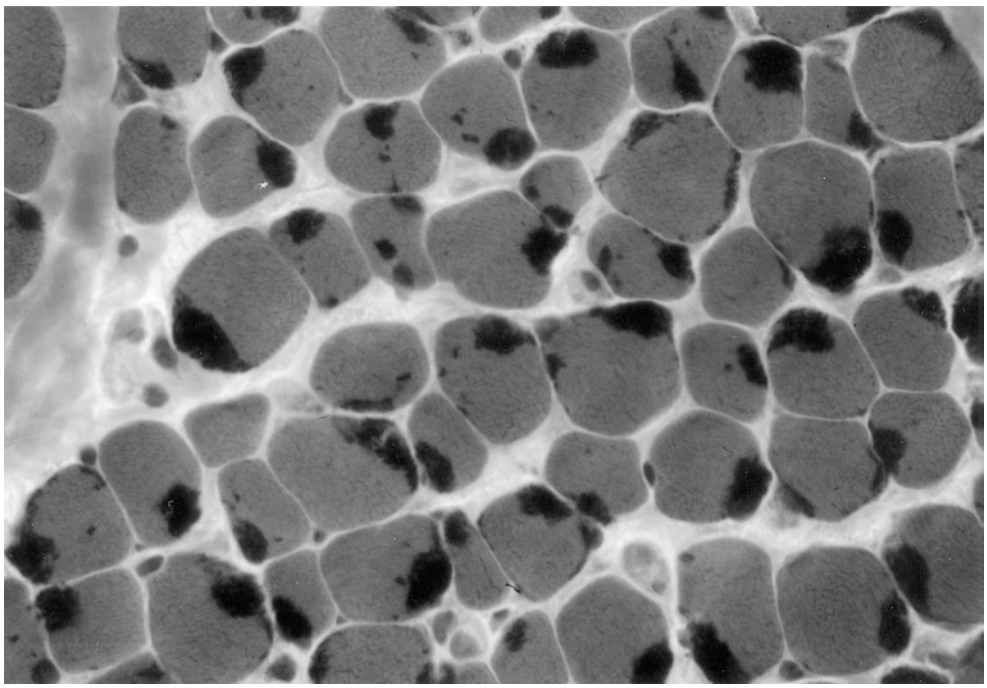

Fig. 62.3 Nemaline myopathy. This biopsy specimen is from a 4-year-old boy with marked weakness and mild skeletal anomalies. The granular nemaline rods stain reddish and tend to accumulate along one side of the myofibers. Modified trichrome × 550 (original magnification)

are composed of compactly aggregated parallel filaments with periodic cross-striations. At their free ends, nemaline rods are in continuity with thin actin filaments. In transverse section, the nemaline rods display a quadratic latticework configuration. Biochemical and immunohistochemical studies have demonstrated the presence of alpha-actinin [49, 50]. A defect in the control mechanisms that normally restrict alpha-actinin to the Z disks may be responsible for the formation of nemaline rods [51]. Rod structures, though characteristic of nemaline myopathy, are not specific for the disease and can be seen in a variety of other situations including other myopathies, normal extraocular muscles, and in normal muscle fibers near myotendinous insertions. Nemaline rods as well as central cores have been seen in tenotomized animals [52].

Genetics

There are currently seven genes known to be associated with nemaline myopathies. Six of the seven genes encode proteins involved with the thin filaments of the sarcomere. The seventh gene is KBTBD13 and the function is not yet known. There are probably more genes to be identified as there are patients with nemaline myopathies who do not have any of the known mutations [43]. Other than the fact that ACTA1 mutations are associated with the intranuclear rods and that the sporadic late-onset nemaline myopathy (SLONM) appears to be an autoimmune disorder, genotype-phenotype correlations are not easily made [41]. The genes associated with nemaline myopathies include:

1. TPM3 Slow alpha-tropomyosin (in first family with NM described) is a dominant mutation. Widely variable clinical presentation, Rods only in type 1 fibers, fiber-type disproportion, may overlap with "cap myopathy" [53].
2. Nebulin (NEB) mutations cause a widely variable NM from severe congenital to milder forms, with and without specific involvement of distal musculature, the knee extensors, neck muscles, and face [54]. These are recessive mutations and can be the cause of rod-core myopathies [55].
3. Muscle alpha actin gene (ACTA1) mutations are often severe sporadic dominant mutations with the severity of the involvement being dependent on the degree of expression of cardiac muscle actin retained in the skeletal muscles of the patient [56].
4. Beta-tropomyosin gene (TPM2) mutations are associated with dominant distal arthrogryposis and recessive Escobar syndrome with NM [57, 58].
5. The last three mutations are uncommon. They include slow skeletal muscle troponin T gene (TNNT1) mutations, KBTBD13 mutations, and CFL2 mutations in the muscle cofilin-2 gene.

It is important to realize that the molecular diagnosis of NM is complicated by the number of genes, the large size of the nebulin gene and the overlapping of the clinical syndromes. This makes the genetic diagnosis expensive and time-consuming at present. It is presumed that the next generation of sequencing and targeted capture should facilitate this process [59].

Centronuclear Myopathy (Myotubular Myopathy)

This condition was originally described in a 12-year-old boy with weakness, including involvement of facial and

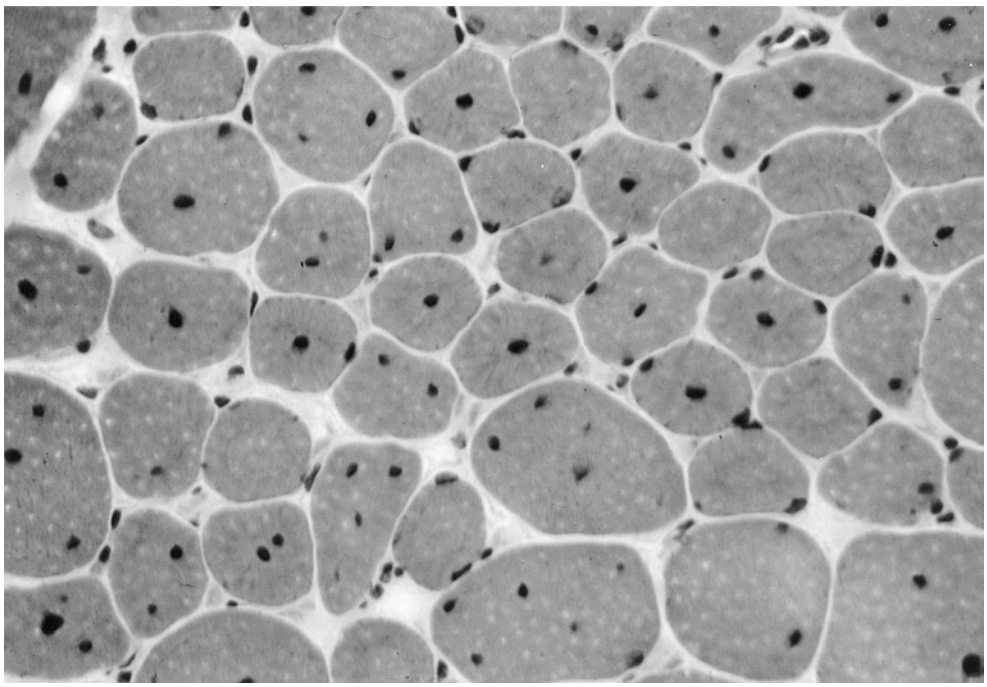

Fig. 62.4 Centronuclear myopathy. This patient and his brother had moderate weakness since infancy. Note the numerous centrally located nuclei and moderate variation in myofiber size. The biopsy specimen also showed type 1 myofiber predominance. H & E × 350 (original magnification)

extraocular muscles and delayed motor development [60]. The authors suggested that the disease resulted from arrested maturation of embryonic muscle and designated the disorder myotubular myopathy. The term centronuclear myopathy (CNM) was soon introduced to describe the disease in two teenage sisters who had weakness, also involving the extraocular muscles, and impaired motor development [61]. The current approach is to label the X-linked infantile form as myotubular myopathy most of which are caused by mutations in the MTM1 (myotubularin 1) gene. The term centronuclear myopathy (CNM) is used for the autosomally inherited later-onset forms, the classical dominant form is caused by mutations in the DNM2 (dynamin 2) gene and the recessive form caused by mutations in the BIN1 (bridging integrator protein) gene [62].

Clinical Features

With subsequent reports the clinical spectrum of the disease has expanded. Three more or less distinct clinical presentations have been delineated [4]. When onset of weakness is in the neonatal period, the clinical course is frequently rapidly progressive, leading to respiratory failure and death [63]. When this presentation occurs, it is usually indicative of the X-linked form of the disease. In the majority of patients, the disease becomes manifest during late infancy or childhood and is characterized by weakness (including extraocular muscles), hypotonia, and delayed motor development. Associated skeletal deformities, such as kyphoscoliosis and pes cavus, may occur. Some patients do not become symptomatic until adulthood. These individuals usually have mild to moderate weakness affecting particularly the lower extremities.

Imaging of the CNMs is most helpful in the MTM1-related cases where there is predominant and prominent involvement of the posterior thigh compartment and anterior medial muscles with preservation of the anterior lateral and gracilis muscles [17]. The imaging features of the dynamin and BNI1-related CNMs are less specific and usually reveal diffuse involvement of the muscle.

Pathological Features

Centronuclear myopathy is histologically characterized by a large but variable number of myofibers that contain rows of centrally placed internal nuclei (Fig. 62.4). The central nuclei are often surrounded by vacuoles that may contain glycogen granules. In some cases, the central nuclei are restricted to the type 1 myofibers; in others, they are found in both fiber types. Centronuclear myopathy often shows type 1 predominance and relatively small type 1 fibers. When viewed in cross section, the affected fibers often show radial striations. This finding may be due to the presence of abnormally small myofibrils in the interior of the myofibers, around and between successive central nuclei [47]. The X-linked form apparent in neonates is characterized by fibers of uncertain type with developing contractile elements around the periphery of the fiber and unstained clear central regions of the fibers resembling myotubes that one might see in developing muscle culture.

Pathogenesis

The gene mutations causing most of the cases of CNM have now been delineated. All are genes that are involved in membrane remodeling and membrane trafficking, perhaps the

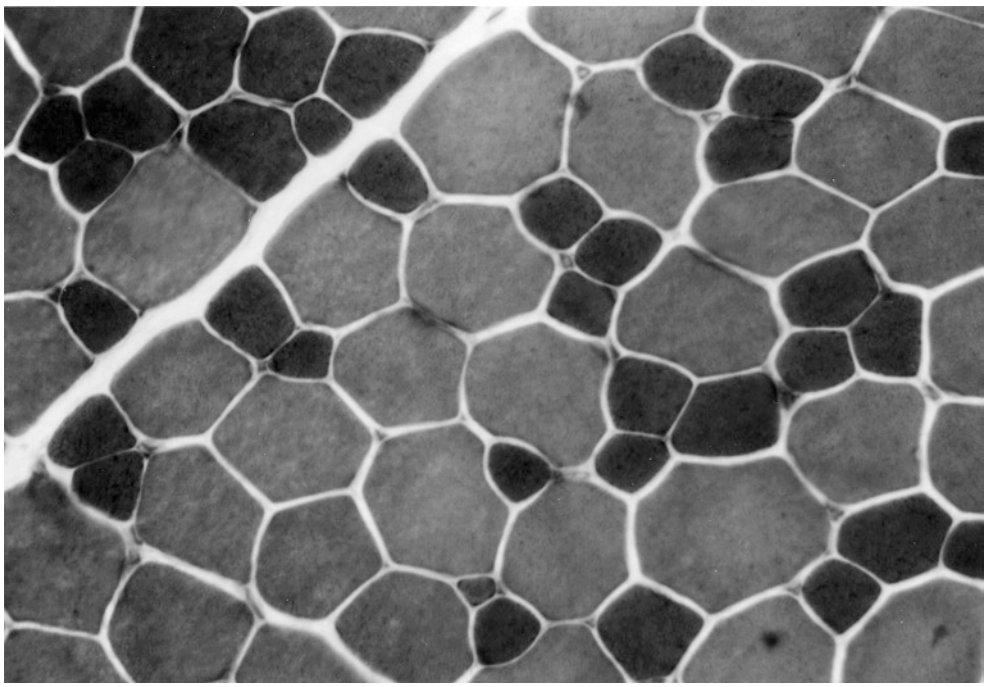

Fig. 62.5 Congenital fiber-type disproportion. This young girl had moderate weakness and hypotonia. The dark staining type 1 myofibers are more than 12 % smaller than the lighter staining type 2 myofibers. Nonspecific esterase × 550 (original magnification)

common pathomechanism involved in the condition although recent data suggests a role for T-tubule dysfunction in the pathogenesis in the X-linked form. The ability to predict the clinical severity based on the gene mutation is not yet well established and mutations in the same gene and similar mutations can be associated with mild or severe phenotypes [64]. Although there is overlap, the triad of pathological features of radial arrangement of sarcoplasmic oxidative enzyme staining, nuclear centralization and internalization, and type 1 fiber predominance and hypotrophy is seen only in the DNM2-related cases of CNM [65].

Congenital Fiber-Type Disproportion

A congenital myopathy in which the chief pathological feature consisted of smallness of type 1 myofibers (where the type 1 fibers are more than 12 % smaller than type 2 fibers) was described and later named by Brooke [66, 67]. Whether congenital fiber-type disproportion (CFTD) is a distinct entity or a part of many other diseases has been controversial, but the term does describe a useful diagnostic category despite the fact that to some degree, fiber size disproportion is a feature of a wide range of conditions [68].

Clinical Features

Infants with CFTD display clinical features that are nonspecific and common to many congenital myopathies. They are hypotonic and weak especially during the first 2 years of life. These children are often short and may have a number of skeletal or morphological abnormalities including high arched palate, kyphoscoliosis, dislocated hips, pes cavus, and contractures of the elbows and knees. CNS abnormalities with mental retardation have been described in some patients with congenital fiber-type disproportion [69, 70]. Congenital fiber-type disproportion has been associated with hyperinsulinemia and peripheral insulin resistance [71]. In those patients with the clinical features of a congenital myopathy and clear-cut fiber-type disproportion on muscle biopsy, the clinical picture is more uniform than is seen in the more common congenital myopathies [2]. There also is a reported association between congenital fiber-type disproportion and rigid spine syndrome [72].

Pathological Features

Histologically the condition is characterized by a disparity in the size of the myofiber types. The type 1 fibers are at least 12–15 % smaller than the type 2 myofibers (Fig. 62.5). Subsequent reports broadened the original definition of the disease and emphasized the occurrence of similar morphologic findings in children with a wide variety of neuromuscular disorders [4]. However, some investigators consider pure fiber-type disproportion to be highly suggestive of a congenital syndrome manifest predominantly by benign hypotonia and nonprogressive weakness [4, 73]. In some cases of congenital fiber-type disproportion, central nuclei have been seen later in the course of the disorder [74]. One of the major unanswered questions with this and some other congenital myopathies is why these patients are weak since their muscle does not show what would ordinarily be considered pathological features or reduction in muscle bulk. In general, the severity of clinical involvement is correlated with the degree

of abnormality of type 1 muscle fibers, though the significance of these findings is still obscure. It has been suggested that this disorder represents a disharmonic maturation of the muscles [70]. If there are rods, cores or central nuclei in the biopsy, the fiber size disproportion is considered secondary and of little importance.

Genetics

Although some cases of CFTD demonstrate autosomal dominant inheritance, most cases are sporadic. There are now several genes which are known to be associated with the finding of CFTD. These include TPM3 (Tropomyosin), RYR1 (ryanodine receptor 1) and ACTA1 (Actin) genes [75–77]. Tropomyosin mutations are the most common gene associated with CFTD and in fact, CFTD is the clinical diagnosis more often in patients with TPM3 mutations than nemaline myopathy. Most of the mutations in which the clinical picture is CFTD are dominant missense mutations and have mild to moderate disease severity [75].

In patients where the gene mutation associated with CFTD is known, there may be specific implications regarding health surveillance such as the need to monitor respiratory function in patients with mutations in the TPM3 gene. In patients with CFTD without known mutations, one can anticipate that the weakness will be only slowly progressive at worst but even here monitoring for scoliosis, joint contractures, cardiac abnormalities, and respiratory muscle weakness is appropriate [78].

Reducing Body Myopathy and FHL1-Related Myopathies

Reducing body myopathy (RBM) as a morphologically distinctive disorder was originally described in 2 weak, hypotonic neonates who died in late infancy [79]. Subsequent reports described similar morphologic features in older individuals with varied clinical manifestations, including a more benign course [80, 81]. Developments in the last few years have delineated several gene defects associated with RBM and a number of related or associated myopathies [82]. We now understand that although several genes can be associated with the presence of reducing bodies as well as other myopathies, the most common gene group is the four and a half Lin-11, Lsl-1, Mac-3 (LIM) domain protein 1 gene (FHL1 gene). The identification of these gene mutations has redefined several clinical phenotypes including at least 4 distinct clinical myopathy conditions including RBM, X-linked myopathy with postural muscle atrophy, Emery-Dreifuss MD (type 6), and scapuloperoneal myopathy. These mutations also have been associated with rigid spine syndrome, and the syndrome of rigid spine, contractures, and cardiomyopathy [82]. MRI study of patients with RBM is distinctive and shows altered density of posterior-medial and soleus muscles with sparing of the glutei muscles which appear hypertrophic in comparison [83].

Pathological Features

Reducing body myopathy is characterized by the presence of a variable number of so-called reducing bodies in the muscle fibers. These structures are round to ovoid masses, measuring 10–70 μm at maximal diameter. Reducing bodies are generally located at the periphery of the myofiber, often near the nucleus. They stain reddish-purple with the modified trichrome technique and are further characterized histochemically by autofluorescence. They also stain for glycogen, nucleic acids, and sulfhydryl groups. Ultrastructurally, reducing bodies are composed of varying proportions of osmiophilic granular and fibrillar material surrounding irregular lacunae. The composition of the reducing bodies is uncertain. They may be derived from ribosomes, viral particles, or myofilaments. Muscle biopsy specimens from these patients also show variation in myofiber size, occasional degenerating myofibers, and type 1 myofiber predominance.

Genetics

There have been at least 26 different mutations in the FHL1 gene. The phenotypes vary considerably; Table 62.2 lists some of the newly discovered genotype-phenotype associations.

Congenital Myopathies with Protein Aggregation

The advances in molecular genetics largely have made the classification of the less well-established congenital myopathies obsolete. As evidenced in the preceding section, mutations in a single gene can cause several distinct phenotypes and conversely, as we will see in this section, a given clinical-pathologic phenotype may be caused by a number of different gene mutations, sometimes affecting the same cellular functions, sometimes the functional relationships are not so clear. A number of congenital myopathies share the aggregation of proteins in the fibers [84]. Among the common proteins accumulated in muscle are AlphaBeta crystallin, desmin, and myotilin which are associated with myofibrillar myopathies including granulofilamentous myopathy, cytoplasmic body myopathy, and spheroid body myopathy, respectively.

Myofibrillar myopathies are known now to be associated with more than a dozen different gene mutations (Table 62.3). The MFM conditions make up the largest group of protein aggregate myopathies to date. These conditions are marked by late onset with a variable progression but including muscle weakness, respiratory failure and cardiomyopathy. The mechanisms of accumulation of protein in these conditions are not established. In some, there may be an abnormal

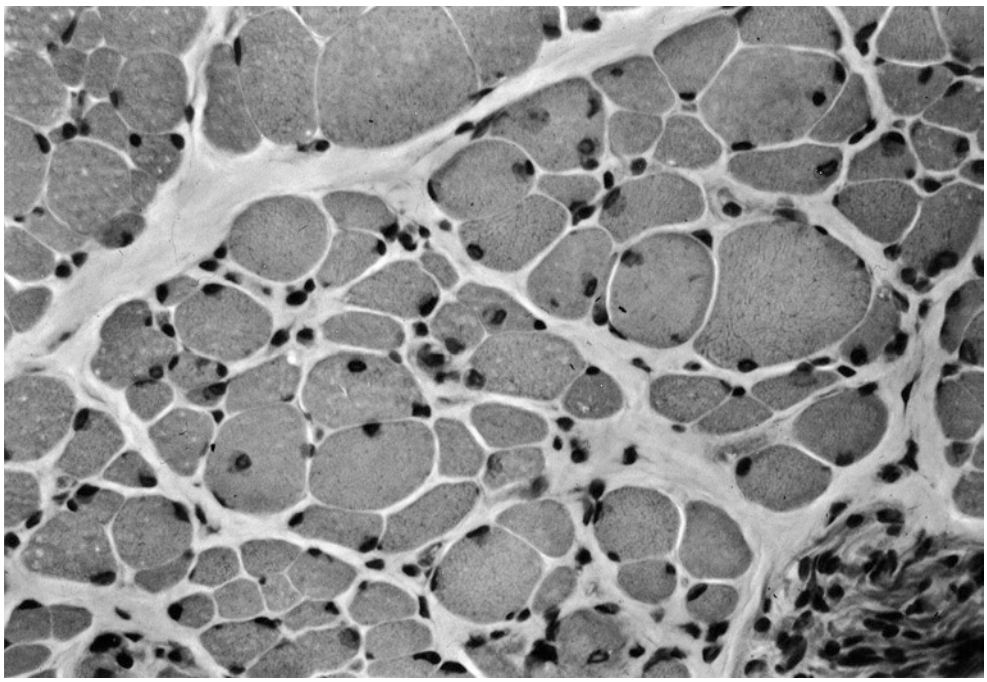

Fig. 62.6 Congenital muscular dystrophy. This biopsy specimen is from a 2-year-old girl with mild weakness and skeletal deformities. Note the variation in myofiber size, increase in internal nuclei, and increased endomysial connective tissue. H & E × 350 (original magnification)

structure of the protein, but it may also represent a defect of muscle protein catabolism [84]. Why the same gene mutation produces protein aggregation in some families and a congenital myopathy in other families is not understood at this time. Table 62.4 gives some examples of known genes that produce both kinds of myopathies.

Congenital Muscular Dystrophy

The term congenital muscular dystrophy refers to a group of congenital myopathies which have what are usually felt to be dystrophic changes on muscle biopsy (Fig. 62.6). These dystrophic changes include muscle fiber necrosis, replacement of muscle tissue by fatty tissue, and fibrosis of muscle. Thus, a congenital muscular dystrophy presents in early life with weakness, hypotonia, and other features of congenital myopathy and is further delineated by the finding of dystrophic changes on biopsy. In the past, the congenital muscular dystrophies were further categorized by the presence or absence of associated cerebral involvement on a clinical basis. While the distinction may be useful on a clinical basis, the classification has now given way to the use of the gene mutation as the primary classification parameter (Table 62.5).

All the congenital muscular dystrophies are associated with muscle weakness, hypotonia, and deformities resulting from intrauterine weakness and decreased movement (arthrogryposis, pes cavus, etc.). Before the deficiency of merosin was identified, two types of congenital muscular dystrophy (CMD) were identified on the basis of clinical severity, mild and severe CMD. The severe form of CMD has now been identified as having a deficiency of merosin (laminin M) as the molecular basis for the myopathy. Current classification would thus identify merosin deficient CMD as a severe form often resulting in extensive disability and not uncommonly leading to respiratory failure and death.

Merosin, or laminin M chain, is a predominantly extracellular protein which forms an essential link between the extracellular matrix and the dystrophin-associated glycoprotein component of the muscle cytoskeleton (see Figure 56.1, chapter 56). The clinical features include hypotonia, weakness, arthrogryposis, and delayed motor milestones. Characteristically, these patients are remarkable for their mental alertness. Although brain involvement has been reported, as these patients get older, it is usually clear that in the majority there is no cognitive impairment [85]. The merosin negative CMDs also have a striking abnormality on cranial MRI scan consisting of diffuse high signal intensity on T-2 weighted images in the cerebral white matter.

The merosin positive form of CMD, or the mild form of CMD, is typically nonprogressive or slowly progressive and usually results in only minor disabilities. There is usually no cognitive impairment and fully 90 % of these patients will be able to ambulate by 4 years of age [86].

The genetic basis of the merosin deficient CMD (MDC1A) is a deletion/mutation of the laminin 2 gene (LAMA2) on 6q22-q23 [87]. The result may be complete deficiency of the merosin in the more severe cases or partial function of the merosin in milder cases [88].

Congenital muscular dystrophy due to abnormal glycosylation of the dystroglycans represents the second group of CMDs. The best known of the CMDs with glycosylation

defects of dystroglycans are Fukuyama CMD (FCMD), Walker-Warburg CMD (WWS), muscle-eye-brain CMD (Santavuori, MEB), congenital muscular dystrophy 1C (FKRP-related or MDC1C), and congenital muscular dystrophy 1D (LARGE-related or MDC1D).

The Fukuyama CMD is most prevalent in Japan and was once thought to be allelic with WWS [89]. The cerebral involvement is characterized by polymicrogyria, lissencephaly, and neuronal heterotopias which result in characteristic MRI features [90]. Seizures are frequently the initial CNS symptom. Affected children are hypotonic at birth, show developmental delay affecting both motor and cognitive developmental milestones and develop progressive muscle weakness and atrophy. Life expectancy is strikingly shortened and most do not survive beyond the first decade. MRI of the brain may be helpful in suggesting the diagnosis in these patients [88].

Another CMD disease which may be distinct from the Fukuyama and Walker-Warburg CMDs was reported as an autosomal recessive disorder by Echenne [89]. These patients had typical CMD with mild intellectual impairment and moderate to severe cerebellar atrophy, strikingly elevated CK in the serum, and normal merosin, dystrophin, and sarcoglycan immunostaining of the skeletal muscle.

Some patients with CMD have a combination of eye and brain anomalies [91]. The cerebral anomalies include disturbances of neuronal migration, hypomyelination, leptomeningeal gliomesodermal proliferation, and pyramidal tract hypoplasia. The ocular anomalies include corneal opacities, severe myopia, congenital glaucoma, pallor of the optic disks, and retinal hypoplasia. Muscle-eye-brain disease has been shown to result from a mutation in POMGnT1 in most cases, but mutations in FKRP and FKTN can also cause this phenotype.

The third group of CMDs is the diseases that result from mutations in the COL6 genes. The spectrum of disease resulting from collagen 6 defects varies from severe (Ullrich CMD) to more mild adult onset (Bethlem Myopathy). These patients are at risk for respiratory failure which may even present prior to the loss of ambulation and requires the physician to be vigilant with regard to the respiratory function. Although there is no diagnostic clinical feature, the MRI of the muscle may show a characteristic "outside-in" pattern of degeneration in which most of the abnormal signal will be at the outer edges of the muscle [88]. These patients also may have contractures of proximal joints with hyperlaxity of the distal joints and often show a characteristic follicular hyperkeratosis of the skin as they get into the second half of the first decade of life.

The fourth category of CMDs is the selenoprotein-related disorders due to recessive mutations of the SEPN1 gene [88]. Clinical characteristics of SEPN1 CMD patients include severe weakness of axial neck and trunk muscles which leads to scoliosis and respiratory failure in the second and thirds decades of life with relatively preserved limb strength. The range of clinical syndromes is large however with the possible phenotypes including rigid spine syndrome, multiminicore disease, desmin-related myopathy with Mallory body-like inclusions and CFTD [92]. Table 62.5 lists some features of the four major groups of congenital muscular dystrophies.

The CK, EMG, and muscle biopsy findings in CMD are similar whether or not there is associated cerebral involvement.

Treatment, Management, and Prognosis

There is no specific treatment for any of the congenital myopathies. Therapeutic interventions consist of symptomatic physical therapy, orthopedic treatment of associated skeletal anomalies, and ventilatory supportive measures (if appropriate) for patients with respiratory muscle weakness. Measures to allow effective sitting or wheel chair fitting are frequently of value in improving the comfort and function of these individuals. There are no established or clinically tested standards of practice for any supportive therapies in the congenital myopathies although the standard of management for muscle disease in general applies to the CMDs generally.

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Metabolic Myopathies

63

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Introduction

Inborn errors of glycogen and fatty acid metabolism that cause exclusively or predominantly neuromuscular disorders are characterized by dynamic or static symptoms. Dynamic symptoms are acute, recurrent, reversible muscle dysfunctions, manifesting as exercise intolerance, myalgia with or without painful cramps (contractures), and often culminating in muscle breakdown and myoglobinuria. In contrast, static symptoms are manifested by fixed, often progressive weakness, sometimes simulating dystrophic or neurogenic processes (Fig. 63.1).

To understand glycogen and lipid storage disorders, a brief review of muscle metabolism at rest and during exercise is helpful.

The "fuel" utilized by muscle depends on several factors, most importantly the type, intensity, and duration of exercise but also diet and physical conditioning. At rest, muscle utilizes predominantly fatty acids. At the opposite end of the spectrum, the energy for extremely intense exercise (close to one's maximal oxygen uptake, or VO_2max, in dynamic exercise or close to maximal force generation in isometric exercise) derives from anaerobic glycolysis, especially when there is a "burst" of activity with rapid acceleration to maximal exercise. During submaximal exercise, the type of fuel utilized by muscle depends on the relative intensity of exertion. At low intensity (below 50 % VO_2max), blood glucose and free fatty acids (FFA) are the primary sources of energy. At higher intensities, the proportion of energy derived from carbohydrate oxidation increases, and muscle glycogen becomes an important fuel; at 70–80 % VO_2max, aerobic metabolism of glycogen is the crucial source of energy, and fatigue appears to set in when glycogen is exhausted. The type of circulating substrate utilized during mild exercise varies with time, and there is a gradual increase in the utilization of FFA over glucose until, a few hours into

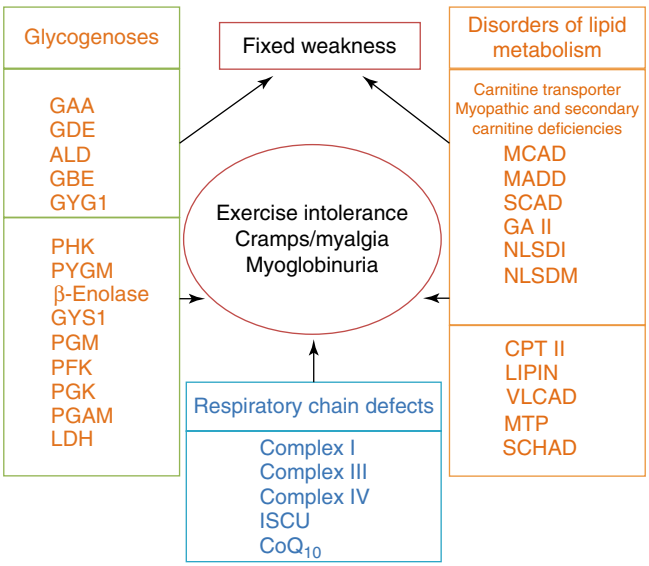

Fig. 63.1 The two major clinical syndromes seen in metabolic myopathies. Deficient enzymes are denoted by abbreviations or gene symbols as follows: *GAA* acid maltase (acid α-glucosidase) (GSD II), *GDE* glycogen debranching (GSD III), *ALD* aldolase (GSD IX), *GBE* glycogen branching (GSD IV), *GYG1* glycogenin (GSD 0), *PHK* phosphorylase kinase (GSD VIII), *PYGM* myophosphorylase (GSD V), *GYS1* glycogen synthetase, *PGM* phosphoglucomutase (GSD IV), *PFK* phosphofructokinase (GSD VII), *PGK* phosphoglycerate kinase (GSD IX), *PGAM* phosphoglycerate mutase (GSD X), *LDH* lactate dehydrogenase (GSD XI), *MTP* mitochondrial trifunctional enzyme, *MCAD* medium-chain acyl-CoA dehydrogenase, *MADD* multiple acyl-CoA dehydrogenase, *SCAD* short-chain acyl-CoA dehydrogenase, *GAII* glutaric aciduria type II, *NLSDI* neutral lipid storage diseases with ichthyosis (Chanarin-Dorfman disease), *NLSDM* neutral storage disease with myopathy, *CPT II* carnitine palmitoyltransferase II, *VLCAD* very-long-chain acyl-CoA dehydrogenase, *SCHAD* short-chain 3-hydroxyacyl-CoA dehydrogenase, *ISCU* nonheme iron-sulfur (Fe-S) protein, *CoQ_{10}* coenzyme Q_{10}

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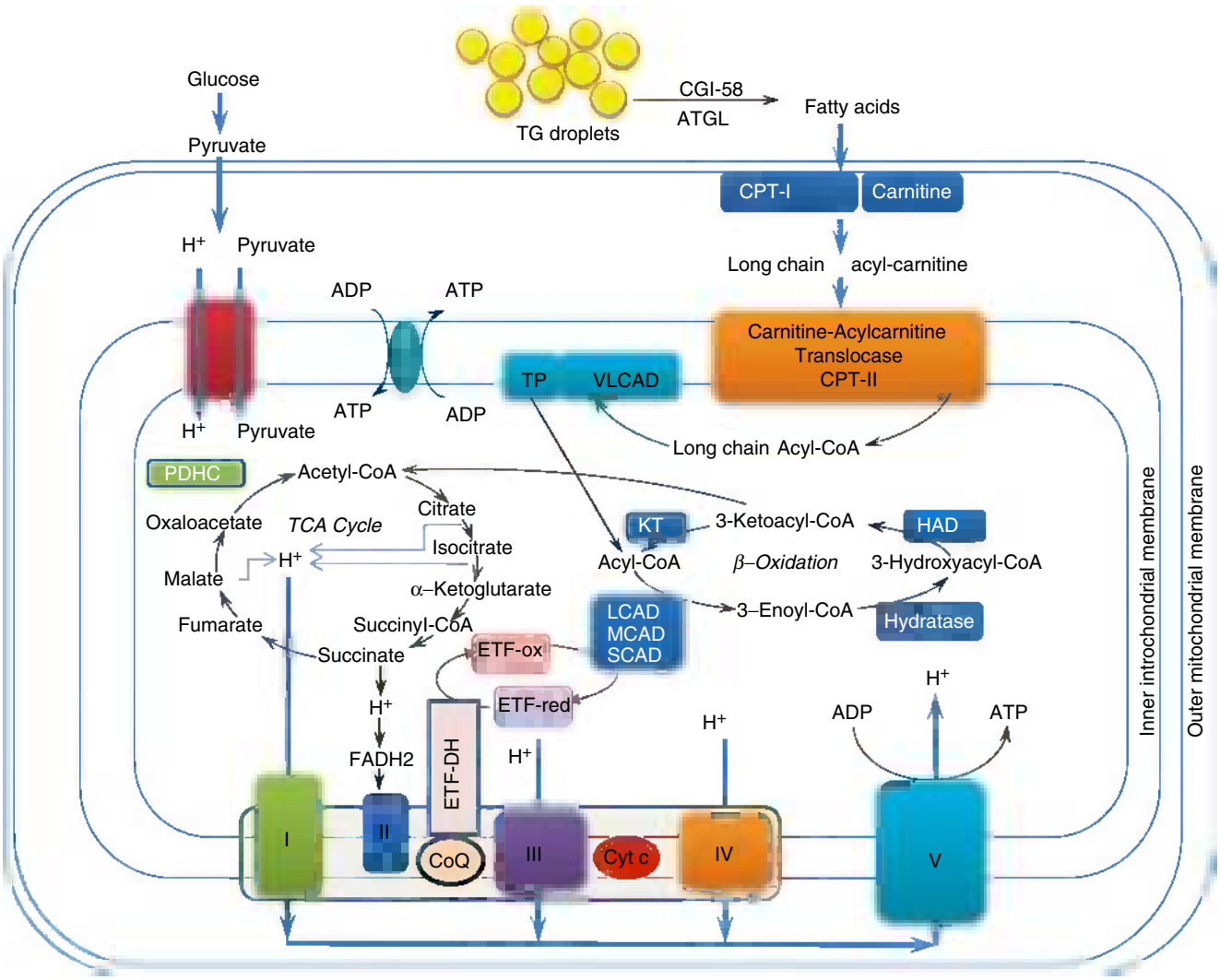

Fig. 63.2 Schematic representation of mitochondrial metabolism. *Abbreviations*: *PDHC* pyruvate dehydrogenase complex, *CPT* carnitine palmitoyltransferase, *VLCAD* very-long-chain acyl-CoA dehydrogenase, *TP* trifunctional protein, *LCAD* long-chain acyl-CoA dehydrogenase, *MCAD* medium-chain acyl-CoA dehydrogenase, *SCAD* short-chain acyl-CoA dehydrogenase, *HAD* 3-hydroxyacyl-CoA dehydrogenase, *KT* 3-ketothiolase, *ETFox* oxidized form of electron transfer flavoprotein, *ETFred* reduced form of electron transfer flavoprotein, *ETFDH* ETF-coenzyme Q oxidoreductase, *CG!-58* is the protein that activates ATGL, *ATGL* adipocyte triglyceride lipase (Reproduced from DiMauro and Haller [198], with permission)

exercise, lipid oxidation becomes the major source of energy. Because the availability of FFA from adipose tissue is virtually unlimited, a normal person can perform moderate dynamic exercise for many hours.

Figure 63.2 illustrates schematically mitochondrial energy metabolism, including the "points of entry" of carbohydrate and lipid fuel. Pyruvate, the terminal product of aerobic glycolysis, is carried across the inner mitochondrial membrane by an incompletely known transporter system. Transport of FFA requires a more complex system, which includes two enzymes (carnitine palmitoyltransferase [CPT] I and CPT II), a carrier molecule (L-carnitine), and a translocase (carnitine-acylcarnitine translocase, CACT). After oxidation of pyruvate through the pyruvate dehydrogenase complex (PDHC) and of fatty acyl-CoAs through ß-oxidation, both carbohydrate and lipid fuels converge into a common central metabolite, acetyl-CoA, which is further oxidized in the Krebs cycle. The reducing equivalents produced in the Krebs cycle and in the ß-oxidation spirals are passed along a chain of proteins embedded in the inner

mitochondrial membrane (the electron transport chain) to molecular oxygen with production of water. The *electron transport chain* consists of four multimeric complexes (I to IV) plus two small electron carriers, coenzyme Q (or ubiquinone) and cytochrome *c*. The energy generated by these reactions is used to pump protons from the mitochondrial matrix into the space between inner and outer mitochondrial membranes. This creates an electrochemical proton gradient across the inner membrane. A fifth multimeric complex (complex V or adenosine triphosphate [ATP] synthase), a tiny rotary engine, converts the energy of the electrochemical proton gradient into ATP, in a process known as oxidation/phosphorylation coupling. The terminal pathway of oxidative metabolism, comprising the electron transport chain and complex V, is known as the *respiratory chain*.

Disorders Causing Exercise Intolerance and Myoglobinuria

In general, there is a good correlation between the circumstances leading to clinical problems and the different roles of glycogen and lipid metabolism in the provision of energy. Thus, the complaints of patients with glycogenoses are almost invariably related to an identifiable, and usually strenuous, bout of exertion, and the muscles that hurt, swell, or cramp up are those that have been engaged in that particular type of exercise.

In contrast, patients with disorders of lipid metabolism, such as CPT II or very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency, often have no warning of an impending episode of myoglobinuria, which usually follows prolonged moderate exercise and may be heralded by myalgia of exercising muscles but is never accompanied by painful cramps. In addition, prolonged fasting in and by itself may cause myoglobinuria, in which case any muscle group may be affected, including respiratory muscles; a few patients with CPT II deficiency have been taken to the emergency room in respiratory distress during an episode of myoglobinuria [1]. The deleterious effect of fasting in CPT II deficiency is easily explained by the increased dependence of muscle on FFA oxidation, which is partially blocked. Conversely, some patients with myophosphorylase deficiency, a glycogen storage disease, note a beneficial effect of fasting on their exercise ability. This is explained by the mobilization of FFA, which facilitates the physiological switch from carbohydrate to lipid utilization.

The *respiratory chain* is indeed the "business end" of mitochondrial metabolism, where the energy generated by carbohydrate and lipid oxidation is released as ATP. This raises an interesting question: if disturbances of glycogen and lipid metabolism cause exercise intolerance, cramps, and myoglobinuria by impairing ATP production, why did it take so long to associate this syndrome with defects in the respiratory chain, the energetic pathway "par excellence"? The answer is that these patients often stay below the clinical radar because they contradict the rules of mitochondrial genetics (see below) [2].

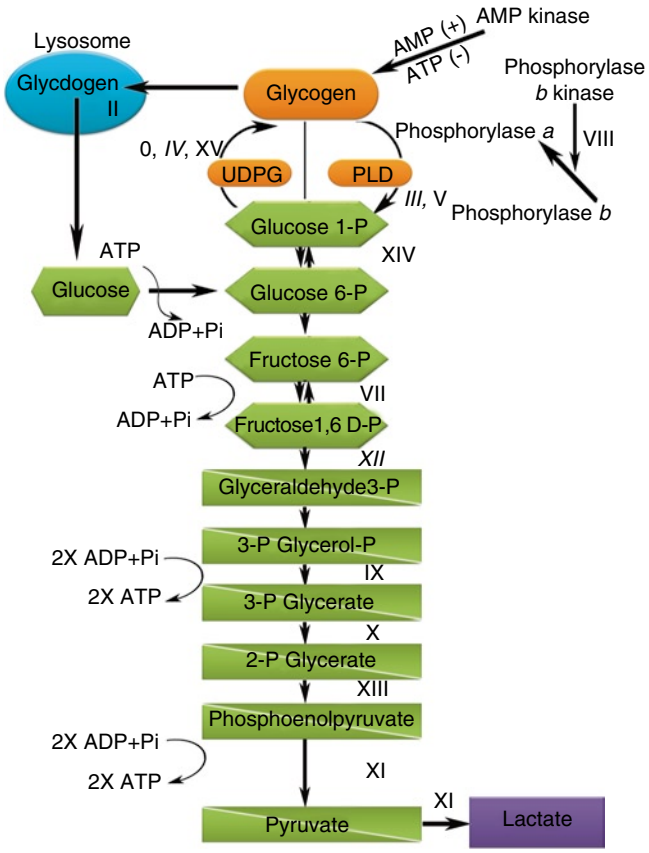

Fig. 63.3 Scheme of glycogen metabolism and glycolysis. *Roman numerals* indicate enzymes whose deficiencies are associated with muscle glycogenoses: *II* acid maltase (GAA, Pompe disease), *III* debrancher (GDE, Cori-Forbes disease), *IV* brancher (GBE, Andersen disease), *V* myophosphorylase (PYGM, McArdle's disease), *VII* phosphofructokinase (PFK, Tarui disease), *VIII* phosphorylase kinase (PHK), *IX* phoshoglycerate kinase (PGK), *X* phosphoglycerate mutase (PGAM), *XI* lactate dehydrogenase (LDH), *XII* aldolase A. *Normal numerals* indicate glycogenoses causing exercise intolerance, cramps, and myoglobinuria; *italic numerals* indicate glycogenoses causing fixed weakness. *Abbreviations*: *UDPG* uridine diphosphate glucose, *PLD* phosphorylase-limit dextrin, *AMP* adenosine monophosphate, *ADP* adenosine diphosphate, *ATP* adenosine triphosphate, P_i inorganic phosphate

Glycogenoses

In reviewing the glycogenoses causing exercise intolerance and myoglobinuria, we follow the metabolic "flow" in the glycogenolytic and glycolytic pathways rather than the historical numeration (Fig. 63.3).

Phosphorylase Kinase (PhK) Deficiency (Glycogenosis Type VIII)

PhK is a key regulatory enzyme in glycogen metabolism because it activates glycogen phosphorylase by phosphorylating a specific serine in response to neuronal or hormonal stimuli. PhK deficiency is associated with four distinct clinical presentations, which are distinguished on the basis of tissue involvement (liver, muscle, heart, or liver and muscle) and mode of inheritance (autosomal or X-linked). This clinical and genetic heterogeneity is explained by the complexity of the enzyme, a decahexameric protein composed of four subunits $(\alpha\beta\gamma\delta)4$: the α and β subunits are regulatory, the γ is catalytic, and the δ- is bound to calmodulin and confers calcium sensitivity to the enzyme. In addition, there are two isoforms for the α subunit (muscle and liver, A1 and A2), both encoded by genes on the X-chromosome, and two isoforms for the γ subunit (muscle and testis, G1 and liver, G2). Both G isozymes and the B-subunit are encoded by autosomal genes.

The purely myopathic variant of PhK deficiency usually manifests as a milder form of myophosphorylase deficiency (McArdle's disease), with exercise intolerance, cramps, and, infrequently, myoglobinuria. One distinguishing laboratory feature is the lactate response to the ischemic forearm exercise test (see Chap. 6), which is usually flat in patients with McArdle's disease, while it is normal or blunted in patients with PhK deficiency. Only about 15 patients with myopathic PhK deficiency have been reported, most of whom were men, suggesting X-linked inheritance. In agreement with this concept, all molecular defects identified thus far were in the *PHKA1* gene [3].

The liver and muscle variant of PhK is an autosomal recessive disorder dominated by hepatomegaly and fasting hypoglycemia with minimal muscle involvement: in one female and four male patients, five distinct nonsense mutations have been identified in the *PHKB* gene [4].

The cardiac phenotype of PhK deficiency is secondary to mutations in the gene (*PRKAG2*) encoding the γ2 subunit of AMP-activated protein kinase (AMPK) [5]. The mechanism of this AMPK-mediated PhK inhibition is unknown.

Myophosphorylase Deficiency (Glycogenosis Type V; McArdle's Disease)

Introduction

Although McArdle did not identify the biochemical defect, never was an eponym more appropriate than in this case. In 1951, on the basis of clinical observations and a few critical lab tests, Brian McArdle gave a remarkably precise description of the metabolic problem. He noted that ischemic exercise resulted in painful cramps of forearm muscles and that no electrical activity was recorded from the shortened muscles, indicating that they were in a state of contracture. He also noted that oxygen consumption and ventilation were normal at rest but increased more than normal with exercise. The astute observation that venous lactate and pyruvate did not increase after exercise led McArdle to conclude that his patient's disorder was "characterized by a gross failure of the breakdown of glycogen to lactic acid." Nor was the specific involvement of muscle lost to McArdle, who noted that epinephrine elicited a normal rise of blood glucose and "shed blood" in vitro accumulated lactate normally, leading him to conclude that "the disorder of carbohydrate metabolism affected chiefly, if not entirely, the skeletal muscles."

Etiology and Pathogenesis

Myophosphorylase deficiency is transmitted as an autosomal recessive trait, and the gene for the muscle isoenzyme of phosphorylase has been localized to chromosome 11 [7]. The apparently autosomal dominant transmission in a few families may be explained by at least two mechanisms: (1) the presence in subsequent generations of homozygous and manifesting heterozygous individuals [8–10] or (2) the presence of one homozygous and one heterozygous parent [11].

The molecular heterogeneity of myophosphorylase deficiency is striking: in the 19 years from the description of the first molecular defects [11, 12], more than 100 different mutations have been reported [13]. The most common mutation in North America and Northern Europe appears to be a cytosine-to-thymine substitution in codon 50 of exon 1, converting an arginine to a stop codon (R50X). This has allowed the use of molecular genetic analysis in leukocytes for diagnostic purposes, thus avoiding the obligatory need of a muscle biopsy [14]. However, as more and more mutations in the myophosphorylase gene are described and leukocytes are increasingly used for diagnosis, it becomes important to establish the relative frequency of the different mutations in ethnic groups. For example, the R50X mutation has never been observed in Japan, where the most common mutation appears to be a 3-bp deletion, TTC at codon 708/709 [15].

The genotype/phenotype relationship in McArdle's disease remains unclear: the most common genetic defect in typical McArdle patients, R50X, was also found in an infant who had the fatal myopathic variant [11] and in a child who died of sudden infant death syndrome (SIDS) [16]. Of course, one cannot exclude that these unusual presentations may be due to additional gene defects. Unlikely as this situation may appear, it has been verified in two children with McArdle's disease (both homozygous for the common mutation), who were also homozygous for the most common mutation associated with adenylate deaminase (AMPD) deficiency [17, 18]. One patient had myoglobinuria at the unusually early age of 2 years; the other was a young man with multiple episodes of myoglobinuria and early onset of weakness. Although AMPD deficiency per se is an inconsistent cause of myopathy, it might have worsened the phenotypic expression of myophosphorylase deficiency.

Phosphorylase activity is virtually absent in muscle biopsies when determined either histochemically or biochemically. Biochemical studies show that the enzyme is lacking in most patients, which is consistent with the most common genetic error, a nonsense mutation (see above). As a consequence, glycogen of normal structure accumulates in muscle, reaching concentrations two or three times higher than normal. Morphologically, the stored glycogen is mostly visible at the periphery of muscle fibers, where it forms subsarcolemmal "blebs." However, glycogen accumulation may be mild enough to escape morphological detection.

Phosphorylase catalyzes the first step in glycogen breakdown by removing 1,4-glucosyl residues phosphorolytically with liberation of glucose-1-phosphate. Hence, lack of phosphorylase impedes glycolysis, as shown by the flat venous lactate response to the ischemic forearm exercise test. Similarly, 31P-nuclear magnetic resonance spectroscopy (MRS) shows lack of acidification during aerobic or ischemic exercise and a greater than normal drop of the phosphocreatine/inorganic phosphate ratio [19].

Two main pathophysiological mechanisms underlie the exercise intolerance of myophosphorylase deficiency: (1) block of anaerobic glycolysis deprives muscle of the energy needed for isometric exercise and (2) block of aerobic glycogen utilization, with the attending shortage of pyruvate and acetyl-CoA, impairs dynamic exercise above certain intensity (approximately 50 % VO_2max). In agreement with the concept that oxidative phosphorylation is curtailed by decreased substrate availability, oxygen extraction and maximal oxygen uptake are decreased in myophosphorylase deficiency but may be at least partially restored by intravenous glucose infusion [20]. Haller et al. have also documented lower concentrations of Na+/K+ pumps in needle muscle biopsies from patients with McArdle's disease than in controls [21]. This finding explains several previous observations in McArdle patients, including the excessive rise of plasma potassium with exercise, the decline in the compound muscle action potential with repetitive stimulation (probably due to extracellular potassium-mediated membrane inexcitability), and the exaggerated increase in heart rate during exercise.

The pathogenesis of contracture and myoglobinuria remains unknown: depletion of high-energy phosphate compounds, especially ATP, has long been postulated to occur, but experimental evidence is lacking.

Resting serum creatine kinase (CK) is consistently elevated in patients with McArdle's disease, indicating that individual fiber necrosis probably occurs even with daily activities, a concept supported by morphological observations. The cumulative effect of this focal muscle damage along the years may explain the appearance of fixed weakness in older individuals; we found that 28 of 52 patients had fixed weakness, with a mean age of 41.5 years, while the mean age of patients without fixed weakness was 28.1 years [22].

Clinical Presentation

The clinical picture of McArdle's disease is rather stereotypical, dominated by exercise intolerance manifested by myalgia, premature fatigue, and stiffness or weakness of exercising muscles, which is relieved by rest. The type and amount of exercise needed to precipitate these symptoms vary considerably from patient to patient, possibly in relation to training and diet, but two types of exertion are likely to cause problems: brief intense isometric exercise, such as lifting heavy weights, or less intense but sustained dynamic exercise, such as walking uphill. Moderate exercise, such as walking on level ground, is usually well tolerated. On the other hand, strenuous exercise often results in painful cramps and muscle swelling, which can last for hours. Myoglobinuria is seen in about half of the patients. In fact, McArdle's disease is the second most common metabolic cause of recurrent myoglobinuria after CPT II deficiency [23]. An interesting phenomenon, almost invariably described by McArdle patients, is the "second wind" that they experience when, at the first appearance of exercise-induced myalgia, they slow down or rest briefly before resuming their activity.

The severity of symptoms may vary markedly in different patients, some of whom have neither cramps nor myoglobinuria but complain only of excessive fatigue and poor stamina, symptoms that are likely to be dismissed as "psychogenic." On the other hand, about 20 % of patients have progressive weakness, usually starting late in life [24]. A distinct clinical variant reported in four children is characterized by severe generalized weakness at or soon after birth, respiratory insufficiency, and death in infancy [25, 26].

Differential Diagnosis

Differential diagnosis includes other metabolic myopathies, especially glycogenoses and disorders of lipid metabolism.

On purely clinical grounds, myophosphorylase deficiency is indistinguishable from defects of glycolytic enzymes, such as phosphoglucomutase (PGM), phosphofructokinase (PFK), phosphoglycerate kinase (PGK), phosphoglycerate mutase (PGAM), β-enolase (EN), and lactate dehydrogenase (LDH). Laboratory data may offer useful clues. Patients with PFK deficiency have a compensated hemolytic trait, with hyperbilirubinemia and increased reticulocyte count. With the ischemic forearm exercise test, patients with defects of terminal glycolysis (PGK, PGAM, and LDH deficiencies) have an abnormally low but not absent venous lactate response, and patients with LDH deficiency show a low lactate but excessive pyruvate response.

McArdle's disease should be distinguished from the most common metabolic cause of recurrent myoglobinuria in adults, i.e., CPT II deficiency. In patients with myophospho-

rylase deficiency, myoglobinuria is invariably triggered by exercise, usually of high intensity. Patients with CPT II deficiency, however, have episodes of myoglobinuria not only after exercise (which can be of moderate intensity but is usually prolonged) but also after prolonged fasting without exertion or after a combination of exercise and fasting. Furthermore, the ischemic forearm exercise test is normal in patients with CPT II deficiency.

Exercise-related myoglobinuria may occur in dystrophinopathies and in malignant hyperthermia. In patients with dystrophinopathies, serum CK levels between attacks are usually much higher than in patients with myophosphorylase deficiency, and transmission is X-linked recessive. In patients with malignant hyperthermia, there is usually a family history of characteristic attacks related to the administration of volatile anesthetics, and inheritance is autosomal dominant.

Intolerance to exercise without myoglobinuria can be due to adenylate deaminase (AMPD) deficiency. In patients with AMPD deficiency, the ischemic forearm exercise test causes a normal rise of venous lactate, in contrast with a lack in the rise of ammonia. Because of the high frequency of the adenylate deaminase deficiency trait, its association with myophosphorylase deficiency may occur and this "double trouble" may aggravate the clinical phenotype [17, 18].

Exercise intolerance without myoglobinuria is a common complaint of malingering and hysterical patients and is the cardinal symptom of the "chronic fatigue syndrome." However, these diagnoses should be used prudently and only after finding normal serum CK and lactate levels and a normal ischemic forearm exercise test.

Evaluation and Diagnosis

The ischemic forearm exercise test is a valuable but not specific diagnostic test, because absent or abnormally low rise of venous lactate is seen in all defects of muscle glycogenolysis or glycolysis.

Until recently, definitive diagnosis required muscle biopsy showing lack of myophosphorylase immunostaining. Our present knowledge of multiple genetic defects allows us to identify many suspected patients using genomic DNA from white blood cells. However, it is important to keep in mind the ethnic origin of the patient in order to screen for the most likely mutations.

Treatment and Management

Most patients learn to adapt their lifestyles to their limited exercise tolerance, and, within this framework, they can lead nearly normal lives. Late in the course of the disease, fixed weakness, usually moderate and affecting proximal more than distal muscles, may become a problem.

Acute renal insufficiency is the most important complication, occurring in about 50 % of patients with myoglobinuria. In those cases, abundant fluid intake to induce diuresis may suffice, but renal dialysis is often necessary. Uncomplicated episodes of myoglobinuria are followed by complete functional recovery.

There is no specific therapy for McArdle's disease. Regular moderate aerobic training (resulting in a heart rate of no more than 60–70 % of maximal) is effective because it optimizes alternate fuel delivery and utilization [27]. Another promising therapeutic agent, at least in cases with residual phosphorylase activity, is vitamin B6, because the overall body stores of pyridoxal phosphate (PLP) are depleted in McArdle's disease due to the frequent lack of enzyme protein (to which PLP is bound) [28–30]. Naturally, patients should be warned about the risks of strenuous exercise and advised to seek medical attention at the first appearance of pigmenturia, especially if accompanied by oliguria. Sucrose ingestion shortly before exercise is beneficial but must be used sparingly to avoid weight gain [31]. The ketogenic diet improved exercise tolerance in one patient but has not been subjected to a formal therapeutic trial [32].

There are two spontaneous animal models of McArdle's disease, Charolais cattle and Merino sheep. Recently, a knock-in mouse model of the R50X mutation has been obtained that recapitulates faithfully the human disease [33]. This model will provide valuable information on the pathophysiology and allow therapeutic experimentation.

Phosphoglucomutase (PGM) Deficiency (Glycogenosis Type XIV)

A single patient with biochemically and genetically proven PGM deficiency had two exercise-induced episodes of myoglobinuria [34]. Nonischemic forearm exercise caused normal rise of venous lactate but excessive rise of ammonia. Muscle biopsy showed moderate increase of normal-looking glycogen.

Phosphofructokinase (PFK) Deficiency (Glycogenosis Type VII; Tarui Disease)

Introduction

In its typical presentation, this disorder, first described by Tarui et al. in a Japanese family [35] and soon thereafter by Layzer et al. in an Ashkenazi Jewish American patient [36], is clinically indistinguishable from McArdle's disease. Minor clinical differences include lack of a typical "second wind" phenomenon; more common report of nausea and vomiting accompanying the exercise-induced crises of myalgia, cramps, and weakness; and lower frequency of myoglobinuria attacks. Much more useful in distinguishing PFK deficiency from McArdle's disease are a few simple laboratory tests, such as increased bilirubin concentration and reticulocyte count (reflecting compensated hemolytic anemia).

Etiology and Pathogenesis

The reason for the hemolytic trait in PFK deficiency is that PFK is a tetrameric enzyme under the control of three autosomal loci: a locus on chromosome 1 encodes the muscle (M) subunit; a locus on chromosome 21 encodes the liver (L) subunit; and a locus on chromosome 10 encodes the platelet (P) isozyme [37]. The three subunits are variably expressed in different tissues. Mature human muscle expresses only the M subunit and contains only the homotetramer M4, while erythrocytes express both the M and L subunits and contain five isozymes, the two homotetramers M4 and L4, and three hybrid isoforms. In patients with typical PFK deficiency, genetic defects of the M subunit cause total lack of activity in muscle but only partial PFK deficiency in red blood cells, where the residual activity (approximately 50 % of normal) is accounted for by the L4 isozyme.

The first molecular defect in PFK deficiency (a splice junction mutation resulting in a large deletion) was identified in the Japanese family originally described by Tarui and coworkers [38]. Soon thereafter Raben and her coworkers described two mutations, a splicing defect and a nucleotide deletion, which are common among Ashkenazi Jewish patients [39, 40]. About 20 distinct mutations have been identified in patients of different ethnic origins. The molecular basis of PFK deficiency in patients with infantile or childhood onset remains unknown.

Genetic defects of PFK-M cause virtual absence of PFK in muscle biopsies, when the activity is determined either histochemically [41] or biochemically. The same defects cause partial enzyme deficiencies in erythrocytes, where the L4 homotetramer accounts for the residual activity (about 50 % of the total). Tissues such as liver and platelets express predominantly or exclusively the non-M PFK subunits and are not affected. The lack of clinical cardiomyopathy or encephalopathy, however, is more difficult to explain, because PFK-M accounts for over 90 % of heart PFK and over 50 % of brain PFK [42].

As a consequence of PFK deficiency, glycogen accumulates in muscle, reaching concentrations two to three times greater than normal. Morphologically, the stored glycogen is mostly seen at the periphery of the fibers, where it is revealed by the periodic acid-Schiff (PAS) histochemical reaction and is normally digested by preincubation with diastase. However, a peculiarity of PFK deficiency is the finding, in muscle fibers of some, usually older, patients, of an abnormal polysaccharide, which stains intensely with PAS but is not digested by diastase (*polyglucosan*, PG). Ultrastructurally, PG is composed of finely granular and filamentous material, similar to the amylopectin-like polysaccharide that accumulates in branching enzyme deficiency. The presence of this material has been attributed to the accumulation in muscle of glucose-6-phosphate, an activator of the enzyme glycogen synthetase, which alters the delicate ratio between the two main glycogenosynthetic enzymes, synthetase and branching enzyme [43, 44].

PFK is the rate-limiting enzyme of glycolysis and PFK deficiency blocks glycolysis, thus explaining the flat venous lactate response to forearm ischemic exercise. The accumulation in muscle of phosphorylated monoesters, observed by 31P-nuclear MRS in PFK but not in myophosphorylase deficiency, is easily explained by the sites of the two metabolic blocks: midway in the glycolytic pathway for PFK deficiency and preceding glycolysis for myophosphorylase deficiency.

As in myophosphorylase deficiency, PFK deficiency also impairs both anaerobic and aerobic glycogen metabolism and blocks the fall in muscle pH that normally accompanies heavy exercise. It also results in high levels of adenosine diphosphate (ADP) and increased adenine nucleotide degradation with exaggerated production of ammonia and myogenic hyperuricemia during exercise [45]. It causes substrate-limited oxidative metabolism with fluctuations in exercise and oxidative capacity related to the availability of blood-borne fuels [46]. Finally, PFK deficiency causes exaggerated sympathetic neural responses to exercise associated with enhanced mobilization of extramuscular fuels [47] and exaggerated heart rate, cardiac output, and blood flow relative to the muscle capacity to use oxygen [48].

The negative effect of high-carbohydrate meals on exercise tolerance is attributed to the fact that glucose lowers the blood concentration of free fatty acids and ketones, which are alternative fuels in PFK-deficient patients. Thus, not only is glucose ineffective in alleviating exercise intolerance (in contrast to myophosphorylase deficiency), but it is actually harmful, a situation dubbed "out-of-wind" phenomenon [46].

The pathogenesis of contracture and myoglobinuria in PFK remains unknown: depletion of high-energy phosphate compounds, especially adenosine triphosphate, has long been postulated to occur, but experimental evidence is lacking. Abnormal accumulation of metabolites such as adenosine diphosphate may be an important trigger of premature fatigue.

Clinical Presentation

Typically, there is intolerance to intense exercise, often accompanied by cramps of exercising muscles, which is relieved by rest [37]. Although careful history reveals that exercise intolerance is present since childhood, patients usually do not come to medical attention until adolescence, and the diagnosis is most commonly established in young people. Symptoms are more likely to occur with isometric exercise (such as pushing a stalled car) or intense dynamic exercise (such as walking uphill). The exercise intolerance appears to worsen with high-carbohydrate intake [46]. In contrast to patients with McArdle's disease, patients with PFK deficiency do not experience a "second wind" [49].

A few patients may be jaundiced as a consequence of the hemolytic trait that accompanies PFK-M deficiency, and a few may suffer from gouty arthritis due to hyperuricemia.

Fixed weakness of late onset has been described in a few patients who suffered from exercise intolerance earlier in life [50–54]. A strikingly different clinical presentation consists of severe myopathy in infancy or early childhood, with respiratory failure and death before 2 years of age. This variant has been reported in several children [37]. Although they all had severe myopathy with muscle PFK deficiency, clinical and biochemical data were rather heterogeneous, possibly reflecting different molecular etiologies.

In patients with typical muscle disease, serum CK is usually increased. There is moderate reticulocytosis and increased serum bilirubin, reflecting the hemolytic trait. Uric acid is increased in most patients.

The ischemic forearm exercise test is a useful but not specific test. In patients with PFK-M deficiency (but also in patients with myophosphorylase deficiency or other defects of muscle glycolysis), the increase of venous lactate is absent or inadequate. It is important to keep in mind that the test depends on the patient's ability and willingness to exercise vigorously.

Needle electromyography (EMG) may be normal or show "myopathic" abnormalities (small and short-duration motor unit action potentials). Furthermore, no electrical activity is recorded from maximally shortened muscles during contractures induced by ischemic exercise.

Studies of ^{31}P-nuclear MRS show the accumulation, even with mild exercise, of glycolytic intermediates in the form of phosphorylated monoesters, which occurs also in other defects of glycolysis but not in myophosphorylase deficiency [55].

Differential Diagnosis

The differential diagnosis is similar to that outlined above for McArdle's disease. Few laboratory data may offer useful clues because of the compensated hemolytic anemia that accompanies PFK and aldolase deficiency, with consequent hyperbilirubinemia and increased reticulocyte count. Of all the other glycogenoses, only PGK and aldolase deficiency causes a hemolytic trait [56].

Muscle PFK deficiency should be included in the differential diagnosis of late-onset proximal limb weakness. Usually these patients have a history of lifelong exercise intolerance and cramps. Laboratory signs of a hemolytic trait, an abnormal ischemic forearm exercise test, and abundant polyglucosan in the muscle biopsy are clues to the correct diagnosis.

Evaluation and Diagnosis

The ischemic forearm exercise test is a valuable but not specific diagnostic test. In patients with an abnormal ischemic forearm exercise test (i.e., no rise of venous lactate), laboratory evidence of hemolytic anemia suggests PFK deficiency. Documentation of partial PFK deficiency in erythrocytes bolsters this conclusion, but, until recently, definitive diagnosis required biochemical documentation of the enzyme defect in muscle (keeping in mind that PFK is notoriously labile and PFK deficiency is often a spurious finding if muscle is not flash frozen at the time of biopsy). Present knowledge of multiple molecular defects in the PFK-M gene allows identification of many suspected patients using genomic DNA isolated from white blood cells.

Treatment and Management

Most patients learn to adapt their lifestyles to the limited exercise, and, within this framework, they may lead nearly normal lives. In the fifth or sixth decade, some patients develop proximal limb weakness, which can limit their functional independence but is rarely disabling.

Although myoglobinuria is rare in this condition, acute renal insufficiency may occur in patients with myoglobinuria, requiring forced diuresis or renal dialysis. Uncomplicated episodes of myoglobinuria are followed by complete functional recovery.

There is no specific therapy. Glucose administration is not only useless because the metabolic block is halfway in the glycolytic pathway but is in fact detrimental because glucose lowers the blood concentration of alternative fuels, such as free fatty acids and ketone bodies [46].

High-protein diet and aerobic training [57] have proved beneficial in patients with myophosphorylase deficiency and should be tried in patients with PFK deficiency.

A 2-year-old boy with the infantile form of PFK deficiency benefited remarkably – as had a patient with McArdle's disease [32] – from a ketogenic diet, which was instituted to provide muscle and brain with ketone bodies as alternative fuels [58]. There was clear improvement in strength, EMG features, and electroencephalogram (EEG) pattern. Unfortunately, the child worsened suddenly at 35 months of age and died of complications of pneumonia. Still, a ketogenic diet should be considered in children with the more severe infantile variant of PFK deficiency.

Aldolase (ALD) Deficiency (Glycogenosis Type XII)

Two children with muscle and erythrocyte aldolase deficiency have been reported [59, 60]. Both had transfusion-requiring nonspherocytic hemolytic anemia, muscle weakness, exercise-induced myalgia, and increased serum CK, especially during febrile illnesses (2,620 U/L in one patient and 13,800 U/L in the other). One patient was alive at 4 and ½ years [59], the other died at 4 years during an episode of myoglobinuria and hyperkalemia [60]. Both children were compound heterozygous for mutations in *ALDOA*, the gene that encodes

aldolase A, the only aldolase isozyme present in muscle and erythrocytes. The mutant enzyme is more thermolabile than normal, thus probably explaining the vulnerability of patients to febrile illnesses.

Phosphoglycerate Kinase (PGK) Deficiency (Glycogenosis Type IX)

Primary myopathy is not a common presentation of PGK deficiency, an X-linked recessive disorder most commonly (11 of 33 reported patients) presenting as nonspherocytic hemolytic anemia and central nervous system (CNS) dysfunction. However, purely myopathic presentation is a close second (9 of 33 patients), while isolated blood dyscrasia was reported in 6 patients and the association of myopathy and CNS dysfunction in 4 patients [56]. All myopathic patients complained of exercise intolerance, with cramps and myoglobinuria. Molecular defects were documented in several recent patients, and one, T378P (PGK Afula), caused the peculiar association of myopathy and severe juvenile Parkinsonism [61, 62].

The wide spectrum of clinical phenotypes in PGK deficiency is difficult to explain because PGK is a monomeric enzyme encoded by a single gene on Xq13 and expressed in all tissues except the testis (a testicular isozyme, PGK2, is encoded by a gene on chromosome 19). Different amounts of residual activities in different tissues do not fully explain the clinical heterogeneity [56]. While lack of myoglobinuria in patients with severe hemolytic anemia and brain dysfunction may be attributed to their inability to exercise, it is more difficult to explain the converse situation, lack of blood dyscrasia, or brain disease in patients with myopathy.

Phosphoglycerate Mutase (PGAM) Deficiency (Glycogenosis Type X)

In contrast to PGK deficiency, PGAM deficiency affects only muscle, causing exercise intolerance, cramps, and recurrent myoglobinuria [63]. This is because PGAM is a dimeric enzyme composed of a muscle-specific (M) and a brain-specific (B) subunit, and normal muscle contains predominantly the MM homodimer, which accounts for 95 % of the total activity. The only other tissues containing substantial amounts of the M subunit are heart and sperm, but there is no evidence of cardiomyopathy or male infertility in patients with PGAM deficiency. A dozen patients have been reported, most of them from the United States [64]. All US patients have been black and they harbor one common mutation (W78X) in the *PGAM-M* gene (encoded by a gene on chromosome 7), suggesting a founder effect [64]. Different mutations were found in two Italian families [65, 66], in a Japanese family [67], and in a Pakistani patient [64, 68].

Despite the abundance of PGAM in muscle, we have observed exercise intolerance in heterozygous relatives of PGAM-deficient patients [64, 67]. A second unusual feature of PGAM deficiency is the frequent (33 % of patients) occurrence of tubular aggregates, which have never been associated with other, more common glycogen storage diseases: the relationship between this morphological abnormality and the enzyme defect remains unexplained.

Cycle exercise responses in two patients were markedly different from those of patients with clinically similar McArdle's disease: the PGAM-deficient patients had virtually normal cycle exercise and oxidative capacity, no second wind, and no improvement of their exercise capacity with lipid or lactate supplements [69].

The first mutation in the PGAM-B subunit of PGAM has been reported in a patient with hereditary spherocytosis [70].

Beta-Enolase Deficiency (Glycogenosis Type XIII)

A single patient with adult-onset exercise intolerance and generalized weakness but without episodes of myoglobinuria had a flat lactate response to forearm ischemic exercise. Muscle ultrastructure showed subsarcolemmal accumulations of glycogen, and muscle biochemistry revealed an isolated severe deficiency of enolase activity (5 % of the normal mean). Over 90 % of the muscle enzyme is accounted for by the β-enolase form, which is encoded by the *ENO3* gene. The patient was compound heterozygous for two missense mutations, probably reducing the stability of the mutant enzyme [71].

Lactate Dehydrogenase (LDH) Deficiency (Glycogenosis Type XI)

The discovery of this glycogenosis was due to the astute observation that a patient with myoglobinuria had predictably sky-high values of serum CK but extremely low values of LDH [72]. LDH is a tetrameric enzyme composed of various proportions of a muscle-specific subunit (LDH-A) and a cardiac subunit (LDH-B). LDH-A is encoded by a gene on chromosome 11, and three different mutations have been identified in Japanese patients [73–75], while the only two described white patients had two distinct mutations [76]. In addition to muscle symptoms, three affected Japanese women suffered from dystocia necessitating cesarian sections, and a few patients had dermatologic problems [77].

Muscle Glycogen Synthetase (GS) Deficiency (Glycogenosis Type 0)

Although glycogen synthetase (GS) deficiency of the liver was described almost 50 years ago and aptly called "glycogenosis" (i.e., lack of glycogen), the first cases of muscle glycogenosis were reported only 5 years ago in a Swedish family, and the condition was dubbed glycogenosis type 0 [78]. Of three siblings, a boy died of sudden cardiac arrest at 10 years of age, his brother suffered from exercise intoler-

ance and hypertrophic cardiomyopathy, and his sister was asymptomatic. Muscle biopsies from the younger siblings showed conspicuous lack of glycogen by periodic acid-Schiff histochemistry and by electron microscopy, as well as increased numbers of mitochondria. All three children harbored a homozygous nonsense mutation in the muscle GS gene (*GYS1*), which encodes the muscle and heart isoform of the enzyme.

The fourth patient was an 8-year-old previously asymptomatic boy who unexpectedly collapsed and died while climbing up and down the stairs at school [79]. A sister had died at 6 days of age from unknown cause. Muscle morphology showed mitochondrial proliferation and – in retrospect – lack of glycogen by EM. The diagnosis of glycogenosis type 0 is complicated by the mild muscle symptoms (exercise intolerance), the scarce attention paid by morphologists to lack of glycogen (as opposed to glycogen storage), and the misleading clue of the reactive mitochondrial proliferation.

The fifth patient was a Japanese girl who died at age 12 of cardiac arrest [80]. She had had normal early development but suffered from two generalized tonic-clonic seizures at 2 and 4 years. Since age 5, she had recurrent rather stereotypical syncopal episodes after brief exercise. Loss of consciousness lasted a few hours and was followed by muscle weakness and pain. Muscle biopsy showed lack of glycogen by PAS and negative histochemical stain for myophosphorylase, which depends on the presence of endogenous glycogen. Glycogen synthetase activity was 2 % of normal, and glycogen concentration was barely detectable. The modified Gomori trichrome stain showed abundant subsarcolemmal mitochondria. Molecular genetic analysis revealed a compound heterozygous mutation in *GYS1*.

Glycogenin Deficiency (Glycogenosis Type XV)

The primer of glycogen synthesis is a glycosyltransferase that uses uridine diphosphate glucose as a substrate in an autoglycosylation reaction to generate a short (about 10 glucosyl units) glucose polymer, the kernel of the new glycogen molecule. There are two isoforms of glycogenin, the muscle isozyme glycogenin-1 and the liver isozyme glycogenin-2, which are also expressed partially in the heart.

The first pathogenic mutation in the gene encoding glycogenin-1 (*GYG1*) was described 2 years ago in a young man who was slower than his peers as a child, suffered from exertional dyspnea, and at age 27 had a life-threatening episode of ventricular fibrillation and was equipped with a permanent defibrillator [81]. Skeletal muscle was devoid of glycogen, whereas the heart showed large accumulation of a poorly structured PAS-positive material, presumably a novel form of abnormal polysaccharide due to the presence in the heart of some glycogenin.

Disorders of Lipid Metabolism

Carnitine Palmitoyltransferase II (CPT II) Deficiency

Introduction

CPT II deficiency (rather, CPT deficiency, because at the time we could not distinguish CPT I and CPT II activities) was identified in 1973 in two brothers with recurrent exercise-induced myoglobinuria whose muscle biopsies had shown no glycogen storage and normal phosphorylase and PFK activities [82, 83]. A hindsight reevaluation of their clinical histories revealed interesting differences from patients with glycogenoses: (1) neither brother had any weakness nor any problem with brief intense exercise; (2) neither complained of cramps but described muscle tenderness preceding myoglobinuria; (3) both had problems with prolonged and not necessarily strenuous exercise; (4) both identified fasting as a precipitating factor, usually in combination with exercise. Their histories summarize the main clinical features of CPT II deficiency, except that additional precipitating factors may also include emotional stress, lack of sleep, and cold exposure.

Etiology and Pathogenesis

CPT II is a key enzyme in the *carnitine cycle*, needed for the transport of long-chain fatty acids from the cytosol into the mitochondrion. The carnitine cycle is comprised of four elements: (1) carnitine palmitoyltransferase I (CPT I), on the inner aspect of the outer mitochondrial membrane, which catalyzes the esterification of palmitoyl-CoA to palmitoylcarnitine; (2) the carrier molecule L-carnitine; (3) carnitine palmitoyltransferase II (CPT II), on the inner aspect of the inner mitochondrial membrane, which catalyzes the reverse reaction of CPT I, regenerating palmitoyl-CoA and liberating carnitine; and (4) a carnitine-acylcarnitine translocase (CACT), capable of exchanging acylcarnitine and carnitine across the inner mitochondrial membrane (Fig. 63.2).

Although the existence of two CPT enzymes, one outside and the other inside the inner mitochondrial membrane, was never questioned, for many years it was uncertain whether the two enzymes were distinct proteins under separate genetic control or a single protein with different milieus. It is now known that CPT I and CPT II are different proteins: CPT I is encoded by a gene on chromosome 11q [84], while CPT II is encoded by a gene on chromosome 1p32 [85].

Although by 1990 it was apparent that CPT deficiency was an important cause of recurrent myoglobinuria [23], a vexing question was why the defect of such a key enzyme in lipid metabolism should affect skeletal muscle selectively, especially since there was no evidence for the existence of tissue-specific CPT isozymes. The situation is now clearer. CPT I deficiency does, in fact, cause life-threatening hypoketotic hypoglycemia of infancy induced by fasting and often accompanied by lethargy, coma, and seizures [86]. CPT II

deficiency can also cause two different and severe infantile phenotypes: (1) a rapidly lethal neonatal form with hypoketotic hypoglycemia, generalized steatosis, and multiple malformations and (2) an infantile hepatomuscular form characterized by episodes of hypoketotic hypoglycemia, lethargy, seizures, hepatomegaly, cardiomegaly, and cardiac arrhythmias [86]. However, these variants are rare compared to the adult myopathic phenotype. Molecular genetic analysis has revealed more than 30 pathogenic mutations in patients with myopathic CPT II deficiency. Of these, the S113L mutation is common in American patients [87], and screening genomic DNA from white blood cells in suspected patients may eliminate the need for a muscle biopsy. The large predominance of affected men in CPT II deficiency has been perplexing and has suggested a hormonal influence; it is, therefore, interesting that studies of the CPT II promoter region do, in fact, suggest that gene expression may be hormonally regulated [88].

Clinical Presentation

The more common, myopathic form of CPT II deficiency usually presents in adolescents or young adults, predominantly males, with recurrent myoglobinuria following prolonged, though not necessarily strenuous, exercise, prolonged fasting, or a combination of the two conditions. Other precipitating factors include cold exposure, lack of sleep, and, especially in children, intercurrent illnesses with high fever. Between attacks, these patients have normal physical and neurological exams. At difference from the glycogenoses, the attacks of myoglobinuria are not heralded by painful cramps. In addition, exercising muscles are not necessarily the only ones undergoing acute necrosis, and a few patients have been admitted to the hospital in respiratory distress. Another distinguishing feature from the glycogenoses is the normal level of serum CK between attacks of myoglobinuria. Muscle biopsy is usually normal.

Differential Diagnosis

The differential diagnosis includes other inborn errors of metabolism characterized by recurrent myoglobinuria, especially glycogenoses and defects of the mitochondrial respiratory chain. Several features distinguish CPT II deficiency from the glycogenoses: (1) whereas in the glycogenoses, myoglobinuria is always triggered by exercise, in CPT II deficiency, myoglobinuria may follow prolonged fasting or, less frequently, cold exposure, lack of sleep, emotional stress, or intercurrent illness; (2) painful cramps of exercising muscles are not described by patients with CPT II deficiency, who, therefore, lack a useful warning sign of impending myoglobinuria; (3) fixed weakness is much less common in CPT II deficiency than in the glycogenoses; (4) between episodes of myoglobinuria, serum CK is usually normal in CPT II deficiency while it is variably but consistently increased in the glycogenoses. Patients with defects in the mitochondrial respiratory chain typically complain of exercise intolerance and premature fatigue, whereas patients with CPT II deficiency have no problem with brief exercise, even when this is strenuous, and their everyday life is usually normal. CPT II deficiency is a "silent disease" that manifests itself only in extreme situations because the presence of 15–20 % residual enzyme activity in muscle is sufficient to support fat oxidation at rest but does not allow the increase in fat oxidation needed to supply muscle energy during dynamic exercise [89]. Also, patients with CPT II deficiency have no central nervous system involvement, unlike patients with CoQ10 deficiency, in whom recurrent myoglobinuria is usually associated with seizures, ataxia, or mental retardation [90].

Therapy is based on a low-fat, high-carbohydrate dietary regimen, medium-chain triglyceride (MCT) instead of long-chain oil, or triheptanoin as an anaplerotic compound [91]. Another therapeutic approach is based on the upregulation of mitochondrial biogenesis by bezafibrate [92].

Very Long-Chain Acyl-CoA Dehydrogenase (VLCAD) Deficiency

The clinical picture of CPT II deficiency may be indistinguishable from that of some defects in the first step of ß-oxidation, including very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency and trifunctional protein deficiency.

VLCAD is associated with the inner mitochondrial membrane and is specific for C14–C24 fatty acyl-CoAs. Age at onset and clinical severity of VLCAD deficiency depend on the amount of residual enzyme activity. A severe infantile form is characterized by cardiomyopathy and high mortality. A milder childhood form with hypoketotic hypoglycemia and rare cardiac involvement has a more benign outcome. The adult myopathic form causes recurrent myoglobinuria triggered by prolonged exercise or fasting, thus closely simulating CPT II deficiency [86, 93]. The diagnosis can be made by tandem mass spectroscopy detecting long-chain acylcarnitines (especially C14) in blood or in fibroblasts incubated with long-chain acylcarnitines [94].

The muscle biopsy is usually normal or nonspecifically altered as in patients with CPT II deficiency, but the diagnosis can be established by immunohistochemistry [93].

Mitochondrial Trifunctional Protein (MTP) Deficiency

Mitochondrial trifunctional protein (MTP) comprises three enzyme reactions, enoyl-CoA hydratase, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), and acyl thiolase, and generates acetyl-CoA and an acyl-CoA shortened by two carbon atoms, which is ready to enter a new β-oxidation cycle. Most patients with MTP have isolated LCHAD

deficiency, usually due to one mutation (E510Q) in the *HDHA* gene encoding the α subunit of the enzyme [95]. A fatal infantile presentation is dominated by encephalopathy and hepatopathy. The childhood presentation is characterized by recurrent myoglobinuria, often accompanied by cardiomyopathy, pigmentary retinopathy, and sensorimotor axonal neuropathy. The episodes of myoglobinuria may be precipitated by exercise, fasting, or intercurrent illnesses and are often accompanied by life-threatening respiratory distress. Because of the concurrent neuropathy, the muscle biopsy shows features of denervation but only rarely lipid storage.

Phosphatidic Acid Phosphatase (LIPIN) Deficiency

It has long been known that many cases of recurrent myoglobinuria, especially in children, go undiagnosed at the molecular level [96]. It is, therefore, important that a new cause of childhood myoglobinuria has now been added, mutations in the *LPIN1* gene that encodes the muscle-specific phosphatidic acid phosphatase: this enzyme converts phosphatidate to diacylglycerol in the triacylglycerol pathway [97]. Affected children had episodes of myoglobinuria between 15 months and 7 years of age, usually precipitated by febrile illnesses. Muscle biopsy was essentially normal. It has been proposed that the enzyme defect during stress periods causes accumulation of lysophospholipids, which act as detergents, thus favoring muscle breakdown.

Respiratory Chain Defects

While exercise intolerance is a common complaint in patients with mitochondrial encephalomyopathies, it is often overshadowed by other symptoms and signs [98]. Only relatively recently we have come to appreciate that exercise intolerance, myalgia, and myoglobinuria may be the sole presentation of respiratory chain defects. These may affect complex I, complex III, or complex IV, although they seem to be more commonly associated with complex III deficiency [2, 99].

Complex I Deficiency

Increased blood lactic acid at rest (5.2 mEq/L; normal, less than 2.2) was the only objective indication for a muscle biopsy in a 38-year-old man who complained of severe lifelong exercise intolerance [100]. He was otherwise completely normal, including muscle strength and bulk, resting serum CK, and EMG. He had never noticed pigmenturia, and his mother and siblings had no muscle problems. The muscle biopsy showed intensely cytochrome *c* oxidase (COX)-positive ragged-red fibers (RRF) and an isolated moderately severe defect of complex I activity. Molecular analysis identified a heteroplasmic (54 % of muscle mitochondrial DNA) nonsense mutation (G11832A) in the gene encoding subunit 4 of complex I (ND4). Single-fiber polymerase chain reaction (PCR) showed that the mutation was much more abundant in RRF than in normal fibers, thus confirming the pathogenicity of this base change.

In 1990, Bet et al. [101] had reported a similar case: a 43-year-old man with lifelong exercise intolerance, myalgia, mild proximal limb weakness, and negative family history. His muscle biopsy also showed abundant RRF and an isolated defect of complex I activity (40 % of normal). Molecular analysis of his muscle revealed a novel pathogenic mutation in the ND1 gene of mtDNA, a seven nucleotide intragenic inversion that alters three highly conserved amino acids [102].

Complex III Deficiency

In 1993, Bouzidi et al. [99] found low complex III activity in the muscle of a 25-year-old man with exercise intolerance in whom they later identified a missense mutation (G15615A) in the cytochrome *b* gene (the only mtDNA-encoded subunit of complex III) [100]. In the years that followed, 14 more patients were reported with different mutations in the cytochrome *b* gene of mtDNA (*MTCYB*) but with the same clinical picture: isolated myopathy with exercise intolerance and sometimes myoglobinuria [99]. The muscle biopsy in all patients showed complex III deficiency and "ragged-blue" fibers with the SDH stain, which were also COX positive. The lack of maternal inheritance and of multisystem involvement keeps these patients under the radar for the diagnosis of mtDNA-related disorders.

Complex IV (COX) Deficiency

Starting at age 15, a 16-year-old woman had four episodes of muscle cramps and myoglobinuria precipitated by prolonged exercise or viral illness [103]. Rather surprisingly, she had only "mildly reduced endurance." Between attacks, both physical and neurological exams were normal, as were routine laboratory tests, including serum CK and lactate. Interestingly, no tissue other than muscle was clinically affected, and family history was entirely negative. A muscle biopsy at age 16 showed numerous ragged-red fibers, which stained intensely for the succinate dehydrogenase (SDH) reaction but not at all for the cytochrome *c* oxidase reaction. Biochemical analysis showed a marked and isolated defect of COX activity (14 % of normal), and molecular genetic analysis identified a 15-bp microdeletion in the mtDNA gene encoding subunit III of COX (*COX III*). The deletion affected 92 % of the mtDNA in muscle and 0.7 % in leukocytes but was not detected in the patient's fibroblasts or in her mother's leukocytes.

We studied a very similar case [104], except that our patient was a 34-year-old man who had suffered from exercise intolerance since childhood. He also had an isolated myopathy with recurrent episodes of exercise-induced myoglobinuria, normal neurological exam between attacks, and

Table 63.1 Pathogenic mutations in mitochondrial DNA protein-coding genes causing exercise intolerance, weakness, and myoglobinuria

Respiratory complex	Age, sex	Mutation	AA change	Mut. load	Inher.	Reference
I-ND4	38, M	c.11832G>A	W358X	54	S	[100]
I-ND1	43, M	7 nt inversion	NLA>GKV 199-201	80	S	[102]
III-MTCYB	nd	c.15150G>A	p.W135X	60	S	[190]
	nd	c.15197T>C	p.G165X	80	S	
	18, M	c.14849T>C	p.S35P	85	S	[191]
	38, F	c.15762G>A	p.G339E	85	S	[192]
	27, M	c.15059G>A	p.G190X	63	S	[193]
	43, M	c.15498_15522del	p.G251_A259delinsA	50	S	[2]
	52, F	c.14846G>A	p.G34S	85	S	
	38, F	c.15168G>A	p.W141X	70	S	
	32, M	c.15084G>A	p.W113X	87	S	
	51, M	c.15723G>A	p.W326X	87	S	
	40, F	c.15170G>A	p.G142X	>99	S	[194]
	24, F	c.15800C>T	p.Q352X	45	S	[195]
	19, F	c.15761G>A	p.G339X	73	S	[196]
	29, M	c.15615G>A	p.G290D	80	S	[197]
IV-COIII	16, F	15-bp deletion	5 aa deletion	92	S	[103]
IV-COI	34, M	c.5920G>A	W---X	61	S	[104]
IV-COII	14, M	c.7671T>A	M29L	90	S	[105]
IV-COI	34, F	c.6708G>A	G269X	90	S	[106]
IV-COII	30, M	c.7989T>C		n.d.	S	[107]

negative family history. Muscle biopsy showed scattered RRF but numerous COX-negative fibers severely reduced COX activity (13 % of normal), and molecular studies revealed a heteroplasmic nonsense mutation (G5920A) in the *COX I* gene of mtDNA.

A third case of isolated myopathy due to a mutation in *COX II* was described in a 14-year-old boy with mild weakness of shoulder and pelvic girdle muscle and exercise intolerance without myoglobinuria [105]. Family history was negative, and although lactate in the CSF was mildly elevated, there was no evidence of brain dysfunction and brain MRI was negative.

A fourth case of isolated mitochondrial myopathy with weakness, myalgia, and one episode of myoglobinuria regarded a 34-year-old woman with no family history of similar disorders. Muscle histochemistry showed over 90 % COX-deficient fibers, and molecular genetic analysis identified a heteroplasmic nonsense mutation in *COX I* [106].

Reevaluation of a 30-year-old man with exercise-related recurrent myoglobinuria and no family history revealed a mutation (m.7989T>C) in subunit II of COX. Single-fiber PCR showed that COX-negative fibers contained >90 % mutant mtDNAs compared to 52 % in COX-positive fibers [107].

The clinical and molecular characteristics of all reported patients with exercise intolerance and mutations in mtDNA protein-coding genes are summarized in Table 63.1. All patients had pure myopathy, with no evidence of multisystem involvement. The myopathy was dominated by exercise intolerance with premature fatigue and myalgia. Myoglobinuria occurred in a few patients. Fixed weakness was also rare and appeared nonprogressive. All patients were sporadic cases with no family history of similar disorders.

Iron-Sulfur Cluster Scaffold Protein (ISCU) Deficiency

In 1991 and 1993, Haller and coworkers described a young man with lifelong exercise intolerance, dyspnea, cardiac palpitations, and episodes of myoglobinuria [108, 109]. The syndrome, which is common in northern Sweden, was dubbed "mitochondrial myopathy with succinate dehydrogenase and aconitase deficiency" and correctly attributed to altered metabolism of iron-sulfur (Fe-S) cluster proteins, which are prosthetic groups present in complexes I, II, and III and in the Krebs cycle enzyme aconitase. Accordingly, histochemical analysis of muscle showed SDH deficiency, and biochemical analysis showed deficiencies of complex II, complex III, and aconitase. In 2008, homozygosity mapping revealed a single pathogenic mutation in the *ISCU* gene in three Swedish families [110]. Two years later, Kollberg et al. [111] defined SDH deficiency and accumulation of iron in muscle as the morphological hallmarks of the disease. They also observed that these features transiently disappeared after rhabdomyolysis, warning that false-negative histochemical results may be obtained if muscle biopsies are taken soon after episodes of myoglobinuria.

Coenzyme Q10 (CoQ10) Deficiency

CoQ10, which is encoded by the nuclear genome, transfers electrons from complex I and complex II to complex III (Fig. 63.2). CoQ10 is also the final acceptor of electrons

derived from ß-oxidation via the electron transfer flavoprotein (ETF) and the ETF dehydrogenase (Fig. 63.2), and, in this sense, it is part of lipid metabolism. The coexistence of ragged-red fibers and lipid storage in muscle biopsies of patients with the myopathic variant of CoQ10 deficiency underscores the dual metabolic nature of this disorder. Also, CoQ10 deficiency, though first described in 1989 [112], was "rediscovered" in recent years and may have been underestimated as a cause of recurrent myoglobinuria [113, 114]. In the five patients described thus far, primary CoQ10 deficiency in muscle was characterized by the triad: (1) exercise intolerance and recurrent myoglobinuria; (2) central nervous system dysfunction, with seizures or mental retardation; and (3) RRF and markedly increased lipid droplets in the muscle biopsy. Biochemical analysis of muscle shows a partial block at the level of complex III and variably severe deficiency of CoQ10.

Isolated lipid storage myopathy without myoglobinuria has been described in a few patients [115–118]. The report by Gempel et al. [118] implied that myopathic CoQ10 deficiency could be secondary to multiple acyl-CoA dehydrogenase deficiency (MADD) due to mutations in the gene encoding the electron-transferring-flavoprotein dehydrogenase (*ETFDH*), but this generalization has been contradicted [119, 120].

More common and severe presentations of primary CoQ10 deficiency include infantile encephalomyopathy, childhood-onset cerebellar atrophy and ataxia, and glomerulopathy [90].

Miscellaneous

Adenylate Deaminase Deficiency

Adenylate deaminase (AMPD) deficiency is a muscle disease with variable manifestations [121]. Some patients have no symptoms. The most common complaints are muscle cramping, stiffness, or pain after exercise. In others, fixed weakness, hyporeflexia, paresthesias, periodic paralysis, and repeated infections in childhood have been reported. The serum CK concentration may be increased, but myoglobinuria is extremely rare. Muscle biopsy is usually normal, but a specific histochemical stain facilitates the diagnosis and shows that the enzyme defect is often encountered in virtually asymptomatic subjects. In keeping with this observation, molecular genetic analysis has shown that a common mutation (Q12X) in the *AMPD-1* gene, which encodes the muscle isozyme, can explain the 2 % incidence of myoadenylate deficiency encountered in the general population. As mentioned above, two children, who were homozygous for pathogenic mutations in the myophosphorylase gene (glycogenosis type V, McArdle's disease) or in the muscle phosphofructokinase gene (glycogenosis type VII, Tarui disease), were also homozygous for the *AMPD-1* mutation. Interestingly, both children had unusually severe phenotypes, with early episodes of myoglobinuria. This suggests that the per se mild AMPD-1 mutation may have worsened the clinical expression of the two glycogenoses. Thus, it is important to keep in mind the possibility of genetic "double trouble" between adenylate deaminase deficiency and other metabolic errors.

Disorders Causing Fixed Weakness

All but one of the glycogenoses causing exercise intolerance and myoglobinuria are due to muscle-specific enzyme defects, whereas all but one of those causing fixed weakness are due to generalized enzyme defects (Fig. 63.3). This suggests the possibility that factors other than defective substrate utilization may play a role in the etiology of weakness. One such obvious factor is the severe involvement of spinal motor neurons in the infantile form of acid maltase deficiency (Pompe disease) [122, 123]. A more subtle neurogenic involvement may occur in debrancher deficiency, where glycogen storage has been documented in intramuscular nerves [124] and in both Schwann cells and axons of sural nerve biopsies [125, 126]. Subclinical cardiomyopathy may contribute to weakness in both debrancher [127] and, possibly, brancher deficiencies. Similarly, liver dysfunction with hypoglycemia in debrancher deficiency, and with chronic hepatic failure in brancher deficiency, will undoubtedly contribute to the lack of stamina of these patients.

Whereas glycogen storage is mild (sometimes hardly detectable) in the glycogenoses associated with exercise intolerance, it tends to be more severe in the glycogenoses associated with weakness, especially in the infantile and juvenile forms of acid maltase deficiency and in debrancher deficiency.

Glycogenoses

Acid Maltase (α-Glucosidase, GAA deficiency), Glycogenosis Type II

Introduction The fatal infantile form of acid maltase (acid α-glucosidase, GAA) deficiency was first described in 1932 in separate papers by Pompe and Putschar, who called attention to the severe glycogen storage in the heart [128, 129]. In 1963, Hers documented the defect of GAA in liver, heart, and skeletal muscle of children with "cardiomegaly glycogenosis" [130] and, together with Lejeune and Tines-Sempoux, showed that GAA was a lysosomal enzyme [131]. Thus, GAA deficiency became the prototype of inborn lysosomal diseases [132]. In the years that followed, GAA deficiency was recognized in both children and adults with myopathy but without cardiac involvement, and, by 1973, the three main clinical variants of GAA deficiency were clearly defined [133]. The eponym *Pompe disease* should be limited to the infantile form, but it is now used to indicate the disease as a whole.

Etiology and Pathogenesis Acid maltase deficiency is a hereditary condition transmitted as an autosomal recessive trait. The gene encoding GAA is localized on the long arm of chromosome 17, and a variety of molecular defects have been described in both infants and adults [134].

The genotype/phenotype correlation is hard to establish, partly because of the frequency of compound heterozygotes. In general, there is good correlation between the severity of the mutation and the severity of the clinical phenotype. Thus, deletions and nonsense mutations are usually associated with infantile GAA deficiency, whereas "leaky" mutations, such as the common IVS1(−13T->G) splice site mutation, are associated with the adult-onset variant of the disease.

GAA has both α-1,4-glucosidase and α-1,6-glucosidase activity and is, therefore, capable of digesting glycogen completely to glucose. Like other lysosomal enzymes, GAA, a glycoprotein, is synthesized as a high-molecular-weight precursor, which is extensively modified posttranslationally as the protein travels from ribosomes to primary lysosomes through endoplasmic reticulum and Golgi apparatus. Posttranslational processing includes glycosylation, acquisition of a mannose-6-phosphate recognition marker, phosphorylation, and proteolytic trimming. Through these steps, in cultured fibroblasts, a 95-kd precursor is converted into two enzymatically active 76- and 70-kDa glycoproteins [135, 136].

One intriguing question is: why non-muscle tissues in childhood and adult acid maltase deficiency are spared? In agreement with the concept that there are no tissue-specific isozymes of acid maltase, GAA activity is markedly decreased in all tissues not only in infantile acid maltase deficiency but also in the adult form [137]. The difference in clinical expression and pathology between infantile and later-onset forms of GAA deficiency has been attributed to the presence of a small but crucial amount of residual GAA activity in childhood and adult cases but not in infantile cases. The difference in residual activity, first observed in muscle specimens [138], is more evident in fibroblast and muscle cultures from patients with the different variants [139].

A second question concerns the pathogenesis of weakness. Muscle biopsy shows a vacuolar myopathy in all three forms of AMD. In the infantile form, all muscles and all fibers contain many, often confluent vacuoles, resulting in a "lacework" appearance. In childhood and adult GAA deficiency, vacuoles are less numerous and tend to be smaller. Furthermore, in the adult variant, biopsies from clinically unaffected muscles may appear normal, despite the marked decrease of GAA activity. The vacuoles contain PAS-positive material and stain intensely for acid phosphatase, another lysosomal enzyme. The positive acid phosphatase stain is a useful diagnostic clue in otherwise normal biopsy specimens. In agreement with morphological appearance, glycogen content is massively increased in muscle from patients with infantile GAA deficiency, often reaching a level ten times higher than normal. Muscle glycogen concentrations are generally lower in the childhood form and may be normal in the adult variant.

A central riddle regards the pathogenesis of weakness: is it simply due to the mechanical disarray of the contractile system caused by the glycogen-laden lysosomes or rather to an energy defect? The energetic hypothesis is supported by the notion that GAA activity normally releases glucose into the cytoplasm. A compelling scenario for the pathogenesis of acid maltase deficiency, as well as other lysosomal diseases [140], involves a disruption of the vital autophagic process, with accumulation of autophagosomes resulting from defective autophagosome-lysosome fusion [140, 141]. In fact, Nishino and colleagues went as far as stating that "Pompe disease can no longer be viewed simply as a glycogen storage disease," but rather as a problem in handling excessive numbers of autophagosomes [142].

In infantile GAA deficiency, accumulation of free and intralysosomal glycogen occurs in all tissues and is especially severe in the heart. In the CNS, anterior horn cells of the spinal cord and neurons of brainstem nuclei are more severely affected than neurons of the cerebral cortex [122, 123, 143]. This probably contributes to the flaccid quadriplegia of these infants and may explain why mental retardation does not become apparent within their short life span.

Clinical Presentation *Infantile Pompe disease* manifests in the first weeks or months of life with diffuse hypotonia and weakness, giving these infants a "rag doll" appearance (floppy infant syndrome). However, muscle bulk may be increased, and macroglossia is common. There is massive cardiomegaly and less severe hepatomegaly. Despite their extreme weakness, these infants are usually alert and interested in their environment. Respiratory muscle weakness increases susceptibility to pulmonary infections, and death due to cardiac or respiratory failure occurs invariably before 2 years of age and usually within the first year.

Glycemia and the response of blood glucose to epinephrine or glucagon administration are normal. Serum CK is markedly increased. Needle EMG shows myopathic motor unit action potentials (MUAPs) associated with fibrillation potentials, positive waves, complex repetitive discharges, and myotonic discharges. Electrocardiography shows a short P-R interval, giant QRS complexes, and signs of left ventricular or biventricular hypertrophy. Chest radiography shows massive cardiac enlargement.

In *childhood GAA deficiency*, weakness starts in infancy or early childhood but is less severe than in the infantile form, and progression is slower. Motor milestones may be delayed. Some patients have calf enlargement and, in boys, the clinical picture may suggest the diagnosis of Duchenne

muscular dystrophy. Respiratory muscles are affected early and respiratory failure is the usual cause of death within the second or third decade. There is no cardiomegaly, and both hepatomegaly and tongue enlargement are much less frequent than in infantile AMD.

Serum CK is variably but consistently increased. On needle EMG, the association of myopathic MUAPs with signs of abnormal irritability and myotonic discharges should raise the suspicion of acid maltase deficiency.

The clinical hallmark of *adult-onset GAA deficiency* is a slowly progressive myopathy, starting in the third or fourth decade, but occasionally later, including a few patients with onset in the sixth or seventh decade. Weakness predominates in truncal and proximal muscles, sometimes involving bulbar muscles and causing dysphagia. Respiratory muscles are selectively affected, and respiratory insufficiency may be the presenting complaint, with morning headache or exertional dyspnea [144, 145]. The initial diagnosis in most cases is limb-girdle dystrophy or polymyositis. There is no visceromegaly. Glycogen accumulation in the smooth muscle of cerebral arteries may lead to the formation of intracranial aneurysms, which have been described in a few families [146].

Serum CK is variably increased in most patients. The ischemic forearm exercise test causes a normal rise of venous lactate, indicating that phosphorolytic glycogen breakdown and glycolysis are normal. On needle EMG, fibrillation potentials, positive waves, and myotonic discharges are useful clues to the diagnosis and may be more evident in paraspinal muscles. Studies of pulmonary function show restrictive ventilatory insufficiency, with reduced maximal static inspiratory and expiratory pressures, and early diaphragmatic fatigue. Whole-body muscle MRI can provide an accurate picture of the muscles involved in the course of the disease [147].

Differential Diagnosis Infantile GAA deficiency has to be distinguished from other causes of the floppy infant syndrome, including spinal muscular atrophy type I (Werdnig-Hoffmann disease) and other metabolic or congenital myopathies. The massive cardiomegaly distinguishes acid maltase deficiency from most of these disorders. Some infants with cytochrome *c* oxidase deficiency have both myopathy and cardiomyopathy, but cardiomegaly is usually less marked and there is lactic acidosis. Muscle biopsy is virtually pathognomonic for acid maltase deficiency.

AMP-dependent protein kinase (AMP) deficiency can present with massive glycogen storage and cardiomegaly in infancy, but muscle weakness is modest and muscle biopsy shows only minor glycogen storage [5].

Childhood GAA deficiency may simulate Duchenne muscular dystrophy in boys with calf pseudohypertrophy. In Duchenne muscular dystrophy, however, family history may suggest X-linked transmission, serum CK tends to be higher, and needle EMG does not show myotonic discharges. Muscle biopsy clearly differentiates the two conditions.

Other metabolic myopathies of childhood include debrancher deficiency, phosphorylase *b* kinase deficiency, and carnitine deficiency. Debrancher deficiency myopathy is often accompanied by hepatomegaly and fasting hypoglycemia; there is no response of blood glucose to epinephrine or glucagon administration, and if feasible to do, the ischemic forearm exercise test shows no rise of venous lactate. Differential diagnosis from phosphorylase *b* kinase deficiency and from carnitine deficiency requires morphological and biochemical studies of muscle.

Muscle biopsy is also required to distinguish childhood GAA deficiency from congenital myopathies, because several patients with Pompe disease have a thin body habitus, elongated facies, and high-arched palate that are commonly seen in congenital myopathies, such as myotubular myopathy, nemaline myopathy, and central core disease.

Adult GAA deficiency is an important consideration in patients thought to have limb-girdle dystrophy or polymyositis. The early and often selective involvement of respiratory muscles and the EMG features, especially in paraspinal muscles (fibrillation potentials, positive waves, complex repetitive discharges, and myotonic discharges), are useful clues to acid maltase deficiency [145].

A disorder resembling acid maltase deficiency but not due to acid maltase deficiency is characterized by X-linked dominant "cardiomyopathy, mental retardation, and autophagic vacuolar myopathy" [148]. The molecular defects in this disorder involve the *LAMP-2* gene, which encodes a major lysosomal membrane protein [149].

Evaluation and Diagnosis Diagnostic workup includes serum CK (variably increased in all three forms of GAA deficiency), electrocardiogram (EKG) and chest radiogram in the infantile form, pulmonary function tests in childhood and adult acid maltase deficiency, MRI of spine/paraspinal muscles and needle EMG of paraspinal muscles in the adult variant (looking for fibrillation potentials and myotonic discharges), ischemic forearm exercise test (to exclude other glycogenolytic or glycolytic defects), and muscle biopsy.

In all three forms of acid maltase deficiency, short of a muscle biopsy, the diagnosis may be aided by determination of acid and neutral maltase activities (and calculation of the acid/neutral activity ratio) in lymphocytes [150].

Treatment and Management A generally effective enzyme replacement therapy (ERT) with recombinant human GAA (rhGAA) is now available and widely utilized. There is already a vast literature on the subject particularly in the infantile form of the disease [151]. A few problems have emerged recently, such as the immune reaction to rhGAA in

infants with null mutations and no GAA protein (i.e., no cross-reactive immunological material, CRIM) [152]. A multicentric, randomized, placebo-controlled trial of alglucosidase alfa, a recombinant human GAA, was conducted in 90 patients (8 years of age or older) with the late-onset form of Pompe disease [153]. The two primary end points were motor (6-min walk test) and respiratory (percentage of predicted forced vital capacity). Secondary and tertiary end points were quantitative muscle testing and maximum inspiratory and expiratory pressures. Treatment with rhGAA for 78 weeks was associated with improved walking distance and stabilization of pulmonary function over a period of 18 months. The results were modest but important considering the slow but inexorable progression of the disease [154]. One question remains unanswered: whether to start ERT in presymptomatic late-onset patients [155].

The response of patients with infantile Pompe disease has been much more patchy, as illustrated by the first four children treated [156, 157]. All four children survived until 4 years or longer, thus meeting the provisional end point of the trial. Three of the children are still alive more than 11 years later, but the two who started therapy late (7 and 8 months of age) are paralytic and ventilator dependent. The child who started therapy at 3 months is still able to walk at age 11 and goes to school, although he has some weakness [151]. The UK experience with 20 infants treated between 2000 and 2009 is equally tattered: overall ventilator-free survival was 35 %; 35 % died at a median age of 10 months; 30 % were alive but ventilator dependent. Again, age and clinical severity at the beginning of treatment were of paramount importance. The authors wisely conclude that ERT for infants with Pompe disease has to be pondered carefully [158].

Patients with childhood or adult AMD and respiratory insufficiency may need intermittent or permanent mechanically assisted ventilation [159]. Controversial results have been obtained with high-protein diet and aerobic exercise, which appears to improve strength and respiratory function in some, but not all patients [160].

Debrancher Deficiency (Glycogenosis Type III)

This is usually a benign disease of childhood characterized by hepatomegaly, growth retardation, and fasting hypoglycemia, which tend to resolve around puberty [161]. However, later in life (third or fourth decade), a small proportion of patients develops a myopathy, which is often more distal than proximal. Wasting of leg muscles and intrinsic hand muscles often leads to the diagnosis of motor neuron disease or peripheral neuropathy. This clinical picture, the "mixed" myopathic and neurogenic EMG pattern, and the often slowed nerve conduction velocity reinforce the impression that weakness in these patients may have a neurogenic component [162, 163]. It is, however, surprising that an enzyme that acts "hand in hand" with muscle phosphorylase in the degradation of glycogen should not cause exercise intolerance and myoglobinuria, at least in those patients that are not severely weak.

The debranching enzyme is a single protein that catalyzes two enzymatic reactions, an oligo-1,4-1,4-glucantransferase and an amylo-1,6-glucosidase, and is encoded by a gene on chromosome 1p21. There are three biochemical variants: a rare deficiency of the transferase activity alone (type IIId), a common deficiency of both enzyme activities in both muscle and liver (type IIIa), and a less frequent deficiency of both enzyme activities in liver but not in muscle (type IIIb) [37]. Numerous mutations have been identified: although the molecular basis for the differential tissue involvement in patients with the IIIa and IIIb variants remains unclear, it is interesting that most patients with the IIIb variant (but none with the IIIa variant) have mutations in exon 3 of the debrancher gene, which are expected to result in truncated proteins [164].

Glycogen Branching Enzyme (GBE) Deficiency (Glycogenosis Type IV)

This glycogenosis has a surprising spectrum of clinical phenotypes, considering that GBE is a single polypeptide (encoded by a gene on chromosome 3). The enzyme defect can be silent or affect predominantly the liver, the heart, skeletal muscle, or the brain [37]. GBE deficiency results in the deposition of an amylopectin-like polysaccharide that has fewer branching points and longer outer chains than normal glycogen and is known as polyglucosan (PG). PG is PAS positive and only partially digested by diastase, which makes it easily recognizable in various tissues and offers an important clue to the correct diagnosis.

The "typical" presentation described by most authors is in infancy with hepatosplenomegaly, progressive cirrhosis, and chronic hepatic failure. Cardiomyopathy dominates the clinical picture in a few older children. We now realize that we have vastly underestimated the infantile neuromuscular presentation.

As recognized in a seminal paper published in 2004 [165], there are two main infantile presentations. The first is a perinatal disorder dubbed "fetal akinesia deformation sequence" (FADS), characterized by multiple congenital contractures (arthrogryposis multiplex congenita), hydrops fetalis, pulmonary hypoplasia, craniofacial abnormalities, intrauterine growth retardation, abnormal amniotic fluid volume, and perinatal death. The second form, labeled "congenital," should probably be called "fatal infantile" because it presents at or soon after birth with hypotonia, muscle wasting, neuronal involvement, inconsistent cardiomyopathy, and early death. Of the eight patients reported by Bruno et al. [165], three had FADS, three had the congenital form, and two had childhood myopathy. Interestingly, there was a good correlation between molecular severity and clin-

ical severity, which has been confirmed in several subsequent patients.

It is becoming increasingly clear that patients with congenital GBE deficiency present a clinical continuum from FADS to a rapidly fatal congenital multisystem disorder dominated by profound hypotonia, respiratory failure, and inconsistent cardiomyopathy [165–172]. Detailed neuropathology in a few infants showed PG inclusions in neurons of the basal ganglia and thalamus, oculomotor and pontine nuclei, and periaqueductal neurons [169]. In the medulla, PG deposits were found in the hypoglossal nucleus, the dorsal motor nucleus of the vagus, and the nucleus ambiguous [166, 168]. The motor neurons of the spinal cord are also severely affected [173], thus explaining how one of the patients we studied was initially diagnosed as spinal muscular atrophy type I until mutations in the *SMN1* gene were ruled out [166].

Brain involvement dominates the clinical picture also in a characteristic late-onset (fifth or sixth decade) form of GBE deficiency known as "adult polyglucosan body disease" (*APBD*) manifested by progressive upper and lower motor neuron involvement, sensory loss, sphincter problems, and dementia (see Chap. 22). Although APBD is seen in various ethnic groups, this disorder predominates among Ashkenazi Jews, in whom one common mutation (Y329S) probably reflects a founder effect [174].

There is no specific therapy for GBE deficiency, but the recent creation of transgenic mice models that faithfully recapitulate both the fatal infantile form and APBD will facilitate the development of therapeutic modalities [175].

Disorders of Lipid Metabolism

Primary Systemic Carnitine Deficiency (PCD)

The mean age at onset of this autosomal recessive condition ranges from 1 month and 7 years. Progressive cardiomyopathy is the most common presentation: echocardiography and EKG show dilated cardiomyopathy, peaked T waves, and signs of ventricular hypertrophy. Endomyocardial biopsies or postmortem studies show massive lipid storage, and, when measured, carnitine concentration in the myocardium is less than 5 % of normal. Cardiac function responds poorly to inotropics and diuretics but responds dramatically to carnitine supplementation, with progressive normalization of cardiac function indices within a few months. Some infants may present with acute encephalopathy together with hypoketotic hypoglycemia and hepatomegaly with liver steatosis. Myopathy is usually associated with cardiomyopathy or encephalopathy and is manifested by mild motor delay, hypotonia, or slowly progressive proximal weakness. Serum CK is normal or slightly elevated. Muscle biopsy shows lipid storage myopathy and very low levels of total and free carnitine (below 10 % of normal).

Defective carnitine transport in kidney causes defective carnitine reabsorption and excessive carnitine excretion. Deficient intestinal transport results in poor and delayed carnitine absorption. The combination of defective renal and intestinal carnitine handling causes carnitine levels to fall in blood. Hence, it is important to measure blood carnitine concentrations in all infants and young children with unexplained cardiomyopathy. In vitro, deficient carnitine transport has been documented in cultured skin fibroblasts [176] and in cultured muscle cells [177].

PCD is due to mutations in the *SLC22A5* gene that encodes the high-affinity, sodium-dependent plasma membrane carnitine transporter (organic cation transporter, OCTN2) [178].

Primary Myopathic Carnitine Deficiency

This disorder, characterized by decreased muscle carnitine with normal serum carnitine, was the first example of carnitine deficiency described by A.G. Engel and Angelini in 1973 in a young woman with progressive proximal weakness and lipid storage myopathy responsive to corticosteroids [179]. The existence of this entity, however, is controversial because there is no definitive documentation of an isolated defect of carnitine uptake in muscle. It is possible that patients with the myopathic form of carnitine deficiency have other fatty acid oxidation defects, either generalized or muscle specific. In some of the patients described, symptoms appeared in the first years of life, but in most the onset was between the second and third decade. There was progressive and sometimes fluctuating weakness of proximal limb and axial muscles of variable severity. A few of these patients had associated cardiomyopathy. Muscle biopsy showed accumulation of triglycerides, especially in type I fibers. Muscle carnitine levels were 20 % of normal or less, while plasma carnitine levels were normal or slightly reduced. Some of the patients improved with carnitine administration.

Secondary Carnitine Deficiency

This condition, characterized by decreased levels of carnitine in blood and, often, in tissues, can accompany diverse disorders, including inborn errors of metabolism, acquired medical disorders, and iatrogenic states.

Examples of inborn errors of metabolism include numerous defects of fatty acid metabolism affecting both the carnitine cycle and β-oxidation, disorders of branched-chain amino acid metabolism, and defects of the mitochondrial respiratory chain.

Examples of acquired medical conditions include those causing decreased carnitine biosynthesis (e.g., hepatic cirrhosis or extreme prematurity), those causing decreased carnitine intake (e.g., malnutrition, chronic total parenteral nutrition, strict vegetarian diet, soy protein infant formula,

malabsorption), those causing decreased body stores of carnitine in the face of increased requirements (e.g., pregnancy and lactation, extreme prematurity, infant of carnitine-deficient mother), and those causing increased carnitine loss, such as Fanconi syndrome.

Examples of iatrogenic factors include valproate therapy [180], hemodialysis, and zidovudine administration [181]. It is important to keep in mind these diverse causes of carnitine deficiency because carnitine replacement often results in marked improvement.

Medium-Chain Acyl-CoA Dehydrogenase (MCAD) Deficiency

This relatively common condition presents in childhood as an episodic acute illness with hypoketotic hypoglycemia following intercurrent infection and fasting. The presenting symptoms and signs, in order of decreasing frequency, include lethargy, vomiting, encephalopathy, respiratory arrest, hepatomegaly, seizures, apnea, cardiac arrest, and sudden death. Once the correct diagnosis is established, subsequent crises can generally be prevented, but survivors are at risk for developmental disabilities. In a large retrospective analysis of 120 MCAD patients, weakness was present in 16 % of the survivors [182]. The most effective laboratory test in this, as in other β-oxidation disorders, is the profile of acylcarnitines in plasma as determined by tandem mass spectrometry. The profile is characteristically abnormal both in sick and in well children with MCAD deficiency.

The gene for MCAD has been cloned and assigned to chromosome 1p31. A single mutation (K304E) is present in over 90 % of patients.

Multiple Acyl-CoA Dehydrogenase Deficiency (MADD)

MADD can be due to mutations in either one of two enzymes: electron-transfer flavoprotein (ETF) or ETF/CoQ10 oxidoreductase (ETFDH). Another name for MADD is glutaric aciduria type II. The clinical spectrum ranges from a fatal multisystem disorder of infancy to a less severe disorder of adolescence or adult life. Late-onset MADD often causes severe lipid storage myopathy with proximal and axial weakness. Of considerable practical importance is the riboflavin-responsive form of MADD, which is predominantly associated with ETFDH deficiency [120, 183]. Some of these patients had CoQ10 deficiency in muscle and responded to CoQ10 supplementation alone or together with riboflavin [118], but secondary CoQ10 deficiency is not a consistent finding [120].

Neutral Lipid Storage Disease with Ichthyosis (NLSDI, Chanarin-Dorfman Syndrome)

This disorder was first reported by Chanarin in a Ugandan woman [184], then recognized in several patients from the Mediterranean area [185]. Patients suffer from ichthyosis, steatorrhea, and a neurological syndrome that includes ataxia, nystagmus, neurosensory hearing loss, and slowly progressive proximal limb weakness. The pathological hallmark is massive triglyceride storage in all tissues, including muscle, liver, gastrointestinal epithelium, endometrium, skin, bone marrow, and both fibroblast and muscle cells in culture [186]. The presence of lipid droplets in granulocytes of a blood smear (Jordan anomaly) facilitates diagnosis. The biochemical basis of this condition is a deficiency of the protein (CGI-58) that activates the adipocyte triglyceride lipase (ATGL), which catalyzes the first step in triglyceride hydrolysis, thus liberating fatty acids from triglyceride stores in skeletal muscle and all other tissues. Several mutations in the *CGI-58* gene have been identified [185].

Neutral Lipid Storage Disease with Myopathy (NLSDM)

This generalized lipid storage disease is due to mutations in the gene (*PNPLA2*) encoding the ubiquitous adipocyte triglyceride lipase (ATGL). Although all tissues can be affected, some patients present with "triglyceride deposit cardiomyovasculopathy (TGCV)" or "obesity of the heart" [187], but many patients present with a myopathy that does not start until adulthood and progresses slowly but steadily, such that many patients are confined to a wheelchair late in life. Some patients may also develop severe cardiomyopathy. There is no ichthyosis, but the Jordan anomaly is present in blood smears [120, 188]. Serum CK is increased and was the only consistent abnormality in a young preclinical woman with severe lipid myopathy and a retrotransposal mutation in *PNPLA2* [189].

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Mitochondrial Myopathies

64

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Introduction

The concept of mitochondrial diseases originated in 1962 with the report by Luft and colleagues of a patient with nonthyroidal hypermetabolism due to loose coupling of oxidation (the breakdown of biomolecules such as carbohydrates and fatty acids) and phosphorylation (the production of ATP) in muscle mitochondria [1]. Over the following quarter of a century, numerous clinical and morphological reports described patients with abnormalities of muscle mitochondria. In 1988, the discovery of mutations in the mitochondrial DNA (mtDNA) led to an explosive expansion of research on mitochondrial myopathies. Over the past two decades, the rapid pace of identification of these clinically diverse disorders and their associated gene defects has left many physicians bewildered about these heterogeneous and complex syndromes.

Etiology and Pathogenesis

Structural Considerations

Each mitochondrion is about the size of a bacterium (1–2 μm by 0.5–1 μm) and has two membranes: an external or outer mitochondrial membrane (OMM) and an internal or inner mitochondrial membrane (IMM). The OMM separates the organelle from the cytoplasm. The IMM serves as a barrier to most molecules and contains vital enzymes required for import of molecules and for ATP synthesis. Within the IMM resides the mitochondrial matrix, which harbors mtDNA (actually, mtDNA molecules are organized into discrete assemblies called nucleoids, which are probably tethered to the IMM [2, 3]), as well as many enzymes responsible for housekeeping and metabolic processes.

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Biochemical Properties

The mitochondria are essential to the cell because they harbor the enzymatic machinery necessary for aerobic metabolism, by which fatty acids, carbohydrates, and amino acids are broken down to form CO_2 and H_2O and, most importantly, to convert adenosine diphosphate (ADP) to adenosine triphosphate (ATP), the energy currency of the cell. The biochemical processes of aerobic metabolism may be classified into five major steps: (1) transport; (2) substrate utilization; (3) Krebs, citric acid, or tricarboxylic acid (TCA) cycle; (4) electron transport chain; and (5) oxidation-phosphorylation coupling (Fig. 64.1).

Transport refers to the importation of molecules, including polypeptides and substrates for the TCA cycle, that are necessary for mitochondrial structure and function. Carnitine palmitoyltransferase (CPT) II deficiency is a prototypical example of a substrate transport defect and is described in the chapter on metabolic myopathies (Chap. 63) [4].

Substrate utilization refers to the oxidation of metabolites within the mitochondrial matrix to form acetyl-coenzyme A (acetyl-CoA), which enters the TCA cycle. Specifically, acetyl-CoA is produced through the metabolism of pyruvate by the pyruvate dehydrogenase enzyme complex (PDHC) [5] and through the catabolism of fatty acids in the ß-oxidation pathway.

Krebs cycle enzymes convert the energy stored in the acetyl-CoA to high-energy electrons in the form of NADH and $FADH_2$. Defects in fumarase, aconitase, and

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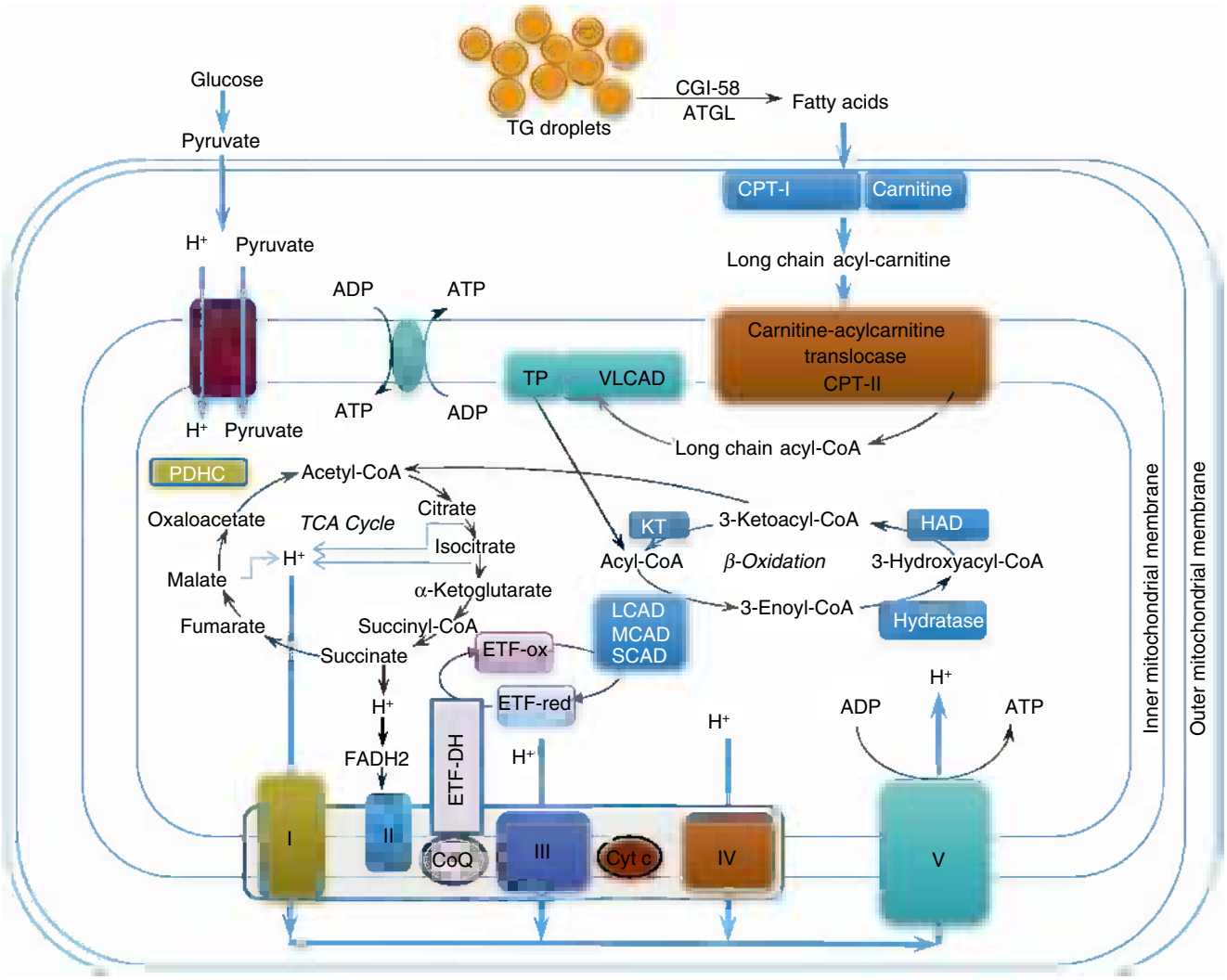

Fig. 64.1 Schematic representation of mitochondrial metabolism. Respiratory chain components or complexes encoded exclusively by the nuclear DNA are solid; complexes containing some subunits encoded by the nuclear genome and others encoded by mtDNA are crosshatched. *Abbreviations*: *PDHC* pyruvate dehydrogenase complex, *CPT* carnitine palmitoyltransferase, *VLCAD* very long chain acyl-CoA dehydrogenase, *TP* trifunctional protein, *LCAD* long chain acyl-CoA dehydrogenase, *MCAD* medium chain acyl-CoA dehydrogenase, *SCAD* short chain acyl-CoA dehydrogenase, *HAD* 3-hydroxyacyl-CoA dehydrogenase, *KT* 3-ketothiolase, *ETFox* oxidized form of electron transfer flavoprotein, *ETFred* reduced form of electron transfer flavoprotein, *ETF-DH* ETF-coenzyme Q oxidoreductase (Reproduced from: DiMauro and Haller [223], with permission)

beta-ketoglutarate dehydrogenase are associated with human diseases [5].

The *electron transport chain* is composed of four enzyme complexes (complexes I–IV) and two small electron carriers, coenzyme Q_{10} (CoQ_{10}) and cytochrome *c*. Reducing equivalents (electrons) are carried along these enzymes to sustain an efflux of protons from the mitochondrial matrix across the IMM, thus generating a transmembrane proton gradient.

Oxidative phosphorylation is the process by which the proton gradient across the IMM is converted into ATP when protons flow back into the mitochondrial matrix through the world's tiniest rotary motor, ATP synthase (complex V). Luft's disease with loose coupling of mitochondrial oxidation to phosphorylation is a classic example of an oxidative-phosphorylation defect. Although the molecular etiology of this exceedingly rare disorder has not been elucidated, defects of complex V have been identified in patients with other forms of mitochondrial encephalomyopathies [6].

While the biochemical features of human mitochondrial disorders are vitally important in understanding the diseases, the identification of mutations in the mitochondrial and nuclear genomes has revolutionized the conceptual framework of mitochondrial myopathies.

Genetic Concepts

Mitochondria originated from aerobic bacteria that formed symbiotic relationships with eukaryotic cells, which benefited from their newly acquired capacity to utilize oxygen. This

relationship is unique because mitochondria are the only mammalian subcellular organelles – aside from the nucleus – that contain genetic material (mtDNA). However, during evolution most of the genes necessary for mitochondrial functions were transferred to the nuclear DNA (nDNA) so that mitochondria are the products of two genomes.

Human mtDNA is a small circular, double-stranded molecule composed of 16,569 base pairs. It contains 37 genes: 13 encode polypeptides; 22 encode transfer ribonucleic acids (tRNA) molecules, and 2 encode ribosomal RNAs (RRNAs) [7]. All 13 mtDNA-encoded polypeptides are subunits of the respiratory chain (seven in complex I, one in complex III, three in complex IV, and two in complex V). The mitochondrial genome differs from nDNA in several aspects. First, there are no introns in the mtDNA, which is therefore tightly packed with information. Second, mtDNA is maternally inherited. Third, each cell contains hundreds to thousands of copies of mtDNA whereas nDNA contains two copies of each autosome and, in the case of normal males, single copies of X and Y chromosomes. Fourth, mtDNA undergoes spontaneous mutations more rapidly than nDNA. These properties of mtDNA are responsible for the unusual genetic features of mitochondrial myopathies.

An important principle of mtDNA genetics is *heteroplasmy*. As each mitochondrion contains two to ten copies of mtDNA and each cell contains multiple mitochondria, there are thousands of copies of mtDNA in each cell. Alterations of mtDNA may be present in some (heteroplasmy) or in all (homoplasmy) of the mtDNA molecules. As a consequence of heteroplasmy, the proportion of a deleterious mtDNA mutation can vary widely. An individual who harbors a large proportion of mutant mtDNA will be more severely afflicted by the mitochondrial dysfunction than a person with a low percentage of the same mutation; therefore, there is a spectrum of clinical severity among patients with a given mitochondrial mutation.

A second factor that may influence the expression of the same mtDNA mutation in different individuals is *the tissue distribution of that mutation*. The best example of different clinical phenotypes due to diverse tissue distribution comes from large-scale single mtDNA deletions. Infants with a high proportion of deleted mtDNA in the blood develop Pearson syndrome (PS, sideroblastic anemia often accompanied by exocrine pancreatic dysfunction) [8]. Presumably, these infants have a high proportion of deleted mtDNA in the bone marrow stem cells. With blood transfusions, some children survive the anemia and subsequently recover because the stem cells with a high proportion of deleted mtDNA are under a negative selection bias. Later in life, however, as mtDNA deletions accumulate in postmitotic tissues, such as brain, heart, and muscle, these same children may develop the multisystem mitochondrial disorder Kearns-Sayre syndrome (KSS) characterized by ophthalmoplegia, pigmentary retinopathy, and cardiac conduction block [9]. Thus, variable tissue distribution broadens the clinical spectrum of pathogenic mtDNA mutations.

The third factor that determines the clinical spectrum of an mtDNA mutation is the *tissue threshold effect*. Cells with high metabolic activities are severely and adversely affected by mtDNA mutations; therefore, these disorders tend to affect disproportionately the brain and muscle (encephalomyopathies).

A fourth characteristic of mtDNA is *maternal inheritance* [10]. During the formation of the zygote, mtDNA derives exclusively from the oocyte. Thus, mtDNA is transmitted vertically in a non-mendelian fashion from the mother to both the male and female progeny. This inheritance pattern is important in determining whether a family is likely to harbor an mtDNA mutation. A caveat to this principle is that maternal relatives harboring lower percentages of an mtDNA mutation may have fewer symptoms (oligosymptomatic) than the proband or may even be asymptomatic. Therefore, in taking the family history, it is important to ask about "soft" symptoms or signs in maternally related family members who might be oligosymptomatic.

These peculiar features of "mitochondrial genetics" contribute to the clinical complexity of mitochondrial disorders. Variable heteroplasmy of mtDNA mutations produces an extensive range of disease severity while tissue distribution and tissue threshold of mtDNA mutations explain the frequent but variable involvement of multiple organ systems. In addition to mtDNA mutations, nuclear DNA (nDNA) defects may also cause mitochondrial dysfunction. In fact, nDNA encodes the following: (1) most electron transport chain subunits and all ancillary proteins needed for proper subunit assembly; (2) factors needed for mitochondrial protein importation; (3) factors needed for mtDNA replication, transcription, and translation ("mtDNA maintenance"); (4) factors controlling the synthesis and assembly of phospholipids in the OMM and IMM; and (5) factors controlling mitochondrial dynamics, i.e., mitochondrial motility, fusion, fission, and mitophagy.

Clinical Presentations

Primary Mitochondrial DNA Mutations

In 1988, the first mtDNA point mutation and large-scale single deletions were described [11, 12]. Since then, there has been an outburst of information relating mtDNA mutations to human mitochondrial disorders. Numerous mtDNA mutations were identified including: single or multiple deletions, and over 250 pathogenic point mutations. Most mtDNA point mutations are in transfer RNA (tRNA) genes. Here, we describe only the most common mtDNA mutations associated with mitochondrial myopathies to illustrate some of the principal features of mtDNA genetics.

Holt and colleagues first identified large-scale single mtDNA deletions ("single" because all mutated mtDNAs in the patient are identical) in patients with mitochondrial myopathy, and soon thereafter, Lestienne and Ponsot [13] and Zeviani and colleagues [14, 15] pointed out the specific association with KSS or chronic progressive external opthalmoplegia (CPEO). Approximately 90 % of KSS patients have large-scale mtDNA deletions, duplications, or both. The mtDNA deletions range from about 2.0 to 10.4 kilobases (kb) in length and are mainly confined to an 11-kb region that does not include the origins of mtDNA replication or mtDNA promoter regions. About one-third of the mtDNA deletions involve an identical 4,977 base pair (bp) segment: this is often referred to as the "common deletion" [16]. Most mtDNA deletions are flanked by direct sequence repeats, suggesting that they may arise from homologous recombination events. Most patients with single deletions of mtDNA are sporadic cases suggesting that the recombination events occur in the oocytes or early in embryogenesis. Large-scale mtDNA deletions are often undetectable in leukocytes; therefore, molecular diagnosis requires muscle biopsy.

The first point mutation in human mtDNA was identified by Wallace and colleagues in patients with Leber's hereditary optic neuropathy (LHON) [11]. This mutation was a guanine-to-adenine (G-to-A) transition at nucleotide (nt) 11778 (m.11778G>A) in subunit 4 of complex I (ND4). We now know that almost all cases of LHON are due to one of three mutations in complex I: m.11778G>A in ND4, m.3460C>A in ND1, or m.144484T>C in ND6 [17].

Myoclonus epilepsy with ragged-red fibers (MERRF) was the first multisystemic disorder to be associated with an mtDNA point mutation, specifically m.8344A>G in the $tRNA^{Lys}$ gene [18]. A second $tRNA^{Lys}$ mutation at nt 8356 (m.8356T>C) was associated with both the MERRF phenotype and a clinical overlap syndrome with features of MERRF and mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) [19, 20]. Two additional mutations in the $tRNA^{Lys}$ have been identified in MERRF patients, one at nucleotide 8363 in two Japanese families [21] and the other at nucleotide 8361 [22]. While the mitochondrial $tRNA^{Lys}$ gene is clearly a hot spot for mutations causing MERRF, a mutation in the $tRNA^{Phe}$ was also identified in a family with MERRF [23]. Overlap syndromes between MERRF and MELAS have also been attributed to point mutations in $tRNA^{Ser(UCN)}$ [24], in $tRNA^{His}$ [25], and in subunit 5 of complex I [26]. Overlap syndromes between MERRF and KSS have been associated with two point mutations in $tRNA^{Leu(UUR)}$ [27, 28].

MELAS was first associated with a specific mtDNA point mutation, m.3243A>G, in the $tRNA^{Leu(UUR)}$ gene [29], and about 80 % of MELAS patients harbor this mutation. However, mutations in at least ten mtDNA genes have been identified in patients with MELAS [30]. These data illustrate how in mitochondrial genetics one phenotype may have multiple genotypes and, conversely, one genotype can cause multiple phenotypes. In addition to MELAS, the m.3243A>G mutation is associated with maternally inherited progressive external ophthalmoplegia (PEO) [31] and with maternally inherited diabetes and deafness (DAD) [32].

The syndrome of neuropathy, ataxia, and retinitis pigmentosa (NARP) is due to the m.8993T>G mutation in subunit 6 of complex V (ATPase subunit 6) [33]. The mutation changes a leucine to arginine and is associated with in vitro decreased ATP synthase activity. In the original NARP patients, the proportion of mutant mtDNA in leukocytes was 82–88 % [33]. When individuals inherit higher proportions of the mutation (around 90 %), they develop a more devastating and earlier-onset disease, maternally inherited Leigh syndrome (MILS) [34]. The relationship between mutational load and clinical phenotypes reinforces the significance of heteroplasmy in mitochondrial genetics. Interestingly, a clinically milder form of NARP/MILS can be caused by a T>C mutation at the very same site (m.8993T>C) [35].

In addition to the mtDNA mutations described above, the already long list of pathogenic point mutations continues to expand [36, 37]. There are recurrent themes in these mutations, which have become widely accepted criteria for pathogenicity. First, most pathogenic mtDNA mutations are heteroplasmic, presumably because the homoplasmic mutant state would be incompatible with life. Second, there are general correlations between levels of heteroplasmy and clinical severity and between tissue distribution of the mutations and syndromic phenotypes. Third, pathogenic mutations generally affect evolutionarily conserved and presumably functionally important sites. Fourth, when the muscle biopsy shows ragged-red or COX-negative fibers, these can be literally "plucked" and used for PCR analysis ("single-fiber PCR") [38]: pathogenic mutations ought to be present in higher proportion in these abnormal fibers (or fiber segments) than in histologically normal segments. A disproportionate number of mutations have been identified in the tRNA genes, and the $tRNA^{Leu(UUR)}$ gene appears to be a hot spot for mutations [36]. Finally, mutations in polypeptide-encoding genes in the mtDNA are emerging as important and not uncommon causes of human diseases [37]. Interestingly, sporadic somatic mutations of polypeptide-encoding genes, particularly in the cytochrome *b* gene, are not uncommon in patients with isolated exercise intolerance [39]. The absence of maternal inheritance and lack of multisystem involvement are strikingly different from our experience with tRNA gene mutations. A full discussion of mitochondrial myopathies due to mutations of mtDNA genes presenting with exercise intolerance, myalgia, or myoglobinuria may be found in Chap. 63 discussing metabolic myopathies.

While much effort was placed on the identification of mtDNA mutations, their pathogenic mechanisms are not

Table 64.1 Overview of the mitochondrial diseases

Genome	Genetic defect	Clinical examples
mtDNA	Single deletions	KSS, sporadic PEO, PS
	Mutations affecting protein synthesis	MELAS, MERRF, LHON
	Mutations in protein-coding genes	NARP/MILS, myopathy
nDNA	Mutations in RC subunits ("direct hits")	LS
	Mutations in RC ancillary proteins ("indirect hits")	LS-plus, GRACILE, leukoencephalopathy, CM
	Defects in intergenomic communication	mtDNA depletion syndromes (myopathy, hepatocerebral syndrome, Alpers syndrome, encephalomyopathy)
		Multiple mtDNA deletion syndromes (AD/AR PEO, SANDO)
		Defects of mtDNA translation (hepatocerebral syndrome, encephalomyopathy, MLASA)
	Defects of the lipid milieu	Barth syndrome
		Megaconial encephalomyopathy
		Sengers syndrome
		Childhood myoglobinuria
		MEGDEL
	Defects of mitochondrial dynamics	DOA, DOA-plus, CMT 2A

Abbreviations: *KSS* Kearns-Sayre syndrome, *PEO* progressive external ophthalmoplegia, *LHON* Leber's hereditary optic neuropathy, *NARP/MILS* neuropathy, ataxia, retinitis pigmentosa/maternally inherited Leigh syndrome, *RC* respiratory chain, *LS* Leigh syndrome, *GRACILE* growth retardation, aminoaciduria, cholestasis, iron overload, and early death, *CM* cardiomyopathy, *SANDO* sensory ataxic neuropathy, dysarthria, and ophthalmoparesis, *MLASA* mitochondrial myopathy, lactic acidosis, and sideroblastic anemia, *MEGDEL* refers to 3-merthylglutaconic aciduria type IV, deafness, and Leigh-like encephalopathy, *DOA* dominant optic atrophy, *CMT* Charcot-Marie Tooth

fully elucidated and questions remain unanswered. For example, why do different tRNA mutations produce different clinical syndromes? All tRNA mutations should decrease mitochondrial protein synthesis, reduce respiratory enzyme activities, and impair ATP synthesis, yet the phenotypic consequences vary considerably. How does one mutation produce multiple genotypes? The m.3243A>G mutation is associated with MELAS, maternally inherited PEO, and diabetes and deafness, but the reasons for this heterogeneity remain unclear.

Defects of Nuclear DNA

The vast majority of polypeptides in the mitochondria are encoded in nDNA; therefore, nuclear mutations are the cause of many, in fact most, mitochondrial myopathies. These mutations have been more difficult to identify, but both traditional sequencing techniques and novel genome-wide or more targeted (mito-exome) "next-generation" sequencing technologies have revealed a bewildering number of mutant mitochondrial genes, most of them responsible for encephalomyopathies but some for myopathies [40, 41].

Historically, Bougeron and colleagues provided the first description of a nDNA gene defect causing a human mitochondrial disease when they identified a mutation in the flavoprotein subunit gene of succinate dehydrogenase (complex II) in two siblings with Leigh syndrome [42].

Table 64.1 shows one rational way to classify nDNA-related mitochondrial disorders into five groups. First, "direct hits" comprise disorders due to mutations in genes encoding subunits of respiratory chain complexes. Second, "indirect hits" refer to those disorders that are due to mutations in genes encoding not respiratory chain subunits but ancillary proteins needed for assembly, stability, or function of individual complexes. Third, defects of intergenomic communication scramble the dialogue between the nuclear genome and the mitochondrial DNA: although transmitted as mendelian traits, these disorders have features of both mendelian and mitochondrial genetics. Fourth, mutations in nuclear genes may alter the lipid milieu of the inner mitochondrial membrane, which is not merely a scaffold for respiratory chain complexes but contributes to their function. Fifth, alterations of mitochondrial dynamics (motility, fusion, and fission) are associated with disease, although the pathogenesis of respiratory chain dysfunction remains unclear.

Mutations in Respiratory Chain Subunits ("Direct Hits")

Complex I

Complex I (NADH-ubiquinone oxidoreductase) comprises 45 subunits, of which 38 are encoded by nDNA, and it generates about 40 % of the proton motive force eventually harnessed by ATP synthetase (complex V). Given its size, it is not too surprising that isolated complex I deficiency is the most frequently encountered RC defect [43].

Pathogenic mutations have been identified in all evolutionarily conserved subunits that comprise the catalytic core and generally result in Leigh syndrome (LS). LS, which reflects the ravages of energy shortage on the developing nervous

system, is defined neuropathologically (or neuroradiologically) by bilateral symmetrical lesions all along the nervous system, but especially in the basal ganglia, thalamus, brainstem, and cerebellar roof nuclei. Microscopically, there is neuronal loss, proportionate loss of myelin, reactive astrocytosis, and proliferation of cerebral microvessels.

Clinically, these children have psychomotor retardation or regression, respiratory abnormalities, hypotonia, failure to thrive, seizures, dystonia, and blindness. Although hypotonia is usually severe, isolated myopathy is not seen in mutations of nuclear genes for complex I whereas it has been reported in several patients with mutations in mtDNA-encoded complex I (ND) genes (see Chap. 63).

Besides LS, four distinct presentations had been attributed to mendelian complex I deficiency: fatal infantile lactic acidosis (FILA), neonatal cardiomyopathy with lactic acidosis, leukodystrophy with macrocephaly, and hepatopathy with renal tubulopathy [43]. It is likely that they represent variations on a common LS theme rather than separate clinical entities, and differences in residual activity may account for the apparent differential tissue involvement.

One important clinical feature common to these disorders is that onset is invariably in infancy or childhood. Usually, these children are fine at birth and early in life, but disease progression is rapid and relentless, leading to death often before 1 year of age. Lactic acid is consistently and markedly elevated both in the blood and in the cerebrospinal fluid (CSF). From a genetic point of view, it is noteworthy that mutations in NDUFA1 cause X-linked LS [44], a most unusual hereditary pattern for RC defects.

Complex II

Complex II (succinate-ubiquinone oxidoreductase) is the smallest multimeric component of the RC, comprising only four subunits. Complex II deficiency is also probably the least common RC defect [45].

Four reported patients had typical LS [46, 47] whereas one child at 5 months developed hypotonia, respiratory distress, hepatosplenomegaly, and cardiomegaly [48]. Two children with psychomotor regression and spastic quadriparesis showed diffuse leukodystrophy by MRI, and a third child presented in the first year of life with stunted growth and lactic acidosis without neurological symptoms. Interestingly, all three children stabilized or improved after riboflavin administration [49]. Two sisters were heterozygous for a mutation in the gene encoding the flavoprotein subunit and showed late-onset optic atrophy, ataxia, and myopathy with a partial defect of succinate dehydrogenase (SDH) [50].

Coenzyme Q_{10} Deficiency

Enzyme defects that impair the biosynthesis of the small electron carrier CoQ_{10} can be considered "direct hits" because they drastically reduce the concentration of CoQ_{10}, thus blocking the flux of electrons in the RC between complexes I and II and complex III (see Fig. 64.1).

CoQ_{10} is a lipophilic molecule composed of a benzoquinone ring and an isoprenoid chain, which in humans contains 10 isoprenyl units. The quinone group is synthesized in mitochondria from para-hydroxy-benzoate, a catabolite of tyrosine, whereas the polyisoprene tail is synthesized in the cytoplasm starting from acetyl-CoA through the mevalonate pathway [51, 52]. CoQ_{10} biosynthesis is carried out by a set of at least eight enzymes encoded by nuclear genes named *COQ*. Pathogenic mutations have been identified in six genes and cause heterogeneous clinical conditions. Five main clinical syndromes have been associated with CoQ_{10} deficiency in skeletal muscle.

The first syndrome is an encephalomyopathy described in 1989 by Ogasahara et al. [53] in two sisters with mitochondrial myopathy and recurrent myoglobinuria, seizures, mental retardation, and ataxia. The triad of mitochondrial myopathy, myoglobinuria, and encephalopathy was then reported in a few other patients [54–57], but responsible genes remain elusive.

The second syndrome is childhood-onset cerebellar ataxia and atrophy, with variable additional symptoms, including neuropathy, seizures, mental retardation, and muscle weakness [58–61]. The molecular basis of this syndrome was identified in some but not all patients, and the mutated gene was *ADCK3*/*CABC1* (*COQ8*) [62–64].

The third syndrome is an infantile encephalomyopathy, first described by Rötig et al. [65] in three siblings with nystagmus, optic atrophy, sensorineural hearing loss, ataxia, dystonia, weakness, and nephropathy. Quinzii et al. found a homozygous missense mutation in the *COQ2* gene in an infant boy who presented with nystagmus at 2 months and, at 12 months, had hypotonia, psychomotor delay, and severe nephrotic syndrome requiring renal transplantation [66]. His neurological condition deteriorated and he developed psychomotor regression, tremor, weakness, and status epilepticus. Brain MRI showed cerebral and cerebellar atrophy and stroke-like lesions. His younger sister had severe nephrosis at 12 months but never developed neurological symptoms. Oral CoQ_{10} administration improved the boy's condition dramatically and presumably protected his sister from developing neurological problems [67].

A similar but rapidly fatal condition was associated with *COQ2* mutations in two siblings. One was a girl with neonatal neurological distress, nephrosis, hepatopathy, pancytopenia, diabetes, seizures, and lactic acidosis, leading to death at 12 days [68]. Her older brother had anemia, liver failure, and nephropathy and survived only 1 day.

COQ1 is composed of two subunits, PDSS1 and PDSS2. Mutations in *PDSS2* were responsible for typical Leigh syndrome and nephrotic syndrome in an infant boy who died at age 8 months of intractable status epilepticus despite CoQ_{10}

supplementation [69]. Mutations in *PDSS1* were associated with early deafness, encephaloneuropathy, obesity, valvulopathy, livedo reticularis, and mental retardation in two siblings, who were 14 and 22 years old at the time of publication [68], and in two much more severely affected siblings, who died at 1 and 12 days with neonatal neurologic distress, liver failure, nephrotic syndrome, diabetes, seizures, and pancytopenia [68].

The fourth syndrome is dominated by severe nephrotic syndrome and is outside the scope of this book. Two patients had mutations in *COQ2* [70] and 13 patients from 7 families had mutations in *COQ6* [71].

The fifth syndrome, characterized by isolated myopathy, was described by two groups [72–74]. Patients have progressive weakness, lipid storage in the muscle biopsy, and respiratory chain dysfunction. Gempel et al. [72] attributed this myopathic presentation to mutations in the gene encoding the electron-transferring flavoprotein dehydrogenase (*EFTDH*) also associated with glutaric aciduria type II (multiple acyl-CoA dehydrogenase deficiency [MADD]) and described a beneficial effect not only of CoQ_{10} but also of riboflavin supplementation. However, this entity is controversial because in some studies patients with MADD and ETFDH mutations had normal CoQ_{10} levels in muscle [75, 76].

Complex III

Two distinct direct hits for complex III (ubiquinol-cytochrome *c* reductase) have been described, one in a single patient and the other in a large consanguineous family. A deletion in the *UQCRB* gene encoding the ubiquinone-binding protein (QP subunit or subunit VII) was identified in an 8-month-old girl with moderate hepatomegaly, hypoglycemia, metabolic acidosis, and lactic acidosis [77]. During a fasting test, she developed hypoglycemia after 19 h, which became symptomatic after 21 h. Lactic acid was also markedly increased (4.16 mmol/L, normal 0.5–2.2), and ketogenesis was impaired, suggesting a functional defect of fatty acid oxidation. At age 4 years, the child was normal and the hepatomegaly had regressed. Complex III activity was decreased in the liver, lymphocytes, and fibroblasts.

Twenty members of a Bedouin family in Israel presented with a uniform encephalomyopathy that was severe but compatible with long survival. These patients were normal at birth and for the first few months, then showed psychomotor retardation and developed extrapyramidal signs, including dystonia, athetoid movements, ataxia, and dementia [78]. There was a homozygous mutation in *UQCRQ*.

Complex IV

It is likely that most "direct hits" in nuclear-encoded subunits of complex IV (cytochrome *c* oxidase) are incompatible with life because years of research have revealed mutations in only one of the 10 nDNA-encoded subunits, COX6B1 [79]. Both siblings with mutations in this gene had had failure to thrive but normal psychomotor development until late childhood, when they developed muscle weakness, cognitive deterioration, visual problems, and lactic acidosis. MRI showed severe cavitating leukodystrophy in both.

Complex V

As for complex IV, "direct hits" of complex V appear to be very rare, having been reported only in one patient, who harbored a homozygous mutation in the *ATP5E* gene and – paradoxically – had a more benign course than patients with "indirect hits" (see below) [80]. This girl was small at birth and had a poor suck, respiratory distress, lactic acidosis, and 3-methylglutaconic aciduria. Although she had recurrent metabolic crises, her clinical course stabilized at 5–6 years, and she completed school and was gainfully employed. At the age of 17 years, she had mild ataxia, horizontal nystagmus, exercise intolerance, mixed axonal and demyelinating polyneuropathy, and mild left ventricular hypertrophy.

Mutations in Genes Encoding Ancillary Proteins ("Indirect Hits")

Pathogenic mutations in proteins needed for the assembly, stabilization, and functional regulation have been identified for all five complexes of the RC.

Complex I

Pathogenic mutations have been reported in 6 assembly subunits [81–86] and in 5 chaperone factors [87–93], and many more mutated genes in both groups will be identified through the increased use of exome sequencing [41, 94].

The clinical manifestations tend to be more heterogeneous than those associated with "direct hits" in complex I, but, again, isolated myopathy is exceedingly rare. Three siblings in a doubly consanguineous Dutch family and an unrelated patient, who harbored mutations in the *ACAD9* gene, had isolated myopathy with exercise intolerance and lactic acidosis responsive to riboflavin [91].

Complex II

Even the tiny complex II requires assembly factors, and mutations have been described in one of them (SDHAF1), which contains a LYR motif and is presumably involved in Fe-S metabolism [95]. The clinical picture was dominated by psychomotor regression, impaired growth, spastic quadriplegia, and moderate cognitive decline. Weakness was not related to a primary myopathy.

Complex III

The first assembly defect in complex III was identified in 2002 in Finnish infants with an extremely severe syndrome named GRACILE, which summarizes the main symptoms

and signs: *g*rowth *r*etardation, *a*minoaciduria, *c*holestasis, *i*ron over*l*oad, and *e*arly death (before 5 months of age). The mutated protein BCS1L is a member of the AAA family of ATPases needed for insertion of the Rieske FeS subunit into the complex [96]. This syndrome was also recognized in British and Turkish children: although symptoms vary somewhat in different ethnic groups, myopathy is not a prominent feature.

In addition, *BCS1L* mutations cause the milder Björnstad syndrome characterized by sensorineural hearing loss and pili torti (flattened and twisted hair shafts) [97]. One patient with a novel homozygous *BCS1IL* mutation had an intermediate presentation with infantile onset of hypotonia, psychomotor retardation, coarse facial features, and hirsutism [98].

A second assembly factor for complex III is tetratricopeptide repeat 19 (TTC19), a protein of the inner mitochondrial membrane, where it interacts with complex III [99]. Four Italian patients with homozygous mutations in *TTC19* had severe encephalopathy, which, although incapacitating, was compatible with life into the second and even fourth decade.

Complex IV

It has long been known that cytochrome *c* oxidase (COX, complex IV) deficiency is a common cause of LS [100, 101]. Yet, years went by before a mutated gene was associated with LS: the gene (*SURF1*) is essential for correct COX assembly, and this was the first example of an "indirect hit" to affect the RC [102, 103].

Mutations in the COX assembly gene *SCO2*, which encodes a metallochaperone involved in mitochondrial copper delivery, cause a severe clinical phenotype that combines neonatal hypertrophic cardiomyopathy with encephalopathy and is fatal in the first weeks or months of life [104].

Importantly, *SCO2* mutations (both in compound heterozygosity and in homozygosity) can simulate spinal muscular atrophy (SMA), and the neurogenic, often SMA-like, histological pattern of the muscle biopsy further complicates the differential diagnosis [105–107]. One postmortem study of the spinal cord showed severe neuronal loss and astrocytosis in the anterior horns [106]. Two distinctive features orient towards the correct diagnosis: clinically, the severe cardiomyopathy and, morphologically, the lack of COX stain in the muscle biopsy. However, in patients with the clinical picture of SMA but without mutations in the *SMN* gene, it is important to consider *SCO2* mutations.

Mutations in several other genes encoding COX assembly proteins have been associated with encephalopathy resembling Leigh syndrome together with involvement of one other tissue, although the reason for this additional tissue vulnerability is not clear. Thus, mutations in *SCO1*, another copper chaperone, cause encephalohepatopathy; mutations in *COX10* cause encephalonephropathy; and mutations in *COX15* cause encephalocardiopathy as do mutations in *C2orf64* [104]. Additional disorders due to "indirect hits" and resulting in generalized COX deficiency, including an unusual "toxic" mechanism of COX inhibition, have been reported (for review, see [104]), but myopathy, if present, is overshadowed by brain and visceral involvement.

Complex V

Mutations in two ancillary proteins, *ATP12* (now known as *ATPAF2*) and *TMEM70*, cause severe infantile disorders involving multiple organs, but myopathy is not a prominent feature [6].

Iron-Sulfur (Fe-S) Cluster Scaffold Protein (ISCU) Deficiency

In 1991 and 1993, Haller and coworkers described a young Swedish man with lifelong exercise intolerance, dyspnea, cardiac palpitations, and episodes of myoglobinuria [108, 109]. The syndrome was called "mitochondrial myopathy with succinate dehydrogenase and aconitase deficiency" and attributed to altered metabolism of iron-sulfur (Fe-S) cluster proteins, which are prosthetic groups present in complexes I, II, and III, and in the Krebs cycle enzyme aconitase. Accordingly, histochemical analysis of muscle showed SDH deficiency, and biochemical analysis showed deficiencies of complex II, complex III, and aconitase. In 2008, homozygosity mapping revealed a single pathogenic mutation in the *ISCU* gene in three Swedish families [110], and 2 years later, Kollberg et al. [111] described SDH deficiency and accumulation of iron in muscle as the morphological hallmarks of the disease.

Defects of Intergenomic Communication

As noted above, the mtDNA is highly dependent for its proper synthesis and replication on numerous factors encoded by nuclear genes. Mutations in these genes cause disorders characterized by qualitative or quantitative alterations of mtDNA. Although these disorders are mendelian, it is important to keep in mind that they show overlap features with mitochondrial genetics because mtDNA is unevenly affected and clinical phenotypes depend on the degree of heteroplasmy. Most of these disorders are generalized, but myopathy is a frequent symptom and extraocular muscles are almost always involved, causing progressive external ophthalmoplegia (PEO) and droopy eyelids (ptosis).

Initially, qualitative mtDNA alterations (multiple mtDNA deletions) and quantitative alterations (mtDNA depletion) were considered separate entities due to distinct molecular defects. However, in the past few years, and especially after the introduction of exome sequencing, it has become apparent that multiple mtDNA deletions and mtDNA depletion often coexist in the same patient and that syndromes

Table 64.2 Main clinical presentations associated with mtDNA depletion or multiple mtDNA deletions (Δ)

Gene	mtDNA depletion	Multiple mtDNA Δ
TK2	Infantile or adult myopathy, SMA phenocopy	Adult AD PEO
DGUOK	Infantile hepatocerebral syndrome	Adult myopathy ± PEO
PEO1	IOSCA, hepatocerebral syndrome	Adult AD PEO-plus
SUCLA2	Infantile encephalomyopathy	
SUCLG1	Infantile encephalomyopathy, MMA	
RRM2B	Infantile encephalomyopathy	Adult AD/AR PEO-plus
MPV17	Infantile hepatocerebral syndrome, NNH	Adult AR PEO-plus
TYMP	MNGIE	MNGIE
POLG	Hepatocerebral syndrome (Alpers syndrome)	Adult AD/AR PEO-plus, SANDO, MIRAS
POLG2		Adult AD PEO
ANT1		Adult AD PEO-plus
OPA1		DOA, adult PEO-plus
MFN2		DOA-plus
GFER		Congenital cataract, encephalomyopathy

Note how mutations in the same gene can cause mtDNA depletion, multiple mtDNA deletions, or both. The proteins encoded by genes are described in the text

Abbreviations: *AR* autosomal recessive, *AD* autosomal dominant, *PEO* progressive external ophthalmoplegia, *IOSCA* infantile-onset spinocerebellar ataxia, *MMA* methylmalonic aciduria, *NNH* Navajo neurohepatopathy, *MNGIE* mitochondrial neurogastrointestinal encephalomyopathy, *SANDO* sensory ataxic neuropathy, dysarthria, and ophthalmoparesis, *MIRAS* mitochondrial recessive ataxia syndrome, *DOA* dominant optic atrophy

considered typical of multiple mtDNA deletions can be caused by mtDNA depletion and vice versa. This is illustrated in Table 64.2.

For the sake of clarity, we will still consider separately the two entities but we will alert the reader about overlap situations.

Disorders Characterized by Multiple mtDNA Deletions

Mitochondrial Neurogastrointestinal Encephalomyopathy (MNGIE)

One of the disorders in which the coexistence of multiple mtDNA deletions and mtDNA depletion was first recognized is MNGIE (mitochondrial neurogastrointestinal encephalomyopathy). This autosomal recessive multisystemic syndrome is characterized by mitochondrial myopathy with ptosis and PEO, peripheral neuropathy, gastrointestinal dysmotility causing severe cachexia, and leukoencephalopathy without cognitive impairment. MNGIE is due to mutations in the gene (*TYMP*) encoding thymidine phosphorylase (TP), resulting in elevated levels of thymidine and deoxyuridine in plasma and tissues [112]. In fact, measurement of these metabolites in plasma and measurement of TP activity in buffy coat are valuable diagnostic tools. The disease starts in young adults and is relentlessly progressive, with an average age of death of 37 years [112]. Muscle biopsy shows COX-negative RRF and combined deficiencies of respiratory chain complexes. Molecular analysis has shown over 50 *TYMP* mutations resulting in mtDNA multiple deletions, depletion, and site-specific somatic mtDNA point mutations in multiple tissues. It has been suggested that the increased levels of thymidine and deoxyuridine imbalance the mitochondrial deoxynucleotide triphosphate pool, resulting in mtDNA instability.

This devastating mitochondrial disorder is amenable to therapy. Transient biochemical benefit is obtained with hemodialysis, which eliminates the offending nucleosides from the blood. Permanent benefit derives from allogeneic hematopoietic stem cell transplantation (AHSCT). Bone marrow transplantation in a few MNGIE patients has raised blood levels of TP activity to heterozygous levels and normalized plasma thymidine and deoxyuridine. Seven years after AHSCT, one patient had markedly improved gastrointestinal function and improved exercise tolerance and nerve function (assessed clinically and electrophysiologically) [112].

Mutations in ANT1

Mutations in the gene for one isoform of the adenine nucleotide translocator (*ANT1*) have been identified in patients with autosomal dominant PEO, sometime associated with psychiatric disorders [113–115]. In the seminal paper by Suomalainen et al., multiple mtDNA deletions were most abundant in the brain, followed by cardiac and skeletal muscle [114]. Sporadic PEO may also infrequently be due to mutations in *ANT1* [116], and the association of mitochondrial myopathy and cardiomyopathy, even in patients with recessive inheritance and without PEO, should raise the question of *ANT1* mutations [117].

Mutations in PEO1

In 2001, autosomal dominant PEO with multiple mtDNA deletions was associated with mutations in the gene (*PEO1*), encoding a mitochondrial helicase called Twinkle [118], an essential factor for mtDNA maintenance and for the regulation of mtDNA copy number [119]. A review of 33 patients from 26 families showed that the most common symptoms were ptosis (97 %) and ophthalmoparesis (94 %), followed by exercise intolerance (52 %) and mild proximal weakness (33 %) [120]. Central nervous system involvement was infrequent and included visual impairment, migraine, lethargy, hearing loss, and epilepsy. Cardiac problems were noted in 24 % of the patients. It was

also noted by several investigators that multiple mtDNA deletions are often not revealed by Southern blot and require long-range or real-time PCR. When 67 patients with multiple mtDNA deletions in muscle (with mitochondrial myopathy but with or without PEO) were screened for mutations in *ANT1*, *PEO1*, *POLG1*, and *POLG2*, it was found that mutations in *PEO1* accounted for 27 %, mutations in *ANT1* for 15 %, and mutations in *POLG* for 10 % of familial cases [121]. However no mutations in known genes were found in 54 % of cases (this study preceded mitoexome screening).

Infantile-onset spinocerebellar ataxia (IOSCA) was described in the 1970s in Finland (reviewed in reference [122]): between 9 and 18 months, children develop acutely or subacutely ataxia, hypotonia, athetosis, and areflexia, and by teenage years they lose independent ambulation. Additional symptoms include PEO, optic atrophy, sensorineural hearing loss, cognitive impairment, sensory neuropathy, and autonomic nervous system dysfunction. Neuroradiology shows cerebellar atrophy. In 2005, this autosomal recessive disorder was attributed to mutations in *PEO1* [123]. Although no mtDNA alteration was initially identified [123], it was later found that both the brain and the liver showed mtDNA depletion [124]. In fact, an early-onset hepatocerebral presentation similar to Alpers-Huttenlocher syndrome has also been associated in two siblings with recessive *PEO1* mutations and mtDNA depletion in the liver [125]. Although muscle showed only mild mtDNA depletion, these children had hypotonia and PEO.

Mutations in POLG

Mutations in the gene encoding the only mitochondrial polymerase, polymerase γ (*POLG*), have emerged as major causes of a vast array of mitochondrial disorders [126]. Over 150 mutations have been described in all three domains of the gene, exonuclease, linker, and polymerase, and may cause either autosomal dominant or autosomal recessive PEO, a syndrome comprising autosomal recessive sensory ataxic neuropathy, dysarthria, and ophthalmoparesis (SANDO) [127, 128], mitochondrial recessive ataxia syndrome (MIRAS) [129], or parkinsonism with or without PEO [130–134].

Mutations in *POLG* can cause multiple mtDNA deletions – as in the diseases mentioned above – or mtDNA depletion as in Alpers-Huttenlocher syndrome (AHS), a severe autosomal recessive hepatocerebral disorder of childhood defined by the tetrad of refractory seizures, episodic psychomotor regression, cortical blindness, and hepatopathy with micronodular cirrhosis [135]. It is crucially important not to expose these children to valproate, which often precipitates fulminant hepatic failure. This interaction of gene and environment contributes to the extreme clinical heterogeneity of POLG mutations [127]. As if the many syndromes listed above were not enough, *POLG* mutations can mimic other mitochondrial disorders, including MNGIE [136, 137] and MERRF [138].

From the neuromuscular point of view, *POLG* mutations have to be considered in the differential diagnosis of autosomal dominant and autosomal recessive PEO and SANDO, but also isolated myopathies [139]. The extraordinary clinical spectrum of *POLG* mutations, the relationship of the different phenotypes to the three functional domains of the gene, and the vulnerability of the gene to environmental factors are discussed in several reviews [140, 141].

In human mitochondria, polymerase γ is part of an enzyme complex containing an accessory subunit of 55 kDa, p55, which is encoded by the *POLG2* gene. A dimer of p55 binds to polymerase γ and stimulates its catalytic activity. Heterozygous mutations in *POLG2* have been reported in two patients with remarkably similar clinical histories: both women were in their 60s and had developed bilateral ptosis in midlife, followed by PEO and facial weakness in one patient [142] but not in the other [143]. Both patients had proximal muscle weakness, COX-negative fibers in the muscle biopsy, and multiple mtDNA deletions by long-range PCR.

Mutations in OPA1

One unexpected gene was recently added to those described above and associated with myopathy and PEO, *OPA1*. Why unexpected? Because mutations in *OPA1* were initially associated with a purely ophthalmological condition, dominant optic atrophy (DOA) or Kjer disease [144, 145], and because the gene product was a mechanoenzyme associated with mitochondrial fusion rather than with mitochondrial maintenance.

However, a syndromic disorder, often dubbed DOA-plus, has emerged, which is characterized more or less sequentially [146] by optic atrophy with visual failure, sensorineural deafness, ataxia, myopathy, axonal sensory-motor polyneuropathy, and PEO [147–150]. Muscle biopsy in these patients shows scattered ragged-blue, COX-negative fibers, and multiple mtDNA deletions are demonstrable by long-range PCR. Interestingly, the proportion of COX-negative fibers is much higher in patients with DOA-plus than in those with non-syndromic DOA. The relationship between this defect of mitochondrial dynamics and altered mitochondrial maintenance is intriguing. Two explanations have been proposed, decreased ability by the organelles to repair stress-induced mtDNA damage or accelerated accumulation of pre-existing age-associated somatic mtDNA mutations [151].

Mutations in RRM2B

An identical mutation in a gene (*RRM2B*, encoding the small subunit, p53R2, of the p53-inducible ribonucleotide reductase protein), which had been typically associated with autosomal recessive mtDNA depletion syndromes (see

below), was recently reported in two unrelated families with autosomal dominant PEO [152]. The patients in the first family had only PEO with or without ptosis manifesting in adulthood. Muscle biopsies showed COX-negative fibers and multiple mtDNA deletions by long-range PCR. The propositus from the second family was more severely affected: besides PEO, he also had hearing loss, gait ataxia, depression, and moderate cognitive impairment. Mutations in *RRM2B* are not a rare cause of PEO because screening this gene in 75 patients with molecularly unexplained PEO, COX-negative fibers, and multiple mtDNA deletions showed that 12 of them (16 %) were either compound heterozygous (2 patients with autosomal recessive PEO) or heterozygous (10 patients with autosomal dominant PEO) for pathogenic mutations [153]. A single patient with PEO, the child of first cousins, had a homozygous missense mutation in RRM2B [154].

Mutations in TK2

Whole exome sequencing also revealed that two sisters with late-onset PEO, ptosis, proximal weakness, dysarthria, and dysphagia were compound heterozygous for two pathogenic mutations in the *TK2* gene, which is typically associated with infantile myopathy and mtDNA depletion (see below). Muscle biopsy showed mosaic distribution of COX-negative fibers, and multiple mtDNA deletions were seen by Southern blot [155].

Mutations in MPV17

Although mutations in this gene are typically associated with multisystemic infantile mtDNA depletion, they have also been described in two adult patients with peripheral neuropathy (both patients), steatohepatopathy (both patients), leukoencephalopathy (one patient), ptosis, PEO, diabetes mellitus, depression, parkinsonism, and gastrointestinal dysmotililty (one patient) [156, 157]. Both patients had ragged-blue COX-negative fibers and multiple mtDNA deletions but no evidence of mtDNA depletion.

Mutations in GFER

The *GFER* gene encodes a sulfhydryl oxidase (DRS) of the mitochondrial intermembrane space, which is involved in mitochondrial protein import. A homozygous mutation of GFER caused congenital cataract, progressive muscle hypotonia, sensorineural hearing loss, and developmental delay in three siblings of a consanguineous family [158]. The pathogenic relationship between this gene and the multiple mtDNA deletions observed in muscle biopsies is not clear.

Disorders Characterized by mtDNA Depletion

These disorders are characterized by paucity of mtDNA, but the residual molecules are normal. mtDNA depletion syndromes (MDS) are phenotypically and genotypically heterogeneous. Transmission, however, is autosomal recessive in all forms. From the very first documentation of mtDNA depletion [159], it looked like myopathy or hepatopathy were the predominant presentations, but some children have multisystem involvement.

Myopathic MDS

Patients usually present in the first year of life with failure to thrive, hypotonia, weakness, and sometimes PEO. They usually die in childhood from pulmonary insufficiency, but severity of weakness and survival vary considerably [160]. The myopathic MDS is most commonly due to mutations in the gene (*TK2*) encoding mitochondrial thymidine kinase. About 20 mutations have been reported in as many patients. Notably, mutations in *TK2* can also cause a phenocopy of spinal muscular atrophy (SMA) [160–162]. It is notable, in this respect, that a *TK2* knockin mouse has more severe involvement of the central nervous system than of muscle [161]. It is also of practical importance to sequence the *TK2* gene in patients with SMA but without mutations in the *SMN1* gene.

Muscle biopsies in early-onset patients are uniformly COX-negative and do not react to DNA antibodies [162], whereas in later-onset patients some fibers appear normal and others lack both COX activity and mtDNA. Ragged-red fibers are not always present in early biopsies but may appear later. Biochemical analyses show combined defects of respiratory chain complexes containing mtDNA-encoded subunits. Of practical importance, serum CK levels tend to be elevated (2–30 times normal) in patients with myopathic MDS: this is an important diagnostic clue because CK levels are normal or only mildly elevated in other mitochondrial myopathies.

However, mutations in *TK2* can also cause adult-onset myopathy with mtDNA depletion [163] and even – as mentioned above – late-onset PEO with multiple mtDNA deletions rather than mtDNA depletion [155].

Muscle is almost invariably involved – though not in isolation – in patients with mtDNA depletion due to mutations in *RRM2B* (see above). Infants are hypotonic and children are weak, but there is usually also renal involvement [164–166] and central nervous system involvement with microcephaly, seizures, and developmental delay. As mentioned above, mutations in *RRM2B* can also be associated with autosomal dominant or recessive PEO and multiple mtDNA deletions [152–154]. One such case had multisystem involvement mimicking KSS [167].

Encephalomyopathic MDS

Two variants of this condition are both due to a defect of succinyl-CoA lyase activity in the Krebs cycle. Mutations in the gene (*SUCLA2*) encoding the ATP-dependent succinyl-CoA lyase SUCLA2 cause severe psychomotor retardation,

muscle hypotonia, hearing loss, generalized seizures, knee and hip contractures, mild ptosis, lactic acidosis, and methylmalonic aciduria. There is moderate mtDNA depletion (about 30 %) in muscle, and MRI of the brain is suggestive of Leigh syndrome [168–171].

Mutations in the gene (*SUCLG1*) encoding the GTP-dependent isoform SUCG1 cause a much more severe and rapidly fatal phenotype with mtDNA depletion in both muscle and the liver, characterized clinically by dysmorphic features, congenital lactic acidosis, and methylmalonic aciduria [172–174]. A less dismal course, more like the SUCLA2 phenotype, is correlated to the degree of residual activity [175, 176].

Hepatocerebral MDS

Alpers syndrome is the most important form of hepatocerebral MDS, and it has been described above. Mutations in two other genes, *DGUOK* and *MPV17*, also cause liver and brain involvement. Mutations in *DGUOK*, encoding the mitochondrial deoxyguanosine kinase (dGK), were first reported in 2001 [177], and by 2007 15 different mutations had been identified in 12 kindreds [178]. Severe mutations cause fatal infantile hepatopathy and brain involvement whereas milder mutations cause isolated liver disease and are compatible with longer survival, suggesting that the encephalopathy is largely secondary to the liver dysfunction.

Skeletal muscle is not directly affected in infants, and the only reported myopathy was due to a most unusual "double trouble," the association of McArdle disease and *DGUOK* mutations in an infant with hepatopathy and muscle glycogenosis [179]. However, exome sequencing has revealed *DGUOK* mutations in five adult patients with PEO and mitochondrial myopathy with multiple mtDNA deletions: only one of these patients had had liver problems in childhood [180].

Mutations in *MPV17*, which encodes a small mitochondrial membrane protein of unknown function, cause a rather typical hepatocerebral syndrome in Caucasian children [181] but is associated with a peculiar neurohepatopathy in the Navajo population. Navajo neurohepatopathy (NNH), which has a prevalence of 1 in 1,600 live births, was attributed to mtDNA depletion [182] and is due to a homozygous *MPV17* mutation [183]. The clinical features of NNH include peripheral and central nervous system involvement, acral mutilation, corneal scarring or ulceration, liver failure, and immunologic derangement [184]. As mentioned above, *MPV17* mutations can also impair mtDNA maintenance and cause mtDNA multiple deletions in adults [156, 157].

Defects of mtDNA Translation

Clinically, these disorders came to the attention of pediatricians because they cause severe infantile syndromes, often similar to those associated with mtDNA depletion even though mtDNA is normal both qualitatively and quantitatively.

A thorough update on this rapidly expanding group of diseases can be found in a recent Workshop Report [185], in which the authors classify the mutated proteins into six types according to the translational step affected and list the most common clinical features. Onset is usually in infancy or early childhood, and the course is rapidly fatal. Encephalomyopathy is the most common presentation, although cardiomyopathy and hepatopathy are occasionally seen. Lactic acidosis is almost invariably present.

Skeletal muscle is not a target organ, except in the disorder known as MLASA (mitochondrial myopathy, lactic acidosis, and sideroblastic anemia). MLASA is an autosomal recessive condition due to mutations in the gene (*PUS1*) encoding pseudouridine synthase 1 [186]. PUS1 is an enzyme located both in the nucleus and in the mitochondria: it converts uridine to pseudouridine in cytosolic and mitochondrial tRNAs, thus increasing the efficiency of protein synthesis in both compartments [187]. Detailed clinical descriptions of two affected brothers showed similar features but different severity. The older brother had severe hypotonia at 6 months and at 5 years developed sideroblastic anemia unresponsive to vitamin B6 administration. At 10 years, he had marked growth retardation despite growth hormone supplementation, generalized muscle weakness and wasting, winged scapulae, waddling gait, and Gowers sign. Blood lactate was markedly increased but CK was normal. He developed severe restrictive ventilatory syndrome and died at the age of 12 years. A muscle biopsy showed ragged-blue COX-negative fibers and a combined defect of complexes I and IV. His younger brother had cognitive impairment but milder myopathic involvement and was still alive at age 13, although he complained of exercise intolerance and had incipient ventilatory insufficiency [187].

Defects of Lipid Milieu Composition

The phospholipid components of the inner mitochondrial membrane (IMM) do not simply act as a scaffold for the respiratory chain, but participate in its structural and functional integrity. Phospholipid metabolism and the lipid composition of the IMM have been relatively neglected in the study of mitochondrial diseases, but there has been a recent awakening to this subject, and several new disorders have been discovered, thanks in part to exome sequencing (Table 64.2).

Barth Syndrome

Cardiolipin is the most abundant phospholipid component of the IMM. Alterations in cardiolipin biosynthesis resulting in

loss of tetralinoleoyl-cardiolipin [188] have been associated with Barth syndrome, due to mutations in the *TAZ1* gene that encodes the monolysocardiolipin transacylase [189]. Barth syndrome is an X-linked disorder characterized by mitochondrial cardiac and skeletal myopathy, cyclic neutropenia, and growth retardation [190]. Two commonly associated laboratory abnormalities are urinary excretion of 3-methylglutaconic acid and hypocholesterolemia.

A second disorder of the mitochondrial lipid milieu was recently identified in 15 patients with a congenital myopathy characterized clinically by early-onset muscle weakness and mental retardation with protracted course (most patients were alive at the time of publication and only four had died between the ages of 2½ and 28 years). The hallmark of the disease was the presence in muscle of greatly enlarged mitochondria displaced to the periphery of the fibers [191, 192].

Ten of the patients were Turkish, 4 Japanese, and 1 British, and they all harbored various mutations in the gene (*CHKB*) encoding choline kinase beta, the enzyme that catalyzes the first step in the *de novo* biosynthesis of phosphatidyl choline (PtdCho) and phosphatidylethanolamine (PtdEtn) via the Kennedy pathway.

A new homozygous *CHKB* mutation was found in an American patient, who also had weakness and psychomotor delay and was alive at 2 years [193]. The American patient had COX deficiency in muscle, and impaired RC enzyme activities were documented in muscle from mice harboring a loss-of-function mutation in the ortholog gene *Chkb* and which were affected with retrocaudal muscular dystrophy (rmd) [194].

Sengers syndrome, an autosomal recessive disorder described in 1975 [195] and consisting of congenital cataracts, hypertrophic cardiomyopathy, skeletal myopathy, exercise intolerance, and lactic acidosis, has now been attributed to mutations in the gene (*AGK*) encoding acylglycerol kinase. AGK phosphorylates diacylglycerol and monoacylglycerol to produce phosphatidic acid and lysophosphatidic acid, which are deficient in Sengers syndrome and result in a secondary decrease of the adenine nucleotide translocator (ANT1) in the IMM [196].

A fourth genetic alteration of phospholipid metabolism helped explain many cases of recurrent myoglobinuria in children, which are often not due to known metabolic myopathies [197]. Mutations in the gene (*LPIN1*) encoding the muscle-specific phosphatidic acid phosphatase cause accumulation of phosphatidic acid and lysophospholipids in muscle. Interestingly, carriers of *LPIN1* mutations are prone to develop myoglobinuria upon statin administration [197].

The most recent – but certainly not the last – defect of lipid milieu is associated with a syndrome characterized by 3-methyglutaconic aciduria (3-methylglutaconic aciduria type IV [198], deafness, and Leigh-like encephalopathy, which was dubbed MEGDEL). This syndrome is caused by mutations in the phospholipids remodeling gene *SERAC1*, a key player in intracellular cholesterol trafficking and a member of the mitochondria-associated ER membranes (MAM) [199]. The differences in cardiolipin species composition found in fibroblasts from patients are reminiscent of Barth syndrome and probably explain the respiratory chain dysfunction observed in MEGDEL patients.

Defects of Mitochondrial Dynamics

In keeping with their bacterial origin, mitochondria move, fuse, and divide, often forming tubular networks that may favor a balanced distribution of energy throughout the cell [200]. In fact, mitochondria fuse and split constantly, such as – to quote David Chan – "the identity of any individual mitochondrion is transient" [201]. Any interference with mitochondrial motility, fusion, or fission results in disease, and especially neurological disease, both because the nervous system is highly dependent on oxidative energy and because neurons have long processes and mitochondria have to travel long distances along central axons and peripheral nerves.

In agreement with this concept, most disorders of mitochondrial dynamics involve either the central or the peripheral nervous system. Under "Disorders Characterized by Multiple mtDNA Deletions," we have already discussed the wide phenotypic expression of mutations in *OPA1*, encoding a mitochondrial guanosine triphosphatase (GTPase) involved in mitochondrial fusion and first associated with dominant optic atrophy (DOA) [144, 145]. Mutations in a second gene (*MFN2*) also encoding a mitochondrial fusion protein, mitofusin 2, result in Charcot-Marie-Tooth (CMT) type 2A neuropathy [202], but mutations in *MFN2* have also been associated with a multisystem disorder that includes mitochondrial myopathy with multiple mtDNA deletions [203].

Mutations in KIF5A, whose product, a kinesin, moves mitochondria along microtubules, were associated with a long-tract disorder, autosomal dominant hereditary spastic paraplegia (HSP) type 10 (SPG10) [204].

Mutations in the gene (GDAP1) encoding the ganglioside-induced differentiation-associated protein 1 (GDAP1), a regulator of mitochondrial fission, are responsible for CMT4A, the most common recessive type of CMT [205, 206].

Interestingly for myologists, a form of centronuclear myopathy (CNM) has been associated to mutations in the gene encoding dynamin 2 (*DNM2*) and shows – besides the typical features of CNM – mitochondrial changes with ragged-blue COX-negative fibers [207, 208]. Curiously, DNM2 mutations also cause CMT that may be axonal (CMT2M) or dominant intermediate (CMTDIB) [202, 209]. Dynamin 2 is a GTPase involved in plasma membrane endocytosis, intracellular membrane trafficking, actin assembly, and centrosome cohesion.

The increasing role of altered mitochondrial dynamics in neurological diseases has been reviewed in several recent articles [210–212].

Zidovudine Myopathy

Zidovudine or azidothymidine (AZT) administration is associated with a ragged-red-fiber (RRF) myopathy [213]. This nucleoside analogue lacks a 3′-hydroxyl group and inhibits infectivity of retroviruses (e.g., HIV-I) by incorporating into the replicating viral DNA and causing premature termination of the elongating DNA chain. Patients on AZT with RRF myopathy have reduced amounts of mtDNA in muscle, an iatrogenic form of mtDNA depletion [214]. It was shown that the drug is incorporated into mtDNA in vitro by the DNA polymerase gamma, one of the enzymes responsible for mtDNA replication [215].

Therapeutic Considerations and Conclusions

Therapy for mitochondrial diseases is woefully inadequate. A trite but true statement is that incurable diseases are not untreatable diseases. Two eminently treatable mitochondrial conditions are some of the CoQ_{10} deficiencies and MNGIE [112]. Palliative therapy for other mitochondrial disorders includes pharmacology (i.e., antiepileptic drugs), surgery (i.e., blepharoplasty for ptosis), and physical therapy (i.e., aerobic exercise) [216, 217]. "Cocktails" of vitamins and antioxidants are commonly used, and the pervasive administration of CoQ_{10} in high doses is justified by its safety, by evidence that CoQ_{10} levels are decreased in patients with mitochondrial diseases [218], and by a small randomized therapeutic trial [219]. However, a Cochrane Review concluded that no therapy had shown convincing beneficial results [220].

The history of mitochondrial diseases after the opening of the molecular era in 1988 has been a succession of exciting discoveries [221]. After most of the mtDNA-related disorders had been described, the mitochondrial disorders due to mutations in nuclear DNA have revealed surprising numbers of disease paradigms, from mutations affecting the respiratory chain directly and indirectly to defects of the crucial interaction between the two genomes, to alterations in the phospholipid composition of mitochondrial membranes, and to disorders of mitochondrial dynamics and quality control. The sheer number of nuclear genes controlling mitochondrial structure and function has made progress rather slow, but the advent of exome sequencing is propelling our knowledge of new diseases by leaps and bounces.

Despite recent progress, our knowledge of pathogenesis remains limited; we have not yet tackled the new field of epigenetics [222], and therapy remains our greatest challenge.

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Inflammatory Myopathies

65

Namita Goyal and David A. Chad

Introduction

The inflammatory myopathies comprise three major categories of muscle disease: polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM), conditions that are pathogenetically, histologically, and clinically distinct [1]. Although the inflammatory myopathies are uncommon diseases, they demand attention for several reasons. First, PM and DM are eminently treatable, but improvement and ultimate favorable outcome depend on early diagnosis and prompt initiation of immunotherapy. Although IBM is therapy resistant, accurate diagnosis is critical so that side effects from long-term therapy with potent immunosuppressive drugs are avoided. Second, DM and PM may be associated with disorders of the lungs and heart, as well as with specific connective tissue diseases or neoplasms. Thus, accurate diagnosis of the myopathy should lead the physician to a careful exploration and systematic search for these potentially treatable illnesses before onset of irreversible morbidity. Third, a number of different myopathic and some neurogenic disorders may cause weakness resembling these myositides, particularly PM and IBM. Thus, familiarity with the clinical nuances that characterize PM, DM, and IBM allows the physician to establish an early and accurate diagnosis.

Clinical Features

PM and DM are characterized by subacute (over several weeks to months), progressive, proximal muscle weakness (Table 65.1). There is a bimodal age distribution: one peak occurs in children 5–14 years of age, and a second, larger peak occurs between 45 and 64 years of age [2]. The annual incidence is 5–10 new cases per million per year in the United States. Women outnumber men by 2 to l; moreover, black women have a greater risk for developing this disease than do white women, with the former group showing a higher mortality [2, 3]. IBM progresses more slowly than either PM or DM, on average 6 years from the onset of symptoms to diagnosis. It shows a male predominance, is more common in the white than black population, and is the most common acquired inflammatory muscle disease in patients over the age of 50 years [1, 2, 4–6]. It represents 30 % of inflammatory myopathies referred to a tertiary care center [7].

Table 65.1 Clinical features of polymyositis (PM) and dermatomyositis (DM)

Clinical characteristic	Description
Time course	Weeks to months
Distribution of weakness	Proximal muscles and neck flexors, dysphagia in 30 %, weakness may not be obvious in DM (amyopathic form)
Rash	In DM: heliotrope, V sign, shawl sign, Gottron's sign (all may be subtle)
Childhood form	Yes, primarily DM
Other organ involvement	Interstitial lung disease and cardiac conduction defects most commonly
Associated diseases	Malignancy (especially in DM), connective tissue disease (especially scleroderma)
Diagnostic process	Straightforward for DM, complex for PM with broad differential diagnosis
Response to immunosuppressive treatment	Usually good

In all three forms, weakness of the neck flexors, limb girdle, and proximal muscles is common; in IBM, there is also a predilection for distal muscle involvement (Table 65.2). Dysphagia from involvement of the striated muscle of the upper esophagus and pharynx occurs in 30 % of patients with PM and DM and up to 60 % of patients with IBM [1]. Respiratory muscle involvement is rare but is occasionally seen in the most advanced cases of PM and DM and may occur with an acute form of DM. Although mild facial weakness is occasionally encountered, pronounced facial

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Table 65.2 Clinical features of inclusion body myositis

Clinical characteristic	Description
Time course	Months to years
Distribution of weakness	Proximal muscles and neck flexors; dysphagia in up to 60 %; weakness and wasting tend to be distal, asymmetric, predilection for volar forearm and quadriceps
Rash	None
Childhood form	Very rare
Other organ involvement	Not typically described
Associated diseases	No increase risk of malignancy; connective tissue diseases do occur
Diagnostic process	Often difficult with delay in diagnosis, simulates amyotrophic lateral sclerosis
Response to immunosuppressive treatment	Poor

weakness is not a part of the clinical picture, and extraocular muscles are unaffected; indeed, prominent involvement of cranial muscles should raise the suspicion of another diagnosis. IBM is further distinguished from the other inflammatory myopathies by early and asymmetrical involvement of the finger flexors, wrist flexors, knee extensors, and ankle dorsiflexors [7, 8]. In contrast to PM and DM, where proximal muscles tend to be more affected than more distal groups, in IBM, the shoulder abductors are stronger than the forearm muscles, and the hip flexors perform better than the quadriceps [8]. Indeed, frequent and unexpected falls, a result of pronounced weakness involving the quadriceps, are common complaints in IBM. For reasons not entirely clear, there appears to be a higher incidence of peripheral neuropathy (as indicated by distal sensory loss, attenuated ankle reflexes, and low-amplitude sural nerve action potentials) in IBM compared to PM and DM [8].

A wide range of myopathic disorders may simulate PM and include endocrine myopathy, toxic myopathy, Becker and some limb-girdle dystrophy, late-appearing congenital myopathy, and some metabolic myopathies [9]. The main differential diagnostic consideration for IBM is usually (amyotrophic lateral sclerosis), given the propensity for the former to present with asymmetrical, distal weakness. Distinguishing these two diseases may at times be especially challenging because the electromyographic (EMG) signature of a chronic denervating disease like ALS may be found in some patients with long-standing IBM [10] (see below).

Dermatomyositis is characterized by proximal muscle weakness with a skin rash. The rash often precedes the onset of weakness by weeks to months. Early in its course, rash and muscle enzyme elevations may be the sole manifestations of DM [11]. The rash occurs in light-sensitive areas and is erythematous, edematous, and sometimes pruritic; in the later, healed stages of DM, there may be atrophy of the skin [12, 13]. It characteristically occurs over the knuckles, knees, elbows, anterior chest ("V" sign), back and shoulders ("shawl sign"), malar regions, and bridge of the nose. A pathognomonic heliotrope or purplish discoloration with periorbital edema often involves the upper eyelids. Inspection of the nail beds (aided by magnification) typically discloses dilated capillary loops at the base of the fingernails (periungual abnormalities) with irregular thickened and distorted cuticles. The Gottron sign (also known as Gottron's papules or plaques) refers to symmetric, scaling, erythematous, violaceous raised papules and plaques over bony prominences, especially knuckles, proximal interphalangeal joints, and distal interphalangeal joints but can also be seen on the elbows, knees, and ankles (Fig. 65.1) [12]. "Mechanic's hands" or a rough, cracking appearance of the skin of the fingertips may develop. A less well-recognized eruption seen in DM is an erythematous, scaling, and atrophic rash (known as poikiloderma), particularly over extensor surfaces and upper back [14]. Calcium deposits within the skin, known as calcinosis cutis, may occur in juvenile DM but are uncommon in adult DM.

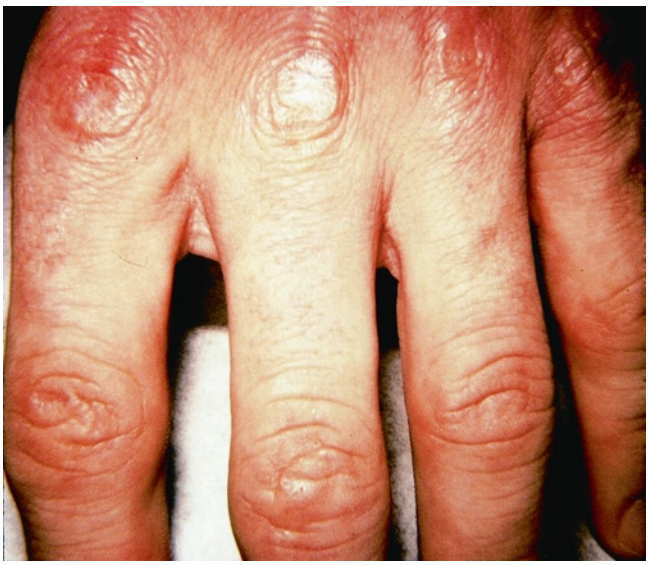

Fig. 65.1 Gottron sign. There is a scaly raised plaque on the middle finger joint. Over the other joints, there is a violaceous erythema

Other Organ Involvement

In both PM and DM, the lungs [14–17] may be involved (Table 65.3). Respiratory symptoms occurring in PM and DM may have a number of different causes, some pulmonary and others non-pulmonary. For example, in the latter category, there may be frank ventilatory insufficiency due to generalized respiratory striated muscle weakness, or dyspnea may result from the rare development of congestive heart failure in the setting of severe cardiac involvement [13].

Table 65.3 Causes of respiratory symptoms in polymyositis and dermatomyositis

Non-pulmonary	Pulmonary
Respiratory muscle weakness	Chronic aspiration
Congestive heart failure	Pyogenic and atypical infections
	Methotrexate toxicity
	Interstitial lung disease

Pulmonary causes comprise parenchymal pulmonary changes stemming from chronic aspiration, pyogenic and atypical lung infections (related to immunosuppressive therapeutics), medication toxicity (notably methotrexate), and interstitial lung disease (ILD) [13].

The prevalence of ILD depends upon the method used to detect lung pathology, with an overall frequency of 5–10 % by radiographic evidence and as high as 30–40 % when pulmonary function testing is employed [17]. ILD may be associated with rapidly progressive respiratory failure. An important serum marker is the anti-Jo-1 antibody (see below), present in more than 50 % of patients with ILD [17–19].

Although clinically symptomatic cardiac involvement in PM and DM, such as congestive heart failure, pericarditis, pulmonary hypertension, and valvular disease, is uncommon, electrocardiographic abnormalities occur in up to 40 % of patients [13]. They comprise nonspecific ST-T wave changes (most frequently), varying degrees of heart block and bundle branch block, and tachyarrhythmias.

Associated Connective Tissue Disorders

The inflammatory myopathies are associated with connective tissue diseases in about 20 % of patients [2]. This so-called overlap group is rather heterogeneous because of the wide variety of conditions that have been linked to PM and DM. They comprise scleroderma, systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjögren's syndrome, and mixed connective tissue disease [18]. Patients with the overlap syndrome are more likely to present with arthralgia, and arthritis and their muscle disease is often milder than in isolated PM or DM and more responsive to therapy.

Although symptoms of muscle pain and weakness are frequent complaints in patients presenting with one of these connective tissue diseases, active myositis is uncommon in scleroderma (5–17 %), SLE (<10 %) and rheumatoid arthritis (13 %), and rare in Sjögren's syndrome [20].

It has become increasingly clear that IBM is also associated with autoimmune diseases like Sjögren's syndrome [21] and SLE [22]. It is also associated with autoantibodies as well as with monoclonal gammopathies, which often recognize various muscle components, especially myonuclei, suggesting disturbed immunoregulation [23, 24].

Association with Malignancy

Although the validity of a possible cause and effect relationship between cancer and inflammatory myopathy has been questioned [25], there is probably a substantially and statistically significant increased association between cancer and DM compared to the normal population. Devere and Bradley [26] found that 40 % of patients over the age of 39 with DM had cancer, whereas only 3.4 % of older patients with PM were found to have a neoplasm. Callen suspects that "roughly 25 % of patients with DM have had, will have, or will develop an internal malignancy," in contrast to only a small increased risk in PM [27]. IBM has not been associated with an increased risk of malignancy [7].

The diagnosis of malignancy can precede or follow the myopathy by months to several years, but most malignancies are identified within 2 years of the presentation of myositis. It is generally thought that ovarian cancer may be overrepresented in women with DM. Callen's review of the literature, however, indicates that any type or site of malignancy is possible, that the tumor site is determined by the prevalence of the tumor in the population, and that sites involved are age related [27]. Several clinical and laboratory features are negatively associated with malignancy, including an accompanying connective tissue disease, pulmonary fibrosis, and a myositis-specific antibody (see below) [27].

We recommend undertaking a careful screening for malignancy in patients presenting with PM or DM, especially the latter. This should include a thorough general physical examination, including the rectum, pelvis, breast, and testicles. Laboratory testing includes routine hematological and biochemical studies, stool analysis for occult blood, chest roentgenogram, mammography and pelvic ultrasound in women, and prostate-specific antigen. Further radiological procedures such as computerized tomography and magnetic resonance imaging studies of the chest, abdomen, and pelvis may be indicated if the initial screening studies reveal a suspicious structural alteration from normal appearance. Early tumor recognition is obviously crucial, and there are reports of improvement in DM with tumor resection [27].

Association with Autoantibodies

Myositis-specific autoantibodies (MSA) are directed primarily against cytoplasmic ribonucleoproteins involved in the process of protein synthesis and are found almost exclusively in patients with myositis (the PM and DM forms, not IBM) [18, 19]. They are heterogeneous with each one occurring in only a small proportion of patients with PM and DM (Table 65.4). It is rare for a patient to have more than one MSA, and hence each one defines a specific subgroup of patients [28]. Although the absence of an MSA cannot exclude

Table 65.4 Myositis-specific autoantibodies in polymyositis and dermatomyositis

Autoantibody	Clinical features
Anti-synthetase (anti-Jo-1)	20 % of DM and PM patients, acute onset in spring, association with interstitial lung disease and nonerosive arthritis, frequent relapse during prednisone taper
Anti-SRP	5 % of PM, onset in autumn, acute weakness with myalgias, frequent myocarditis, resistance to prednisone, poor prognosis (25 %, 5 year survival)
Anti-Mi-2	5–10 % of DM, acute onset with florid rash, good response to immunosuppressive therapy

DM dermatomyositis, *PM* polymyositis, *SRP* signal recognition particle, *Mi* nuclear helicase

Table 65.5 The laboratory diagnosis of idiopathic inflammatory myopathy

Laboratory feature	Finding(s)
Serum CK	Elevated: 5- to 50-fold in PM and DM, 3- to 5-fold in IBM, rarely normal in early or mild DM
ESR	Usually normal, may be elevated in presence of connective tissue disease or malignancy
Electromyography	Abnormal in the majority showing a combination of increased insertional activity/positive waves/fibrillation potentials and short-duration/low-amplitude/polyphasic MUAPs and early recruitment; sometimes, mixed with large MUAPs when chronic
Muscle biopsy	Abnormal in the vast majority with unique histology for DM and IBM and inflammation with muscle fiber necrosis and degeneration/regeneration common to all forms

the diagnosis of PM or DM, their presence has strong predictive value defining subgroups of patients with similar clinical manifestations, disease severity, and response to therapy.

Clinically, the most important MSAs are the *anti-synthetase antibodies*, found in 25–30 % of patients with PM/DM; the *anti-SRP* (*signal recognition particle*) *autoantibody* detected in 4–5 % of cases of PM; and the *anti-Mi-2* (*nuclear helicase*) *autoantibody* found in 5–10 % of DM patients [19]. A fourth autoantibody, the *anti-PM-Scl autoantibody*, is more appropriately designated myositis associated (rather than specific) because it is most closely associated with connective tissues disease and is found in the overlap syndrome—PM associated with scleroderma. Fifty percent of autoantibody positive patients have this clinical combination, others have an undifferentiated connective tissue disease, and some have scleroderma without myositis [28]. Anti-U1RNP has a strong association with myositis in the context of mixed connective tissue disease (features of scleroderma, SLE, rheumatoid arthritis) but is also not specific [19]. Similarly, anti-Ro/SSA autoantibody is more closely associated with connective tissue disease than myositis per se.

Among the five anti-synthetases that have been defined, *anti-aminoacyl tRNA synthetase* (*anti-Jo-1*) MSA is the most prevalent, occurring in 20 % of patients with PM and DM. The anti-Jo-1 autoantibody is directed at histidyl-tRNA synthetase, the cytoplasmic enzyme responsible for catalyzing the formation of histidyl-tRNA from histidyl and its cognate RNA. Anti-Jo-1 positive patients often have a constellation of clinical features, termed *the anti-synthetase syndrome*, comprising the acute onset of myositis in the spring, associations with a nonerosive symmetrical small joint arthritis, low-grade fevers, Raynaud's syndrome, mechanic's hands, frequent relapse with tapering of corticosteroids (see below), and perhaps, most importantly, interstitial lung disease (found in 50–75 % of patients who are anti-Jo-1 positive) [18, 19, 28]. A small number of patients with anti-Jo-1 autoantibody have no evidence of myositis but have other features of the syndrome.

Patients with the anti-SRP autoantibody, almost exclusively in PM, present with acute onset of severe weakness and myalgias in the autumn [19]. Their disease is characterized by frequent cardiac involvement (myocarditis), resistance to immunotherapy, and poor prognosis. Patients with anti-Mi-2 autoantibody (unique because it is directed at a nuclear antigen, in contrast to the other MSAs) virtually all have DM and present with weakness and a florid rash (50 % have the shawl sign and nearly 100 % the V sign). Response to therapy is good and the prognosis is favorable.

Diagnosis

Laboratory Features

Routine hematological and clinical chemistry laboratory and radiologic studies are generally normal unless there is an underlying neoplasm or overlap syndrome with associated connective tissue disease. In the event of the latter, the ESR may be elevated and testing for antinuclear antibodies may be positive. Creatine kinase (CK) is a very sensitive serum enzyme for the diagnosis of myositis, found to be normal in only 4.6 % of patients with PM and DM described by Bohan and colleagues [29]. Nearly 90 % of patients with myositis have CK elevation [30]. Normal values may be found in those with mild or early disease, particularly in instances of DM or IBM [11]. In most patients with PM and DM, CK levels are elevated 5–50 times above normal [11], while in the majority of those with IBM, the CK elevations are mild, usually three- to fivefold normal, rarely exceeding tenfold increases (Table 65.5) [7]. Although other enzymes including lactate dehydrogenase, the transaminases, and, notably, the highly sensitive aldolase are also elevated in active myositis, the CK is most reliable, correlating best with clinical course and other markers of disease activity [29].

Table 65.6 Electromyography in idiopathic inflammatory myopathy

Stage of the disease	Findings
Acute	Fibrillation potentials and positive waves; complex repetitive discharges
	Short-duration, low-amplitude, polyphasic MUAPs
	Early recruitment of motor unit action potentials
Chronic	As above with addition of a population of high-amplitude, long-duration, polyphasic MUAPs (mixed potentials)
Long standing (end stage)	Features of acute and chronic stages and a reduction of motor unit action potentials with reduced recruitment

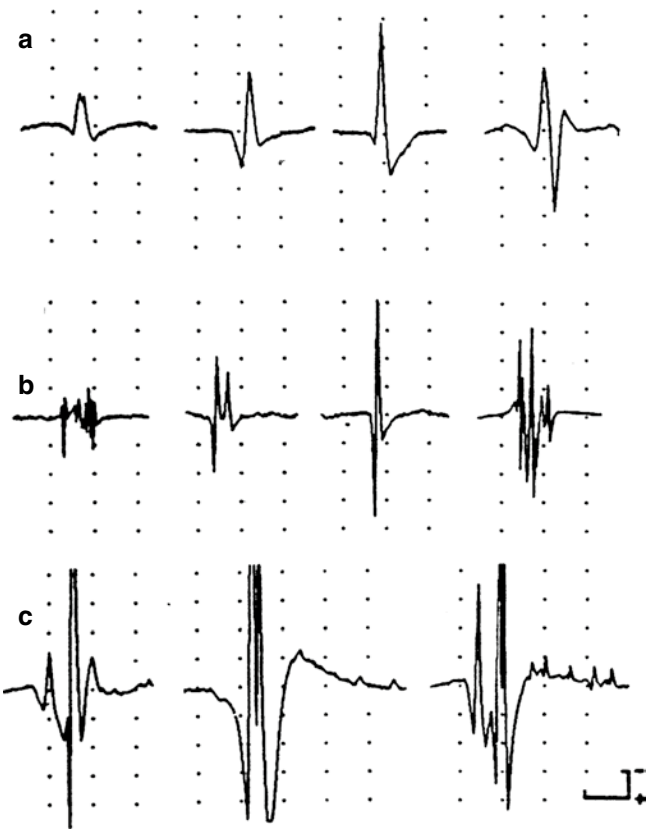

Fig. 65.2 Motor unit action potentials (MUAPs) typical of active myositis (**b**). The MUAPs are short in duration, low to moderate in amplitude, "spikey," and polyphasic. Contrast with normal MUAPs (**a**) and large-amplitude, long-duration MUAPs seen in neurogenic disease (**c**) (Reproduced with permission from Bromberg and Albers [37])

Electromyography

Needle electromyographic (EMG) study is of great importance in the evaluation, diagnosis, and management of the inflammatory myopathies (Tables 65.5 and 65.6). The classic needle EMG changes in the acute stages of active myositis comprise three major abnormalities [31–37]:

1. *Increased insertional activity*, *positive sharp waves*, *fibrillation potential activity*, *and complex repetitive discharges*. Although these electrodiagnostic features have long been viewed as the hallmarks of acute neurogenic disease, they may also be produced by segmental necrosis of muscle fibers [38]. In this latter case, the necrotic muscle segment separates a distal, healthy portion of the muscle fiber from the part carrying the end plate. An important observation is that fibrillation potentials in myositis are most frequent in paraspinal muscles, so that the study of these muscles should be part of every work-up for myositis (see below) [34–41].
2. *Short-duration*, *low-amplitude*, *and polyphasic motor unit action potentials* (*MUAPs*)—so-called "myopathic" MUAPs (Fig. 65.2). These changes are thought to result from a decrease in the number of functioning muscle fibers per motor unit and from the loss of synchronous firing of the remaining fibers whose function is impaired [36].
3. *Early or rapid recruitment of MUAPs*, where more MUAPs than expected are discharging for a given level of force (Fig. 65.3). This behavior is a reflection of the decreased number of functioning muscle fibers in each motor unit [36, 37, 42].

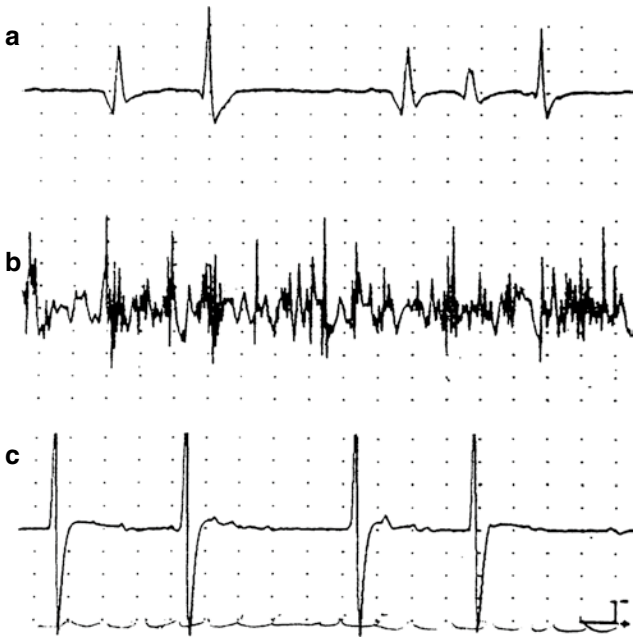

Fig. 65.3 Early or increased recruitment of MUAPs in myositis with many short-duration polyphasic MUAPs despite low level of force (**b**). Contrast with normal recruitment with three MUAPs firing (**a**) and decreased recruitment with one high-amplitude MUAP firing rapidly in neurogenic disease (**c**) (Reproduced with permission from Bromberg and Albers [37])

In the chronic stages of myositis (histologically defined by ongoing muscle fiber necrosis and inflammation), some of the MUAPs are high in amplitude, long in duration, and polyphasic with satellite potentials (Fig. 65.4) [10, 42–44]. These alterations in MUAP appearance probably result from reinnervation by secondary collateral sprouting to the previously denervated muscle fiber segments (see above). Indeed, single-fiber EMG studies in PM [45] and IBM [10, 46] disclose increase in fiber density, increased jitter, and blocking.

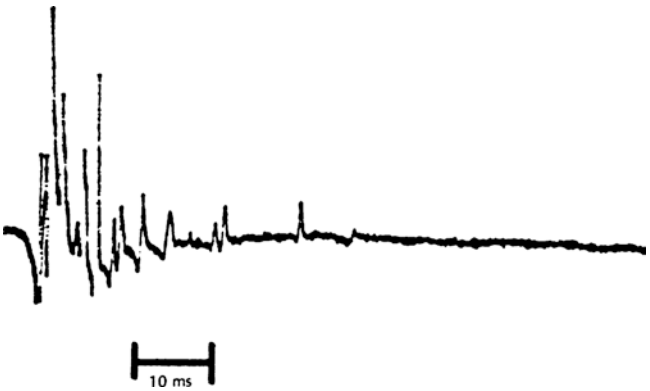

Fig. 65.4 A highly complex MUAP with satellite components gives the total motor unit a long duration (Reproduced with permission from Daube [42])

Table 65.7 Approach to the EMG diagnostic study for inflammatory myopathy

Test	Goal/rationale
Sensory nerve conduction studies	Exclude polyneuropathy (expected to be normal in PM and DM, occasional abnormalities in IBM)
Motor nerve conduction studies	Exclude polyneuropathy and Lambert-Eaton myasthenic syndrome (expect to be normal in PM, DM, IBM except when there is pronounced distal muscle involvement)
Repetitive nerve stimulation	Exclude myasthenia gravis and Lambert-Eaton myasthenic syndrome (expect to be normal in PM, DM, IBM)
Needle EMG	Cast a broad net and always include paraspinal muscles
	Examine most proximal, proximal, mid-limb, and distal in arms and legs
	Examine one side, leaving the other for muscle biopsy

Increased jitter and blocking probably reflects necrotic segments receiving new axonal sprouts, while the increase in fiber density is likely produced by fiber atrophy (as more fibers are close to the recording electrode) and fiber splitting [45, 47]. After two or more years of myositis (PM, DM, and IBM), it is common to encounter in the same muscle the combined presence of long- and short-duration MUAPs, also known as mixed potentials [7]. Finally, in end-stage muscle, loss of all the fibers belonging to some units will lead to a net loss of MUAPs, the EMG signature of which is reduced recruitment.

The electrodiagnostic examination in a patient with, or suspected of, inflammatory myopathy begins with nerve conduction studies (Table 65.7). Sensory amplitudes, distal latencies, and conduction velocities are expected to be normal, unless there is a coexisting poly- or mononeuropathy. In IBM, several studies found an increased incidence of a mild axon-loss peripheral neuropathy [8, 10, 46]. Because conventional motor nerve study parameters are usually measured from distal—small hand and foot—muscles, motor amplitudes are typically normal or only mildly attenuated in myositis. If there is substantial distal muscle involvement, however, motor amplitudes might be reduced. Marked generalized attenuation of motor amplitudes should raise the possibility of Lambert-Eaton myasthenic syndrome and prompt further detailed testing of neuromuscular transmission. Yet, even if distal amplitudes are within the normal range, we generally proceed with repetitive nerve stimulation in the evaluation of the suspected inflammatory myopathy patient because disorders of the neuromuscular junction—both myasthenia gravis and Lambert-Eaton myasthenic syndrome—may present with limb-girdle and proximal muscle weakness.

The needle EMG electrode examination should "cast a broad net." The distribution of EMG findings in PM and DM correlates with the pattern of weakness detected by clinical examination, so that fibrillation potential activity and abnormal MUAPs follow a proximal to distal gradient [37]. In IBM, however, the EMG abnormalities are often strikingly asymmetrical, multifocal, and distally predominant. The needle EMG examination study should always include paraspinal muscles, an approach that derives from the work of several groups [29, 40], notably Streib et al. [41]. These authors performed detailed needle-electrode examinations on 40 patients with inflammatory myopathy. In each patient, eight or more muscles were studied. In 35 % of patients, fibrillation potential activity was found in all examined muscles; in another 35 %, more than ½ of the muscles examined revealed these potentials; in 20 % of patients, <½ of the muscles revealed fibrillation potentials; and in 10 % of patients, fibrillations were found in only one or two muscles. In every patient, fibrillation potentials were found in at least one muscle. The yield of fibrillation potential activity was greatest for paraspinal muscles (93 % of tests performed) and lowest for the first dorsal interosseous (47 %). The yield was greater than 75 % each for each of the spinati, biceps, triceps, and brachioradialis; approximately 75 % for each of the glutei and iliacus; 70 % for the tibialis anterior; 50 % for the gastrocnemius; and 64 % for the vastus lateralis.

The EMG provides an excellent gauge of disease activity [36]. In the phase of active myositis, fibrillation potential activity, positive sharp waves, and increased insertional activity all tend to be widespread and abundant along with "myopathic" MUAPs (Fig. 65.5). With successful treatment (see below), there is a trend toward a decrease in features of "membrane irritability" and a diminution in the proportion of "myopathic" MUAPs. Another indication of treatment response is the presence of only small-amplitude positive waves or fibrillation potentials, in contrast to the 100- to 200-μV size fibrillation potentials seen in the acute phase following partial muscle fiber necrosis [35]. The EMG may also be helpful in determining if the clinical deterioration in a previously stable prednisone treated patient is caused by

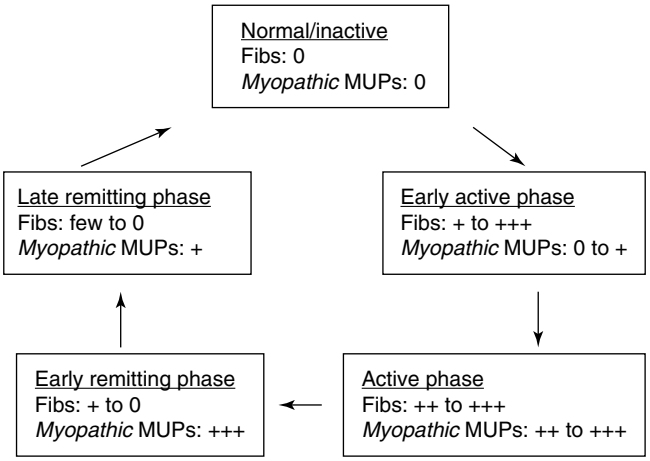

Fig. 65.5 The cycle of EMG changes during stages of polymyositis (Modified with permission from Wilbourn [36]).

Table 65.8 Muscle biopsy findings in the idiopathic inflammatory myopathies

Histopathologic finding	Distinguishing features
Mononuclear cell inflammation	In PM and IBM, inflammation is endomysial; in DM, it is perivascular and interfascicular
Muscle fiber degeneration/regeneration	In PM and IBM, scattered throughout fascicles; in DM, perifascicular; in IBM, there are rimmed vacuoles
Fiber size variation	In IBM, small fibers tend to group or cluster
Oxidative enzyme staining alterations	In DM, occur in perifascicular regions
Capillary damage	Characteristic for DM is capillary endothelial cell damage (with tubuloreticular inclusions by EM) and immune deposits; no alterations in PM and IBM
Muscle nuclei	In IBM, intranuclear (and intracytoplasmic) filamentous inclusions

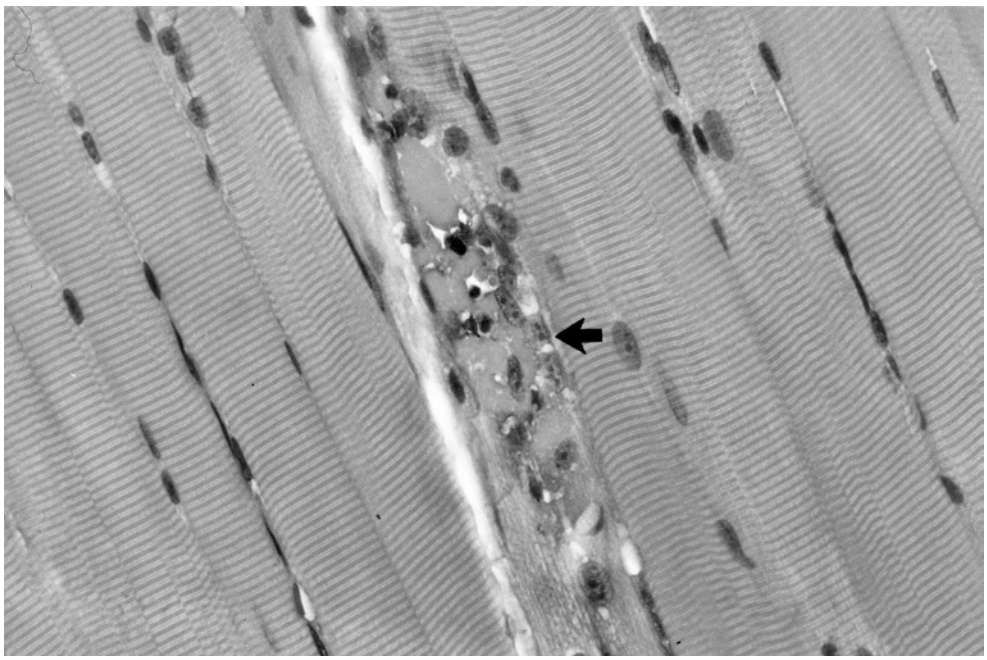

Fig. 65.6 Polymyositis. Segmental necrosis. There is a necrotic muscle fiber (*arrow*) in the center of the photomicrograph surrounded by healthy-appearing muscle fibers. The necrotic fiber has lost normal cross striations. Hematoxylin and eosin × 100 (original magnification)

recrudescence of myositis (disease activity) or instead marks the onset of a superimposed corticosteroid-related myopathy. Steroid myopathy would be favored by finding no evidence of positive waves or fibrillation potentials in the face of the early recruitment of short-duration, low-amplitude MUAPs, while prominent fibrillation potentials with a similar voluntary MUAP pattern would favor recurrent myositis.

Muscle Biopsy

This diagnostic tool is of great importance in the evaluation of a suspected inflammatory myopathy (Table 65.8). Not only does it help exclude other potential causes for the patient's symptoms but also it reveals abnormal histological features unique for DM, IBM, and PM [11]. In general, the inflammatory myopathies are characterized by *segmental muscle fiber necrosis* (Fig. 65.6), *muscle fiber regeneration*, *and mononuclear cell inflammation* (Fig. 65.7). In PM, the inflammatory cells are found among muscle fibers (Fig. 65.8), while in DM, the inflammation is primarily perivascular (Fig. 65.9) and interfascicular [1, 2].

Both DM and IBM have histologically distinctive features of an inflammatory nature so that the diagnosis of these myositides may be suspected in the setting of typical clinical and histopathologic pictures even in the absence of inflammation. Two histologic patterns of muscle fiber injury are characteristic of DM: perifascicular atrophy (Fig. 65.10) and, less

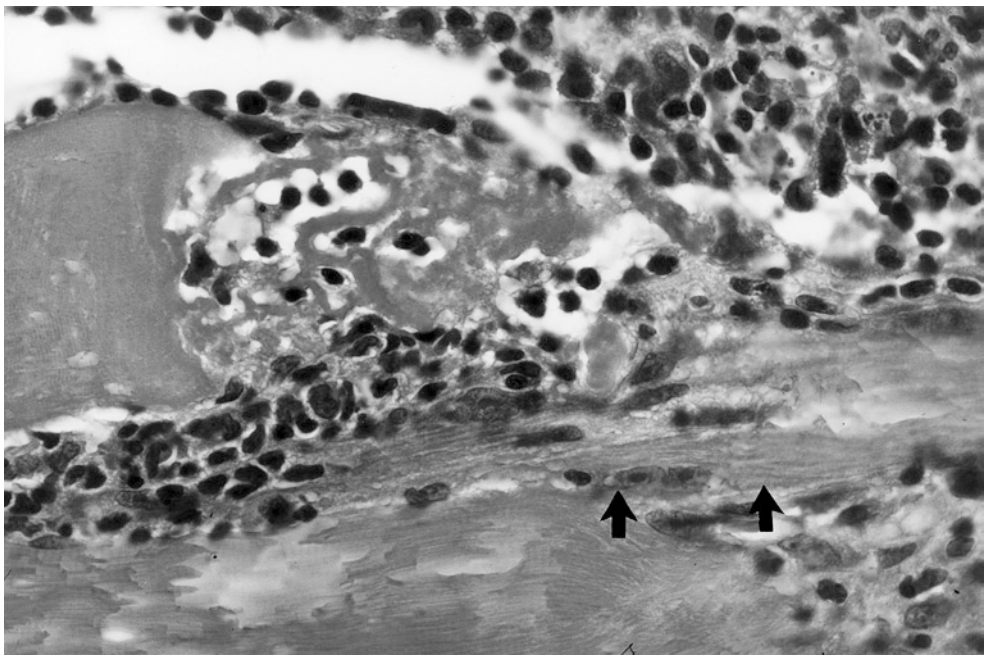

Fig. 65.7 Polymyositis. There is a necrotic muscle fiber surrounded and invaded by mononuclear inflammatory cells. A regenerating fiber is seen adjacent to the necrotic segment (*arrowheads*). Hematoxylin and eosin × 150 (original magnification)

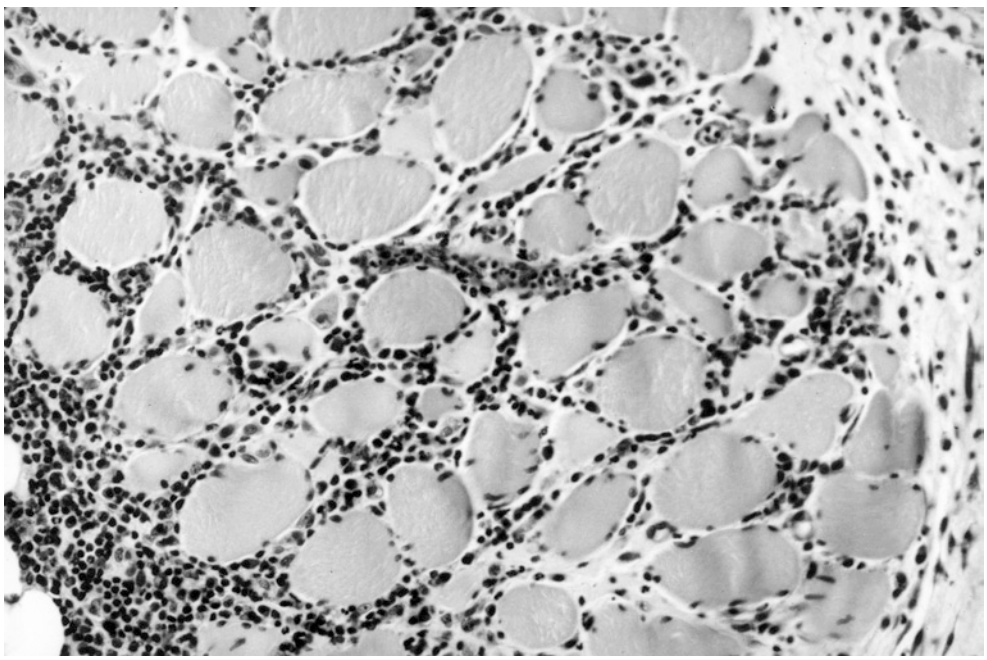

Fig. 65.8 Polymyositis. Inflammatory mononuclear cells surround nonnecrotic muscle fibers. There is pronounced variation in muscle fiber size, and many fibers are atrophic. Hematoxylin and eosin × 50 (original magnification)

commonly, wedge-shaped muscle microinfarcts [11]. Both reflect the presence of a primary abnormality of blood vessels causing ischemic injury to muscle fibers. Perifascicular atrophy is characterized by two to ten layers of atrophic fibers at the periphery of the fascicles [11].

The histologic picture of IBM resembles PM in that in endomysial lymphocytic inflammation, fiber necrosis with phagocytosis and regeneration are present, although these features may be variable and even absent. The characteristic light microscopic features of IBM are *rimmed vacuoles* (Fig. 65.11) within a variable number of muscle fibers [4–7]. Electron microscopy reveals the presence of bundles of 15–18 nm diameter tubular filaments (Fig. 65.12) in the vicinity of the rimmed vacuoles or in the nuclei [4–7].

Intracellular amyloid deposits have been demonstrated in muscle fibers of IBM with Congo red [48]. They were mostly intracytoplasmic, but some were also present in the nucleus. Recent studies have demonstrated that rimmed vacuoles in

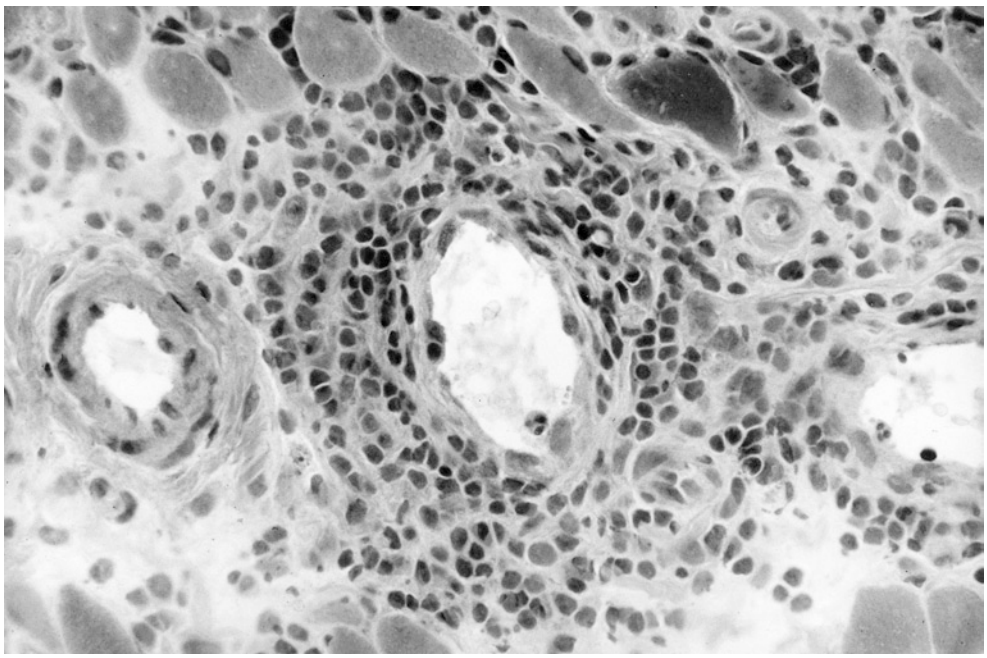

Fig. 65.9 Dermatomyositis. There is pronounced perivascular inflammation in the interfascicular space. Hematoxylin and eosin × 50 (original magnification)

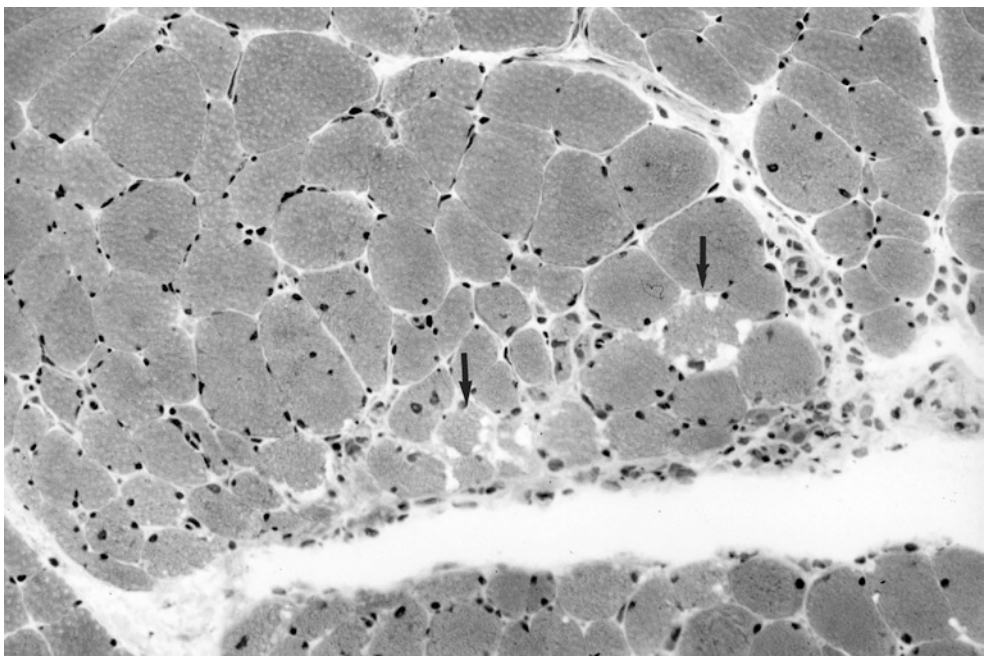

Fig. 65.10 Dermatomyositis. Perifascicular atrophy. Many muscle fibers at the edge of the fascicles are atrophic. Some degenerating fibers are vacuolated (*arrows*). Hematoxylin and eosin × 50 (original magnification)

IBM may show immunoreactivity for "brain-specific" proteins such as β-amyloid, prion protein, phosphorylated tau, ubiquitin, and apolipoprotein E [49]. In some biopsies, there are mitochondrial alterations, manifested by cytochrome oxidase-negative fibers, scattered ragged-red fibers, and an increased number of mitochondria, some containing paracrystalline inclusions noted by electron microscopy [50]. Mitochondrial deletions have also been found in at least half of the patient population with IBM [51].

In PM, the histological findings of fiber necrosis and regeneration lack the requisite specificity for a diagnosis to be established without primary endomysial inflammation being present in at least one muscle biopsy specimen [11]. In some instances (12.5 % in the study of Bohan and colleagues in 1977 [29]) in otherwise typical PM or DM, the muscle biopsy is normal or only mildly and nonspecifically abnormal. Although for some patients the explanation may relate to the mild nature of their disease or to sampling errors, in

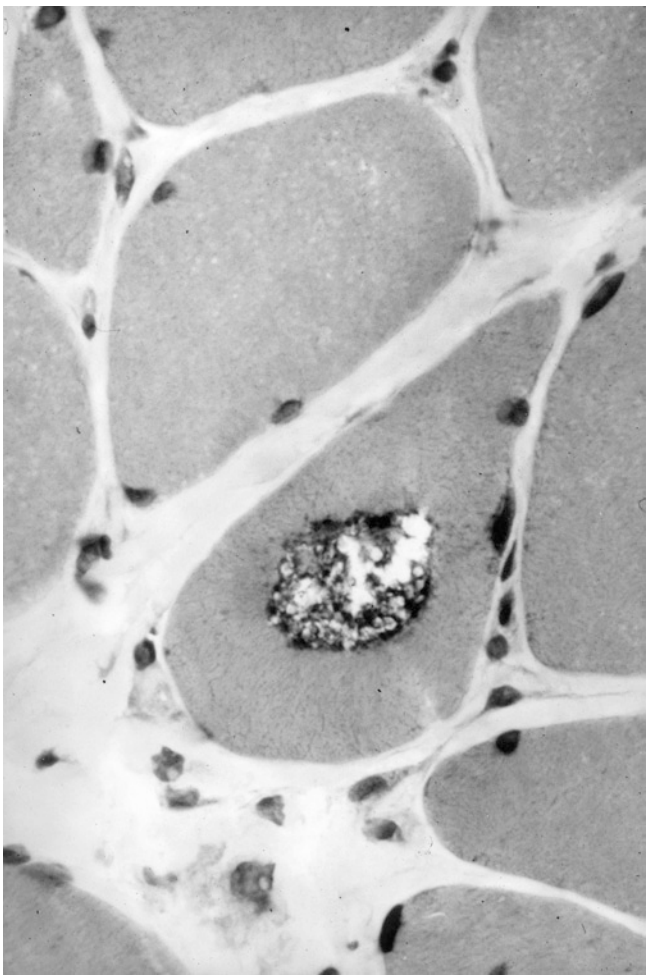

Fig. 65.11 Inclusion body myositis. A vacuole containing basophilic granules ("rimmed vacuole") is seen within a muscle fiber. Hematoxylin and eosin × 1,000 (original magnification)

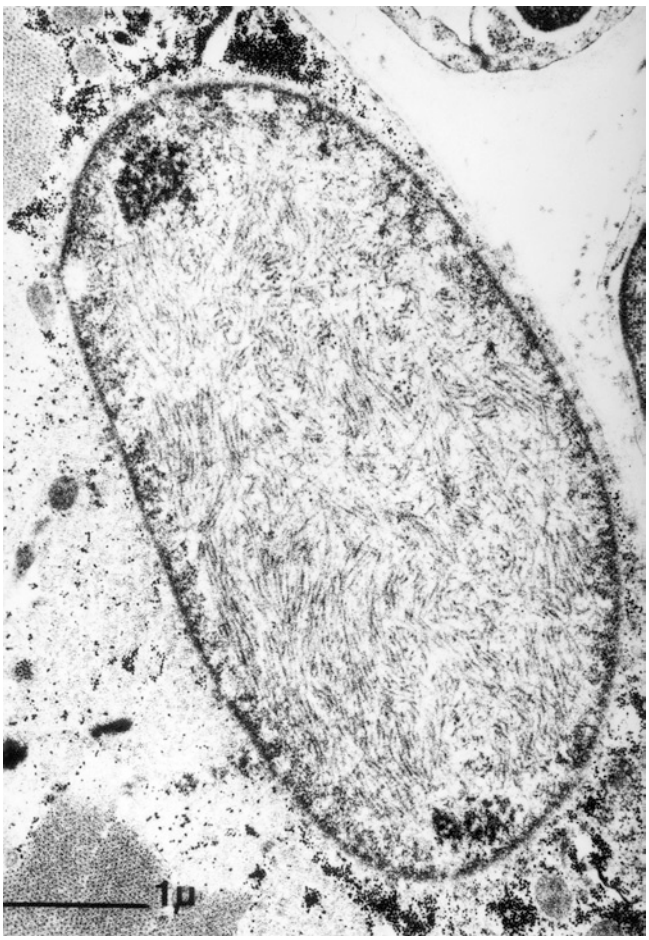

Fig. 65.12 Inclusion body myositis. Intranuclear tubular inclusions, 13–18 nm in diameter × 16,000 (original magnification)

others, a satisfactory reason remains elusive. When reading muscle biopsies, it is important to bear in mind that some of the cardinal features of myositis (necrosis, regeneration, and inflammation) may also be found in the muscular dystrophies and the chronic neurogenic atrophies.

Pathogenesis

Although the exact mechanism of fiber damage is not completely known, there is evidence for an immune pathogenesis in the inflammatory myopathies. In DM, the intramuscular microvasculature is believed to be the early and specific target of a humorally mediated process involving the complement membrane attack complex (MAC) [52–54]. The earliest lesion that precedes inflammation or structural changes in muscle fibers is deposition of the C5b-9 membrane attack complex (MAC) in intramuscular capillaries [55]. Complement deposition leads to necrosis, and thrombosis of capillaries, small arteries, and venules found predominantly in the periphery of the fascicle, resulting in ischemia, myofiber destruction, and perifascicular atrophy. Consistent with the notion that dermatomyositis is mediated largely by humoral immunity is that the inflammatory infiltrate is composed mainly of B cells and helper T cells.

In PM and IBM, histologic findings suggest a cell-mediated immune response directed against muscle fibers [1]. The majority of inflammatory cells are made up of T cells and macrophages. These cytotoxic and suppressor T cells are thought to recognize antigenic targets associated with major histocompatibility complex 1 antigen in muscle fibers, as they surround and destroy healthy, nonnecrotic fibers. In IBM, the filamentous inclusions resemble myxovirus nucleocapsids, and therefore a viral pathogenesis has been suggested but never proven. Immune and degenerative mechanisms appear to be involved in the pathogenesis of IBM, but the relative importance of each is not clear. The observation that quantitative studies of the major histological alterations in IBM reveal a several fold more frequent occurrence of invasion of nonnecrotic fibers by T cells than

Congo-red-positive fibers indicates that immune-mediated mechanisms may be important [56]. On the other hand, the decrease in inflammation during the course of prednisone treatment for IBM while the number of vacuolated and amyloid-positive fibers increases suggests that immune mechanisms are secondary and that the disease is primarily degenerative [57].

Differential Diagnosis

The presence of characteristic weakness and rash, elevation of CK, abnormal EMG, and distinctive histopathology establishes the diagnosis of definite DM. The condition is deemed mild or early DM if there is a characteristic rash and minimal weakness, mild CK elevation, and equivocal abnormalities on EMG, in the setting of a nonspecifically abnormal biopsy that does not show the characteristic pathology of DM (see above) [11]. The diagnosis of IBM is suggested by the clinical characteristics of a long course, distal involvement and asymmetries, the modest CK elevation, myopathic EMG, and the unique histological appearance (see above). Not uncommonly, however, IBM is initially diagnosed as PM, usually because the muscle biopsy specimen fails to disclose the clues of rimmed vacuoles and myopathic grouping and electron microscopy is either not done or does not reveal the characteristic cytoplasmic inclusions. In these cases, lack of response to immunotherapy leads to reconsideration of the diagnosis and a second muscle biopsy, which may establish the diagnosis. The diagnosis of PM is most challenging of all [58]. Without characteristic cutaneous manifestations, a unique distribution of weakness, a defining EMG signature, or a specific pathological appearance, PM may simulate the dystrophies and metabolic myopathies. In addition, infection of muscle, sarcoidosis, endocrinopathies, and the effects of certain drugs and toxins may all produce a similar pattern of muscle weakness. The presence of a myositis-specific autoantibody in patients undergoing an evaluation for suspected inflammatory myopathy has assisted in establishing the diagnosis of PM [19].

Necrotizing myopathy (NM) is a distinct entity in which the dominant histological feature is muscle fiber necrosis; in contrast to DM, IBM, and PM, there is no inflammation and yet NM is thought to be an immunologically mediated condition [59]. It may occur as a manifestation of a paraneoplastic disorder and may be seen in some patients with anti-SRP antibodies and the anti-synthetase syndrome. NM has also been described in a small percentage of patients with a history of statin use. The clinical scenario among this subset of patients taking statins is that following the onset of weakness, the drug is appropriately discontinued and yet weakness persists, and this leads to the decision to undertake a muscle biopsy; the histological picture is one of muscle fiber necrosis without inflammation. When patients are treated with aggressive immunosuppressive therapy, many respond suggesting to investigators that the most appropriate designation for this myopathic disorder is "statin-associated, immune-mediated necrotizing myopathy." Further support for the role of immunity in the pathogenesis of statin-associated NM is its association with autoantibodies directed to a 100-kDa antigen identified as the 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) protein [60].

Treatment

The natural history of PM and IBM without therapy has not been formally studied. It is possible that in some patients, these diseases may improve or resolve spontaneously. Corticosteroid treatment of PM and DM is started when weakness interferes with activities of daily life. Patients with minimal weakness may be closely followed without specific treatment. We recommend prednisone at 1 mg/kg per day taken as a single morning dose and institute corticosteroid precautions.

Although some patients may improve within days to a couple of weeks, improvement in others may be delayed for 4–6 weeks. It is difficult to know when to start reducing the dose of prednisone, but we generally maintain a high daily dose for 3–4 weeks (unless an unacceptable side effect develops) [1]. Once a clear sustained improvement in muscle strength occurs and the serum CK level falls, one may gradually taper the dose of prednisone over a period of 10 weeks to a dose of 1 mg/kg every other day [1]. If improvement continues during the period of conversion, one can then continue to taper by 5–10 mg every 3–4 weeks until the lowest possible dose which controls the disease is reached. A patient destined to have a good response generally shows substantial return of function in the first 4–6 months of treatment.

In patients on long-term corticosteroid therapy, corticosteroid myopathy is a consideration when an increase in weakness occurs without a major change in serum CK, especially if the urinary creatine is elevated [61]. If a trial of reduced corticosteroid therapy leading to improvement is demonstrated, the diagnosis of corticosteroid myopathy is confirmed. These patients usually also have other steroid side effects. An EMG may also help to distinguish corticosteroid myopathy from more severe inflammatory myopathy. In the latter, abundant fibrillation potentials are expected in weak muscles, whereas in the former, these potentials are usually absent.

Some patients with PM and DM will fail to respond to prednisone even after 12 weeks of high-dose daily treatment [29]. A number of cytotoxic immunosuppressive agents have been used with varying degrees of success in this situation, and these include azathioprine, methotrexate, cyclophosphamide,

chlorambucil, and cyclosporine [1, 11, 62]. Although successful in some, in other patients, improvement may be only partial and slow in coming. In refractory cases of PM, intravenous gamma globulin (IVIG) was demonstrated to have a beneficial effect in uncontrolled studies [63]. For DM, a placebo-controlled study showed dramatic improvement in muscle strength and skin rash [55]. Repeated muscle biopsies showed improvement in the muscle fiber diameters with resolution of the immunopathology [63]. More recently, several small case series or case reports have shown clinical improvement using rituximab in both DM and PM [64–67].

Despite the inflammatory component on muscle biopsy, IBM has been noted to be relatively resistant to traditional immunosuppressive therapy. A number of immunosuppressive agents have been evaluated in therapeutic trials for IBM; however, none have shown significant clinical improvement. A double-blind, placebo-controlled crossover study of IVIG in IBM failed to show a statistically significant improvement in overall muscle strength. There was, however, a trend toward improvement in swallowing and lower limb strength [68] suggesting that a role may yet be found for IVIG in IBM, perhaps as a stabilizing modality [69]. Another double-blind, placebo-controlled study of IVIG and high-dose corticosteroids failed to show changes in muscle strength and concluded that the combination of prednisone and IVIG was ineffective in treating IBM [70].On a positive note, one study showed that the inflammatory myopathy with cytochrome oxidase (COX)-negative muscle fibers, which resembles IBM clinically with slow progression and resistance to corticosteroids, showed improved muscle strength in response to methotrexate therapy [71].In general, empiric treatment with immunotherapy can be attempted in patients with IBM; however, if muscle strength continues to decline, therapy should be discontinued given the risks of long-term steroid and immunosuppressive therapy along with the lack of supportive clinical evidence that immunotherapy is beneficial in IBM.

Prognosis and Outcome

Although features such as the severity of the weakness at onset of the disease, degree of elevation of the CK, and degree of abnormality of the muscle biopsy do not correlate with outcome, a number of unfavorable prognostic factors have been identified [72] (Table 65.9). First, patients with PM and DM associated with malignancy have a significantly higher mortality rate than those without a neoplasm. Second, patients with myositis-specific autoantibodies, specifically anti-synthetase autoantibodies, and anti-SRP autoantibody have a poorer prognosis and are less likely to respond to corticosteroids. Patients with anti-Jo-1 autoantibody are at increased risk for interstitial lung disease, which may be a cause of increased morbidity and mortality. Third, patients with a delay to diagnosis greater than 18 months have a poor chance of complete response to prednisone. Fourth, in the last decade, it has become clear that IBM responds poorly, if at all to treatment with corticosteroids and immunosuppressive agents [4–7, 57]. Because IBM may be diagnosed initially as PM [8], it is possible that patients designated as unresponsive PM in earlier studies actually had IBM.

Table 65.9 Prognostic factors in idiopathic inflammatory myopathies

Unfavorable prognostic factors
Malignancy
Myositis-specific autoantibody (especially anti-SRP)
Interstitial lung disease
Cardiomyopathy
Delay to diagnosis of >18 months
IBM

For patients with PM or DM without unfavorable prognostic factors, however, the outlook for a favorable response to treatment is good, with 70–80 % responding completely or at least partially to corticosteroids [62]. In one of the landmark studies from 1975, two-thirds of corticosteroid treated patients improved to the point of having no functional disability, three or more years after the institution of treatment [26]. For the 20–30 % of patients whose disease remains active despite optimum dose and duration of corticosteroid treatment, one or more of the immunosuppressive agents mentioned above often prove helpful, and in the last few years, IVIG has emerged as an additional effective modality.

Although discontinuation of all medication may ultimately be possible for some patients, most will require a low dose of corticosteroid or immunosuppressive drug or both to remain asymptomatic or at least stable at a partially improved state. Indeed, PM or DM alone or associated with a connective tissue disease (overlap group) may be reactivated (relapse) after a period of stability, leading to deterioration in strength, reappearance of the rash of DM, increase in CK, or some combination of these features [73]. Relapses (2–6 per patient) were noted in 60 % of patients over periods of up to 13 years. Although they could occur at anytime during the course of the illness, they were most frequent during the stable stage of drug maintenance.

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Paraspinous Myopathies: The Dropped Head and Bent Spine Syndromes

66

Numthip Chitravas and Bashar Katirji

Introduction

Neck extensor weakness was initially described in late 1980s and early 1990s [1, 2] as "dropped head syndrome" or "floppy head syndrome [3]." This syndrome is characterized by severe weakness of neck extensor muscles resulting in a "chin-on-chest" deformity in the standing or sitting position correctable by passive extension. In contrast to neck extensor weakness, Babinski and Souques coined the term "camptocormia" (derived from the Latin *camptos* meaning bent forward and *cormos* for trunk) [4] in 1916 to describe trunk extensor weakness that resulted in a bent forward posture observed in World War I soldiers attributed to what was believed to be a hysterical conversion reaction [5]. Thereafter, this condition was not well recognized until 1991when Laroche et al. provided evidence of its presence in organic disease and documented abnormal fatty infiltration of the paraspinal muscles [6]. Currently, the terms "bent spine syndrome" and "camptocormia" are used interchangeably to describe pathologically abnormal involuntary forward flexion of the trunk in the upright, but not recumbent, position.

Over the past two decades, both the dropped head and bent spine conditions have received considerable attention. The syndromes have been identified in a broad spectrum of neurological, musculoskeletal, and movement disorders including, in particular, Parkinson's disease, motor neuron disorders (e.g., amyotrophic lateral sclerosis), and primary or secondary congenital or acquired muscle diseases [7–11]. When these conditions are discovered in isolation, the terms isolated neck extensor myopathy (INEM) or isolated trunk extensor myopathy (ITEM) have been utilized [12]. Although it is unclear whether these two conditions share a similar pathogenesis, we find it preferable to use the term "isolated paraspinous myopathy" because it inclusively describes weakness of the cervical, thoracic, and/or lumbar extensor muscles [13, 14].

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Clinical Presentation

Isolated Paraspinous Myopathy

Paraspinous myopathy has been reported as a feature in various neuromuscular diseases in both adults and children with variable symptom onset and clinical presentation depending on the underlying cause. Table 66.1 summarizes the neurological conditions that have been reported in association with prominent dropped head or bent spine syndromes. Note that the majority of data are derived from small case series or case reports.

It remains unclear if a gender predilection exists for *isolated cervical paraspinous myopathy*. Patients usually present with the initial symptoms in the sixth decade or later [1, 12, 15, 16]. Patients with congenital myopathies tend to have an earlier age of onset of symptoms. In mild cases, the patient may simply notice difficulty keeping the head erect such as while standing, walking, watching television, driving, or, merely, engaging in conversation (Fig. 66.1). In more extreme cases, the paraspinal musculature completely "gives way," causing the chin to fall forward until it rests firmly against the anterior chest wall. This is at times referred to as the "chin-on-chest" deformity (Fig. 66.2). As a result of the

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Table 66.1 Neurological conditions that may be associated with prominent dropped head or bent spine syndrome

Motor neuron diseases
Amyotrophic lateral sclerosis
Progressive spinal atrophy
Spinal muscular atrophy
Peripheral nerve disorders
Chronic inflammatory demyelinating polyneuropathy
Neuromuscular junction disorders
Myasthenia gravis
Muscle diseases
Polymyositis
Dermatomyositis
Inclusion body myositis
Focal myositis
Isolated paraspinous myopathy
Adult acid maltase deficiency (Pompe's disease)
Carnitine deficiency myopathy
Facioscapulohumeral muscular dystrophy
Myotonic dystrophy
Limb-girdle muscular dystrophy type 2B
Nemaline myopathy
Multicore myopathy
Mitochondrial myopathy
Cushing's disease
Hypothyroid myopathy
Severe hypokalemic myopathy
Movement disorders
Parkinson's disease
Systemic disease
Primary amyloidosis

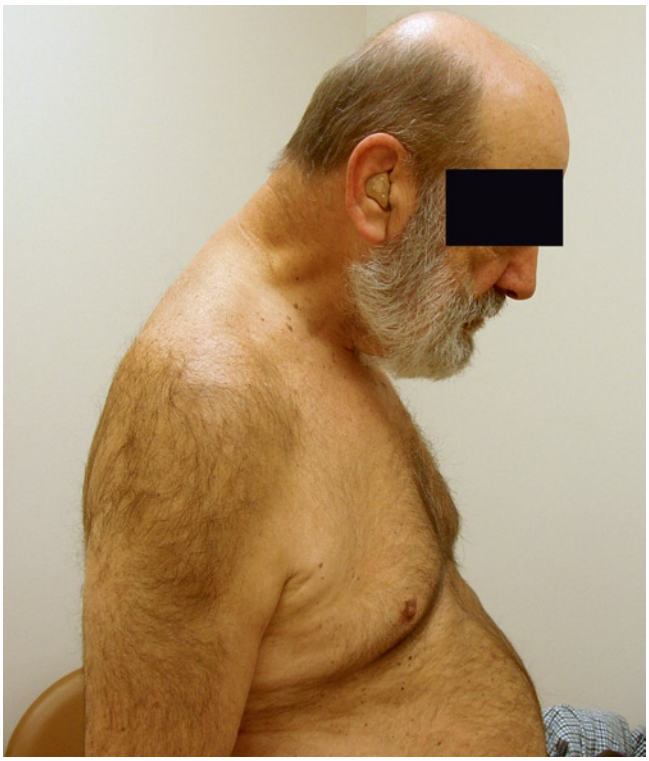


Fig. 66.1 Patient with moderate isolated neck extensor myopathy. He is able to keep head erect forcefully but when resting the head drops

abnormally declined head position, patients experience considerable difficulty looking directly forward especially while speaking to someone or walking. The neck weakness may develop over a period as short as 1 week up to as long as several months [12]. Dull neck discomfort or burning posterior cervical pain is common. Weakness is essentially restricted to the neck extensor muscles with normal passive head extension, and this differentiates the isolated form from other neurologic or spine conditions. Mild deltoid and sternocleidomastoid muscle weakness have been noted in a few reports [1, 12], but these should not be the prominent symptoms. Dysphagia, another common complaint in isolated cervical paraspinous myopathy, mostly reflects interference of the normal swallowing mechanism by the flexed neck posture rather than actual pharyngeal or esophageal involvement. It usually resolves with passive elevation of the head.

Similar to isolated cervical paraspinous myopathy, *isolated thoracic and/or lumbar paraspinous myopathy* also has a tendency to affect elderly individuals, generally, in the sixth decade or later [4, 10, 17–21] with the youngest reported patient being a 56-year-old woman [22]. The largest case series in the current literature is a retrospective collection of patients over a 10-year period by Laroche and Cintas [23]. Forty patients with delayed-onset, isolated thoracic and/or lumbar paraspinous myopathy were identified with a female dominance (female to male ratio of 3:1). The mean age of patients was 69 years and the mean duration of symptoms was 4.5 ± 4 years. An additional affected family member was identified in up to 40 % of cases. All of the patients in this series presented with weakness in thoracic or lumbar regions or both, resulting in the inability to stand upright (Fig. 66.3). The deformity fully resolves in the recumbent position, and forward flexion of the trunk is often augmented with ambulation. This abnormal posture is exaggerated by activities that require back extension, such as walking up an incline or pulling a shirt over the head (Fig. 66.4). Back pain is also occasionally reported at the onset of weakness. Only a minority of patients have proximal limb muscle weakness, which is more commonly seen in the pelvic rather than scapular distribution. The clinical course is usually benign and patients remain ambulatory with the use of a walking assistance device.

The occurrence of combined dropped head and bent spine syndrome has been reported infrequently [13, 14]. As mentioned earlier, it is unknown whether these two conditions represent disorders within the same clinical spectrum [10, 14, 17].

Fig. 66.2 Patient with severe isolated neck extensor myopathy with "chin-on-chest" deformity. She is not able to raise her head against gravity but the passive range of movement is full

Fig. 66.3 Patient with isolated trunk extensor weakness. Her truncal extensor weakness is worse when she holds her arm foreword, such as while carrying any light object (such as her clinical chart)

Paraspinous Myopathy in Parkinson's Disease

Over the last decade, there has been significant increased awareness of dropped head or bent spine syndromes in patients with Parkinson's disease (PD). The incidence of camptocormia was reported as high as 6–7 % of Parkinson patients [24, 25]. As PD is more prevalent in men, the gender predilection of paraspinous myopathy in PD patients also appears to be male. The latency between onset of PD and the onset of paraspinous myopathy ranges widely from several weeks up to three decades [3, 26, 27]. In one study, the mean duration of paraspinous myopathy in PD was 13.5 years [26].

Fig. 66.4 Patient with isolated trunk extensor weakness leans forward when attempting to remove his shirt. The unusual motion is necessary because lumbar weakness prevents him from extending his back to pull the shirt over his head

The vast majority of the patients develop classic extrapyramidal symptoms of PD, such as resting tremor and bradykinesia, prior to head drop or bent spine. Significant neck or back pain attributed to the abnormal forward flexion of the torso predominates and is often the leading patient complaint. Quite clearly, these symptoms create a significant, additional physical disability with resultant further difficulty in activities of daily living in PD patients. The clinical course is usually slow and progressive. From within the movement disorder community, it has been postulated that the bent forward or "stooped" position manifests due to abdominal muscle rigidity or flexor-dystonia as opposed to weakness of neck or back extensors from a paraspinous myopathy. However, more recent studies claimed that PD patients with paraspinous myopathy did not display any sensory signs (e.g., geste antagoniste) which usually indicate dystonia in PD. Moreover, despite good responses of parkinsonian symptoms from levodopa or with bilateral deep brain stimulation (DBS) in the subthalamic nucleus (STN), the

stooped posture does not usually improve with any of these treatments [26]. A recent review also demonstrated consistent "myopathic" changes in the muscle biopsies of paraspinal muscles in idiopathic PD patients with camptocormia [28]. Whether paraspinous myopathy is a clinical manifestation of PD remains a subject to debate.

Evaluation and Diagnosis

Because neck extensor muscle weakness may be a manifestation of many neurological disorders (see Table 66.1), a careful initial neurological examination is recommended. Occasionally, serial neurological evaluation is helpful. In mild cases, the neck extensor weakness is best demonstrated with the patient attempting to extend the neck while in the prone position with the head hanging off the bed. This maneuver isolates the involved extensor neck muscles. Truncal weakness is also best demonstrated with the patient in the prone position by the inability (or difficulty) to raise the torso off the examination table without the aid of the hands and arms.

Electrodiagnostic study is very helpful for accurate diagnosis and to exclude other neuromuscular disorders. Nerve conduction studies and repetitive nerve stimulation tests are normal in isolated paraspinous myopathy. Interestingly, sensory axonal neuropathy was reported in 70 % of the patients in one study [23]. This has to be cautiously interpreted as there is a higher prevalence of sensory axonopathy from any etiology in the elderly population. A decremental response on repetitive nerve stimulation should warrant a diagnosis of neuromuscular junction disorders (e.g., myasthenia gravis). Often, the needle examination demonstrates the presence of "myopathic" changes in cervical and/or thoracic and/or lumbar paraspinal muscles. The abnormality includes positive sharp waves and fibrillation potentials with low amplitude, short duration motor unit action potentials (MUAPs) (Fig. 66.5) [12]. The limb muscles usually are often normal, but less prominent myopathic changes in deltoid, biceps, or gluteus muscles may be seen [1].

Laboratory studies usually reveal a normal creatinine kinase (CK) level to mild elevation up to 1.5–2 times of upper normal limit [23]. Acetylcholine receptor antibodies, anti-muscle-specific tyrosine kinase (anti-MUSK) antibodies, erythrocyte sedimentation rate (ESR), and C-reactive protein are unremarkable.

Imaging studies include magnetic resonance imaging and computed tomography through affected spinal regions that demonstrate atrophic changes as well as heterogeneous fatty infiltration of the paraspinal muscles extending along the length of the affected spinal segments (Fig. 66.6) [22, 23, 29]. Occasionally, the infiltration extends to the posterior thighs and gluteus muscles [23]. Edematous changes as well as abnormal enhancement after administration of gadolinium contrast on T1-weighted images may be seen. The abnormal enhancement and edematous changes were also reported in the idiopathic PD patients with paraspinous myopathy [12, 26, 30, 31].

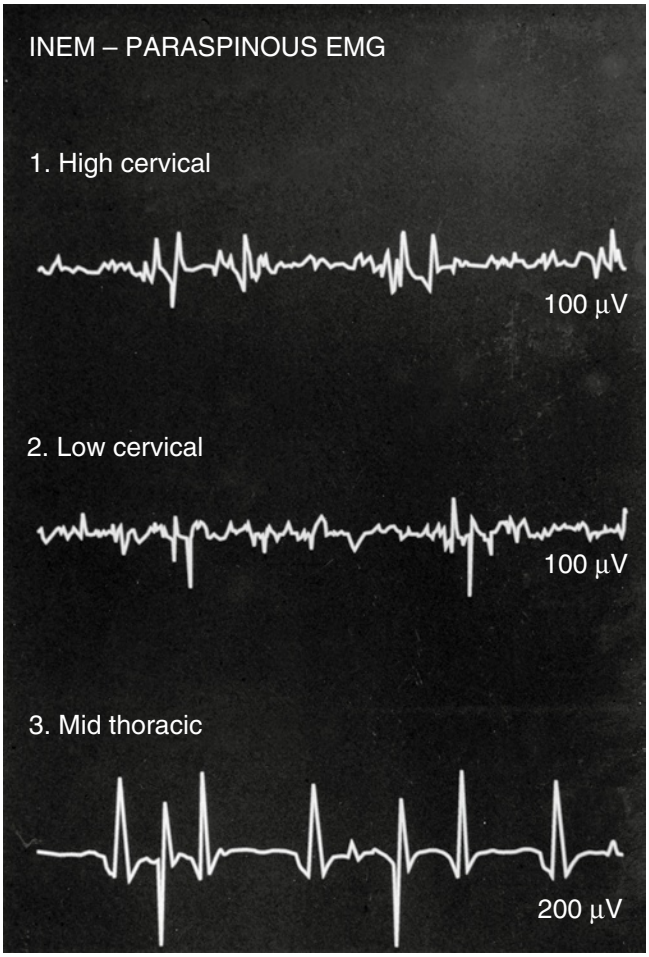


Fig. 66.5 Electromyography of the paraspinal muscles in isolated cervical paraspinous myopathy demonstrates. There are myopathic motor unit action potentials, maximal in the cervical region. The mid-thoracic area is normal

To date, muscle biopsy remains the gold standard for diagnosis for paraspinous myopathy. Due to an easily accessible approach, it is primarily performed in the cervical or thoracic paraspinal muscles. For isolated cervical paraspinous myopathy, as the superior belly of the trapezius muscle normally covers the underlying affected paraspinal muscles, the surgeon may obtain the biopsy specimen from the splenius capitus or the semispinalis in the affected mid-lower cervical region by lifting the lateral edge of the trapezius. Paraspinal muscles in the thoracic and lumbar regions can be approached directly. Deltoid, biceps, gluteus, and quadriceps biopsies may also be obtained to rule out other neuromuscular disorders (e.g., inclusion body myositis). Some authors recommend to perform an MRI of the spine

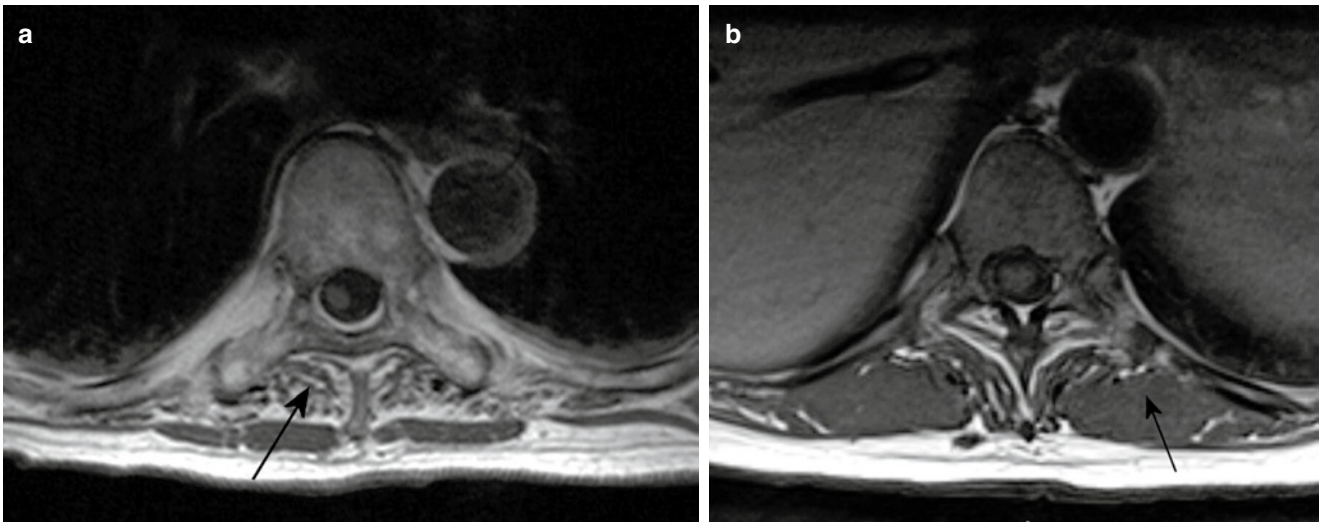


Fig. 66.6 MRI, axial T1-weighted sections of the lower thoracic regions in a patient with isolated trunk extensor paraspinous myopathy (**a**) and an age-matched control (**b**). Note the fatty replacement and atrophied paraspinal muscles in patient comparing to control (*arrows*)

prior to muscle biopsy in order to localize affected tissue and maximize pathological yield (see Fig. 66.6).

Histopathological findings in the majority of patients demonstrate a myopathy marked by variation in fiber size, fiber splitting, increased numbers of internal nuclei, degenerating fibers, proliferation of connective tissue, type 2 fiber atrophy, cyclooxygenase (COX)-deficient fibers, lobular endomysial fibrosis, and fatty replacement [10, 12, 17, 19, 23]. These findings are nonspecific and may sometimes be seen in normal elderly individuals with or without advanced cervical or lumbar spondylosis [32]. When the biopsy reveals angular, esterase-positive fibers with grouped atrophy or fiber-type grouping and targetoid fibers, it is suggestive of a neurogenic process such as amyotrophic lateral sclerosis [22]. Less commonly, nemaline myopathy, inclusion body myositis, or primary amyloidosis is detected on paraspinal muscle biopsy (Fig. 66.7) [29, 31, 33]. Specific analysis with Congo red stain, ubiquitin-binding protein P62 immunohistochemistry, or molecular DNA analysis may be helpful in making these unusual diagnoses.

Muscle inflammation is an uncommon finding. Perivascular and/or endomysial inflammation with or without muscle fiber necrosis has been reported [13, 30, 34, 35]. The inflammation is usually focal and restricted to the paraspinal muscles. It is rarely widespread into the limb muscles. Note that the inflammatory cases often responded favorably to an immunosuppressive treatment, either with steroid or other immunomodulating agents.

In Parkinson's disease with camptocormia, the biopsy revealed uniform muscle pathology. Wrede et al. reported recently that the main histopathological features in PD patients are type 1 fiber hypertrophy, loss of type 2 fiber, loss of oxidative enzyme activity (SDH, NADH, and COX), and increase acid phosphatase reactivity [28]. There was a correlation between the severity of the endomysial fibrosis and the severity of the camptocormia in PD patients. Ultrastructurally, myofibrillar disorganization, Z-band streaming, and electron-dense patches were observed. These findings were consistently found in PD patients who developed paraspinal symptoms, but not in the age and sex-matched, postmortem control paraspinal biopsy. There was also no evidence of inflammation or mitochondrial changes in the affected paraspinal muscles. Interestingly, a higher number of ragged red and COX-deficient fibers were found in the paraspinal muscles of the postmortem control group. This abnormality was also found more in the paraspinal muscles than in deltoid muscles in the same control patients. This raises the possibility that ragged red fibers and COX-deficient muscle fibers may be a normal finding in the paraspinal muscles of the elderly and should not be interpreted as a sign metabolic or mitochondrial myopathy.

Despite an effort to investigate camptocormia in PD, a clear etiology of the paraspinous myopathy has not been elucidated. It is possible that the paraspinous myopathy is a manifestation of Parkinson's disease, but coincidental disorder is also possible [3].

Differential Diagnosis

The differential diagnosis of dropped head or bent spine syndromes includes musculoskeletal and neurological disorders. Osteoporosis, ankylosing spondylosis, and vertebral fracture are the primary differential diagnoses when the observed kyphosis is fixed without resolution while in the supine position. Increased awareness of this condition over the last two decades has led to the current differential diagnoses listed in Table 66.1. An approach algorithm is shown in Table 66.2.

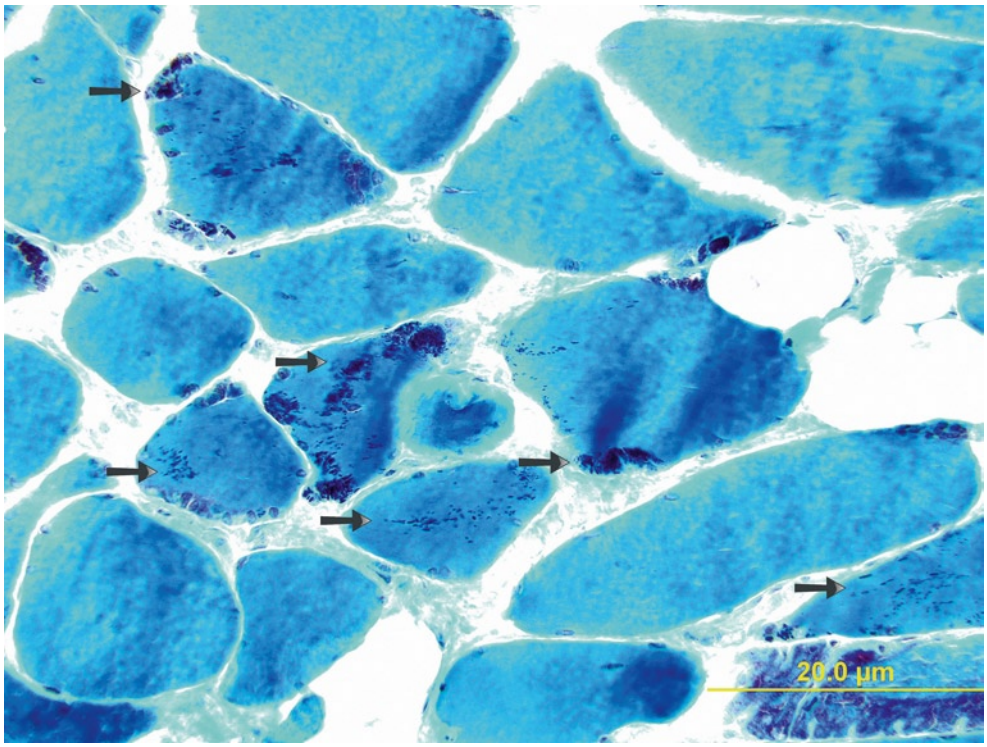
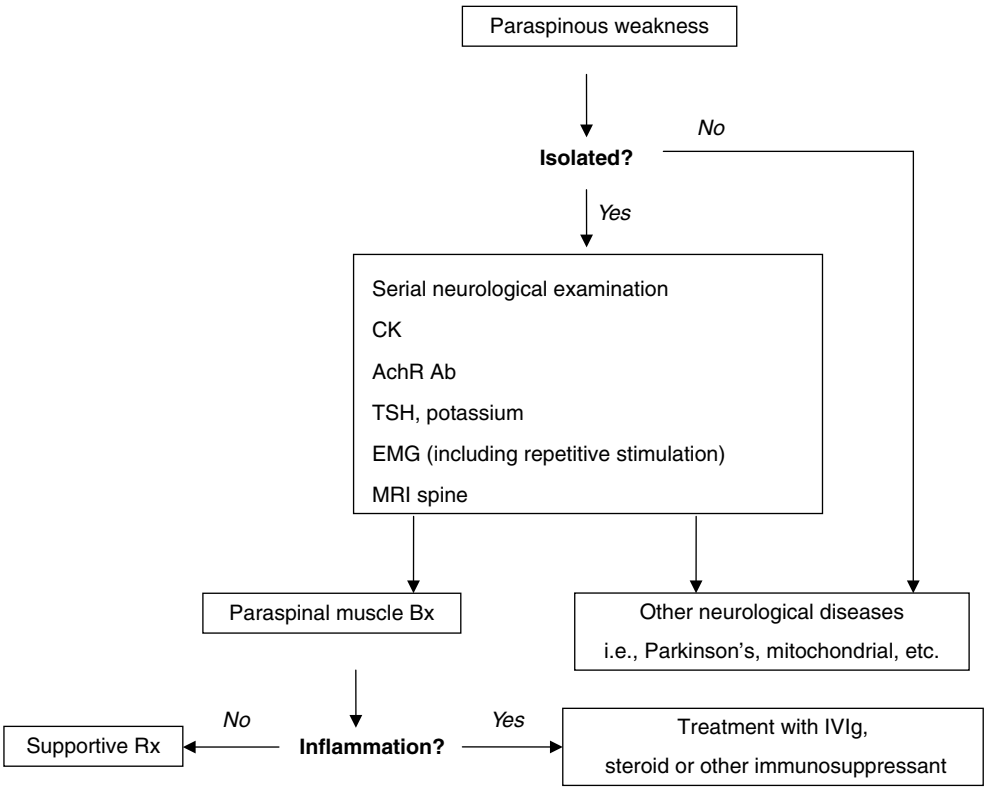


Fig. 66.7 Photomicrograph of the cervical paraspinal muscles from a patient with isolated cervical paraspinous myopathy demonstrating variation in myofiber diameter as well as deposit of nemaline bodies (*arrows*, Trichrome, X 200)

Table 66.2 Approach for paraspinous myopathy



The presence of weakness in regions other than the neck or trunk implicates the diagnosis of a generalized neuromuscular disorder. Myasthenia gravis (MG), amyotrophic lateral sclerosis (ALS), and idiopathic Parkinson's disease are the common neurological disorders associated with paraspinous myopathy. It is estimated that neck weakness is the presenting complaint in 3 % of MG patients [36], 1.3 % of ALS patients [37], and 6 % of idiopathic PD [24, 25]. MG should

be suspected when there is associated ptosis, ophthalmoparesis, generalized weakness, or bulbar dysfunction, while ALS should be considered when there are muscle fasciculations, hyperreflexia, or evidence of a neurogenic process associated with weakness in regions outside of the neck. In PD, patients often have overt extrapyramidal signs prior to the onset of camptocormia and paraspinal muscle weakness [3, 26–28, 38–40].

On the rare occasion, cervical paraspinal weakness can be a primary manifestation of mitochondrial, inflammatory, congenital or metabolic myopathies, chronic inflammatory demyelinating polyneuropathy, or spinal muscular atrophy (see Table 66.1) [33, 41–47].

A significantly elevated CK warrants a diagnosis of polymyositis or other myopathies, while elevated acetylcholine receptor antibodies or voltage-gated calcium channel antibodies are diagnostic of myasthenia gravis or Lambert-Eaton myasthenic syndrome, respectively. Electrodiagnostic (EDX) investigations in patients presenting with isolated neck or trunk weakness may reveal subclinical evidence of diffuse anterior horn cell disease, widespread myopathy, or impaired neuromuscular transmission even before a more extensive clinical findings become evident.

The characteristic anteriorly flexed head posture seen in isolated cervical paraspinous myopathy may also be seen in spasmodic torticollis. However, in torticollis, there is typically a component of rotational or lateral deviation. While torticollis is easily excluded by the presence of extensor weakness, the distinction is important. A local injection of botulinum toxin into the neck flexors in patients with cervical paraspinous myopathy may have devastating effects, as these patients rely on these muscles to support the head from a reclined position.

Etiology

The cause of isolated paraspinous myopathy is still unknown. Familial clustering described in these cases lead to speculation that this may be a distinct paraspinal muscular dystrophy [17, 26]. Ragged red fibers suggesting a mitochondrial myopathy have been described in small numbers of patients [10, 48]; however, the significance of this abnormality in elderly patients remains uncertain. These pathologic findings may very well be coincidental and irrelevant because ragged red and/or COX-negative fibers are commonly seen in the paraspinal more than limb muscles in the normal aging population [17, 32]. Desmin deposits have also been noted in a single biopsy of a patient with dropped head syndrome [49], but it is unclear if this represents an alternative etiology. Others have also postulated that both cervical and thoracolumbar paraspinous myopathies are variant forms of a focal polymyositis [1, 13, 19, 30, 33, 50–52]; however, muscle inflammation is only occasionally seen. Isolated paraspinous muscle weakness may be also the leading or only manifestation of a large number of neuromuscular disorders including congenital myopathies, facioscapulohumeral muscular dystrophy, limb-girdle muscular dystrophy, mitochondrial myopathies, inflammatory myopathies, metabolic myopathies, chronic inflammatory demyelinating polyneuropathy, or spinal muscular atrophy [29, 53].

Katz et al. have postulated that mechanical processes may cause isolated cervical paraspinous myopathy [12]. Once the head begins to fall forward due to aging or because of weakness, the effect of gravity exerts an increasing downward pull. This posture leads to overstretched paraspinal muscles that are no longer able to generate adequate contractile force according to the Starling curve [54, 55]. Prolonged overexertion from the combination of abnormal posture and weakness may also result in myonecrosis. Factors that increase susceptibility to the onset of such a process might include loss of elastic tissue with aging [56], the acquired posture of the head or trunk with aging or disease, or senile degeneration of the spinal column. Similarly, camptocormia in Parkinson's disease may be explained by a poor function of mechanical load receptors or proprioceptive dysregulation of paraspinal muscles. As known, Parkinson patients have an impaired central mechanism that influences the muscle tone via the polysynaptic reflexes. The poor accuracy of movement of a joint may lead to the "overstretch" position causing repetitive and chronic muscle injury which eventually creates myopathic changes and result in loss of muscle strength. Future research is warranted to verify this hypothesis.

Treatment and Management

There is no proven treatment for cervical or thoracolumbar paraspinous myopathy. Corticosteroids and pyridostigmine (Mestinon®) are generally ineffective. Responsiveness to corticosteroids, either with or without additional immunosuppressant therapy, has been previously reported, most notably in a patient whose biopsy showed histological evidence of inflammation suggestive of focal polymyositis [30, 50, 57]. Rarely, intravenous immunoglobulin (IVIg) was used as a treatment modality. It provided great improvement in one patient whose thoracic paraspinal muscle biopsy showed multiple foci of endomysial and perivascular chronic inflammatory cells [13]. Vitamin C, vitamin E, and coenzyme Q supplementation have also been reported to provide benefit in one individual with isolated cervical paraspinous myopathy. In this case, the diagnosis of mitochondrial myopathy was made based on histologic evidence of ragged red fibers.

Invasive mechanical treatment with cervical spine or cervicothoracic fusion and instrumentation is an alternative

treatment [58, 59]; however, the data is very limited and may not be an option if the patient has significant osteopenia or osteoporosis.

Katz et al. have witnessed a clinical improvement in a patient with cervical paraspinous myopathy after a prolonged hospitalization [12]. They attributed the response to "unloading" of the weight of the head during the time he was bedridden. Soft and hard neck collars are uncomfortable for the patient as the chin can fall into the collar and interfere with speech and rotational neck movements. In Fig. 66.8, the patient designed a special brace supporting the head and neck from behind using a rigid backboard attached to a harness worn around the trunk and forehead. In isolated thoracolumbar paraspinous myopathy, patients may benefit from physical therapy to improve range of motion. The use of a cane or wheeled walker is typically necessary for maintaining upright posture, ambulation, and daily activities.

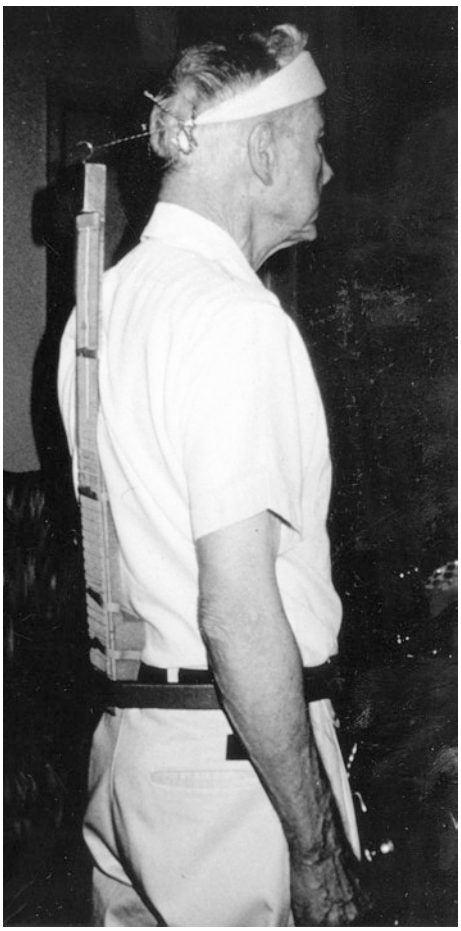


Fig. 66.8 Homemade orthotic device used to support the head from behind in dropped head syndrome. Note that the patient is wearing a belt with a rod arising from it. A headband attached to the rod supports the head

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Endocrine Myopathies

67

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Endocrine disorders are associated with a wide range of clinical presentations, including neuromuscular disorders and particularly myopathies [1, 2]. The wide spectrum of potential endocrinopathies, which includes over- or underproduction of specific hormones, with complex and often overlapping molecular and cellular pathophysiologies, emphasizes the need for a comprehensive assessment of any patient presenting with suggestive symptoms (including fatigue, myalgia, and cramps) and signs (such as wasting or weakness), coupled with a high index of suspicion for an underlying endocrine etiology. In addition to endogenous endocrinopathies, the therapeutic use of glucocorticoids in the treatment of inflammatory conditions frequently results in disabling iatrogenic complications, which can only be minimized through careful patient assessment and management. This chapter highlights the underlying pathophysiology of the most common endocrinopathies, with a particular emphasis on their clinical presentation, relevant investigations, treatment, and prognosis.

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Muscle Disorders Associated with Glucocorticoid Abnormalities

Glucocorticoid Excess

The observation that chronic glucocorticoid use directly produces muscle weakness is long established and is commonly noted by clinicians treating patients for a wide range of inflammatory conditions (particularly asthma and rheumatoid arthritis). The causative association is clear, particularly as asthma is not inherently linked with myopathic symptoms, and the iatrogenic myopathy of rheumatoid disease is independent of the degree of debility or duration of this condition. Once flares of disease are successfully treated and high doses of glucocorticoids are reduced to more physiological levels, muscle weakness and wasting reverses [3].

Over the past decade, there have been marked advances in our understanding of the molecular mechanisms of glucocorticoid-induced myopathy, via studies using in vitro cell culture techniques, with results validated using in vivo animal and human models. They have shed light on the important role of glucocorticoids in both normal muscle physiology and in the pathophysiology of muscle wasting in glucocorticoid excess and other disease states including cachexia, sepsis, and disuse atrophy. This research has highlighted potential therapeutic avenues towards the treatment of this common and important phenomenon.

Physiology and Pathology

The principal endogenous glucocorticoid is cortisol, release of which is regulated by the hypothalamic/pituitary/adrenal (HPA) axis. Neurones from the suprachiasmatic nucleus connect with the paraventricular nucleus of the hypothalamus to regulate corticotrophin-releasing hormone (CRH) secretion. CRH stimulates the pituitary to secrete adrenocorticotropic hormone (ACTH) in a pulsatile manner, leading to cortisol secretion from the adrenal cortex. There is a circadian rhythm of secretion, resulting in peak cortisol levels in the early morning with decline through the day until a nadir is reached

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late at night. The HPA axis is under negative feedback control, with cortisol acting on the pituitary and hypothalamus. The axis is further stimulated by mediators of the stress response, particularly proinflammatory cytokines, such as TNF-α, IL-6, IL-1, and LIF.

Glucocorticoid hormones are derived from cholesterol and synthesized in the adrenal cortex, reaching skeletal muscle and other target organs via the blood and because of their lipophilic nature pass the cell membrane by simple diffusion. Further regulation of glucocorticoid actions is provided at the pre-receptor level by the 11beta-hyrdroxysteroid dehydrogenase types 1 and 2 (11beta-HSD) isozymes, which are responsible for the inter-conversion of inactive cortisone and active cortisol at multiple tissue sites, including skeletal muscle [4].

Within the muscle, the hormone binds to steroid hormone receptors, which are the mediators of glucocorticoid action. The hormone receptors form a complex with chaperones (heat shock protein 90), which have well-described functions in protein folding and prevention of aggregation. The hormone receptors are transcription factors that can activate or inhibit expression of target genes via at least three mechanisms: first, the complex of glucocorticoid and steroid receptor binds to chromatin-organized DNA sequences (hormone response elements) within the regulatory region of target genes. This binding initiates chromatin remodeling leading to the activation or inhibition of transcription of the target gene. Second, through protein-protein interactions with other transcription factors, the glucocorticoid-receptor complex can regulate the activity of other genes. During stress or inflammatory conditions, including infection, glucocorticoids may modulate muscle gene transcription. Third, the glucocorticoid with its receptor may influence other signal transduction pathways [5].

Glucocorticoids act to alter the balance of muscle protein turnover by reducing synthesis and increasing breakdown, with muscle atrophy as an active process characterized by the stimulation of specific gene programs. Glucocorticoids stimulate muscle proteolysis largely by activating the ubiquitin-proteasome system (UPS), with contributions from lysosomal and calcium-dependent systems [6].

Activation of components of the UPS by glucocorticoids results both in degradation of myofibrillar proteins and those involved in apoptotic pathways [7]. Further sites of action include key steps in myogenesis by reducing mRNA expression of the myogenic transcription factors (MRF), myogenin and MyoD, with preservation of the negative regulator, the DNA-binding protein Id1 [8, 9].

Glucocorticoids additionally activate forkhead box transcription factors (FOXO) by dephosphorylation [10, 11]. FOXO cause upregulation of a variety of genes involved in muscle atrophy known as “atrogenes” including the muscle-specific E3 ubiquitin ligases, muscle RING finger-1 (MuRF-1), and muscle atrophy F-box (MAFbx/Atrogin-1) through specific promoter-binding events [11, 12]. MuRF-1 and MAFbx/Atrogin-1 associate with components of myosin chain proteins, leading to protein degradation [13]. There is evidence that MuRF-1 is critical for the development of glucocorticoid-induced muscle atrophy, as mice with targeted deletion of this gene are protected from loss of muscle mass when compared to those of a wild-type background [14].

Dexamethasone additionally upregulates the expression of regulated in development and DNA damage responses (REDD1), which subsequently inhibits mammalian target of rapamycin (mTOR), resulting in reduced phosphorylation of its downstream targets ribosomal protein S6 kinase 1 (S6K1) and eIF4E-binding protein-1 (4E-BP1) [15]. Binding of 4E-BP1 to the eukaryotic initiation factor eIF4E inhibits the rate-limiting stage of protein synthesis [16].

As mentioned previously, pre-receptor glucocorticoid regulation via 11beta-HSD1 is involved in the regulation of proteolysis and atrogene expression in both primary human and murine myotubes. Treatment with cortisone increases proteolysis and MuRF-1 and MAFbx/Atrogin-1 expression while pretreatment with the 11beta-HSD1 inhibitor, carbenoxolone, attenuates these effects [17]. Other potential regulators of these pathways include glycogen synthase kinase 3 beta (GSK3beta) and the transcription factor C/EBPbeta. GSK3beta appears to be required for the induction of skeletal muscle atrophy by glucocorticoids, as evidenced by a series of experiments using pharmacological inhibitors and gene knock down approaches in a murine skeletal muscle cell line [18]. GSK3beta is a target for phosphorylation by Akt, leading to inhibition of activity. C/EBPbeta expression is increased in various states characterized by muscle wasting. Silencing its expression in rat skeletal myotubes inhibits dexamethasone-induced proteolysis and MuRF-1 and MAFbx/Atrogin-1 expression [19].

Glucocorticoid actions are likely to be partially mediated via indirect pathways, including via the actions of insulin growth factor 1 (IGF-1), in which production in muscle is suppressed in states of glucocorticoid excess [20]. IGF-1 increases protein synthesis via PI3k/Akt/mTOR and GSK-3beta signaling and satellite cell proliferation [21, 22]. It also increases phosphorylation of Akt, leading to inhibition of FOXO and subsequent effects on downstream signaling which result in reduced proteolysis [23, 24]. Similarly, recent data suggests that impaired insulin signaling via IRS-1/PI3K plays an important role in muscle atrophy induced by glucocorticoids [25]. Interventions that act to increase IGF-1 signaling attenuate glucocorticoid-induced muscle atrophy in animal models. Rats treated simultaneously with recombinant human growth hormone and glucocorticoids and those induced to have local overexpression of IGF-1 in skeletal muscle have preservation of muscle mass [20]. Although there are hints of efficacy in small-scale trials [26], growth hormone treatment in humans with glucocorticoid-induced myopathy has not been assessed in large-scale randomized trials.

Myostatin, a secreted growth factor known to negatively regulate muscle mass, has also been shown to be an important modulator of glucocorticoid-induced muscle atrophy. The effects on muscle were identified via several routes, including the observation that inactivating mutations of the gene in "Belgian Blue" cattle are associated with a "double-muscling phenotype" [27]. Transgenic mice with an absent myostatin gene have muscle fiber hypertrophy or hyperplasia, and targeted overexpression of myostatin in skeletal muscle leads to tissue atrophy [28]. Rats with dexamethasone-induced muscle atrophy have dose-dependent increases in mRNA and protein expression of myostatin. Furthermore, myostatin gene deletion prevented glucocorticoid-induced muscle atrophy in transgenic mice [29]. In vitro data demonstrate that myostatin antagonizes IGF-1 and results in activation of genes involved in proteolysis. Myostatin has been implicated in the pathogenesis of preferential muscle-fiber-type atrophy, with evidence of its close association with the myosin heavy chain isoform IIb in normal muscle [30] and of increased expression in type II fibers in disease [31]. Inhibition of myostatin has therefore emerged as a potential therapeutic strategy in type II diabetes mellitus, obesity, and also muscle atrophy [32].

Fasting and inactivity worsen the course of clinical and experimental steroid-induced myopathy, which is observed to decrease the synthesis and increase the breakdown of both myofibrillar and soluble muscle protein in rats. Recovery of muscle from starvation requires a reduction in glucocorticoid levels for muscle to convert from a catabolic to an anabolic state [33]. However, starvation or severe dietary protein and energy restriction do not alter the muscle catabolism seen with high-dose steroid treatment [34], suggesting that the effects of starvation and glucocorticoid treatment are additive but not synergistic. The clinical implications are that dietary supplementation of a patient with an otherwise adequate protein intake will not reverse steroid-induced myopathy, but starvation or protein deprivation will accelerate steroid myopathy, and steroid treatment will slow or prevent the recovery of muscle mass in a previously malnourished person who is being refed.

Although it is well known that glucocorticoids preferentially induce type 2 fiber atrophy, the reasons for this are not clear. Skeletal muscle contains a high concentration of glucocorticoid receptors [35], but differential receptor numbers do not explain this effect. Soleus muscle is predominantly composed of type 1 fibers yet has a higher density of glucocorticoid receptors than does extensor digitorum longus, which expresses a large percentage of type 2 fibers. Effects may in part be mediated through physical activity, as it is well established that inactivity worsens clinical and experimental steroid myopathy [36]. Type 2B fibers are active less frequently than type 2A or type 1 fibers [37], and the differences in normal activity patterns may contribute to the greater steroid-induced atrophy seen with type 2B fibers [38]. A possible explanation for the increased sensitivity of inactive muscles to glucocorticoids is that inactivity leads to an increase in the concentration of glucocorticoid receptors [37]. The additive effects of inactivity and glucocorticoid treatment on muscle function may also partially explain why patients who receive neuromuscular blocking agents tend to develop steroid myopathy particularly quickly.

Conversely, increased muscle activity may partially prevent glucocorticoid-induced atrophy [39]. Therefore, physical therapy may be useful in preventing and treating muscle weakness and wasting in patients receiving glucocorticoids. Studies have demonstrated that resistance exercise training 6 months after heart transplantation restored fat-free mass to a level greater than before transplantation and dramatically increases skeletal muscle strength [40]. Endurance and resistance training attenuate steroid-induced muscle atrophy [41].

ACTH excess may have directly myopathic effects, distinct from its induction of glucocorticoid synthesis [42, 43]. This is evidenced by patients treated for Cushing disease with adrenalectomy, who subsequently developed clinical, electrodiagnostic, or histological evidence of myopathy. These patients had proximal weakness and wasting, but other aspects of their clinical presentation were different from steroid myopathy as some patients had sharp waves or fibrillation potentials on EMG and biopsy of three patients revealed prominent subsarcolemmal lipid deposits. Furthermore, ACTH administration to rabbits results in focal necrosis of muscle fibers with extensive deposition of fat, which is not a characteristic of steroid myopathy [44]. In rat phrenic nerve-diaphragm preparations, excessive amounts of ACTH impair neuromuscular transmission by decreasing the quantal content [45]. The underlying pathogenic mechanisms of ACTH on muscle are not known.

Androgens may partially antagonize the catabolic actions of glucocorticoids. These anabolic steroids may act by displacing glucocorticoids from their cytosolic receptors or directly via androgen receptors in muscle. In some animal studies, androgens partially prevented glucocorticoid-induced muscle atrophy, impaired ribosomal function, and increased 3-MeHis production in rats [46]. In other studies, androgens did not prevent glucocorticoid-induced muscle atrophy [47]. Overall, however, anabolic steroids have not been very successful in treating iatrogenic steroid myopathy [48]. A possible explanation for the unsuccessful results is that androgens will correct the ribosomal defect but not the mitochondrial dysfunction produced by glucocorticoids. One study found that a combination of anabolic steroid and vitamin B complex was more effective than an anabolic steroid alone in preventing steroid myopathy in rats [49].

Clinical Presentations

Glucocorticoid excess most commonly results from exogenous administration during treatment for a wide range of conditions [50]. Other cases result from adrenal overproduction

of cortisol, either secondary to adrenal nodular tumors, hyperplasia or neoplasia, or adrenocorticotropic hormone (ACTH) overproduction by pituitary or other neuroendocrine tumors. Glucocorticoid excess leads to a wide range of tissue effects, including osteoporosis, central obesity, skin manifestations, and the induction of the metabolic syndrome. Cushing first noted that patients with endogenous glucocorticoid excess developed proximal muscle wasting and weakness [51], with patients experiencing difficulty with climbing stairs or combing their hair, and subsequent reports described a similar syndrome in patients with ectopic production of ACTH.

The onset of weakness is usually insidious. The weakness is primarily proximal, with the legs more severely involved than the arms; cranial-nerve-innervated muscles and sphincters are spared. Myalgias frequently accompany the weakness. Serum levels of muscle-associated enzymes (lactate dehydrogenase (LDH), creatine kinase (CK) and aldolase) are usually normal but may be reduced as outlined below [52]. The same patterns of muscle involvement and enzyme activity are found in patients with iatrogenic steroid myopathy and endogenous glucocorticoid excess [3].

Steroid myopathy has been reported in patients ranging from 2 to 84 years of age and has occurred in patients suffering from a variety of diseases treated with glucocorticoids [53]. Between 50 and 80 % of patients with Cushing disease develop appreciable muscle weakness [3]. The incidence of muscle weakness associated with chronic steroid treatment among studies varies from 2.4 to 21 %. These figures indicate only those patients who developed severe weakness and, therefore, are likely to underestimate the actual incidence of steroid-induced weakness. Isolated respiratory muscle weakness may occur with inhaled corticosteroids [54]. When patients treated with glucocorticoids are monitored with quantitative strength testing, a majority of patients show a significant decline in strength after a few weeks of treatment [55]. Women are more likely to develop steroid myopathy with the same glucocorticoid dose [56].

Acute myopathy, developing within a few days of administration of glucocorticoid treatment, has been described in patients treated with large doses of steroids for asthma [57]. Many of these patients received mechanical ventilation and neuromuscular blockade with curare-like agents in this context. Several factors appear to contribute to the rapid onset of weakness and wasting, including prolonged immobility, the use of curare-like agents which may potentiate the action of glucocorticoids, and concurrent sepsis, which may accelerate muscle proteolysis.

Differential Diagnosis

In many clinical situations, the diagnosis is usually straightforward. However, it is often difficult to decide whether deterioration in strength of a patient with inflammatory myopathy treated with steroids is the result of steroid myopathy or a flare in the inflammatory myopathy. As steroid myopathy takes time to develop, weakness that occurs at the onset of steroid treatment is probably caused by an exacerbation of the inflammatory disease and is best treated by continuing or increasing the dose of steroid. Similarly, if the weakness occurs without any other stigmata of steroid usage, it is probably not steroid induced. Elevation in the serum levels of muscle-associated enzymes suggests that the weakness is at least partially due to the inflammatory myopathy.

Recent studies have demonstrated statistically significant reductions in serum CK and plasma myoglobulin in patients with Cushing's disease and also in healthy volunteers who were treated with short-term dexamethasone, as compared to healthy controls. Despite these variations, the majority of the patients had muscle enzyme levels that remained within the laboratory normal reference range [58, 59]. Furthermore, normal enzyme levels do not rule out a flare in the inflammatory myopathy. Muscle biopsy is helpful in distinguishing inflammatory myopathy from steroid myopathy but only if there is an active inflammation, which may be difficult to find in the context of steroid treatment. EMG may be useful in distinguishing steroid myopathy from inflammatory myopathy, as fibrillation potentials are not a feature of steroid myopathy but are often present in inflammatory myopathies.

Creatine excretion is elevated in both steroid and inflammatory myopathy, but the creatine excretion may be useful in differentiating the two myopathies. A change in the creatine excretion value can precede a change in strength by weeks. If the weakness is steroid induced, decreasing the steroid dosage will lower the creatine excretion, which will be followed by clinical improvement. Lowering the steroid dosage in a patient with flare of inflammatory myopathy should produce increased creatine excretion followed by further weakness.

Evaluation and Diagnosis

For endogenous disease, the diagnostic approach requires both the definite recognition of Cushing's syndrome and the subsequent identification of the underlying etiology. Accepted screening tests include 24-h collection for urinary-free cortisol (minimum duplicate testing), late-night salivary cortisol (again, minimum duplicate testing), and the 1 mg dexamethasone suppression test (DST) [60]. The next step is to distinguish between ACTH-dependent and ACTH-independent etiologies. Suppressed serum ACTH levels are suggestive of ACTH-independent disease and should be followed by computerized tomography (CT) of the adrenals. Detectable ACTH levels are suggestive of ACTH-dependent disease and can be followed by a corticotrophin-releasing hormone (CRH) test in combination with a 48-h DST and magnetic resonance imaging (MRI) of the pituitary. Bilateral inferior petrosal sinus sampling is the gold standard for distinguishing between ACTH secretion from pituitary and

ectopic sources, but cannot reliably lateralize secretion within the pituitary and is an invasive procdure [60, 61].

Among patients with steroid myopathy, there is a wide variation in the dose and duration of steroid treatment associated with the onset of weakness. However, patients who have received steroids for less than 4 weeks rarely develop severe steroid myopathy [57]. Lowering the steroid dose or reducing endogenous glucocorticoid production usually corrects the weakness.

EMG findings are variable, typically finding normal insertional activity and motor unit potentials, with the latter occasionally of low amplitude and short duration. Despite reports of fibrillation potentials accompanying the brief duration motor unit potentials, spontaneous electrical activity is typically absent [50]. Noninvasive electrophysiological tests have been used to assess changes in glucocorticoid-induced myopathy, including a recent study estimating muscle fiber conduction velocities (MFCV) from surface EMG measurements, which were significantly reduced in patients with Cushing's disease in comparison to healthy controls (mean relative differences 26 % in vastus lateralis and 11.6 % in tibialis anterior) [58]. These differences contrasted with the lack of changes observed on needle electromyography in these patients, with the authors attributing this to the relative lack of sensitivity of this technique to type II fiber pathology.

Histological studies in either iatrogenic steroid myopathy or in Cushing's disease find selective atrophy of type 2 fast twitch glycolytic muscle fibers. Lipid droplets are infrequently seen in type 1 fibers. Increased muscle glycogen is noted in type 2 fibers. Electron microscopic studies find mitochondrial aggregation, swelling and vacuolization, and myofibrillar degeneration [62]. The motor nerve axons and terminals appear normal even when there was severe muscle atrophy and muscle spindle atrophy is only found in type 2 fibers.

Treatment and Prognosis

Glucocorticoid excess is associated with significant morbidity, with 5-year survival rates as low as 50 % in early series. Modern management and treatment of Cushing's disease has led to a significant improvement in these figures, with a near normalization in mortality [63]. The management of steroid-induced myopathy is primarily treated by decreasing steroid dosage to the lowest possible level, which can be challenging depending on the underlying inflammatory condition. During the phased reduction, the possibility of adrenal suppression should also be considered and excluded where possible. Although any commonly used glucocorticoid can cause steroid myopathy, the fluorinated steroids, triamcinolone, betamethasone, and dexamethasone appear more likely to produce weakness [57]. Patients develop weakness when switched from other steroids to equivalent doses of triamcinolone or dexamethasone and recover from dexamethasone or triamcinolone-induced weakness when converted to an equivalent anti-inflammatory dose of another steroid [64]. Therefore, switching to a nonfluorinated agent is prudent, and where possible, an alternate-day treatment regimen should be instituted.

Often this is not an option, and patients are often dependent on glucocorticoid therapy for the treatment of their underlying condition. Recent years have seen a great focus on the development of novel therapeutic strategies for the prevention and treatment of glucocorticoid-induced muscle atrophy. Much of the present data is at a preclinical stage of use, with robust clinical trial data awaited. Research includes the development of dissociated glucocorticoids, in which the trans-repression function of the glucocorticoid receptor on gene transcription of proinflammatory transcription factors (believed to be responsible for beneficial effects) is segregated from the trans-activation function (believed to be responsible for the adverse side effects). Many compounds which have shown initial promise in vitro have not translated into in vivo benefits [65]. It has since been recognized that trans-activation also appears to play a role in the anti-inflammatory effects of glucocorticoids [66].

Other potential pharmacological approaches attempt to target pathways involved in glucocorticoid-induced myopathy. These include hormonal therapies such as GH and androgen therapy, myostatin inhibitors [67], selective 11beta-HSD1 inhibitors [68], growth hormone peptide-2 (GHRP-2), clenbuterol, branched chain amino acids (BCAAs), and creatine. Testosterone has anabolic actions in a range of disease states characterized by cachexia and muscle wasting. Administration blocks glucocorticoid-induced protein degradation in cell lines and muscle atrophy in animal models, potentially by blocking changes in expression of the translational repressor protein REDD1, by reducing mTOR inhibition, and by increasing muscle IGF-1 [69–71]. Administration of the adrenal androgen, dehydroepiandrosterone (DHEA), to those taking chronic glucocorticoid therapy has been proposed for over a decade, but robust clinical trials are still awaited [48]. Selective 11beta-HSD1 inhibitors have been developed as potential therapies for type II diabetes mellitus, obesity, and the metabolic syndrome, and their assessment in muscle atrophy would be of interest [68], but no large-scale randomized trials have been published to date.

GHRP-2, a GH secretagogue inhibitor receptor (GHS-R) agonist, attenuates dexamethasone-induced MuRF-1 mRNA in rat soleus muscle and MAFbx/Atrogin-1 and MuRF-1 expression a murine muscle cell line [72]. The use of this agent is currently at the preclinical stage. The well-established actions of catecholamines in inhibiting skeletal muscle protein breakdown have been investigated in studies using the selective beta-2 adrenoceptor agonist clenbuterol, finding opposing effects to glucocorticoids on muscle mass and fiber-type switching in mice [73], effects potentially mediated

via increases in muscle cAMP levels and reductions of the ubiquitin-proteasome system (UPS) activity [74]. These promising observations are tempered by questions surrounding the cardiovascular effects of such treatment in humans [75]. BCAAs were found to protect against dexamethasone-induced soleus muscle atrophy in rats, with attenuation of atrogin-1 expression [76]. Creatine supplementation was shown to attenuate dexamethasone-induced gastrocnemius and diaphragm muscle weight losses and the loss of type IIb fibers in rats [77].

Resistance exercise therapy prevents corticosteroid-induced myopathy in some patients and should be encouraged in patients receiving glucocorticoids. Patients with myopathy should therefore still receive physical therapy [40], although recovery may take many weeks to months. In one study, exercise training attenuated dexamethasone-induced muscle extensor digitorum longus atrophy, markers of insulin resistance, and muscular glycogen loss in rats [78]. In a separate study, exercise prior to steroid treatment attenuated effects on body and muscle weight, type II muscle cross-sectional area in plantaris, and myofibrillar protein content. The adaptations of muscle to exercise are partly attributed to stimulation of some of the pathways outlined earlier including by modifying local growth factors such as IGF-1 and modifying PI3K/Akt/mTOR signaling [79].

Adrenal Insufficiency

Pathology

In primary adrenal insufficiency (Addison's disease), the defect is adrenal in origin, whereas in secondary insufficiency, the defect is at the level of the hypothalamus or pituitary. The causes for primary insufficiency are wide ranging, with the most common etiology autoimmune (65 %, including polyendocrine deficiency syndromes types I and II), followed by tuberculosis (20 %), and the remainder of causes relating to infiltrative processes (such as malignancy, sarcoidosis, amyloidosis, fungal infection), or genetic/congenital disorders (particularly congenital adrenal hypo- and hyperplasia, ACTH resistance, adrenoleukodystrophy) [80].

The commonest cause of secondary adrenal insufficiency relates to hypothalamic-pituitary-adrenal suppression following exogenous steroid use, usually in the context of oral steroid use; however, it has also rarely been described in association with inhaled or intranasal steroid use [81, 82]. Other causes include lesions in the region of the hypothalamus and pituitary, trauma, and isolated ACTH deficiency.

Muscle weakness and fatigue caused by loss of adrenal hormones are related to impaired muscle carbohydrate metabolism, water and electrolyte balance, and muscle blood flow [50]. Anorexia and fasting hypoglycemia occur because of adrenal insufficiency [83]. In the absence of glucocorticoids during fasting, amino acids are not metabolized from muscle for hepatic gluconeogenesis resulting in hypoglycemia. Additionally, subjects with Addison's disease appear to have an enhanced sensitivity to insulin partly as a result of increased affinity of the sarcolemmal insulin receptor further exacerbating hypoglycemia.

Acute withdrawal of hydrocortisone replacement therapy in patients with established Addison's disease results in decreased energy expenditure and urea production, increased glucose oxidation, and insulin sensitivity, suggesting that muscle and body weight loss is due to an alternative mechanism such as reduced appetite [84]. Muscle glycogen stores are depleted, and epinephrine activation of glycogen phosphorylase in both skeletal muscle and liver is suppressed [85]. Further effects are likely to result from the adrenergic insensitivity which occurs during adrenal insufficiency, with hypotension a frequent consequence of hypovolemia and reduced adrenergic vasoconstriction [86]. The vasculature is sensitive to locally released vasodilators, so that blood pressure may decline with exercise, partially accounting for the diminished work capacity associated with adrenal insufficiency.

Patients with adrenal insufficiency disease are prone to hyponatremia, hypovolemia, and hyperkalemia, which have potentially important effects on muscle function. The hyponatremia state is multifactorial, resulting from both the inability to deal with water loads stemming from the loss of glucocorticoid antagonism of antidiuretic hormone and a reduction in the glomerular filtration rate [87] and excessive renal excretion of sodium as a consequence of reduced mineralocorticoid activity, further exacerbating hypovolemia [86]. Hyperkalemia has two principal causes, including the inability to increase physiological mineralocorticoid output to compensate for higher potassium loads and a reduced capacity for muscle to take up potassium as a consequence of glucocorticoid deficiency-induced effects on membrane Na^+, K^+ pump content and activity [88], leading to potassium depletion of muscle tissues. The resultant weakness may be exacerbated by prolonged sarcolemmal depolarization secondary to the hyperkalemic state, leading to sodium channel inactivation and loss of membrane excitability [89, 90].

Clinical Presentations

Thomas Addison included descriptions of muscle weakness in his seminal description of patients diagnosed with adrenal insufficiency [91], and subsequent reports have highlighted the spectrum of neuromuscular and musculoskeletal symptoms and signs associated with the syndrome, including muscle contractures, muscle pains, and arthralgias [92–94]. Reports of the incidence of muscle dysfunction in adrenal insufficiency vary, with some reports stating that weakness and fatigue are nearly universally found [95] and with other reports suggesting a range between 25 and 50 % experiencing generalized weakness, muscle cramping, and fatigue [83].

Although adrenal insufficiency frequently occurs in association with other endocrine disorders, which can complicate the clinical assessment of a weak patient, the finding of muscle weakness and fatigability in patients with isolated ACTH deficiency indicates that hypoadrenalism in isolation can lead to significant weakness [83]. Adrenal insufficiency may produce isolated respiratory muscle weakness [96] or may precipitate underlying myasthenia gravis, as described in several challenging clinical cases [97–99]. Further complications can result from electrolyte disturbances, including the well-recognized association of hyponatremia, when severe, with rhabdomyolysis [100]. The co-occurrence of these features appears to be rare in clinical practice, with only three published case reports of this triad occurring together [101–103]. The etiology of adrenal insufficiency-associated rhabdomyolysis has been attributed primarily to cellular edema secondary to the hypo-osmolar extracellular fluid. The cause remains speculative, particularly as cases of adrenal insufficiency coexisting with rhabdomyolysis in the absence of significant hyponatremia have been published, suggesting alternative independent mechanisms [104].

Joint flexion contractures are commonly observed and have even been reported as the initial manifestation of adrenal insufficiency [105–109], including unusual cases of abdominal-crural contractures [110, 111]. These commonly reported features may well be a consequence of a connective tissue disorder rather than a primary muscle phenomenon. Adrenal insufficiency has also presented alongside Guillain-Barre syndrome [112], and other modes of presentation include migratory myalgia, sciatica-like pain, and low back pain [83]. Cardiomyopathy has be observed in the context of adrenal insufficiency, with both pediatric and adult cases reported [113–115].

Further clinical phenotypes include presentations of adrenal insufficiency in conjunction with defects of the mitochondrial and somatic genome, including X-linked congenital adrenal hypoplasia (CAH). This rare developmental disorder of the human adrenal cortex is caused by deletion or mutation of the DAX-1 gene, which encodes a nuclear hormone receptor. CAH occurs as part of a contiguous gene syndrome together with glycerol kinase deficiency and Duchenne muscular dystrophy. Most boys present with salt wasting and hyperpigmentation during the neonatal period, with aldosterone deficiency usually preceding cortisol deficiency. The ACTH test may be necessary to detect cortisol deficiency in infants [116]. Other mitochondrial disorders include Kearns Sayre syndrome, which presents with ophthalmoplegia, pigmentary retinopathy, heart block, and ataxia, with associated adrenal insufficiency (and other endocrinopathies such as growth hormone deficiency, hypogonadism, diabetes mellitus, and hypoparathyroidism) described [117, 118].

Differential Diagnosis

The spectrum of clinical presentations is very wide, as highlighted above, and the differential diagnosis is correspondingly broad. This requires a high index of suspicion and highlights the importance of "thinking endocrine" when considering patients presenting with apparent neuromuscular weakness [2].

An important condition to consider – particularly in the acute setting – is hyperkalemic periodic paralysis, which may occur in association with adrenal insufficiency. A flaccid quadriparesis associated with hyperkalemia is described in patients with primary adrenal insufficiency [119], which resembles familial hyperkalemic periodic paralysis, with triggers including potassium intake or exercise. In contrast, however, these patients do not have a family history of periodic paralysis, and the condition resolves with glucocorticoid replacement. Lowering the serum potassium by glucose administration or other means usually reverses the paralysis. Between attacks of weakness, membrane hyperexcitability is seen in both familial and Addisonian hyperkalemic periodic paralysis. Paramyotonia congenita also present with hyperkalemic paralysis, clinical episodes of flaccid weakness, paradoxical myotonia, and cold-induced weakness and EMG may show myotonic discharges. Paramyotonia and hyperkalemic periodic paralysis are caused by mutations of the skeletal muscle sodium channel [120].

Evaluation and Diagnosis

The diagnosis of adrenal insufficiency requires plasma cortisol, renin, ACTH assays, and ACTH stimulation test. Myopathy secondary to adrenal insufficiency is diagnosed clinically since serum muscle enzymes are usually normal, as are electrodiagnostic studies.

One published study of muscle function in patients with adrenal insufficiency found that patients had preserved maximum voluntary quadriceps forces but altered contractile properties and decreased endurance [121]. In a more recent review of 16 cases, a wide range of neurophysiological abnormalities were identified, although EMG studies were normal in a large proportion of patients (8 out of 14 cases examined). Other findings included myogenic features, continuous firing, or denervation. Nerve conduction studies were normal in 6 out of 10 cases, with a wide range of motor and/or sensory conduction abnormalities in the remaining 4 cases. Muscle biopsies were normal in 3 cases, with variably reduced numbers and/or atrophy of either type I or type II fibers in the remaining 4 cases [122].

Treatment and Prognosis

Management of patients with adrenal insufficiency in association with weakness should be directed at treating the underlying cause of adrenal dysfunction, which should improve weakness. Patients with primary insufficiency

require both glucocorticoid and mineralocorticoid replacement, while glucocorticoid replacement is nearly always sufficient for secondary adrenocortical insufficiency. In the acute clinical scenario, treatment of the paralytic condition may necessitate intensive care management for cardiac and respiratory complications and should focus on the correction of electrolyte abnormalities first followed by hormonal replacement. Dramatic improvements in muscle function are seen with replacement of hydrocortisone; however, treatment may be chronic and lifelong depending on etiology. Long-term muscle stiffness has been reported in some cases [122].

Muscle Disorders Associated with Thyroid Disease

Physiology and Pathology

The thyroid gland releases thyroid hormones, primarily thyroxine (T4), into the circulation. In the periphery, T4 is converted to the more bioactive triiodothyronine (T3). T4 and T3 enter the skeletal muscle by active transport [123], to act at several potential cellular sites, including the plasma membrane, cytoplasm, mitochondrion, and cell nucleus. These sites of action are generally categorized as genomic if they involve binding to intranuclear thyroid hormone receptors and nongenomic at other sites. A full description of the underlying molecular mechanisms of action is outside of the scope of this review, but is comprehensively described in Cheng et al. [124] and Davis et al. [125]. The genomic actions are mediated via thyroid hormone nuclear receptors (TRs), which are found as four T3-binding isoforms (α1, β1, β2, and β3) (alpha1, beta1, beta2, and beta3). Receptor transcriptional activity is regulated at multiple levels, via T3 itself, thyroid hormone response elements, tissue-dependent expression of TR isoforms, and co-regulatory proteins (both corepressors and co-activators). Nongenomic actions are similarly complex, including functions at the plasma membrane which involve the integrin αvβ3 and ERK-dependent pathways, resulting in ion channel modulation (particularly the activity of the Na^+/H^+ exchanger) [126] or linking into downstream nuclear events, including cellular division.

Thyroid hormones have long been known to increase the basal metabolic rate, skeletal muscle heat production, and mitochondrial oxygen, pyruvate, and malate consumption, and these properties are reflected in actions of T3 at the mitochondria. Recent studies suggest that these effects may be mediated by mitochondrial T3 receptors, linking into the glucose transporter 2 (GLUT2) and components of ATP-sensitive potassium channels [127]. Overall effects on skeletal muscle properties include increased glucose uptake and glycolytic activity, with stimulation of glycogenolysis.

The full complexity of the effects of thyroid hormones on skeletal muscle has been revealed in recent microarray studies using both animal models and human patients.

A transcriptional survey of ten patients who underwent thyroidectomy with subsequent thyroxine supplementation to physiological levels found that 607 genes were differentially expressed following thyroxine replacement. Sixty percent of genes were positively regulated, with 40 % negatively regulated, with a significant proportion of genes having roles in energy and fuel metabolism [128].

Hyperthyroidism

Hyperthyroidism is a common disorder, affecting approximately 2 % of women and 0.2 % of men. The most common cause is Grave's disease – autoimmune thyroid disease – in which the action of thyrotropin (TSH) stimulating autoantibodies results in the overproduction of thyroxine (T4) and (T3). Less commonly, toxic nodular goiters lead to hyperthyroidism through localized autonomous overproduction of thyroid hormone. A female predominance of 3:1–4:1 with a mean age of onset near the end of the fifth decade has been noted in numerous epidemiological studies. Thyrotoxicosis accelerates muscle protein degradation. Increased degradation of skeletal muscle protein is also seen in patients without myopathy and therefore is not a consequence of muscle weakness. Fat oxidation and lipoprotein lipase activity are increased in thyrotoxic patients [129].

Clinical Presentations

Acute Thyrotoxic Myopathy

Muscle weakness and atrophy are commonly found in hyperthyroidism, with several large patient surveys describing neuromuscular complaints in up to 80 % of patients, with marked muscle weakness in over half [130, 131]. The incidence of weakness and wasting increases with the duration of illness and is more commonly observed in older patients. The actual degree of weakness does not generally correlate with the biochemical severity of the thyrotoxicosis.

The weakness is primarily proximal and is often out of proportion to the amount of muscle wasting, although severe wasting may occur in some cases. Distal weakness may occur but usually develops in the latter stages and is less prominent than associated proximal weakness. Myalgia, fatigue, and exercise intolerance are common complaints. Breathlessness is a common symptom of patients with hyperthyroidism, with up to 90 % of patients complaining of dyspnea at the time of diagnosis, although overt respiratory insufficiency requiring ventilatory support due to respiratory muscle weakness and fatigue is rare [132]. Bulbar muscle involvement has been reported in thyrotoxicosis, although investigating alternative causes (including myasthenia gravis)

is important in patients with dysarthria, dysphagia, or dysphonia. Sphincter function is not involved. Severe acute hyperthyroidism – sometimes termed a "thyroid storm" – can be associated with rhabdomyolysis with myoglobinuric renal failure [133]. Rarely, an inflammatory myopathy occurs with thyrotoxicosis, which may necessitate corticosteroid therapy [134]. This presentation can occasionally lead to a coincident diagnosis of polymyositis and thyroid disease (both cases of hyper- and hypothyroidism have been reported in these cases) [135].

Association of Thyroid Disorders with Myasthenia Gravis

There is a significantly greater incidence of thyroid disorders in patients with myasthenia gravis than expected by chance, with 5.7 % of myasthenic patients hyperthyroid, 5.3 % hypothyroid, and 2.1 % having a nontoxic goiter [136]. There have been several reports of sudden onset of generalized weakness with bulbar palsy in thyrotoxic patients, and it is likely that some of these are acute presentations of myasthenia gravis, coincident with thyrotoxicosis. These patients had dramatic responses to neostigmine, and thymic hyperplasia was found in one of the two anticholinesterase-sensitive patients who were studied postmortem [50].

Thyroid Eye Disease

Thyroid eye disease (TED), also known as thyroid-associated ophthalmopathy and Graves' ophthalmopathy/orbitopathy, is a chronic inflammatory condition of orbital tissue and is nearly always associated with immune thyroid disease, although patients may be hyperthyroid (80 %), hypothyroid (10 %), or euthyroid (10 %) [137, 138]. The condition is restricted to the orbit, with no involvement of skeletal muscles beyond the extraocular muscles. Clinically evident ophthalmopathy occurs in approximately 50 % of patients with Graves disease, although subclinical disease is detectable using imaging modalities such as orbital infrared imaging, MRI, ultrasound, or radioisotope imaging in up to 90 % of patients [139–141].

The clinical features are wide ranging, in both their presentation and severity. Proptosis is most classically seen, with a degree of restrictive ophthalmoplegia. Severe exophthalmos is associated with prominent chemosis and eyelid edema, which can produce corneal ulceration. If swelling of orbital contents becomes severe, optic nerve compression may occur.

The causes of TED remain unclear, with a range of environmental (including smoking) and genetic risk factors identified [139]. The cellular pathophysiology has been defined, to some extent, with lymphocytes and macrophages identified within the retro-orbital connective tissue, secreting cytokines. Orbital fibroblasts appear integral to the pathological process, with proliferation leading to enlargement of extraocular muscles. The secretion of glycosaminoglycans into the extracellular space is associated with tissue edema and an increase in perimysial connective tissue. Extraocular muscle fibers are not directly damaged. Several potential antigenic targets expressed in extraocular muscle and orbital fibroblasts are found, but their precise role in disease development is unknown. Recent studies suggest that autoantibodies directed against the insulin-like growth factor 1 receptor (IGF-1R), which is overexpressed on fibroblasts derived from patients with TED, may be important mediators of the condition, although this is controversial [142].

The treatment of TED is tailored to the severity and rate of progression of symptoms. Mild manifestations usually respond to topical adrenergic blocking agents, with or without dark glasses and prisms. Systemic glucocorticoids reduce orbital swelling if adrenergic blockers fail and are particularly indicated in patients at high risk of visual deterioration [143]. Small trials of second-line agents, including anti-cytokine therapies, suggest that Rituximab may be an effective therapy [141, 144]. Indications for orbital decompression surgery potentially include compressive optic neuropathies not responsive to glucocorticoids, exposure keratopathies, and cosmesis [145].

Thyrotoxic Periodic Paralysis

Thyrotoxic periodic paralysis (TPP) is a relatively rare but important form of thyroid-associated weakness. Patients with TPP – who are typically male, South East Asian Ethnic origin, and aged 20–40 years – experience recurrent attacks of proximal weakness of variable duration (minutes to days). The actual incidence or prevalence of the condition is unclear, although a large case series reported that nearly 10 % of 432 Oriental patients with thyrotoxicosis manifest episodes of periodic paralysis [146]. Despite the emphasis of the disorder being more common in Oriental patients, a case series from Argentina suggests that TTP may be underappreciated in Caucasian populations [147].

Attacks may be precipitated by heavy carbohydrate intake, muscle cooling, or rest after exercise, although mild exercise may actually prevent an impending attack. The weakness is typically generalized but can also be relatively focal and limited to groups of muscles that were exercised. Bulbar, respiratory, and sphincter function are rarely compromised [148]. Hypokalemia is almost uniformly present, and hypophosphatemia and mild hypomagnesemia are also common features of TPP [149]. Thyroid function tests are often only mildly deranged.

Recent studies suggest that TPP results from a complex interaction of genetic susceptibility, thyrotoxicosis, and environmental factors (diet or exercise). The condition is linked to mutations in the inwardly rectifying potassium channel Kir2.6 (encoded by the KCNJ18 gene). This protein is transcriptionally regulated by T3, leading to increased protein expression in the thyrotoxic state [150]. The dynamic nature

of the muscle tissue changes was demonstrated in a recent study showing that in TPP several neurophysiological (voltage-gated currents and conductance) and muscle biopsy (histochemical fiber type) parameters were similar to those found in patients with hypokalemic periodic paralysis, which normalized once a euthyroid state was achieved [151]. These studies therefore strongly suggest that mutations in the expressed gene result in functional changes in channel current densities and/or alterations in downstream intracellular signaling properties, leading to the clinical manifestations of TPP [152].

Treatment for TTP involves supportive therapy for the acute event, with cautious correction of potassium and magnesium levels (to avoid rebound hyperkalemia), followed by treatment directed at the hyperthyroid state [149]. Nonselective beta-adrenergic blockers such as propranolol are a useful adjuvant until full control of thyroid function – which should cure TPP – is established using standard therapies.

Differential Diagnosis

The potential clinical features of thyrotoxicosis are wide ranging [153], requiring a high index of suspicion in milder cases, and the myopathy associated with hyperthyroidism should be distinguished from other myopathies, myasthenia gravis, polymyositis, myopathy of adrenal insufficiency, and steroid-induced myopathy. The pattern of weakness, progression of symptoms, disproportion between muscle weakness and atrophy, fold of skin above the weak muscle, and deep tendon reflex examination are useful in differentiation. Hyperthyroid myopathy can be confirmed with thyroid hormone assay and resolution of symptoms with return to the euthyroid state.

Evaluation and Diagnosis

In a typical clinical practice, thyrotoxicosis is usually straightforward to establish, using a high-sensitivity TSH assay as a screening test, finding low levels in significant thyrotoxicosis. Serum levels of CK, SGOT, LDH, and myoglobin are usually normal or low – unless the patient presents with rhabdomyolysis and acute renal failure. Assays for autoantibody titers typically find that 95 % of patients with Grave's disease have positive TPO-microsomal antigen antibodies and 50 % have positive antithyroglobulin antibodies.

The literature on neurophysiological features of thyrotoxic myopathy was shaped by the 1979 study of Puvanendram and colleagues, in which 48 thyrotoxic patients were evaluated clinically and neurophysiologically [154]. The majority of patients had abnormal proximal muscle EMG measurements, with short duration motor unit potentials and increased polyphasic potentials; in contrast only about 20 % of patients have abnormal distal muscle needle EMG patterns. The abnormalities were particularly marked in patients with significant clinical weakness, and other EMG features, such as spontaneous electrical activity (including fibrillations or fasciculations), were rare. Following treatment of the hyperthyroid state, EMG patterns normalized. Although well established in the literature, these relatively clear-cut views have been challenged by a more recent study, which found that 24 % of patients had neuropathic changes by needle EMG, further complicated by 19 % of patients manifesting a sensorimotor axonal neuropathy [131].

Histological appearances are variable, with both light and electron microscopic studies of muscle finding normal appearances or occasionally showing varying degrees of fatty infiltration, fiber atrophy, and nerve terminal damage [155]. These nerve terminal changes had previously been hypothesized to potentially account for the observed worsening of myasthenia gravis by thyrotoxicosis [156].

Treatment and Prognosis

Following diagnosis, three forms of therapy are commonly used, including destruction of the thyroid using radioiodine, blockade of hormone synthesis using antithyroid drugs, and surgical resection or removal of the thyroid gland. Adrenergic blocking agents may improve muscle strength acutely, especially of respiratory muscles, and glucocorticoids – which block the peripheral conversion of T4 to T3 – may be useful in the acute treatment of thyrotoxicosis [157, 158]. However, the specific treatment for thyrotoxic myopathy is returning patients to the euthyroid state. Within 4 months of treatment, all symptoms of weakness resolve and persistent weakness is rarely reported [131].

Hypothyroidism

Hypothyroidism is a common endocrine condition, second only to diabetes mellitus, with a prevalence approaching 18 per 1,000 in the general population [159]. As with hyperthyroidism, hypothyroidism has a female predilection, with a female/male incidence ratio of approximately 10:1. The prevalence increases with age, with 2–3 % of older women diagnosed with hypothyroidism [160]. The condition is most commonly primary, usually related to Hashimoto's thyroiditis, although it may result from several iatrogenic causes (both medical and surgical).

Pathology

Metabolic changes of hypothyroidism affect muscle function in multiple ways, reducing oxygen consumption and basal metabolic rate through actions on mitochondrial oxidation capacity, muscle oxidative enzyme activity, and glucose uptake [161]. Muscle glycogenolysis is impaired, resulting in fasting hypoglycemia and possible accumulation of glycogen. In addition, hypothyroidism produces an insulin-resistant state, with likely effects detailed previously. Hypothyroidism reduces the

number of adrenergic receptors on muscle cells, resulting in diminished glycogenolysis [162] which may contribute to development of muscle cramps and fatigability. Both protein synthesis and degradation are reduced with net protein catabolism. Hypothyroidism reduces Na^+-K^+ pump activity and renal sodium resorption in the distal tubule, leading to relative hypovolemia, decrease in the cardiac output, and myokymia [50].

It is well known that hypothyroidism markedly prolongs the tendon reflex relaxation time [163]. This occurs in non-myxedematous patients and likely reflects the slowing of calcium sequestration by sarcoplasmic reticulum and prolongation of the twitch rather than mechanical damping by excess connective tissue.

Clinical Presentations

Muscle stiffness, aching, and slight weakness are present in the majority of hypothyroid patients and occasionally are the only indication of thyroid disease. The primary manifestations of myopathy in hypothyroidism are proximal weakness, stiffness, myalgia, myoedema (local contracture produced by tapping or fatigue, slowed pinching the muscle), and, less commonly, cramps and muscle enlargement [50, 131, 164]. Reflex changes are common, and severe weakness with muscle enlargement occurs in few cases. Hypothyroidism may present with rhabdomyolysis or respiratory muscle weakness [165, 166]. Long-standing hypothyroidism may produce a slowly progressive proximal myopathy, and muscle disease can occur without features of myxedema.

Reported EMG findings in hypothyroid myopathy are highly variable, ranging from normal through to low amplitude polyphasic motor unit potentials and sporadically increased insertional activity and positive waves. Fibrillations or fasciculations may occur but probably suggest a coexistent neuropathy. These are commonly found in hypothyroidism (and are typically sensorimotor axonal in character); furthermore, about a quarter of patients have neurophysiological evidence of carpal tunnel syndrome [131]. The incidence of neurophysiological myopathic changes is controversial. One report of 16 untreated hypothyroid patients found myopathic changes in 46.6 % [167]. In a further prospective study of 23 neurologically asymptomatic patients with hypothyroidism, myopathic changes were found (without spontaneous activity) in 74 % of patients, with abnormalities most commonly found in the deltoid muscles and less commonly identified in the vastus lateralis (39 %) and tibialis anterior (26 %) muscles. Neuropathies were identified in 52 %, principally of a motor demyelinating pattern, with 30 % of patients having a carpal tunnel syndrome [168].

In contrast, in a more recent study of 40 patients with untreated primary hypothyroidism, 30 % of patients had clinical muscle weakness, 45 % with diminished (or absent) deep tendon reflexes, 15 % had a neuropathy, and only 7.5 % had a myopathy. Carpal tunnel syndrome was again commonly found in 32.5 % [169]. It was speculated that the low incidence of myopathy in this cohort may have related to early diagnosis of the condition, prior to the development of complications.

The neurophysiological features of myoedema – defined as stationary muscle mounding after muscle percussion without electrical muscle activity – are unremarkable, even by single fiber EMG. These findings are common – they were observed in 88 % of surveyed patients with a range of neurological diseases. Myoedema is therefore not specific to hypothyroidism, although is more clinically prominent in this condition [170, 171].

Light microscopy of involved muscles demonstrates a variety of changes: atrophy, necrosis or hypertrophy of fibers, increased number of nuclei, ring fibers, glycogen accumulation, and increased interstitial connective tissue [172]. Basophilic inclusions without limiting membranes are sometimes seen in type 1 fibers. The neuromuscular junction generally appears normal in hypothyroidism. Ultrastructural studies have frequently demonstrated multiple abnormalities, including mitochondrial swelling and inclusions, myofibrillar disorganization and fragmentation, glycogen accumulation, lipoid granules, dilation of the sarcoplasmic reticulum, autophagic vacuoles, central core changes, and T-tubule proliferation [173]. Some of these changes have been observed to resolve with thyroid replacement therapy.

Differential Diagnosis

Other endocrine, toxic, inflammatory, and limb-girdle myopathies are within the differential diagnosis of hypothyroid myopathy. Myoedema (see above) occurs in about one-third of hypothyroid patients but is also seen in a variety of disorders associated with malnutrition and wasting. Hypothyroidism should be considered in patients with rhabdomyolysis, but other etiologies – as detailed in previous sections – should always be considered.

Evaluation and Diagnosis

Hashimoto's thyroiditis is usually investigated via standard thyroid function tests (TSH and T4 levels) in combination with antithyroid peroxidase (TPOAb) and antithyroglobulin (TgAb) antibody testing [174]. Primary hypothyroidism is characterized by high TSH and low free and total T4, whereas but in secondary hypothyroidism, TSH and total T4 are both in the low range indicating hypothalamic or pituitary dysfunction. Antithyroglobin antibodies are useful pointers to autoimmune thyroiditis. Serum CK activity is elevated in many hypothyroid patients, with levels up to tenfold higher than normal, even in the absence of overt muscle disease [163, 175]. This may become a less frequent finding than previously reported, as the increased use of screening tests is likely to lead to patients with milder disease at the point of diagnosis [131]. Serum myoglobin has been found to be elevated in some patients with severe hypothyroidism, although creatine excretion is usually not elevated [176].

Treatment and Prognosis

The only effective treatment is to restore the patient to a euthyroid state, with a reasonable prognosis for recovery, with CK levels correcting rapidly with thyroid replacement. A prospective study found that, after a mean of 6 months of treatment, the majority of patients had made a good recovery, although a quarter of patients still experienced neuromuscular symptoms at 1 year, with more than 10 % having weakness on formal examination [131].

Muscle Disorders Associated with Pituitary Dysfunction

Growth Hormone Excess

Physiology and Pathology

Human growth hormone (GH) is a single-chain 191 amino acid polypeptide secreted from eosinophilic (somatotroph) cells in the anterior lobe of the pituitary. GH acts primarily by stimulating the formation of locally synthesized somatomedins, also known as insulin-like growth factors (IGF), of which IGF-1 is the most important. Blood levels of IGF-1 therefore correlate with circulating levels of GH. IGF-1 binds to the cell surface tyrosine kinase IGF-1 receptor [177], resulting in auto-phosphorylation and recruitment of insulin receptor substrate (IRS) proteins. Downstream targets include Ras/Raf/MEK and ERK, which are involved in proliferation; PI3K/AkT, which have effects on protein synthesis; NFkB, which inhibits apoptosis; and MyoD/P21, which has effects on differentiation [178].

GH is an important regulator of protein metabolism and is the primary anabolic hormone during stress and fasting [179], potentially via effects on fatty acid oxidation and oxidative and glycolytic carbohydrate metabolism, thus reducing glucose utilization, with associated insulin resistance. Excessive amounts of GH increase protein synthesis and possibly retard protein breakdown in muscle [180].

The most striking finding of GH excess is the resultant decreased force-generating ability, despite increased fiber diameters [181]. Impaired carbohydrate metabolism and possibly restricted muscle blood flow may partially explain this deficit. In rats with excess GH, for example, proximal and trunk muscle hypertrophy develop, yet muscles have reduced twitch and tetanic tensions [181–183]. Thus, increased protein content does not improve contractile ability, which may result from several factors. In rat muscle, chronic GH administration may decrease myofibrillar ATPase activity, despite the increased concentrations of actin and myosin [184]. Studies in humans are more limited, although a case report from a single acromegalic patient found that intercostal muscle fibers were slightly depolarized, with an elevated action potential threshold [185]. Thus, excessive amounts of GH may both decrease surface membrane excitability and impair myofibrillar contractile ability.

Experimental and clinical studies support growth hormone as a regulator of cardiac muscle function. Transgenic mice, which overexpress growth hormone, demonstrate systolic contractile dysfunction, and ultrastructural studies of the heart show mitochondrial abnormalities. Acromegalic cardiomyopathy is characterized by myocardial hypertrophy with interstitial fibrosis, lympho-mononuclear infiltration, and areas of monocyte necrosis which often result in biventricular concentric hypertrophy [186].

Clinical Presentations

Pierre Marie first described the presentation of acromegaly in 1886, which included two personal cases and five from prior literature [187]. The clinical features included preserved muscle bulk, hypotonia, and increasing proximal weakness as the disease progressed. These early clinical observations of acromegalic patients have been replicated in numerous studies, with more recent reports using MRI and dual-energy x-ray absorptiometry (DXA) finding increased total lean mass but normal total muscle mass compared to normal controls [188].

Proximal weakness and decreased exercise tolerance occurs in approximately 50 % of patients, without apparent racial predilection, and is typically insidious in onset and gradually progressive. Respiratory muscles are also affected, with reduced inspiratory and expiratory muscle function in the presence of an increased total lung capacity [189]. Extraocular myopathy is a rare presenting feature of acromegaly, with case reports finding symmetrical involvement [190, 191]. Assessment is complicated by the frequent incidence of rheumatological signs and symptoms, including musculoskeletal pain (90 %), neck pain (50 %), and osteoarthritis of the hip (84 %) and knee (34 %) [192]. The classic coarsening of facial features and costochondral enlargement are common signs of GH excess [193–195].

Cardiovascular disease, characterized by cardiomyopathy, concentric left ventricular hypertrophy (LVH), and diastolic dysfunction, is commonly associated with acromegaly and account in part for the reduced exercise performance seen in such patients [196].

Evaluation and Diagnosis

For screening and follow-up of acromegaly, basal GH and age-matched IGF-1 levels are the most convenient tools. The most accurate test for diagnosis and prediction of outcome after therapy is the lack of GH suppression during oral glucose tolerance test [197, 198]. Serum levels of CK or aldolase may be slightly elevated [194, 199, 200]. Creatine excretion is normal or only slightly increased.

Approximately 50 % of acromegalic patients have myopathic changes on needle EMG; in other cases, findings are

either nonspecific or normal [194, 200, 201]. Short duration motor unit potentials and an increased frequency of polyphasic potentials are occasionally found in clinically unaffected patients [202]. Diffuse hypertrophic neuropathy or nerve entrapment, usually of the median nerve, occurs in about half of patients. The neuropathy and myopathy usually develop independently and follow separate courses.

Muscle histology may show atrophy of both type I and II fibers [202], mixed fiber-type hypertrophy and atrophy [201], or preferential type II fiber loss [194]. Light microscopic evaluation of muscle reveals isolated fiber necrosis, vascular degeneration, nuclear enlargement with prominent nucleoli proliferation and hypertrophy of satellite cells, increased muscle glycogen, lipofuscin accumulation, and, rarely, round cell infiltrates. Ultrastructural studies show excessive amounts of lipofuscin and glycogen, loss of myofibrils, thickening of capillary basement membranes, increase in satellite cells, altered mitochondria (pleomorphism, elongation, metrical pallor and cristae abnormalities), inclusion bodies, and vesicular dilatations. With effective biochemical control of GH secretion post-surgery, resolution of ultrastructural features has been described [203].

Treatment and Prognosis

According to Endocrine Society guidelines, treatment of acromegaly should be individualized and provided by an experienced multidisciplinary team [204]. Modalities include Transsphenoidal surgery (TSS), medical therapy, and radiotherapy, with TSS as the initial treatment of choice in most cases. Medical therapy includes somatostatin analogues (octreotide and lanreotide), dopamine agonists (cabergoline), and a GH receptor antagonist (pegvisomant), with radiotherapy generally used as a third-line treatment option. Current consensus advocates long-term monitoring of biochemical parameters of GH secretion (OGTT, Serum IGF-I), tumor growth (MRI), along with screening for complications such as hypopituitarism, cardiomyopathy, obstructive sleep apnea, and colonic polyps [204].

Acromegaly is associated with an overall increase in mortality and morbidity resulting from effects on cardiovascular, musculoskeletal, neurological, and endocrine systems. The overall mean standardized mortality ratio (SMR) in a recent meta-analysis was 1.72 (95 % CI 1.62–1.83) [205], with correlations between GH levels and mortality risk. Growth hormone has critical affects on cardiac muscle, and cardiovascular abnormalities represent the major cause of death in patients with acromegaly [205, 206].In a study of 205 patients with acromegaly, patients had reduced left ventricular ejection fractions and just under a 12-fold increased prevalence of LVH compared with normal controls. Increased disease duration was most closely associated with cardiomyopathy [207]. A separate study showed that higher serum IGF-1 levels were associated with higher rates of cardiomyopathy, suggesting that the association is dose dependent [208]. Effective biochemical control of excess GH secretion by TSS and medical therapies, including somatostatin analogues and pegvisomant, has been shown to reduce LVH and improve cardiac function [209].

In treated patients, marked changes in body composition are seen by 1 year, with significant reductions in skin, muscle, and visceral organ mass and a corresponding increase in adipose tissue mass [210]. The myopathy usually resolves when GH levels return to normal; however, deficits may still be detectable years after effective remission of biochemical disease [199, 202].

Hypopituitarism

Pathology

The causes of adult hypopituitarism include thrombosis of the pituitary circulation, pituitary region tumors, head injury, granulomatous destruction, surgery, radiotherapy, iron overload, congenital abnormalities, encephalitis, and meningitis. Pituitary failure in adults causes severe weakness and fatigability with disproportionate preservation of muscle mass. The muscle manifestations of hypopituitarism are primarily attributable to loss of thyroid and adrenal hormones, which are outlined elsewhere in this chapter, with resultant deficits potentially reversed by hormonal replacement.

Clinical Presentations, Evaluations, and Diagnosis

In recent years, however, the particular importance of adult growth hormone (GH) deficiency in causing muscle weakness has been increasingly recognized. GH-deficient patients are weaker, have reduced muscle mass, have increased fat mass, and have impaired exercise capacity and endurance compared to normal individuals [211–214]. Muscle weakness is thought to be secondary to reduced muscle mass, as intrinsic fiber strength is not reduced [211].

Hypokalemic periodic paralysis has been described as an atypical presentation of muscle involvement in GH deficiency [215]. Activation of the Na^+/K^+ ATPase by insulin/IGF-I signaling, resulting in increased transport of K^+ into cells, was proposed as a potential mechanism and symptoms reversed with GH replacement and optimization of glycemic control.

Screening for GH deficiency in patients with fibromyalgia has been advocated following studies suggesting an increased prevalence in this population. In one large study, 34 % of patients ($n=493$) were found to have subnormal IGF-I levels, while 22/127 (17 %) had evidence of GH hyposecretion on insulin tolerance testing, eight of which had severe deficiency [216]. A small-scale study of GH replacement in fibromyalgic patients found significant effects on a range of

disease-related symptoms, but results from larger scale studies are awaited [217].

Several studies have examined the neurophysiological features of GH deficiency. In one study, EMG findings at baseline in GH-deficient patients showed reduced mean frequencies compared to normal controls, with proposed mechanisms including reduced cross-sectional fiber area, reduced type 2 fibers, and increased intramuscular fat deposition [214]. No significant changes in EMG results were seen after 6 months GH treatment. In a separate study, 14 out of 20 patients with GH deficiency had abnormal EMG and/or interference pattern analysis (IPA) studies. Seven of these patients had repeat IPA studies after 12 months of GH treatment, of which six had normal results, with the remaining patient showing improvement [218].

Treatment and Prognosis

Current evidence suggests that short-term treatment with recombinant GH leads to improvements in muscle strength, improved exercise capacity – as measured by maximal power output and oxygen uptake – and increases in lean mass [212, 213]. These results should be interpreted cautiously, as the data on long-term follow-up of GH replacement originates from open-label studies, with controlled studies limited to short-term follow-up periods [213]. It is likely that long-term treatment (beyond 5 years) is required to normalize strength to age-predicted levels [219, 220].

There is a complex interplay between anterior pituitary hormones and their effects on muscle mass and strength. GH is known to reduce total body 11beta-HSD1 activity, resulting in a reduction in local active glucocorticoids and possible pro-anabolic effects [221]. GH deficiency is therefore characterized by activation of glucocorticoids, which may partly explain the observed increased central adiposity and muscle wasting. Testosterone therapy for hypogonadism results in increased lean mass and reduced fat mass and has also been shown to improve grip strength compared to placebo [222]. Effects of androgen therapy on muscle may result from potentiation of GH/IGF-I signaling pathways.

Previously studies have raised interest in the role of GH replacement to prevent age-related sarcopenia, in light of the physiological reduction in GH secretion with age – the so-called somatopause. This treatment is not currently recommended, however, in view of lack of functional improvements and long-term safety concerns [223].

Prepubertal panhypopituitarism is usually idiopathic or associated with a suprasellar tumor and is characterized by dwarfism, with lack of muscular and sexual development. Panhypopituitarism in children produces muscle wasting, with a reduction in cell number and size. In contrast to the disease in adults, GH replacement is essential to correct the muscle disorder because of the critical role of GH (and/or IGF) in muscle development [177, 211, 224–226].

Muscle Disorders of Calcium and Vitamin D Metabolism

Physiology

Parathyroid hormone (PTH), along with vitamin D and calcitonin, collectively controls calcium homeostasis, with important roles in bone metabolism and structure, resulting in a tightly maintained serum calcium level. Vitamin D is found in two forms which are important in humans – vitamin D_2 (ergocalciferol) and D_3 (cholecalciferol) which have actions on the intestine, kidneys, parathyroid glands, and bone, with more recently described effects on skeletal muscle. The two forms have similar biological properties, but are not bioequivalent (reviewed in Houghton et al.) [227], and the related literature, particularly related to therapeutic supplementation, therefore, needs to be interpreted with great caution. Vitamin D_3-related metabolic pathways involve the production of 7-dehydrocholesterol, which isomerizes under the action of UV radiation exposure in the skin to produce cholecalciferol (the inactive, unhydroxylated form of vitamin D_3). Alternatively, cholecalciferol can be obtained from a range of dietary sources. Cholecalciferol binds to the vitamin D-binding protein and is transported to the liver where it is hydroxylated by cholecalciferol 25-hydroxylase to calcifediol (also known as calcidiol, 25-hydroxyvitamin D_3), followed by further hydroxylation in the kidney by 25-hydroxyvitamin D-1α-hydroxylase to calcitriol (1,25-hydroxyvitamin D_3). Calcitriol is the most active form of vitamin D_3 and exerts its principal actions by binding to the vitamin D receptor (VDR), a member of the steroid hormone receptor of ligand-activated transcription factors to modulate the activity of numerous genes and gene products, increasing calcium absorption in the gut, bone resorption, and renal reabsorption of phosphate [228–230]. The VDR can be found in both the cytoplasm and nucleus of many cells, and as with many other hormone receptors, sites of action are typically classified as genomic or nongenomic. Binding of calcitriol to the VDR promotes the association of VDR with the retinoid X receptor (RXR), resulting in binding of the complex to vitamin D response elements present in DNA. Co-regulatory proteins (both co-activators and repressors) associate with the complex to modulate gene transcription (reviewed in Pike et al.) [231].

PTH is an 84 amino acid peptide secreted by the chief cells of the parathyroid glands and functions to increase extracellular calcium concentrations. The hormone binds to the parathyroid hormone receptors – two PTH receptor genes PTH1R and PTH2R are found in mammals – to activate adenyl cyclase and phospholipase C [229] and direct mineral and ion transport of the bone and kidney as well as through indirect pathways on the small intestine through actions on vitamin D synthesis. The full range of actions of PTH on

in vivo gene transcription are extremely wide, with microarray studies finding that approximately 1,000 gene sets are modulated, leading to differential cell signaling, gene transcription, and cytokine production [232].

In contrast to the physiological actions of PTH, calcitonin, a 32 amino acid peptide secreted by the parafollicular cells of the thyroid, reduces blood calcium levels, largely through antagonistic pathways, activated through binding to high-affinity calcitonin receptors (reviewed in Naot et al.) [233]. Although clearly bioactive, the absolute physiological relevance of calcitonin in mammals is the subject of debate (reviewed in Hirsch et al.) [234].

Effects of Vitamin D on Muscle

The unequivocal demonstration of the direct effects of vitamin D on muscle followed the identification and cloning of the VDR from skeletal muscle cell lines [235–237]. The genomic effects include influences on muscle calcium uptake, phosphate transport across the cell membrane, and muscle cell proliferation and/or differentiation [238]. Calcium uptake is mediated through altered activity of calcium pumps, both within the sarcoplasmic reticulum and sarcolemma, changing the contractile properties of muscle [239]. Activation of the nuclear VDR results in the increased production of certain proteins, including calcium-binding proteins, which include calbindin and calmodulin [240, 241].

Further actions of vitamin D on muscle occur rapidly – within minutes – and are not antagonized by RNA/protein synthesis inhibitors, suggesting nongenomic effects. The underlying molecular pathways are not clear, but may involve the modulation of calcium entry into the cell at the membrane, G protein-mediated activation of phospholipase C, and/or the activation of mitogen-activated protein kinase (MAPK) signaling pathways [242, 243].

PTH stimulates protein degradation in skeletal muscle [244]. The PTH effect is partially mediated by elevated intracellular calcium which may result from activation of calcium channels by cAMP and a PTH-induced increase in mitochondrial calcium permeability [245]. The increased intracellular calcium may in turn activate intracellular proteases, and cAMP-dependent phosphorylation of the inhibitory subunit of troponin modulates the calcium sensitivity of the calcium-binding subunit of the protein [50].

Primary and Secondary Hyperparathyroidism and Metabolic Bone Disease

The muscle disorders associated with primary and secondary hyperparathyroidism and metabolic bone disease are grouped together because of their clinical similarities, although the clinical and pathological characteristics of these disorders are described separately to emphasize variations in their presentation, with the overall etiology and pathogenesis considered together [50].

Pathology

This category of muscle disorders results from elevations in parathyroid hormone (PTH) (primary and secondary hyperparathyroidism) and impairment of vitamin D activity (secondary hyperparathyroidism and osteomalacia). As would be expected, the similarity of the muscle disorders associated with primary hyperparathyroidism, uremia, and osteomalacia is likely to reflect the parallel and overlapping effects of PTH excess and vitamin D deficiency on muscle metabolism. Animal models have confirmed that isolated Vitamin D deficiency leads to muscle wasting, with impaired muscle force generation, and delayed relaxation. The extent of weakness does not correlate with electrolyte (calcium or phosphate) levels, and dietary replacement of these agents does not correct the disorder [246]. Excitation-contraction coupling is deranged, with calcium uptake ability and storage capacity of mitochondria impaired [247], along with depressed myofibrillar ATPase activity [248]. Muscle wasting may be a consequence of overall reduced protein synthesis. The close similarity of clinical presentations is mirrored in animal models of both uremia and vitamin D deficiency [247].

Studies in human subjects are generally more complex to perform, and results occasionally contradictory. Many have been performed in patients with renal failure, who are unable to convert 25-hydroxyvitamin D_3 to the bioactive 1,25-hydroxyvitamin D_3 [229]. Muscular weakness and other less specific musculoskeletal symptoms including aches and cramps are well-recognized features of patients with chronic renal failure [249], but the underlying pathogenesis is likely to be multifactorial. Muscle biopsies of patients with renal failure demonstrate abnormalities of muscle energy metabolism which are partially due to alterations in the function of key enzymes of oxidative and glycolytic metabolism [250].

Early small-scale studies suggested that vitamin D supplementation of patients with renal failure led to an improvement in muscle strength, including an improvement of EMG parameters, without causing significant changes in calcium or phosphate levels [251].

Primary Hyperparathyroidism

Primary hyperparathyroidism is a common endocrine disorder, typically resulting from a benign parathyroid adenoma (in 80 % of cases) or more rarely from multiglandular involvement or parathyroid carcinoma. Women are more

commonly affected than men (with a ratio of 3:1), with a peak incidence of diagnosis between the ages of 50 and 60 years. When severe, the resultant hypercalcemic state leads to a wide range of systemic symptoms classically associated with the condition, including polyuria, constipation, nausea, and kidney stones. Hypercalcemia is frequently associated with depressed serum phosphate levels, elevated serum alkaline phosphatase levels, and hypercalciuria. Urinary creatine excretion is elevated, but serum levels of CK and aldolase are usually normal [252]. Osteopenia may be manifest on bone radiographs and may even suggest the diagnosis.

In modern clinical practice, patients are frequently asymptomatic at diagnosis, with the diagnosis made following a screening serum calcium level for an unrelated problem [253]. Relatively mild and/or nonspecific neuromuscular symptoms, particularly muscle cramps, weakness, and fatigability, are commonly reported by patients with mild primary hyperparathyroidism, but overt signs of muscle disease are far less common [252]. When evident, examination may reveal symmetric proximal muscle weakness and atrophy, and severely affected patients may develop a waddling gait or be unable to walk. Of note, the severity of the clinical weakness does not usually correlate with the magnitude of the electrolyte disturbance. Bulbar and sphincter function are usually spared.

EMG studies in patients with primary hyperparathyroidism frequently show decreased motor unit potential size and increased frequency of polyphasic potentials without spontaneous activity [254]. A further report found that three patients with severe proximal weakness and bulbar involvement had fasciculations and a reduction in the number of recruitable motor unit potentials with normal nerve conduction velocities, suggesting an etiological link to amyotrophic lateral sclerosis (ALS) [255]. However, a subsequent study did not support a relationship, as parathyroidectomy did not alter the clinical course of the underlying ALS [256]. Histological analysis of muscle from patients with hyperparathyroidism generally found no abnormalities, but type 2 fiber grouping with internal nuclei and small group atrophy may be observed [257]. Others report type 2 fiber atrophy, focal areas of atrophy with polymorphonuclear cell infiltrates, vacuolar degeneration, and thickening of arteriolar and endomysial basement membranes with accumulation of glycoproteins [258].

Treatment for primary hyperparathyroidism via parathyroidectomy alleviates symptoms and improves strength [259, 260].

Secondary Hyperparathyroidism: Renal Failure

Patients with chronic renal failure frequently develop secondary hyperparathyroidism with a myopathy that resembles that seen in primary hyperparathyroidism [261]. Initially, lower extremity weakness predominates, but with time all four limbs are affected. Parathyroid hormone excess, uremic toxins, vitamin D deficiency, aluminum toxicity, and carnitine deficiency have all been implicated in the underlying pathogenesis of the myopathy.

Diagnostic tests find electrolyte abnormalities consistent with the degree of underlying renal failure. Hypocalcemia is found, resulting from poor vitamin D production and subsequent phosphate retention by the failed kidneys. Serum levels of CK and aldolase are usually normal [262].

Typically, electrodiagnostic studies show myopathic changes, but patients also frequently have diminished motor nerve conduction velocities and signs of distal sensory neuropathy [261, 263]. The usual form of uremic myopathy is associated with type 2 fiber atrophy. Ultrastructural studies show nonspecific changes of Z-line degeneration and vacuolization [261]. Electron microscopy reveals increased lipofuscin located mostly beneath the cell membrane [262]. The myopathy is characterized by calcium deposits in necrotic muscle, suggesting ischemia and arteriolar and capillary stenosis caused by medial calcification and fibrous intimal proliferation. The vessel changes may represent an extreme, as capillary and arteriolar basement membrane thickening and calcium deposition occur in patients without myoglobinuria or elevated serum CK levels [261].

Treatment of the underlying deficit with vitamin D replacement generally reduces the incidence of myopathy, and renal transplantation may lead to complete resolution of myopathic symptoms.

Osteomalacia

Myopathy may occur in osteomalacia caused by dietary deficiency, malabsorption of vitamin D, or abnormal vitamin D metabolism-associated renal tubular acidosis or anticonvulsant use. Myopathic findings may be present prior to the characteristic bony changes of osteomalacia, which can confuse the diagnosis. Boys with X-linked type 1 hypophosphatemic rickets do not develop weakness, as vitamin D metabolism is normal in this condition, but the kidney does not respond adequately, leading to renal phosphate wasting [50].

Clinical Presentations, Evaluation, Diagnosis, and Prognosis

A significant proportion of patients with osteomalacia complain of weakness or myalgia, with the majority experiencing a gradual onset of proximal weakness [247, 264]. The frequently nonspecific presentation, with generalized malaise, fatigue, myalgia, and general weakness, can overlap with a wide range of other conditions, including fibromyalgia, polymyalgia rheumatica, and psychiatric disorders. Patients with osteomalacia have elevated serum calcium and phosphate levels, with increased or normal PTH levels [247].

Serum alkaline phosphatase is often increased, but not invariably, and serum levels of vitamin D are required to confirm the diagnosis [264].

Needle EMG shows short duration, low amplitude, and polyphasic motor unit potentials [265]. In contrast, the light and electron microscopic findings are usually minimal, but may show type 2 fiber atrophy, with fatty infiltration, interstitial fibrosis, variation in fiber size, proliferation of fiber nuclei, loss of myofibrils, and Z-line thickening [266]. The myopathy of osteomalacia improves with vitamin D replacement but may take more than 6 months [264].

Hypoparathyroidism

Hypoparathyroidism is most commonly iatrogenic, resulting from surgical excision of the parathyroid glands or occasionally from vascular injury. Idiopathic hypoparathyroidism also exists as an isolated entity, in association with thymic agenesis and wide range of other systemic abnormalities, such as DiGeorge syndrome, or as part of familial condition associated with deficiency of adrenal, thyroid, and gonadal function [267, 268]. Pseudohypoparathyroidism is characterized by signs of hypoparathyroidism in association with distinctive skeletal anomalies and, frequently, intellectual impairment. PTH levels are normal or elevated in pseudohypoparathyroidism as the disorder results from a defective cellular response to PTH. A mutation of a guanyl nucleotide-binding protein gene is a cause of some forms of pseudohypoparathyroidism [269]. In both pseudo- and true hypoparathyroidism, patients are hypomagnesemic, with associated muscle tetany [270] and occasional signs of chronic myopathy.

The nerve axon hyperexcitability is caused by electrolyte disturbance, with decreased serum free calcium and magnesium concentrations. The voltage-sensitive channels in nerve are controlled by the transmembrane electric field. Depolarization of the cell decreases the electric field, which triggers the opening of voltage-sensitive sodium channels. Decreased free serum calcium will reduce normal amount of surface charge screening, which will reduce transmembrane electric field just as depolarization does. Therefore, hypocalcemia or hypomagnesemia reduces the action potential threshold without changing transmembrane potential.

Tetany

Hypocalcemia and hypomagnesemia produce hyperexcitability of nerve fibers with spontaneous and repetitive discharges, which results in perioral and distal sensory disturbance, carpopedal spasm (extension and adduction of the fingers with associated flexion of metacarpophalangeal joints), and diffuse muscle cramping [270]. Latent tetany can be provoked through hyperventilation, by tapping the facial muscles (Chvostek sign) or by occluding venous return from an arm resulting in carpopedal spasm (Trousseau sign). Ischemia lowers the threshold of nerve fibers and combined with hypocalcemia could account for Trousseau signs [50]. Normocalcemic tetany may occur as a familial disorder [271]. Alkalosis in dialysis patients and postoperative hypocalcemia after thyroidectomy are common causes and may be prevented with vitamin D and calcium supplementation [272].

The treatment of choice is a slow intravenous infusion of calcium, which can be administered as a slow intravenous push with cardiac and blood pressure monitoring for severely deficient cases. Hypomagnesemia should also be treated, with dose reductions in the presence of renal impairment. Chronic treatment of hypocalcemia requires dietary supplement of calcium and vitamin D. After several weeks, treatment doses are adjusted to achieve a physiological blood calcium level. If the patient does not initially respond to vitamin D_2 supplementation, then 1- or 1,25-hydroxyvitamin D_3 may be tried to circumvent impaired vitamin D activation.

Chronic Myopathy in Hypoparathyroidism

The diagnosis of hypoparathyroidism is usually straightforward, manifest with reduced serum calcium, phosphate, and barely detectable serum parathyroid levels. Myopathy rarely complicates hypoparathyroidism. Weakness and CK elevation may be relatively mild, and muscle biopsy may be normal or show atrophic fibers [273]. The condition partially resolves with calcium and vitamin D treatment, which correct underlying electrolyte abnormalities [274]. A similar syndrome is described in patients with pseudohypoparathyroidism who have elevated serum CK and LDH activity without weakness.

Muscle biopsies have demonstrated diminished glycogen phosphorylase activation [275]. Serum levels of muscle-associated enzymes normalized with calcium and vitamin D_2 treatment. The relation between these syndromes and hypoparathyroidism or pseudohypoparathyroidism is unclear. Some patients with mitochondrial myopathy have associated hypoparathyroidism [276].

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Toxic Myopathies

68

Ralph W. Kuncl and Gary J. Romano

Introduction

Toxic myopathies continue to be underrecognized clinically even while the number of substances identified as myotoxic increases. One reason is that the literature continues to be crowded with uncritical case reports of toxic "myopathy" that are often nondescript syndromes of a sense of asthenia, fatigue, and/or myalgia in which myopathy is inadequately documented [1]. Toxic myopathies are defined as toxic disorders where the primary clinical feature is weakness and there is compelling morphological, electrophysiological, serum enzymological, or metabolic evidence of muscle disease [2].

Drugs and toxins may cause muscle damage in a variety of ways. They may *directly* injure muscle fibers, as in toxic necrotizing myopathies (Table 68.1 and Fig. 68.1). Alternatively, myotoxic effects may occur *indirectly* through electrolyte derangements (e.g., ethanol), muscle ischemia, excessive muscle activity (e.g., neuroleptics), lysosomal or mitochondrial damage, or immune mechanisms. The effects of muscle toxins may be generalized affecting multiple muscle groups or focal involving only those muscles which were injected with an offending agent. Lastly, the toxic effects on muscle may occur acutely after ingestion or may require chronic exposure.

Table 68.1 Drugs, neutriceuticals, and foods causing necrotizing myopathies

Statins (HMG-CoA reductase inhibitors)[a]
Red yeast rice; Zhibitai; monacolin K
Fibric acid derivatives
Zidovudine
Clevudine
Ethanol
Emetine
Organophosphates
Epsilon-aminocaproic acid
Etretinate
Procainamide
Bupivacaine
Edible mushrooms

[a]Including atorvastatin (Lipitor®), cerivastatin (Baycol®), fluvastatin (Lescol®), lovastatin (Mevacor®), pitavastatin (Livalo®), pravastatin (Pravachol®), rosuvastatin (Crestor®), and simvastatin (Zocor®)

General Principles

Diagnostic Principles

The diagnosis of toxic myopathy is based on key principles:

1. Drug challenge or de-challenge alone does not make a drug-induced myopathy "probable." The symptoms or signs must follow the administration of drug, usually by weeks to months; they must decline or resolve within weeks when the drug is removed or when the dose is decreased; they should recur when/if the drug is rechallenged and monitored. When weakness is the outcome measure, symptoms and signs in necrotizing and vacuolar myopathies resolve within 5–7 weeks of drug discontinuation, following the time course of muscle fiber regeneration.
2. Temporal association or correlation with drug usage, no matter how tempting, does not imply causation. The connection between the drug and the symptom must make pathophysiological sense.

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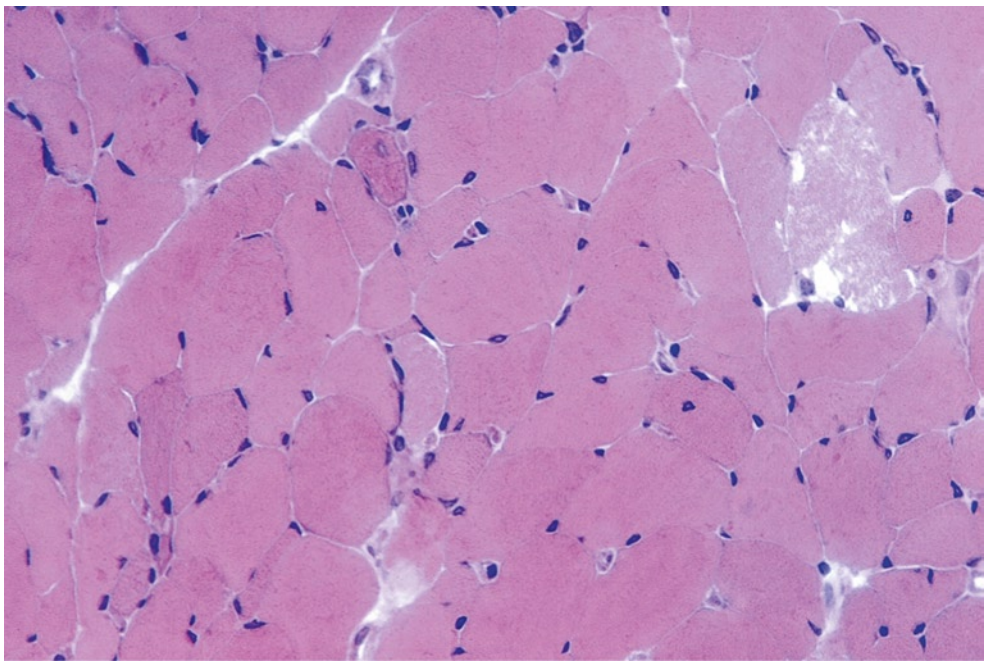

Fig. 68.1 Necrotizing myopathy. Scattered necrotic and regenerating fibers, as seen in HMG-CoA reductase myopathy and other necrotizing myopathies (see text)

3. The determination of creatine kinase (CK) alone, without muscle biopsy, is often insufficient for diagnosis.
4. Toxic myopathy is often a diagnosis of exclusion. For that reason, biopsy is often useful and necessarily so if the differential diagnoses are structurally characteristic or unique (e.g., colchicine, chloroquine, zidovudine).

Differential Diagnosis

In most case series, the most common cause of elevated CK when drug effects are excluded is hypothyroidism. The most common causes of pain in presumed toxic myopathies turn out to be osteoarthritis and cervical or lumbar spondylotic radiculopathy. Cramps and muscle pain are far more common in denervating disorders than in primary myopathies (excluding metabolic disorders of glycogen and lipid metabolism). The differential diagnosis of any suspected toxic myopathy should include consideration of hypothyroidism, hyperthyroidism, hyperparathyroidism, limb girdle muscle dystrophy, the manifesting carrier state of Becker or Duchenne muscular dystrophy, polymyositis, dermatomyositis, inclusion body myositis, and steroid-induced muscle atrophy, all of which have obviously different therapeutic implications.

Creatine Kinase Basics

Vigorous exercise, bruises, needle electromyography (EMG), and intramuscular injections increase serum CK activity in the first 12–48 h. Inactivity decreases the CK level, no matter what the cause of CK elevation is or in fact whether the baseline CK is normal, by one-third to one-half within 3 days. After an insult is removed that caused the CK to rise – even in widespread rhabdomyolysis – the CK declines with a half-life of about 24 h. Therefore, if the CK level is the outcome measure, it nearly always declines by >95 % or normalizes within 5–7 days (i.e., approximately 5 half-lives of CK clearance) (Fig. 68.2). For example, in a reported series of 13 severe statin-induced necrotizing toxic myopathies (7 with acute rhabdomyolysis and 5 of those with myoglobinuria), 1 met the 95 % CK reduction criterion by 3 days, 11 by 5–7 days, and 1 by 8 days [2]. Therefore, a conservative criterion for resolution of a typical necrotizing toxic myopathy is that a 95 % reduction of the CK level occurs 95 % of the time within 1 week of discontinuation of drug.

Terminology Confusion

Myositis and *myopathy* are not synonymous. Muscle *necrosis* is the death of many cells and always secondarily involves inflammatory cells, primarily macrophages, engulfing the already dead myocytes. The process is segmental in the mature myofiber. By contrast, the term myositis denotes an inflammatory myopathy characterized by *non-necrotic* muscle cells that are surrounded and invaded by autoaggressive T lymphocytes and macrophages. This so-called primary inflammation must be observed to make the diagnosis with certainty, although it is usually accompanied by active necrosis as well. This would be a particular distinction to make, with therapeutic importance, in the differentiation of HIV-associated inflammatory myopathy from zidovudine toxic myopathy. Toxic myopathies are most often purely

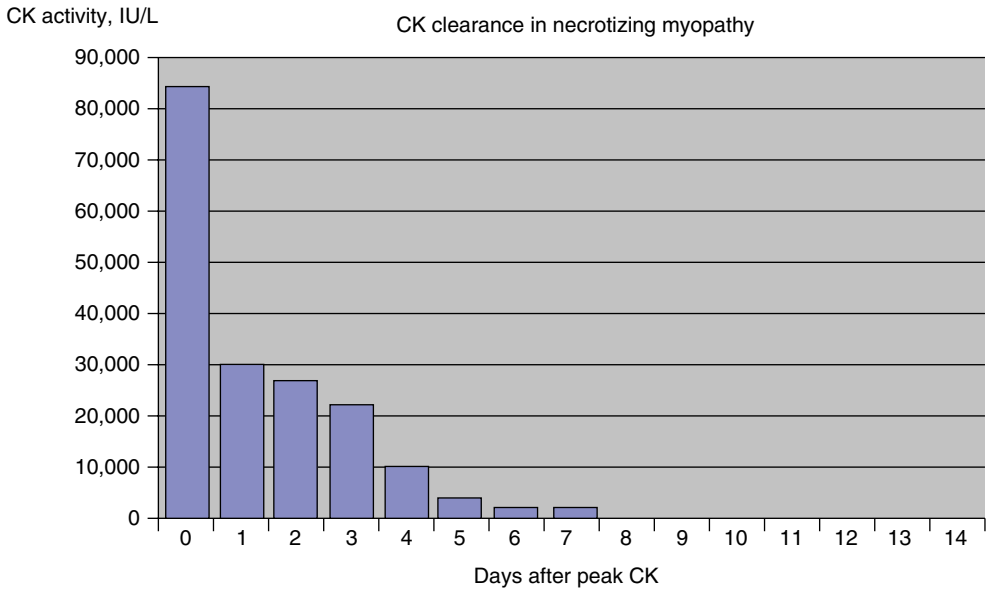

Fig. 68.2 Creatine kinase clearance in necrotizing myopathy. A 68-year-old woman with hypercholesterolemia, hypertension, and obesity was hospitalized with statin-induced acute rhabdomyolysis without myoglobinuria. The peak CK of 84,500 IU/L occurred on the day of admission, at which time the drug was immediately discontinued. By day 5 after discontinuation, the CK had decreased to 3,746 (a 96 % reduction), and it was in the normal range when next tested on day 14. At presentation, she had difficulty even rising from a chair or bed and required assistance to walk. She recovered uneventfully. Within only 3–4 days, she had noticeable improvement in muscle strength and gait. Within 6 days, she was making transfers from chair to bed or standing with minimal assistance. Within 2 weeks, muscle strength testing was markedly improved and she had only mild residual hip flexor weakness but full recovery of the extensors, adductors, abductors, and external rotators of the hips and of all distal leg muscles. At that time, she could walk 250 ft unassisted, could climb 18 stairs, and was fully independent in activities of daily living. She was not further examined until week 11, when her muscle exam was completely normal (Reprinted from Kuncl [2], with permission from Lippincott Williams & Wilkins)

necrotizing or vacuolar. Vacuolar myopathies are so named because the *earliest* pathological change is vacuolation in the absence of necrosis (examples are the small lysosomal accumulations in chloroquine myopathy and the large autophagic vacuole accumulation in colchicine myopathy).

The term *rhabdomyolysis* describes a necrotizing myopathy that is both widespread and fulminantly *acute*, important descriptors that many trialists have ignored. It is often painful, perhaps because of interstitial edema stretching the fascial planes. When it is severe enough to cause the CK to rise to the range of ~50,000 IU/L (or more than about 100 times the upper limit of normal), it is associated with myoglobinuria and pigmenturia, which can cause acute renal failure and death. Myoglobin can be measured in the urine by sensitive immunoassays (as opposed to the orthotolidine dipstick test) whenever the CK is elevated into the thousands; therefore, it is no more significant than the CK level itself and does not in and of itself signal dangerous myoglobinuric renal failure. Rhabdomyolysis is not therefore synonymous with myoglobinuria or necrotizing myopathy. A specific level of CK cannot define the pathology. For example, some clinical trials of statins, for the mere convenience of not mistaking trivial CK elevations on infrequent venipunctures, have operationally defined CK elevations greater than tenfold as myopathy or even as rhabdomyolysis. This is absurd, because the CK may be elevated manyfold by exercise or hypothyroidism or sarcolemmal leakage in muscular dystrophies without the process of necrosis. A host of meta-analyses continue the fiction, combining misleading reports of placebo-level myalgia with rhabdomyolysis, confusing the real picture [3]. Not making these several distinctions can lead to diagnostic confusion and mismanagement.

Lipid-Lowering Agent-Related Myopathies

Necrotizing myopathy can occur in patients treated with a variety of lipid-lowering agents, including 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) and fibric acid derivatives.

Necrotizing Myopathies Induced by Statins

HMG-CoA reductase inhibitors, or "statins," are the mainstay of lipid-lowering therapeutics and are one of the safest and most frequently prescribed classes of drugs in the world. The microsomal enzyme 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA reductase) catalyzes the conversion of HMG-CoA to mevalonic acid, an important step in

cholesterol biosynthesis. A number of fungus-derived inhibitors of this enzyme have been developed for the treatment of hypercholesterolemia, including lovastatin (Mevacor®), pravastatin (Pravachol®), simvastatin (Zocor®), fluvastatin (Lescol®), atorvastatin (Lipitor®), cerivastatin (Baycol®), and more recently rosuvastatin (Crestor®) and pitavastatin (Livalo®). These inhibitors decrease the synthesis of mevalonic acid which is a precursor to cholesterol, ubiquinone, and dolichol.

Clinical Presentation

HMG-CoA reductase inhibitors may cause a mildly elevated CK shortly after treatment is first begun, but this rarely progresses to a necrotizing myopathy in patients who are not taking other predisposing medications. When necrotizing myopathy does occur, patients typically present with the subacute or chronic onset of proximal muscle weakness, with or without myalgia or muscle tenderness. But it is important to note that musculoskeletal aches and pains are common adverse events with *many* drugs, are seen frequently in most placebo groups, and are therefore not likely to be causally relevant. Serum CK is virtually always elevated, but the degree of CK elevation does not define the pathology. Far rarer, fulminant widespread necrosis – that is, rhabdomyolysis – may be diagnosed when CK is greatly elevated in the range of >50,000, a range at which myoglobinuria (pigmenturia and an orthotolidine-positive dipstick test in urine that is not explained by hematuria) may occur and elevated serum creatinine may indicate acute renal failure. EMG of involved muscles may reveal abnormal spontaneous activity (positive sharp waves and fibrillation potentials) and occasionally myotonic discharges. When myopathy occurs acutely, motor unit morphology is normal, but reductions in motor unit action potential (MUAP) duration and amplitude occur in weaker patients with a more insidious course. In that case, the EMG is indistinguishable from that of polymyositis. Muscle biopsies show myofiber necrosis and regeneration.

Myopathy is clearly dose related and usually takes months to develop [4, 5]. Recovery, even from rhabdomyolysis, is complete and rapid, within days or weeks [6]. Frequent talk of prolonged statin myotoxicity comes from noncritical case reports of mainly pain rather than actual myopathy. Statins are not stored and do not have prolonged effects (see below). Two small series have recently been reported in which necrotizing myopathy occurring during statin therapy did not respond to drug discontinuation, but did improve after treatment with immunosuppressive agents [7, 8]. While these cases of "immune-mediated necrotizing myopathy" cannot be definitively attributed to statins because of ubiquitous use of those drugs, analysis of a parallel cohort found that statin use appeared significantly more common in patients with immune-mediated necrotizing myopathy than it was in patients with pathologically confirmed polymyositis, dermatomyositis, or inclusion body myositis [7].

Statin myopathies are greatly overdiagnosed; common mistakes are improper interpretation of the referred musculoskeletal pain of arthritis, radiculopathy- and denervation-induced cramps, or, less commonly, the symptoms of pain in other inflammatory or hypothyroid myopathies. The diagnosis of toxic myopathy is by exclusion of its other mimics, not merely by the association with statins. This can be illustrated by the consecutive series of the last 36 referred cases one of us (RK) has reviewed of *presumed* statin-induced myopathy (based on a combination of statin use with either or both of CK elevation or muscle pain), in which the ultimate diagnoses were based on neuromuscular examinations, on electromyography and muscle biopsy when done, and on whether the CK curve obeyed the principles outlined above (Table 68.2).

It is interesting that only a third of these cases suspected to be statin myopathy actually turned out to be so. Other authors have estimated from large controlled cohort studies that two-thirds (frequency 327 of 480) of all suspected statin myopathies are not attributable to statins but are non-myopathic, mistaken pain diagnoses [9, 10]. In clinical trials, the minor muscle pains reported, often on the order of 5 % of subjects, are equally present in statin and placebo groups [9]. Given all the facts above, we strongly recommend baseline measurement of CK levels (excluding exercise), because a knowledge of asymptomatic baseline elevations helps determine whether the statin is responsible for any later symptom or CK elevation. This is supported by at least one clinical advisory group [11].

Epidemiology

The precise frequency of human statin myotoxicity is unknown, as the literature is fraught with errors of attribution of myalgia as toxicity (see above), biased case ascertainment [12], missing the significance of CK elevations that are less than tenfold elevated (which contains most of the cases of statin myopathy), and operational definitions of myotoxicity that are useful for clinical trials but useless in clinical practice or pathology. It is safe to say that myopathy is rare, on the order of 1 in 10,000–20,000 person-years, and that rhabdomyolysis is far rarer, on the order of 1 in 100,000 person-years, according to meta-analytical data summarizing those clinical trials that use the fraught operational definitions [9]. A much more informative epidemiologic approach was a 6-year cohort study that concluded the risk of myopathy was greatest for the fibrates (relative risk ratio 42) than for statins (relative risk ratio 7.6), for which the risk is 2.3 per 100,000 [10]. The use of the FDA MedWatch Adverse Event Reporting System may underestimate the incidence of hospitalized rhabdomyolysis by some 70–95 % [13] and is fraught with the reporting biases of secular trend,

Table 68.2 Final diagnosis in patients referred for presumed statin myopathy

Final neuromuscular or musculoskeletal diagnosis	*N*		
Statin-induced myopathy	13		
Statin-induced acute rhabdomyolysis		7[a]	
With myoglobinuria			5
Without myoglobinuria			2
Statin-induced chronic necrotizing myopathy		6[b]	
Osteoarthritis with radiculopathy from degenerative cervical or lumbar spine disease	11		
Chronic elevated CK of unknown cause[c]	5		
Polymyositis (1) or dermatomyositis (1)	2		
Rheumatoid arthritis (without inflammatory myopathy)	1		
Hypothyroidism	1		
Exercise-induced CK elevation	1		
Total body pain syndrome	1		
Chronic depression alone	1		
Total	36		

In a consecutive series of 36 patients referred with the presumptive diagnosis of statin-induced myotoxicity, the ultimate diagnosis was based on neuromuscular examinations, EMG and muscle biopsy when done, and whether the CK curve obeyed the principles outlined in the text above

[a]Due to drug interaction with gemfibrozil in 4 of the 7

[b]Due to drug interaction with gemfibrozil in 2 of the 6

[c]Hypothyroidism and other known causes of elevated CK excluded

the newest drug reporting effect, product withdrawals effects, and publicity [13, 14]. A better approach was a side-by-side comparison of 26,562 statin-only subjects against 35,046 placebo subjects comprising 301,372 person-years of follow-up in a meta-analysis of prospective randomized, placebo-controlled trials of statins [15]. The adverse myotoxic effects turn out to be even rarer than previously thought [15], usually minor, but easily recognizable and reversible even when serious. It is therefore safe to say that these drugs have very high safety windows [16], which make them far safer than aspirin by at least an order of magnitude but nevertheless capable of causing severe and even fatal acute necrotizing myopathy.

Mechanistic Hypotheses

The exact biochemical pathophysiological mechanisms of statin myopathy are not fully known, but progress has been made. The most prominent hypotheses being tested relate to the degree of lipophilicity, effects on ion channels in sarcolemma, intracellular calcium homeostasis, potential deficiency of ubiquinone, primary mitochondrial membrane pathology, organic anion transporters, and the catchall category of energy depletion [3, 17]. Statins vary in their potential myotoxicity, but correlational studies among them have not been revealing of the precise incriminating mechanisms. A side-by-side meta-analysis concluded that risk of myotoxicity varied in prospective randomized, placebo-controlled trials of various statins in this order, from most to least: atorvastatin > [pravastatin = simvastatin = lovastatin] > fluvastatin [15]. This did not correlate well with lipophilicity/hydrophilicity partition coefficients or with cytochrome P450 isoform metabolism. Of all the reported pharmacokinetic and pharmacodynamic characteristics of the statins [18], the rank order above is most in line with the fact that atorvastatin has the longest elimination half-life (15–30 h) and can accumulate slightly with daily dosing, whereas fluvastatin has the shortest (0.5–2.3 h). The presumed lipophilicity risk that was once hypothesized based on in vitro data [19] is probably an artifact of in vitro studies of L6 myoblasts, satellite cells, and fibroblasts, which cannot reliably transport hydrophilic statins like pravastatin [20]. Mechanisms of statin absorption, distribution, protein binding, and excretion with short elimination half-lives all predict non-accumulating steady-state concentrations with once daily dosing; therefore, the pharmacokinetic and pharmacodynamic data are incompatible with theories of long-lasting myotoxicity (see above) [18].

It is clear that the myotoxicity is *not* secondary merely to lowering of plasma cholesterol levels or inhibition of cholesterol synthesis by other means, such as inhibition of squalene synthesis [21]. Rather, myotoxicity occurs within the muscle fiber itself and is a more distal effect of HMG-CoA reductase inhibition and the subsequent reduction of the downstream cascades that lower mevalonate, ubiquinone (coenzyme Q10), the isoprenoids farnesol and geranylgeraniol, and squalene [16–18, 22].

Statins have been hypothesized to impair muscle mitochondrial functions secondarily as the result of impaired isoprenylation of ubiquinone. Depletion of isoprenoids has also been invoked to contribute to statin myopathy through suppression of small GTPases such as Rab, which are responsible for trafficking of proteins from the endoplasmic reticulum to Golgi [23]. In in vitro studies supplementation of downstream products like mevalonate, farnesol, and geranylgeraniol mitigated myotoxicity [24], offering rather strong support for the idea that statin myotoxicity, at least for lovastatin and pravastatin, reduced the posttranslational modification by geranylgeraniol of low-molecular-weight proteins that might have regulatory consequences [24]. However, it is a giant step to the in vivo situation in humans. At present the isoprenylation theory remains unproven, and the ubiquinone hypothesis is unsupported, because decreased serum concentrations of ubiquinone did not cause corresponding decreases in muscle tissue ubiquinone during short-term treatment with simvastatin in humans [25, 26]. Coenzyme Q10 supplementation trials have most often been poorly designed, underpowered, or uncontrolled and have not shown any convincing effect [27].

Animal Models

In the rat, the most heavily glycolytic, fast-twitch myofibers (type IIb) are preferentially affected early by necrosis in lovastatin, cerivastatin, and simvastatin [17, 28], whereas the mitochondrial-rich oxidative, slow-twitch myofibers (type I) are relatively spared. Although these differences have been attributed solely to fiber-type metabolic differences, they could also relate to larger fiber diameter as a risk factor, because in the rodent, unlike the human, type II fibers are significantly larger in diameter than type I. The rodent model is well worked out and is not only dose dependent but time dependent [17]. Of course, necrosis always affects mitochondria predominantly and early because of sarcoplasmic edema, disturbance of sarcolemmal ion channels, and their function in accumulating calcium. But a primary and exclusive mitochondrial pathology for statin myopathies is not proven. The earliest ultrastructural change seen in *non-necrotic* myofibers in experimental statin myopathies has been the accumulation of intracellular membranous whirls, myeloid figures, and heterogeneous membranous vacuoles resembling subsarcolemmal autophagy [17, 28]. All such vacuoles contain both mitochondrial remnants and other membranous organelles and hence can be considered secondary effects of disturbed membrane recycling [29]. The absence of mitochondrial respiratory dysfunction after statins in rabbit muscle also suggests mitochondrial mechanisms are not primary [30]. Statin myopathy does not at all resemble the primarily mitochondrial pathology of zidovudine (see below); a single report suggesting a mitochondrial pathology in human biopsies from patients with muscle pain was a misinterpretation of normal lipid and of age-related rare ragged red fibers or COX-negative fibers at frequencies seen in control biopsies [31].

In a robust rat model of statin pathophysiology, chronic treatment in vivo with fluvastatin or atorvastatin decreased rat forearm strength and increased the resting cytosolic calcium concentrations up to 60 % in intact extensor digitorum longus muscle fibers (which are mostly glycolytic and fast-twitch) [32]. As further demonstrated in tendon-to-tendon whole myofibers, this occurred not by affecting sarcolemmal permeability but by increasing caffeine-stimulated Ca^{2+} release from SR and Ca^{2+} permeability from mitochondria via the permeability transition pore. Increased free sarcoplasmic intracellular calcium levels of this magnitude are known to disrupt excitation-contraction coupling and stimulate a host of enzymes, including phospholipase A_2, protein kinase C, and calpains, as further elaborated in an extended review and hypothesis [33].

Genetic Susceptibility

The most definitive pharmacogenetic study used a genome-wide association examination of 300,000 markers in 85 patients who had statin myopathy (defined conservatively as sustained high CK levels above three times the upper limit of normal but five times the baseline level irrespective of muscle symptoms or CK above ten times the upper limit of normal with muscle weakness) from a single clinical trial of high-dose simvastatin [4]. It showed a strong association between instances of simvastatin myopathy and common variants in a single gene, *SLCO1B1*, which encodes the organic anion-transporting polypeptide OATP1B1 that regulates the hepatic uptake of statins [4]. More than 60 % of patients with statin myopathy in this series had the variant single nucleotide polymorphism in the C allele. This worldwide collaborative effort is a signal advance in pharmacogenetics, following upon a series of provocative earlier reports of polymorphisms in solute transporter genes affecting hepatic uptake of statins and other outcomes, but the large collaborative study was well powered and took advantage of a unique clinical trial database to find an unequivocal association [34]. More recently the STRENGTH trial [35] found an association between the SLCO1B1 risk allele and statin "adverse events." Although the primary composite endpoint was quite nonspecific (including discontinuation for *any* adverse event at all, or myalgia or muscle cramps irrespective of CK, or CK elevated greater than three times the upper limit of normal), it is notable that a secondary endpoint specifying musculoskeletal side effects or muscle symptoms alone also showed a statistically significant association.

The SEARCH trial found that severe acute myopathy (narrowly defined as CK greater than 10 times upper limit of normal) occurred 52 times more frequently with high-dose (80 mg) simvastatin than low-dose (20 mg), and such severe myopathy was most likely to occur in the first year of use, presumably because myopathy tends to occur early in patients at risk because they carry the SLCO1B1 variants [4, 5].

Other studies that have hypothesized [36] or purported to find occasional single nucleotide polymorphisms in candidate genes for cytochrome P450 isoforms were unconvincing and confounded by different statin regimens, other concomitant drugs, and the lack of statistical correction for multiple comparisons in the large numbers of candidate genes and single nucleotide polymorphisms that were examined [reviewed in 4, 37, 38]; they were not confirmed by the above genome-wide study [4]. Other disease-causing mutations or carrier states for McArdle disease, carnitine palmitoyltransferase II deficiency, coenzyme Q metabolism, and others [37] seem likely merely to have been discovered as a bystander effect of increased vigilance in statin trials and in selected series in which diagnosis of statin myopathy was less rigorous.

Given that statins differ with regard to their dependence on ion transporters and other metabolic enzymes, it stands to reason that genetic variations predictive of myopathy will likely differ across the statins. Until our understanding of the biology and these genetic risk factors is more complete, it

will not be warranted or cost effective to perform genetic screens on all patients before starting statin therapy. However, with future advances in our understanding of statin biology and the declining costs of genotyping, it will someday be feasible to use genetic markers to guide the personalized use of statins for each patient in order to both optimize lipid-lowering effects and minimize the risk of myopathy.

Drug Interactions

Drug interactions are key concerns for physicians prescribing statins. Statins are capable of causing necrotizing myopathy by themselves, but the vast majority of cases of rhabdomyolysis are caused by drug interactions with fibrates, macrolide antibiotics, azole antifungals, and cyclosporine [39] (Table 68.3). In a comprehensive review of statin rhabdomyolysis, 59 of 74 cases were caused by drug interactions, and 23 of those were attributable to fibrates, most commonly gemfibrozil [39]. The interaction with fibrates may be merely additive with statins, because although theoretically fibrates can impair liver function and decrease hepatic extraction of statins, thus raising plasma drug levels, actual trials of lovastatin with gemfibrozil in combination did not find elevated statin levels, indicating that a pharmacokinetic interaction is unlikely but additivity occurs [18].

The drug interactions with statins are manifold, and the pharmacokinetics and pharmacodynamics that determine them are complex [40]. An important category of drug interaction with statins comprises the long list of other drugs that share a cytochrome P450 metabolism. Lovastatin, simvastatin, and atorvastatin depend on the CYP3A4 isoform of cytochrome P450, and therefore, other drugs that compete with or inhibit that isoform will increase plasma levels of the statin and its toxicity [41]; such drugs include agents from every class, but the more common culprits are cyclosporine, erythromycin, ketoconazole, diazepam, cimetidine, diltiazem, warfarin, amiodarone, verapamil, and compounds in grapefruit juice [42]. Older-generation pravastatin and fluvastatin, or second-generation rosuvastatin and pitavastatin, which do not use the CYP3A4 isoform, represent alternatives. Given the high frequency of hyperlipidemia in transplant patients, cyclosporine represents a special case. It not only inhibits CYP3A4 but inhibits the hepatic transporter for statins, and that double whammy means all statins can interact pharmacokinetically with cyclosporine. The FDA has issued guidance and safety label changes on dose limitations for simvastatin specifying interacting drugs that are contraindicated with high-dose simvastatin based on the SEARCH trial [5].

Table 68.3 Drugs reported to increase the risk of HMG-CoA reductase inhibitor-related myopathy

Category	Drug (common name)
Most common:	
Immunomodulatory	Cyclosporine
Lipid-lowering fibrate	Gemfibrozil
Macrolide antibiotic	Erythromycin
	Azithromycin
	Clarithromycin
Azole antifungal	Itraconazole
	Ketoconazole
Less common:	
Calcium channel blocker	Mibefradil
	Diltiazem
	Verapamil
Antidepressant	Nefazodone
Anxiolytic	Diazepam
Antacid	Cimetidine
Anticoagulant	Warfarin
Antiarrhythmic	Amiodarone
Other	Grapefruit juice

Biomarkers

As outlined above, statin-induced necrotizing myopathy is often confused with nonspecific musculoskeletal symptoms, transient and self-limited myalgias occurring after initiation of statin therapy, and pain due to non-myopathic causes. This diagnostic uncertainty, coupled with the concern about rare, but potentially fatal rhabdomyolysis, often leads to an overly conservative approach to the patient who develops muscle or musculoskeletal symptoms while taking a statin. Unfortunately, the only biomarker in common use is serum creatinine kinase, which has high sensitivity but low specificity except in serious cases of rhabdomyolysis. A predictive biomarker that would allow for diagnosis of patients with the earliest stages of statin-induced necrotizing myopathy would greatly improve diagnosis and management. Such a biomarker would allow identification of patients at risk before rhabdomyolysis occurs and also obviate the need for statin discontinuation in patients whose symptoms are not due to myonecrosis. Several candidate biomarkers of skeletal muscle toxicity are under study, including troponin 1 [43], fatty acid-binding protein 3 [44], and 1- and 3-methyl histidine [45], but all of these are still in early preclinical testing and none has as yet advanced to rigorous clinical validation for statin-induced myonecrosis. An imaging biomarker that may have utility as a research tool is measurement of phosphocreatine exercise recovery kinetics using ^{31}P-magnetic resonance spectroscopy, which has been used to demonstrate prolonged metabolic recovery in patients after statin administration, indicating (secondary) impairment of mitochondrial oxidative function. However, in a very small pilot study ($N = 10$), a significant correlation with muscle symptoms was not apparent [46].

Patient Management

Management of the patient with potential statin-induced myopathy should be guided by a few basic principles: (1)

Other causes of CK elevation or muscle pain should be excluded, including especially hypothyroidism, strenuous physical activity, other necrotizing drug agents (see below), and alcohol abuse; (2) CK levels should be checked at baseline and in all patients with muscle weakness or pain; (3) in patients who are asymptomatic or have tolerable muscle symptoms and CK < 2–3-fold elevated, statin therapy may be continued or the dose reduced, and symptoms and CK levels may be used as a guide to stop or continue therapy. In patients who develop necrotizing myopathy with CK > 3–5-fold elevated, the statin should be stopped and CK monitored for the expected rapid decline of 95 % over 5–7 days. Weakness will recover within weeks. In those patients who present with acute widespread necrotizing myopathy (rhabdomyolysis) (with CK > 10 times the upper limit of normal, or >10,000 IU/L, or with elevated serum creatinine), statin therapy should always be stopped; (4) eliminating any likely interacting drug may be sufficient. (5) A decision whether and how to restart statin therapy should be guided by the severity of the injury – in those with rhabdomyolysis, the decision should be based on the risk vs. benefit for the individual patient; for less severe cases, therapy should be restarted either at a lower dose of the same statin or at an equivalent dose of a statin with lower theoretical risk of toxicity. The National Lipid Association and others have published management algorithms reflecting some of these therapeutic principles [47, 48].

A Note on *Monascus purpureus* ("Red Yeast Rice" Myopathy)

There is now growing evidence that the fungus *Monascus purpureus* is myotoxic. It grows on rice or corn silage and has been cultivated as a fermented food product in China for more than a millennium. The purplish red color of the mold gives it the common name "red yeast rice." It is commonly present in many Asian foods as a colorant or ingredient, such as in pickled tofu, red rice vinegar, Peking duck, and Chinese barbecued pork. The discovery that it contains a family of several monacolin compounds, one of which, monacolin K (the same as the active ingredient in lovastatin), inhibits HMG-CoA, and that it can lower cholesterol levels [49] has led to its use as a so-called "natural" self-administered neutriceutical in the USA. Typical of neutriceuticals, there is controversy whether it is a dietary supplement or ought to be regulated as a drug; other ingredients in red yeast rice may include several sterols, isoflavones, and monounsaturated fatty acids [50]. Currently, commercial preparations are not quality controlled or standardized as to content, dosage of active ingredients, or contaminants. The monacolin K content may be as low as 0.2 % of total product, yielding doses on the order of 10 mg in dietary sized portions. Therefore, red yeast rice should be considered like all impure plant alkaloids and derived foods and herbs – a complex mixture of unknowns. Lovastatin (monacolin K) was isolated from *Aspergillus* when originally produced as Mevacor® but is also found naturally in certain fungi like the edible, nontoxic "oyster" mushroom, *Pleurotus ostreatus*. The FDA does not actively regulate red yeast rice, but it has taken legal action, as has Merck, the original maker of lovastatin, to suppress health claims about cholesterol lowering in commercial preparations that contain significant amounts of monacolin K. The lack of FDA oversight is a barrier to the prevention of the toxicity of red yeast rice.

The traditional Chinese medicine Zhibitai contains red yeast rice equivalent to 10 mg of lovastatin plus Chinese hawthorn, oriental water plantain rhizome, and large-head atractylodes rhizome, and the mixture is claimed to have been equivalent in efficacy and safety to 10 mg of atorvastatin in an 8-week, double-blind, randomized trial, with no myopathy reported in either treatment group [51]. The question arises why one would not take lovastatin alone in pure form rather than an irrational mixture of variable purity and composition.

Organized surveillance, now sometimes coined "pharmacovigilance," revealed four cases of red yeast rice-associated myotoxicity in Italy in a 5-year period [52]. The amount of red yeast rice ingested ranged from 5 to 1,200 mg/day for 2–6 months and was ingested in the form of either *Monascus purpureus* alone or *Monascus purpureus* in a complex mixed supplement (Colestat®, Statinat Crinos®, Armolipid Plus®). The only significant manifestation was modestly elevated CK in the range of 288–401 IU/L. However, the fact that the CK resolved on de-challenge and there were no concomitant medications in these patients raises strong suspicion of myotoxicity. This likely confirms previous single reports of necrotizing myopathy or modest CK increases in more complicated but less well-founded cases [49, 53, 54]. It is tempting to conceive of this myotoxicity as merely statin myopathy, but the complexity of the mold-as-food product means any one of the ingredients of red yeast rice could be the culprit.

Fibric Acid Derivatives

Etiology and Pathogenesis

Clofibrate, bezafibrate, and fenofibrate are branched-chain fatty acid esters that are thought to act by inhibiting hepatic release of lipoproteins, particularly VLDL. The mechanism by which they cause myopathy is unknown, but the finding that these agents induce myotonic discharges in experimental animals suggests that they cause alterations in the sarcolemma [55, 56]. Gemfibrozil is another fibric acid derivative that appears to cause myopathy mainly in patients who are also taking a statin. Since these compounds are associated with disproportionate elevations of serum aminotransferases and even cytolytic hepatitis, myopathy may be

caused by fibrate-associated alteration of hepatic function leading to impaired elimination of HMG-CoA reductase inhibitor metabolites. Alternatively, the two myopathies may be merely additive.

Clinical Presentation

The necrotizing myopathy caused by fibric acid derivatives often presents as painful weakness within 2–3 months of starting the drug (or, in the case of gemfibrozil, when commencing dual therapy with a statin) and is usually associated with an elevated CK and occasionally with myoglobinuria. Needle EMG findings are similar to those associated with statins. In animal models, clofibrate causes myotonic discharges [55, 56].

Predisposing Factors

These compounds are renally excreted, and most patients who develop myopathy while taking clofibrate, bezafibrate, or fenofibrate have some degree of renal failure (the half-life of these compounds increases as much as sevenfold in uremia [57]). In addition, these drugs are bound to albumin, which explains the increased incidence of myopathy in patients with nephrotic syndrome [58]. Gemfibrozil probably does not cause myopathy when taken alone. The myotoxic interaction with statins is well established (above), but large prospective studies of patients taking gemfibrozil in combination with statins demonstrated that the risk of myopathy is relatively low (≤0.4 %) [59, 60].

Treatment/Prognosis

In all reported cases, withdrawal of fibric acid derivatives leads to a fairly rapid clinical improvement and decline in serum CK levels.

Corticosteroid-Induced Muscle Atrophy

Cushing was the first to describe proximal muscle weakness in patients with elevated endogenous glucocorticoid levels. Eventually, the syndrome of muscle weakness and wasting was recognized as a common complication of corticosteroid treatment. The term "steroid myopathy" is a misnomer, as corticosteroids cause damage by atrophy, not cell death or architectural damage.

Etiology and Pathogenesis

Glucocorticoids are lipid-soluble steroid hormones that pass freely through the cell membrane into the cytoplasm where they bind to specific receptors. Glucocorticoid receptors are members of a superfamily of hormone receptors that exert their effects by influencing nuclear gene expression. The hormone-receptor complex binds to specific DNA sequences called "glucocorticoid-response elements" to regulate transcription of steroid-responsive genes.

The mechanisms by which glucocorticoids cause muscle weakness and wasting are related to the important role these hormones play during the fasting state to mobilize amino acids from skeletal muscle protein for direct oxidation and gluconeogenesis. In conjunction with insulin, glucocorticoids mediate these changes in protein turnover through a decrease in protein synthesis and an increase in the rate of proteolysis. Lower rates of protein synthesis are due primarily to decreased rates of peptide chain initiation and primarily affect type 2 muscle fibers [61]. Starvation also leads to increased protein breakdown in muscle, and glucocorticoids are essential for this large activation of proteolysis. Of the three major proteolytic systems active in muscle (lysosomal, calcium-dependent, and the ATP-dependent protease systems), it is the ATP-dependent, ubiquitin-proteasomal pathway that is responsible for the bulk of protein breakdown during fasting. Goldberg and others [62–65] demonstrated that glucocorticoids activate this pathway in fasting and other catabolic states (cachexia, sepsis, disuse, and denervation) by enhancing the expression of components of the proteasomal pathway such as ubiquitin. Corticosteroids affect a host of other growth factors and transcription factors, including downregulation of expression of IGF-1 in muscle (thus decreasing muscle protein synthesis), downregulation of the transcription factor myogenin that plays a role in differentiation of satellite cells, and upregulation of the transforming growth factor-β superfamily member myostatin (thus negatively regulating muscle growth) (for a review of molecular pathways in steroid atrophy, see [66]).

In neural tissues, steroid hormones also have more rapid effects that are mediated through direct effects on the neuronal membrane, rather than through receptor mechanisms. However, to date, such rapid effects have not been described in muscle. Glucocorticoids also cause weakness by affecting membrane excitability and excitation-contraction coupling mechanisms. Although these mechanisms may play a role in the development of acute quadriplegic myopathy [67] (see Chap. 76), the preponderance of evidence suggests that they are not important in chronic steroid atrophy [68, 69].

Clinical Presentation

Corticosteroid atrophy may result from prolonged exposure to endogenous or exogenous elevation of corticosteroid levels. All synthetic glucocorticoids can cause it, but the incidence is higher in patients treated with the 9-alpha fluorinated corticosteroids [70]. Doses equivalent to 30 mg/day of prednisone or higher increase vulnerability, whereas significant

atrophy rarely occurs with doses of 10 mg/day or less and is less frequent with alternate-day regimen [71].

Muscle weakness and atrophy usually occur insidiously and predominantly affect proximal muscles. The legs are usually more severely affected than the arms, and bulbar muscles are usually spared. Reflexes are normal except with severe muscle weakness. Myalgia is uncommon. This pattern of weakness is indistinguishable from that of polymyositis. Patients with corticosteroid atrophy may display other clinical stigmata typical of adrenocorticoid excess including obesity, facial plethora, or easy bruisability, for example.

Differential Diagnosis

Glucocorticoids are frequently employed in the treatment of patients with inflammatory neuromuscular disorders, including the inflammatory myopathies, polymyositis, and dermatomyositis. A common diagnostic dilemma occurs when such patients experience a worsening of weakness following an initial positive response to corticosteroids. In this scenario, the physician must distinguish between steroid toxicity and refractory disease (in which case an increase in dosing may be warranted).

As in other endocrine myopathies (except hypothyroidism), the serum CK level is normal. An elevation in serum levels of muscle enzymes suggests that the inflammatory myopathy remains active, in part. The needle EMG may also be valuable. In patients with inflammatory myopathies, the presence of abnormal spontaneous activity (fibrillation potentials) suggests that muscle fiber necrosis is ongoing and that the myopathy is not responding to the current steroid dose. Finally, muscle biopsy can distinguish inflammatory myopathy from steroid atrophy if the muscle sample contains active inflammation. Nevertheless, both conditions may coexist, so that a clinical trial of corticosteroid dose reduction or switching to another immunotherapy may be required.

Evaluation

Needle EMG examination is normal except in severe cases in which type I fibers are affected. In such cases, small amplitude, short duration polyphasic MUAPs and early recruitment patterns may be seen. Insertional activity is, however, normal and fibrillation potentials are absent, owing to the lack of muscle fiber necrosis.

The primary histological finding in corticosteroid atrophy is type 2 fiber atrophy [70] (Fig. 68.3). Electron microscopy reveals loss of myofibrils, folding of basal lamina secondary to the atrophy, an increase in lipid droplets and subsarcolemmal glycogen, and enlarged mitochondria [72, 73]. In acute quadriplegic myopathy, there is a selective loss of myosin thick filaments (see Chap. 76).

Treatment/Prognosis

The most effective treatment of corticosteroid myopathy is to reduce the dose to the lowest level possible, switching to a non-fluorinated corticosteroid or to alternate-day dosing. Full recovery usually takes at least several weeks, but a dose reduction by half should noticeably affect strength within 2 weeks.

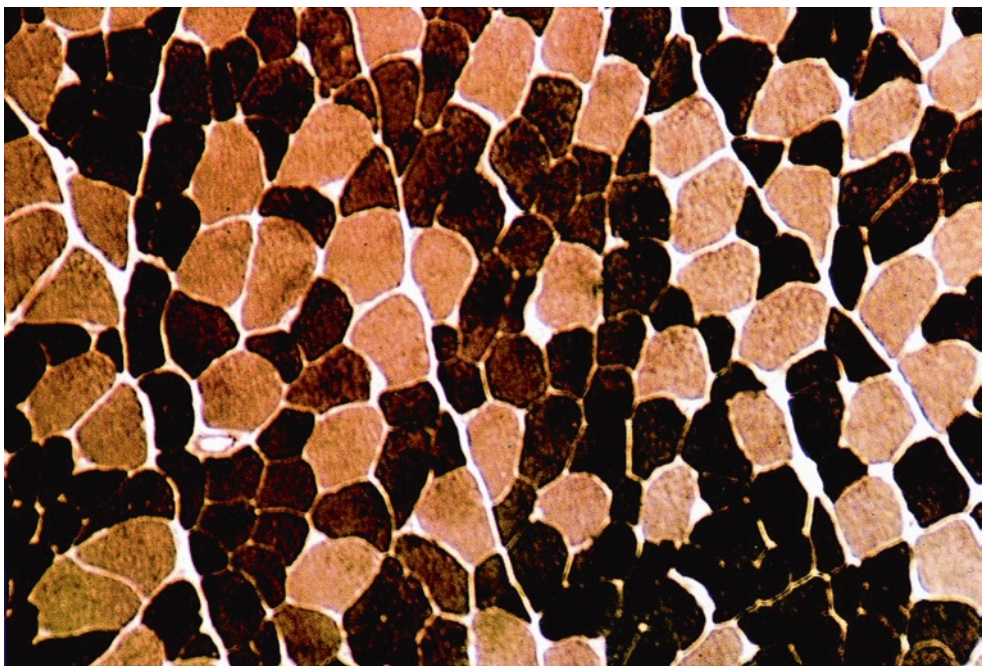

Fig. 68.3 Type II atrophy. ATPase stain at pH 9.4 showing small dark-staining type II fibers, as may be seen in corticosteroid-induced muscle atrophy

Inactivity may worsen corticosteroid myopathy [74], and exercise may be useful in lessening and treating the effects of glucocorticoids on muscle [75].

Amphiphilic Drug Myopathy

Etiology and Pathogenesis

Chloroquine, the antimalarial and antirheumatic drug, was first reported to cause a toxic myopathy in 1948. Since then it became clear that a number of drugs that share structural features with chloroquine cause similar changes in muscle and other tissues (Table 68.4). These compounds are large cationic amphiphiles. They contain both a hydrophobic region and a primary or substituted amine group which can bear a net positive charge. These properties determine how the drugs interact with cell membranes and organelles to cause disease [76].

Effects on Membranes Causing Myofiber Necrosis

The hydrophobic region allows amphiphilic drugs to partition into membranes, where they interact with anionic groups of acidic phospholipids. This may result in conformational changes and a reduction of the surface charge of the plasma membrane. Such changes may then interfere with plasmalemmal function, causing changes in the movement, fusion, permeability, transport, and receptor functions of membranes [76–78].

In skeletal muscle, these effects on surface and internal membranes are recognized as a necrotizing myopathy. In severe and acute cases, such a myopathy may be clinically indistinguishable from other necrotizing myopathies. However, more frequently these drugs cause repeated cycles of segmental necrosis that are not severe enough to present acutely. This manifests as a chronic myopathy, characterized histologically by "myopathic" grouping of longitudinally branched "subfibers" that result from cycles of segmental necrosis, followed by myoblast regeneration and incomplete myotube fusion. Drugs typical of this necrotizing/regenerating response are chlorphentermine, chlorcyclizine, triparanol, and iprindole. Interestingly, these particular amphiphilic compounds have a higher lipid solubility, lower water solubility, and higher pH in solution than are other drugs in this class. All drugs in this class are probably potential causes of necrotizing myopathy, but the clinical significance is uncertain in some instances, because the effects occur at nonpharmacological doses [76–78].

Table 68.4 Drugs causing amphiphilic drug myopathy

Chloroquine, hydroxychloroquine
Amiodarone
Quinacrine
Chlorpromazine
Imipramine
Procainamide
Doxorubicin
Plasmocid
Perhexiline
NVP-LDE225

Effects on Lysosomes Producing Vacuolization

Non-protonized forms of these compounds are able to enter the lysosomal compartment, where they become protonized in the acidic milieu, accumulate, and form complexes with polar lipids of lysosomal contents. By disturbing lysosomal membrane stability, they can cause alkalinization of the lysosomal compartment, inhibiting lysosomal enzymes that require a low pH. These effects are manifest pathologically by the accumulation of vacuoles containing lipid and membranous material, that is, the "lipidosis" which is the hallmark of amphiphilic drugs in other tissues [76–78].

In skeletal muscle, such changes are recognized on histochemical stains as vacuolization of non-necrotic myofibers (Fig. 68.4) and at the electron microscopic level as accumulation of autophagic vacuoles containing a variety of lamellar, reticular, or myeloid lipid-containing inclusions. Interestingly, the drugs that are prone to cause abnormal autophagy have higher water solubility, lower lipid solubility, and lower pH in solution than are the other drugs in the amphiphilic class. Drugs typical of this response include chloroquine, hydroxychloroquine, and doxorubicin, and the myopathies they produce are clinically important.

Similarities to Other "Rimmed Vacuole" Myopathies

Whereas each of the above-described morphological features is not specific by itself and may be seen in many different myopathies, the combined presence of vacuoles, myeloid bodies, and necrosis is characteristic of amphiphilic drug myopathy in both humans and animals. Experimental animal models were produced using several of these compounds [77, 79, 80], the best studied of which is chloroquine myopathy. Experimental chloroquine myopathy received increased attention because of its pathological and biochemical similarities to the so-called "rimmed vacuole" myopathies, such as inclusion body myopathy and the distal myopathies. In addition to their similar morphological features, protein and mRNA levels of certain specific gene products, including tau, beta-amyloid precursor protein, and ubiquitin, are increased in vacuolated fibers in chloroquine myopathy as well as the other "rimmed vacuole" myopathies [81–87]. Yet the two are not pathologically identical, since none of the tubulofilamentous inclusions seen in most rimmed vacuole myopathies are present in chloroquine myopathy. Nevertheless, chloroquine myopathy may prove to be a useful experimental model for the study of the pathogenesis of inclusion body myopathy

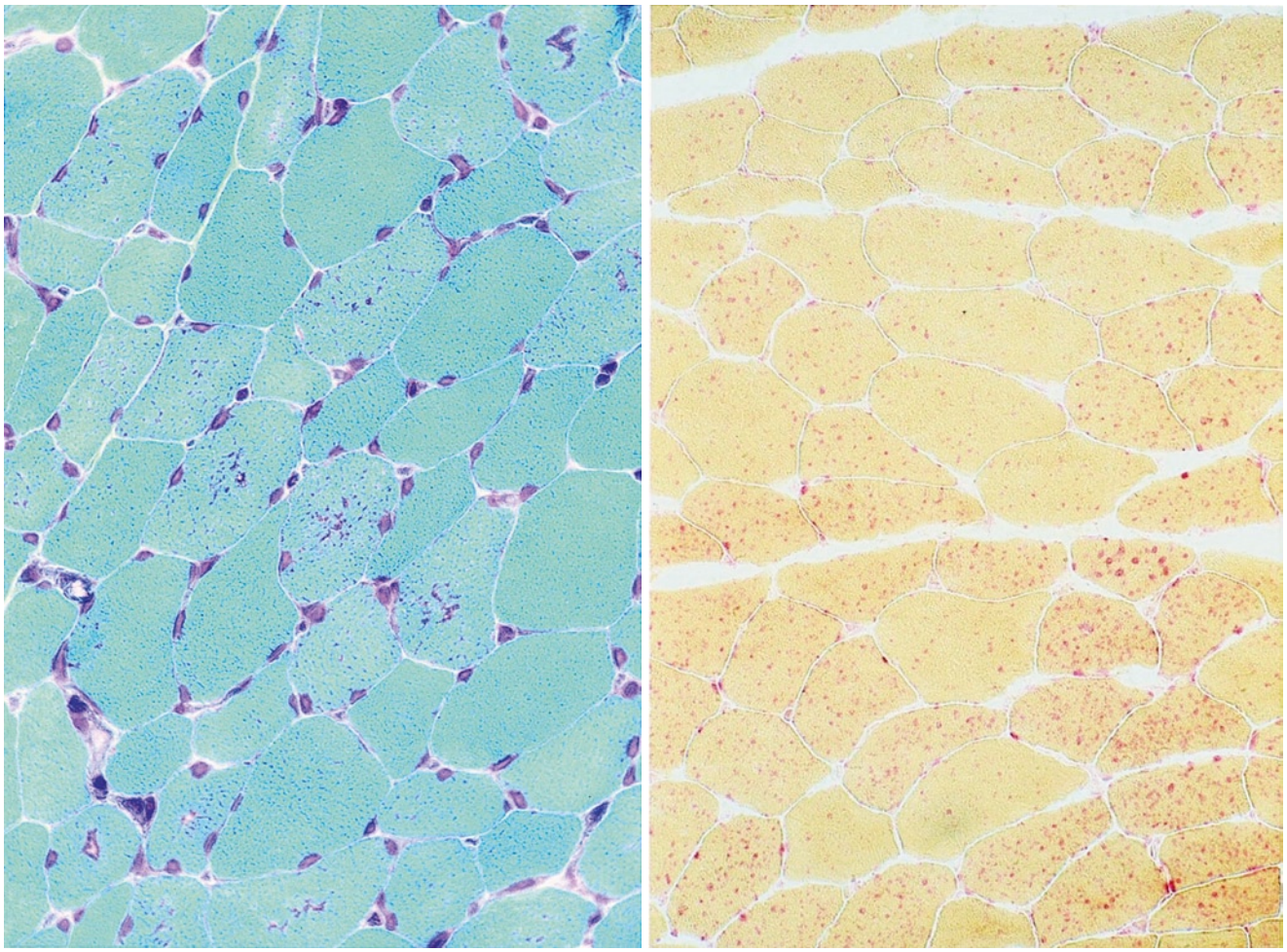

Fig. 68.4 Chloroquine myopathy. Excessive numbers of scattered lysosomes as the primary pathological change (*left panel* modified Gömöri trichrome stain, *right panel* acid phosphatase stain)

and the inherited "rimmed vacuole" myopathies, for which other animal models are unavailable [88].

Clinical Presentation

Chloroquine, Hydroxychloroquine

The frequency of this toxic myopathy has increased in recent years as the utility of these drugs has been rediscovered. It typically presents with slowly progressive proximal weakness after months or years of use at doses as low as the equivalent of 200 mg of chloroquine per day. Serum CK levels are modestly elevated. Needle EMG shows a proximal myopathy with increased insertional activity and fibrillation potentials. It is sometimes associated with an axonal neuropathy, retinopathy, or cardiomyopathy [76, 89].

Amiodarone

The toxicity associated with this antiarrhythmic drug is characterized by phospholipid-containing myeloid inclusions in cells of multiple organ systems, including peripheral nerve, muscle, cardiac muscle, and other tissues. Although the peripheral neuropathy caused by this agent has more functional impact on patients and is more common, amiodarone can also cause an acute, often mild, necrotizing vacuolar myopathy [90–92]. Interestingly, the membrane and lipid inclusions may persist in muscle and nerve as long as 2 years after drug discontinuation, probably due to the long half-life of the drug (40–50 days). Myopathy with amiodarone use may also be secondary to hypothyroidism caused by the drug.

Differential Diagnosis

Since chloroquine is often used in the treatment of rheumatological disorders, this toxic myopathy is most often mistaken for an inflammatory myopathy related to the primary autoimmune disease. A muscle biopsy is necessary for a definitive diagnosis and to determine whether to add further immunosuppressive agents or withdraw chloroquine.

Prognosis

Symptoms slowly resolve many months after chloroquine, hydroxychloroquine, or amiodarone therapy is stopped.

Anti-microtubular Myopathy

Nearly a half century ago, the anti-microtubular agent vincristine was shown to cause a vacuolar myopathy with membranous inclusions [93–97]. However, despite the use of colchicine for treatment of gout since 1763 and knowledge of its anti-arthritic properties by the ancient Greeks, its neuromuscular toxicity in humans has only recently been recognized [98, 99].

Etiology and Pathogenesis

Muscle biopsy shows a distinctive vacuolar myopathy [99, 100]. Unlike the vacuoles seen in other muscle disorders, the vacuoles in colchicine myopathy are very large and spindle shaped. They are typically oriented longitudinally and are highly localized either right below the sarcolemma or in the center of myofibers. These vacuoles stain positively for acid phosphatase and for lipid, indicating that their contents are lysosomal in origin (Fig. 68.5). The changes are not well appreciated in standard paraffin sections but require frozen sections. Necrotic fibers are rare. Electron microscopy reveals remnants of primary lysosomes and spheromembranous bodies in the vacuoles, as well as perinuclear aggregates of densely packed filamentous material. Cytoplasmic deposits of finely granular material immunoreactive for alpha- and beta-tubulin are described [101].

Colchicine is weakly amphiphilic, and there are pathological similarities between colchicine myopathy and that of other amphiphilic drugs. However, a number of observations suggest that colchicine causes myopathy through disruption of muscle microtubular systems rather than through amphiphilic chemical effects. These are (1) its similarity to vincristine myopathy, (2) the well-known interactions of lysosomes with microtubules in most eukaryotic cells and the demonstration of a relevant microtubule network in skeletal muscle [102], (3) colchicine blockade of exocytosis of acetylcholine receptors in lysosomes of cultured rat skeletal muscle at concentrations near the K_d for colchicine binding to tubulin [102], and (4) the cytoplasmic accumulation of tubulin-immunoreactive granular material in colchicine myopathy. The mechanism is now clear. Disruption of a microtubule cytoskeletal network, upon which depends the recycling of membranous material that myofibers abundantly turn over and exocytose, leads to defective movement or localization of lysosomes, resulting in accumulation of autophagic vacuoles [2, 76, 102].

Clinical Presentation

The syndrome of chronic colchicine myopathy was defined in a large series of patients treated for gout [99, 103] and is stereotypic enough to allow easy recognition. Patients are most often men, over age 50, with secondary gout, receiving standard oral doses of colchicine, 0.5–0.6 mg twice a day. They present with the subacute onset of proximal muscle weakness of 1–6 months' duration. The serum CK is always elevated (up to 50-fold in the most symptomatic and one- to threefold in subclinical cases). Needle

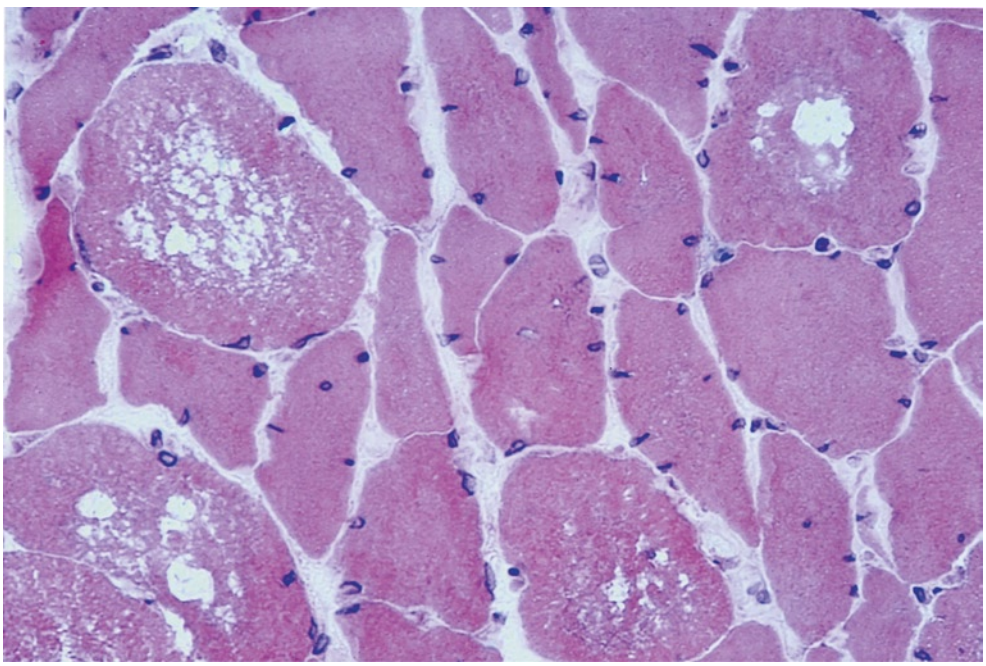

Fig. 68.5 Colchicine myopathy. Large coalescing vacuoles with heterogeneous contents as the primary pathological feature (H and E stain). These can be proven to be lysosomes by acid phosphatase histochemistry (not shown)

EMG shows a myopathy with abnormal spontaneous activity in 60 % of proximal muscles examined [103], simulating polymyositis for which it is commonly mistaken [99]. Both clinical and electrical myotonia may also be present. Most patients have a sensorimotor axonopathy that is functionally less disabling, hence the term *myoneuropathy*.

Although a mild axonal neuropathy is common in patients taking vincristine, myopathy from that drug is relatively rare because it is typically used only intermittently as part of a chemotherapeutic protocol [76].

Predisposing Factors for Colchicine Myopathy

Chronic renal insufficiency, which is commonly associated with gout, is the most identified risk factor [99, 104]. This is probably because colchicine is partially excreted renally and the clearance of the drug from plasma is reduced in renal failure. Occasional cases may be due to *excessive self-dosing* [98]. Because the major route of excretion is hepatic, *liver disease* may eventually become recognized as an important risk factor as more cases of myopathy are seen in patients treated with colchicine for familial Mediterranean fever [101], amyloidosis [105], primary biliary cirrhosis [106], and proliferative vitreoretinopathy [107].

Drug Interactions

Because colchicine is such a commonly used drug, toxicity may be expected to occur frequently in combination with other commonly used drugs. Thus, many cases of toxic myopathy that can be fully explained by colchicine alone but have occurred in the context of other drugs (usually in the clinical context of either renal insufficiency or organ transplantation, as colchicine uses both renal and hepatobiliary excretion) have been attributed without evidence to the concomitant drug itself or to the drug combination. Cyclosporine is such an example, and although a direct myotoxicity of cyclosporine has been hypothesized, it is unsubstantiated. Colchicine myopathy occurs in organ transplant recipients who develop cyclosporine-induced gout [108–110]. All of these patients had some degree of renal insufficiency and all improved following reduction or withdrawal of colchicine.

It should be no surprise that myopathies occur when statins and colchicine are used together, given the ubiquity of use of both drugs. An illustrative case report of myopathy [111] from the combination of simvastatin and colchicine in the context of renal insufficiency postulated the likely cause for interaction. In that case, neither drug alone could be implicated, because both drugs were stopped simultaneously and the patient recovered within 2 short weeks. The fact that the statin had been taken without toxicity for 2 years and the myopathy followed abruptly (within 2 weeks) after the institution of colchicine (it usually takes months for colchicine exposure to cause myopathy) implicated a drug interaction. Both simvastatin and colchicine are dependent on demethylation by the CYP3A4 isoenzyme of the cytochrome P450 system and would therefore compete for this pathway [112]. The same system is used by certain other statins (lovastatin and atorvastatin) [42, 113] as well as many other drugs (see above). By contrast, other statins that do not use the CYP3A4 system, such as fluvastatin and pravastatin, would be predicted not to interact with colchicine and would be better choices in patients with chronic renal insufficiency and gout.

Differential Diagnosis

Colchicine myopathy is frequently misdiagnosed as polymyositis [99]. The original large case series found that the most symptomatic patients with colchicine myopathy were all misdiagnosed as polymyositis and several were inappropriately treated with prednisone. The diagnostic criteria of polymyositis, namely proximal weakness, CK elevation, and myopathic EMG with evidence of membrane instability, are common to both colchicine myopathy and polymyositis. Mistakes in interpretation of these diagnostic criteria for polymyositis arise because they are not equally sensitive or additive in estimating the probability of the diagnosis. In evaluating probable polymyositis, the electromyographer will differentiate colchicine myoneuropathy by searching for evidence of myotonic discharges, mild chronic distal denervation, and abnormal sensory potentials. Finally, a muscle biopsy in polymyositis, if typical – that is, showing primary inflammation and necrosis – should take diagnostic precedence. Other causes of subacute myopathy with axonal neuropathy include chronic uremic myopathy (which rarely causes CK elevation) and toxic myopathies caused by chloroquine, alcohol, amiodarone, and vincristine [99].

Treatment/Prognosis

Both muscle strength and serum CK levels normalize within 4 weeks of a reduction in dose or discontinuation of colchicine in most patients.

Mitochondrial Myopathies

Etiology and Pathogenesis

Zidovudine

The nucleoside analog zidovudine, initially known as AZT (3′-azido-2′,3′-dideoxythymidine), is a reverse transcriptase inhibitor that is a potent suppressor of human immunodeficiency virus (HIV) replication. Early on, it was a

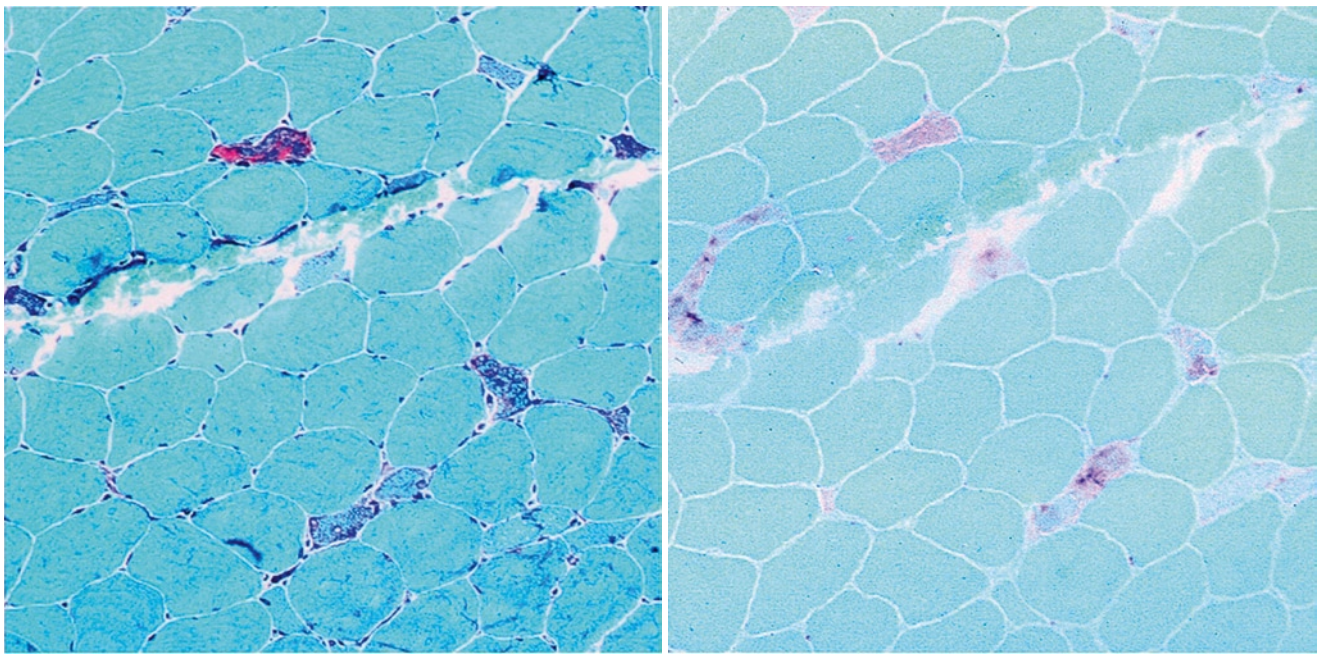

Fig. 68.6 Pseudo-ragged red fibers in zidovudine myopathy. Atrophic degenerating fibers staining red on Gömöri trichrome (*left panel*) and containing abundant lysosomes as shown by serial section stained with acid phosphatase (*right panel*)

principal drug used in the treatment of patients with HIV infection but now is used primarily in developing countries, primarily because of low cost. However, one of the major limitations in the use of zidovudine is a number of potentially severe side effects, including toxic myopathy. Another drug in the class (clevudine, see below) causes similar effects by the same mechanisms.

Because myopathy may occur as a complication of HIV infection in the absence of treatment with zidovudine or other drugs, there was initially some uncertainty as to whether zidovudine caused a distinct myopathy [114–116]. It is now clear that zidovudine causes dose-dependent changes in skeletal muscle consisting of (1) atrophic degenerating fibers filled with lysosomes and degenerating mitochondria, staining red on Gömöri trichrome (pseudo-ragged red fibers, which are smaller and have less "ragged" outpouchings from mitochondrial proliferation than the true ragged red fibers in mitochondrial myopathies) (Fig. 68.6); (2) necrotic fibers; (3) profuse numbers of cytochrome oxidase-negative fibers (Fig. 68.7); and (4) reactive mitochondrial proliferation in a few succinate dehydrogenase-blue or true ragged red fibers. Scattered interstitial lymphocytes typical of HIV-infected tissue, nascent rods caused by denervation, and cytoplasmic bodies typical of cyclic degeneration/regeneration may confuse the picture but are not specific to zidovudine. Zidovudine myopathy is considered a "mitochondrial myopathy" because of evidence of depletion of mitochondrial DNA (mtDNA) [117], a decline in mitochondrial respiratory chain capacity in affected muscle fibers [118], and accumulation of intermyofibrillar lipid droplets consistent with a defect in fatty acid utilization [119]. The depletion of mtDNA is attributed to zidovudine's effects on DNA polymerase gamma, an enzyme found only in the mitochondrial matrix [117]. An independent toxic effect on mitochondria is not ruled out [120].

Dalakas and coworkers suggested that the accumulation of lipid droplets in zidovudine-affected muscle fibers is due to decreased utilization of fatty acids. They showed that degenerating muscle fibers have increased numbers of lipid droplets and decreased total muscle carnitine levels [119]. Furthermore, they showed that L-carnitine protects against the effects of zidovudine on cultured human myotubes and also enhances recovery of zidovudine-associated destruction of myotubes following zidovudine withdrawal [121, 122]. Reductions in both muscle and plasma carnitine levels are described in other mitochondrial myopathies [123, 124], and plasma carnitine levels are reportedly reduced in zidovudine-treated patients [125]. Some suggested that muscle mitochondrial dysfunction leads sequentially to accumulation of coenzyme A esters, formation of acylcarnitine, and finally depletion of muscle carnitine pools [123].

These human pathological features [117, 126] have now been reproduced in an animal model by short-term exposure of rat skeletal muscle cell cultures to zidovudine for only 48 h at concentrations of 10–100 μg/ml [127]. As the authors suggest, this in vitro assay may be an efficient model in which to test potential mitochondrial toxicity of other similarly structured drugs during their development.

Clevudine

Clevudine (Revovir®; Levovir®; 1-[2-deoxy-2-fluoro-b-L-arabinofuranosyl]thymine; 1-[(2*S*,3*R*,4*S*,5*S*)-3-fluoro-4-hydroxy-5-(hydroxymethyl)oxolan-2-yl]-5-methylpyrimidine-2,4-dione),

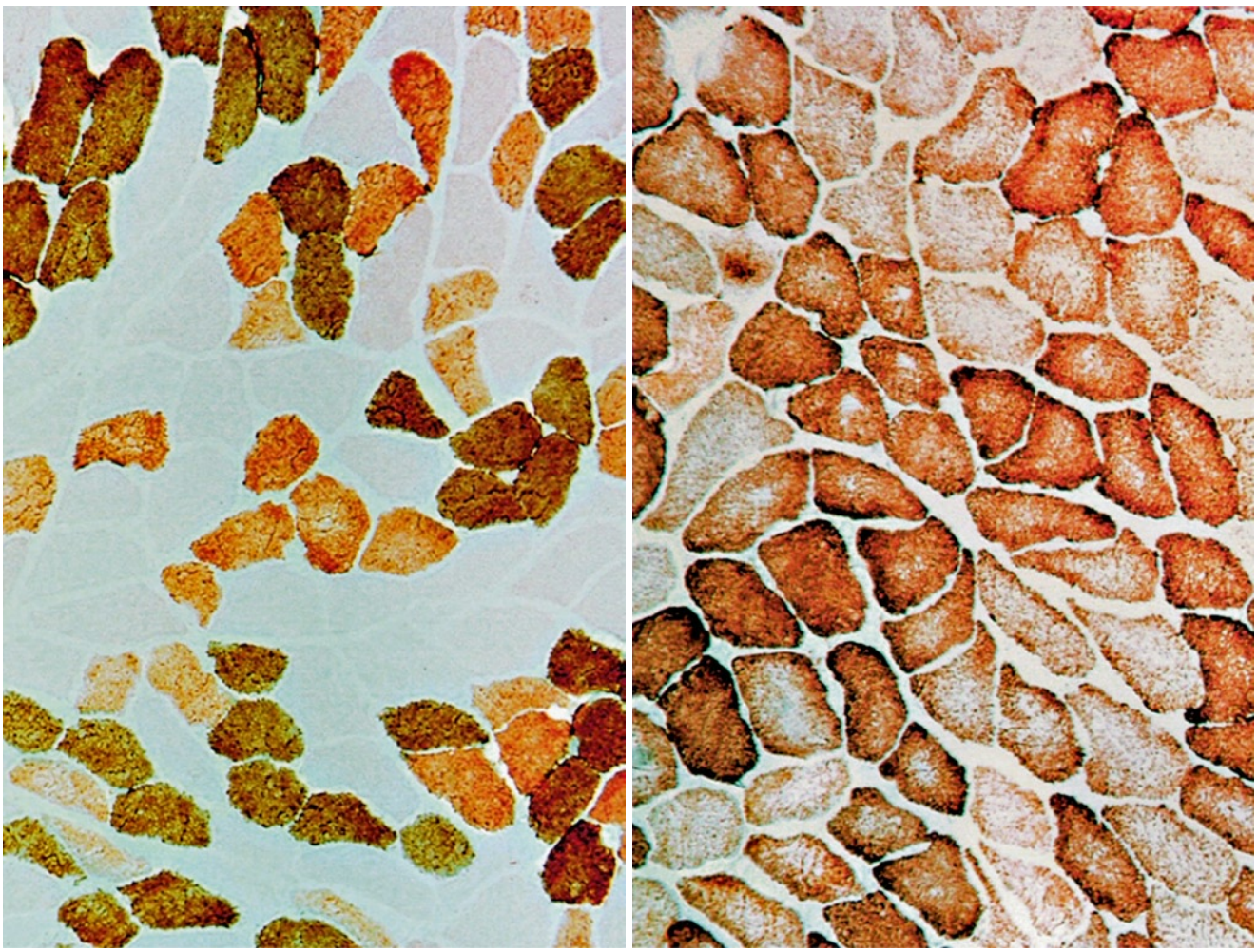

Fig. 68.7 Cytochrome C oxidase-negative fibers in zidovudine myopathy. Innumerable fibers contain no histochemical cytochrome oxidase activity in zidovudine myopathy (*left panel*), as compared to normal cytochrome oxidase activity in HIV-inflammatory myopathy (*right panel*)

a new pyrimidine nucleoside analog drug for hepatitis B, also causes characteristic mtDNA depletion, profuse COX-negative fibers [128, 129], and myonecrosis [130, 131]. The mechanism of myotoxicity is therefore likely to be identical to that of zidovudine.

Clinical Presentation

The spectrum of muscle disease in HIV-infected individuals treated with zidovudine ranges from patients with mild myalgia and CK elevation without muscle weakness to those with frank myopathy [132, 133]. Whether this broad clinical spectrum represents different degrees of zidovudine myopathy or whether it includes patients with overlaps among HIV-associated inflammatory myopathy, zidovudine myopathy, and HIV-related muscle wasting has not always been clear in published reports and cannot be ascertained without muscle biopsy.

Patients who have received a total dose of more than 250 g of zidovudine or a course of treatment ≥9 months are at risk of developing frank zidovudine myopathy [118, 134]. In this unambiguous form, it is characterized by the insidious onset of muscle pain and proximal weakness. Wasting of pelvic and shoulder girdle muscles is usually modest unless HIV wasting syndrome is superimposed. Serum CK levels are near the upper limit of normal to moderately increased, perhaps somewhat suppressed because of superimposed reduction of muscle mass. Needle EMG reveals findings of a myopathy (early recruitment of short duration, small amplitude polyphasic MUAPs) with abundant fibrillation potentials. The needle EMG is therefore indistinguishable from HIV-associated inflammatory myopathy. Nerve conduction studies are normal unless there is an associated HIV distal sensorimotor polyneuropathy [118, 134].

Differential Diagnosis

The differential diagnosis of proximal weakness in an HIV-infected patient includes zidovudine myopathy, the HIV-related inflammatory myopathy identical to polymyositis, HIV-related muscle wasting syndrome, or some combination of these [135]. Occasionally, however, neuropathic processes in HIV patients, such as an acute or chronic demyelinating

inflammatory polyneuropathy, may also present with a pattern of proximal weakness resembling a myopathy.

Myalgia and an elevated CK are insufficient to distinguish between zidovudine myopathy and other myopathic disorders in the HIV-infected patient. Diagnostic criteria for zidovudine myopathy should include the presence of objective muscle weakness, myopathic needle EMG, muscle biopsy documenting a degenerative myopathy *without* primary inflammation surrounding and invading non-necrotic myofibers, and abundant COX-negative myofibers (scores to hundreds per thousand myofibers).

Treatment/Management

The decision whether to discontinue zidovudine in patients with toxic myopathy is not always a straightforward one. An accurate diagnosis, often resting on muscle biopsy, is essential. Although withdrawal of zidovudine does reverse the histological and molecular features of the toxic myopathy [117, 136], and nearly all patients demonstrate substantial improvement in strength, not all achieve complete reversal of clinical manifestations [135]. These presumably include patients with overlapping HIV-related wasting syndrome or HIV-associated inflammatory myopathy. Also, discontinuation of zidovudine may have deleterious effects on the HIV-infected patient not otherwise treated with modern, highly active antiretroviral multidrug regimens. The toxic myopathy is dose/time related and in our experience it nearly always responds to a 50 % dose reduction while the patient's strength is monitored quantitatively for 4–6 weeks. Alternatively, zidovudine can be completely withdrawn. CK should be monitored weekly. If the patient's strength measurably improves and CK normalizes (recognizing that CK may decline from inactivity without clinical improvement), zidovudine can be either retried at a reduced dose or replaced with other multidrug antiretroviral agents. If the patient's strength does not improve, the diagnosis of HIV-associated inflammatory myopathy should be considered.

Alcohol-Related Myopathy

The myotoxic effects of alcoholism are diverse and include the syndromes of acute necrotizing myopathy, myoglobinuria, hypokalemic myopathy, chronic atrophic myopathy, and cardiomyopathy.

Acute Necrotizing Alcoholic Myopathy

Etiology and Pathogenesis

The pathogenetic mechanism of acute alcoholic necrotizing myopathy is unknown. Segmental necrosis of individual muscle fibers is the predominant finding on light microscopic examination – indistinguishable from other necrotizing myopathies. Electron microscopy does not reveal any pathogenetic clues, only the nonspecific separation of myofibrils and other cellular elements by fluid-filled spaces and aggregates of degenerating mitochondria typical of any necrotizing process [137].

Clinical Presentation

Acute alcoholic myopathy is characterized by the sudden onset of focal or diffuse muscle cramps, tenderness, swelling, and weakness. The CK is usually quite high, and when necrosis is severe, transient myoglobinuria occurs.

Predisposing Factors

The incidence of acute alcoholic necrotizing myopathy is probably quite low and almost always occurs in chronic alcoholics *during or immediately after a binge of heavy drinking*. In an experimental rodent model, it occurs only in protein-caloric malnutrition, not in the fed state [137].

Treatment/Prognosis

Following the withdrawal of alcohol, cramps subside within 1–2 days, and the pain and swelling within 1–2 weeks. Muscle power returns in 10–14 days.

Acute Hypokalemic Alcoholic Myopathy

Etiology and Pathogenesis

Hypokalemia is common among patients with alcohol withdrawal symptoms. Muscle biopsy during the acute phase of hypokalemic alcoholic myopathy shows marked vacuolization but only scant necrosis and myophagocytosis (Fig. 68.8).

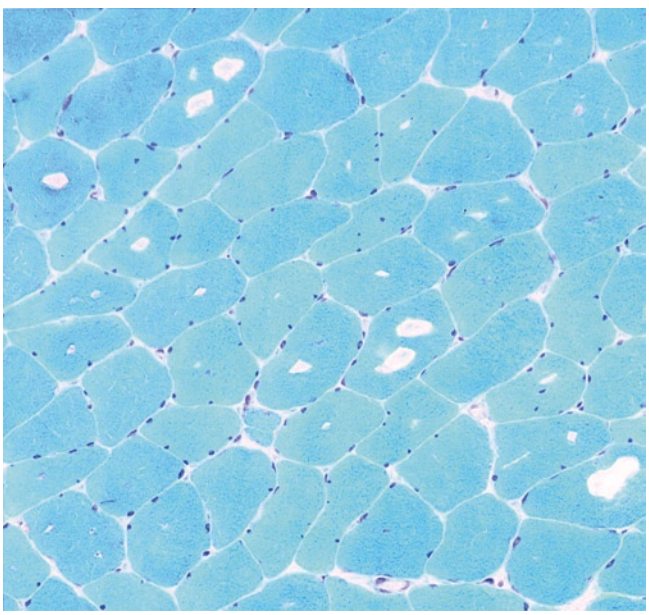

Fig. 68.8 Vacuolar myopathy. Numerous large empty vacuoles are dilated sarcoplasmic reticulum and T-tubules, as seen in hypokalemic myopathy due to alcohol or other agents (Modified Gömöri trichrome stain)

This vacuolar myopathy is due to dilatation of sarcoplasmic reticulum and T-tubules. Other drugs that place patients at risk for severe hypokalemia include laxatives, thiazide diuretics, glycyrrhizate (licorice), amphotericin, and lithium.

Clinical Presentation

In this syndrome, acute muscle weakness occurs *without* cramps, pain, tenderness, or swelling. Serum potassium is typically below 2.5 meq/L. Serum CK and aldolase are markedly elevated.

Treatment/Prognosis

Repletion of serum potassium improves muscle strength within 4–7 days, and complete recovery is achieved within 2 weeks.

Chronic Alcoholic Myopathy

Whether a chronic primary myopathy due to ethanol toxicity exists is debated. The controversy centers around whether the typical histological findings observed in weak muscles of chronic alcoholics – type II atrophy, increased numbers of subsarcolemmal nuclei, variation of fiber size, and occasional necrosis and regeneration of individual fibers – can all be attributed to chronic denervation alone [138]. In favor of a distinct myopathic component are the absence of fiber-type grouping and the lack of a correlation between these histological findings and the presence of clinical neuropathic symptoms or nutritional state [139, 140]. Also, the toxic myopathy in chronic alcoholism is usually dose dependent [141]. In our experience, the chronic myopathies in alcohol users combine the features of the remodeling that occurs after cycles of necrosis and regeneration (fiber size variability and myopathic grouping) with mild vacuolar changes, both characteristics of the acute types of alcoholic myopathy.

Alcoholic Cardiomyopathy

The syndrome of alcohol cardiomyopathy has been attributed to the direct effects of ethanol with chronic use [141], to cobalt poisoning in beer drinkers, or to vitamin B deficiency (beriberi).

Other Less Common Myotoxic Syndromes

Differential Diagnosis

By definition, a toxic necrotizing myopathy results when a substance *directly* causes muscle fiber necrosis (see Figs. 68.1 and 68.2). Syndromes in which muscle fiber necrosis occurs secondarily to other intervening mechanisms, such as the coma-crush syndrome with narcotic drug overdose, should not be included in this category. Common necrotizing toxins like statins, fibric acid derivatives, and ethanol were described above. Most others, like epsilon-aminocaproic acid, procainamide, or etretinate, are far less common now, but a number of these other less common toxic muscle disorders have been well documented (Table 68.5).

Table 68.5 Less common myotoxic syndromes

Epsilon-aminocaproic acid
Etretinate
Emetine (Ipecac®)
Organophosphates
Snake venoms
Bupivacaine
Edible mushrooms
Toxin-associated inflammatory myopathies:
D-penicillamine
Procainamide
Toxic oil syndrome
Eosinophilic myalgia syndrome (contaminated L-tryptophan)
Focal myopathy due to IM injection:
Pentazocine (Talwin®)

Necrotizing Agents

Many substances may cause myonecrosis if the dose is sufficient, as illustrated by the bizarre cases of acute necrotizing myopathy from lindane powder accidentally sprinkled on broccoli (mistaken for monosodium glutamate) [142] and from paraphenylenediamine (used in hair coloring) mistakenly ingested as "coffee" [143]. What are of more importance to the clinician are those substances that, with chronic use, may cause a necrotizing myopathy that may be misdiagnosed. Although necrotizing myopathies probably comprise the most common myotoxic syndromes, the molecular mechanism of myotoxicity in most cases remains unknown.

Emetine

Emetine (*Ipecac*®) causes (usually) painless proximal weakness that is reversible. This is often accompanied by elevated CK and electrocardiographic abnormalities, related to its cardiotoxicity. This myopathy is recognized by morphologically distinct floccular or geographic inclusions [144, 145].

Organophosphates

Poisoning by *organophosphate anticholinesterase compounds*, usually the result of insecticide exposure, causes a necrotizing myopathy [146, 147].

Epsilon-Aminocaproic Acid

Epsilon-aminocaproic acid is a potent antifibrinolytic agent also causes a necrotizing myopathy, sometimes severe enough to cause myoglobinuric renal failure and severe weakness [148, 149]. Myopathy occurs at doses as low as 10 g/day and with usage as little as 14 days, but most cases occurred with more than 24 g/day for more than 4 weeks.

Edible Mushrooms

The first reports from France of the association between ingestion of the edible mushroom *Tricholoma equestre* and subsequent true rhabdomyolysis and cardiac myotoxicity (CK levels in the 50,000–600,000 IU/L range) in 12 patients [150] triggered other confirmative case reports from Poland, Finland, Taiwan, and Alaska. The French syndromes, which occurred over a decade of reporting, were fulminant intoxications presenting about a week after three consecutive meals containing the mushrooms. Myotoxicity was confirmed in mice administered with an aqueous extract from the same mushroom species, which reproduced dose-dependent, mild, but significant 2.5-fold increase in CK in animals that were gavage fed very large amounts of *T. equestre* powder (2–6 g/kg doses) for three consecutive days; lipid-soluble extracts of the mushroom powder produced even more substantial sixfold elevations of CK [150]. More extensive mouse modeling has proven that the causal relationship is more widespread in the mushroom order, showing that the myotoxicity is not species specific but seen in a wide variety of gourmet, edible mushrooms that have been eaten by humans no doubt for centuries and sold commercially, including but probably not limited to the following species: chanterelle (*Cantharellus cibarius*), several *Russula* species, orange birch boletus (*Leccinum versipelle*), and the sheep polypore (*Albatrellus ovinus*) [151]. These many phylogenetically distinct genera of wild, edible mushrooms caused dose-dependent CK elevation at moderately high intake in the mouse diet for substantial 5-day exposures, compared to controls. Variance in the responses suggests individual susceptibility. In these experiments, there was no morphological abnormality by routine paraffin histology, but that is an insensitive technique. In humans, the correlative estimated dosage necessary would be a moderately high dietary consumption over several days, and that is realistically possible. On the positive side of the nutritional ledger, a variety of wild mushroom species have been shown to lower LDL cholesterol levels in rodents. The advocacy for mushrooms as part of a healthy diet, and the value of mushrooms to both gourmands and hobbyists mean vigilance of this new myopathy is warranted.

Toxin-Associated Inflammatory Myopathies

Toxin-associated inflammatory myopathies may occur in patients receiving d-*penicillamine* [152, 153] and *procainamide* [154]. The myopathic manifestations of the epidemic toxic oil syndrome [155] and *tryptophan*-associated eosinophilia-myalgia syndrome [156] were also inflammatory in nature (see Chap. 79).

Focal Myonecrosis

In the wild and in snake handlers, focal myonecrosis is caused by the *snake venom* components single-chain peptides and A_2 phospholipases [157]. The high specificity of venom phospholipases suggests a specific binding to membrane receptors, leading to vacuolization, lysis, and necrosis of skeletal muscle cells. As an iatrogenic occurrence, intramuscular bupivacaine injection in high dose also causes focal myonecrosis and is probably a daily but unrecognized event.

Repeated intramuscular injection of the narcotic *pentazocine* has been reported to cause focal myonecrosis, which in severe cases of self-injection can lead to fibrotic contractures [158].

Newer Agents

Sonedegib® (LDE225, Novartis) is a member of a relatively new class of drugs that are selective antagonists of the smoothened receptor, which is a G-protein-coupled receptor that positively regulates hedgehog signal transduction and is linked to the pathogenesis of several human cancers [159]. Currently in phase I and II trials demonstrating high efficacy against advanced solid-tumor malignancies, Sonedegib has been surprisingly associated with high elevations of serum CK, surprising because preclinical studies did not evidence any myopathy [160]. The mechanism of myotoxicity is as yet unknown. Although substantial CK elevation most often indicates myonecrosis, current evidence completely contradicts a mechanism of acute rhabdomyolysis or any chronic necrosis for that matter with this drug.

Unproven Toxic Myopathic Syndromes

The literature is replete with reports of toxic "myopathy" in which there is no consistent morphological, electrophysiological, serum enzymological, or metabolic evidence of muscle disease. These are typically no more than syndromes in which one or more of the symptoms of fatigue, muscle pain or cramps, and even proximal weakness are present [76].

Fatigue is not a cardinal myopathic symptom, perhaps occurring more commonly from depression, central nervous system disorders, or peripheral and neuromuscular junction disorders. Nevertheless, *solvent-induced myopathies* were

reported solely on the basis of fatigue. A number of solvents including acetone, benzine, naptha, and xylene were implicated as myopathic agents despite normal strength, needle EMG, and muscle histology. CK was minimally elevated in these patients, and 24 % of unexposed controls had CKs above the upper limit of normal [161].

Similarly, pain, myalgia, and cramps are not signs that localize disease to muscle. Yet, "painful myopathies" were attributed to *labetalol* [162], *mercaptopropionyl glycine* [163], and *polyvinyl chloride* [164] without convincing laboratory evidence of muscle injury. In clinical drug trials, aches, pains, or cramps are frequent in placebo groups.

Even the cardinal symptom of proximal weakness is not, by itself, an indication of myopathy, as it can be seen in other neuromuscular disorders and even central nervous system disease. Severe, rapidly reversible weakness attributed to *rifampicin* has been called myopathy without significant electrophysiological, histological, or serum enzymological abnormality [165]. Probable *tetracycline*-induced myasthenia has been mistakenly called myopathy [166]. "*Iron-overload* myopathy" was diagnosed when motor nerve conduction velocities were slowed, muscle fibers were denervated and contained stainable iron, and yet no definitive myopathic features were present [167].

A recurring example of the unproven myopathic syndrome is that associated with *cyclosporine* treatment. A review cites dozens of case reports in which patients treated with cyclosporine reported "muscle symptoms including myalgia, cramps, and muscle weakness, sometimes associated with CK elevation" [168]. In total, these included 34 patients, of whom, only 2 had supposedly taken cyclosporine alone [169, 170]. One of those had only pain, which resolved when the drug was stopped and recurred when it was reintroduced. In the other 32 patients, cyclosporine was administered with other drugs thought to be myotoxic, including colchicine, steroids, and statins. Those few reports purporting to show that removal of cyclosporine improved symptoms (usually muscle pain or other subjective complaints) also involved changes in other drugs which were more likely to be myotoxic. Muscle pathology, which was examined in fewer than half of the cases, was never convincing. Findings included type II atrophy (5/15 patients), rare necrotic fibers (4/15 patients), and excessive numbers of central nuclei (1/15 patients). Finally, needle EMG findings were also rarely convincing. Thus, the existence of a "cyclosporine myopathy" has not been proven.

The widely cited Naranjo scale [171], which is used to estimate the probability of adverse drug reactions, is probably at fault. A case in point is the mistaken attribution of "severe myopathy" to low-dose, short-term use of gabapentin for neuropathic pain [172], when in actuality the more probable cause of a severalfold elevation of CK (no biopsy was performed) was the elderly patient's haloperidol-treated psychomotor agitation and delirium, which are well known, but trivial, causes of motor activity-related CK elevation. Similar errors confusing temporal association with causation have led to reports of "Naranjo-probable" myopathies from many commonly used drugs, including rifampicin, tetracycline, labetalol, proton pump inhibitors (omeprazole, lansoprazole), cyclosporine, solvents, polyvinylchloride, mercaptopropionyl glycine, and even epidural (hence intramuscular) triamcinolone [172]. Generally, such misattributions, based solely on correlation with drug de-challenge, are in case reports that are confused by multiple concomitant drugs (including statins) and complicated medical problems, that lack consideration or control of physical activity or other causes of CK elevation, and that are unfounded by muscle biopsy. Alternatively, if a myopathy did occur, it may be that a drug interaction is to blame, as, for example, via effects on the cytochrome P450 system.

These examples illustrate how toxic myopathies can be *over*diagnosed on precious little evidence. The presence of such unproved syndromes in the clinical literature means that reports of "toxic myopathy" must be critically evaluated.

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Infectious and Granulomatous Myopathies

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Kanokwan Boonyapisit

Viral Myositis

Myalgia is extremely a common symptom in viral infection while pathologically proven myositis is rare. Coxsackievirus in the enterovirus group was the first virus reported to cause muscle inflammation in human. Myalgia was reported in patients with epidemic pleurodynia in the 1940s, but inflammatory change in muscle biopsy was discovered few years later. Myositis associated with influenza virus infection was reported afterwards in the 1950s.

Etiology and Pathogenesis

Several features of the pathogenesis of myositis related to viral infection are still unclear. Details of the penetration of viral particles and the molecular basis of susceptibility or resistance to viral infection remain to be determined. The mechanisms underlying the destruction of the cytoarchitecture are still unresolved. In the case of Coxsackievirus, damage to the contractile proteins and condensation of nuclear chromatin are the initial changes [1, 2], whereas in echovirus infection dilatation of the sarcoplasmic reticulum precedes other changes [3].

Immunopathological mechanisms of acute viral-induced skeletal muscle injury have not been evaluated in detail. The immune response does not appear to play a significant role in the acute phase of viral-induced injury for the following reasons: (1) The early cellular changes in muscle precede any inflammatory response. (2) Younger animals whose immunologic responses are probably less well developed are more susceptible to muscle infection. (3) Immunosuppression does not prevent viral-associated muscle injury and increases the mortality associated with viral infection [4, 5]. However, an initial viral infection may trigger an immune-mediated polymyositis.

The possible causal relation between viral infection and inflammatory myositis comes from early isolation of Coxsackievirus B from the muscle of a child with dermatomyositis [6]. Subsequently, Adams et al. in 1965 and Chou in 1967 discovered eosinophilic intranuclear and intracytoplasmic inclusion in the muscle from the patients with chronic myositis [7, 8]. The inclusions contained aggregates of microtubular filaments with a diameter of 115–118 nm, which resembled paramyxovirus nucleocapsids. However, subsequent attempts to identify viral antigen by immunocytochemical methods were unsuccessful [9].

More recent literatures still focused on relating evidence between viral infection and inflammatory myositis. One recent case control study had demonstrated higher frequencies of detection of EBV genome and anti-Epstein-Barr nuclear antigen in patients with dermatomyositis and polymyositis compared to the matched control group [10]. Viruses in retrovirus group such as human immunodeficiency virus (HIV) and human T lymphocytic virus 1 (HTLV-1) have also been reported related to the development of idiopathic inflammatory myopathy in many case reports [11–15]. Adenovirus type 2 was isolated from muscle biopsy of two patients with inclusion body myositis [16]. Mumps viral antigen also was demonstrated in the sarcoplasm of the muscle with this disorder by immunocytochemical method [17]. However, these findings cannot be reproduced in subsequent studies and so far there is very little evidence to support true relation between viral infection and chronic inflammatory myositis. Nevertheless, it remains possible that a viral infection may trigger an immune-mediated myositis.

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Clinical Syndromes Related to Viral Myositis

Epidemic Pleurodynia

Epidemic pleurodynia first described in the 1940s [18, 19] is also referred to as epidemic myalgia, Bornholm disease, or Devil's grip. The disorder is usually caused by group B Coxsackievirus [20]; however, it may also be caused by some group A Coxsackievirus and echovirus. This syndrome typically occurs in children in the summer or fall. The onset is abrupt in 75 % of the patients, while some patients have prodromal symptoms of headache, anorexia, and mild myalgia for 1–10 days. The major symptom is severe chest wall pain. Deep breathing or coughing accentuates the pain and accounts for the misleading name "pleurodynia," since the pleura itself is not actually involved. Other associated symptoms include fever, headache, cough, anorexia, nausea, vomiting, and diarrhea. Symptoms often last few days up to 2 weeks and then resolve spontaneously. Pleurodynia may also be associated with other sequelae from picornavirus infection such as aseptic meningitis, orchitis, or pericarditis.

Coxsackievirus and echovirus may also cause rhabdomyolysis, which can occur in a wide range of age group [21, 22]. The pathogenesis of myositis caused by Coxsackievirus is still unclear. The evidence of viral infection can be obtained by detection of virus in the stool sample or fourfold rise in the titer from serologic testing.

Routine laboratory tests are usually normal. Muscle pathology is often normal [23] although in some reports, the muscle biopsies revealed inflammatory changes in the muscle [24, 25]. There is no specific treatment for the condition and treatment is mainly supportive and symptomatic.

Benign Acute Childhood Myositis

This clinical syndrome was first reported in the 1950s under the name of "myalgia cruris epidemica" and was later on confirmed to be related to influenza virus infection [26]. Influenza B virus was identified in more than half of the patients, influenza A virus in 10 %, and parainfluenza and adenovirus in the minority of the cases. The disorder usually occurs in children during the epidemic of influenza, and myositis develops in only a small fraction of the children with influenza. Adults are usually not affected, although there were case reports that described this condition in adults [27]. Boys are more affected than girls with a male to female ratio of 2:1. The mean age of onset is 8 years old [28]. The disease is characterized by transient severe pain and tenderness affecting the calves that typically occurs 3–5 days (range 0–18 days) after the onset of an upper respiratory tract infection [28]. The children often refuse to walk. Alternatively, they may toe-walk or ambulate with stiff legs and hold their feet in plantar flex posture. The calves are very tender and may be mildly swollen. Pain lasts for 4–10 days and spontaneously resolves. Approximately one-third of cases, the muscle pain can occur in multiple muscle groups in addition to calves. Recurrent myositis is rare and usually occurs from a different strain of virus that causes the first episode.

Most laboratory tests are normal in benign childhood myositis, including erythrocyte sedimentation rate (ESR). Moderately elevated serum creatine kinase (CK) is frequently found. The serum CK level can be very high in children who develop myoglobinuria. CK level is usually normalized over few weeks. Some children also have elevation of the serum glutamic oxaloacetic transaminase (SGOT) and lactate dehydrogenase (LDH) activity. Needle EMG in severe cases shows low amplitude, brief duration motor unit action potentials (MUAPs), most prominent in calf muscles but are also found in clinically uninvolved muscles in upper and lower extremities [29, 30]. Muscle biopsy is not routinely performed and often reveals nonspecific findings. However, a single report demonstrated that influenza virus could be isolated from muscle tissue in a patient with myoglobinuria [31].

Treatment is symptomatic and consists mainly of bed rest, hydration, and antipyretic agents.

Acute Viral Myositis

Myalgia is common during viral infection. Certain strain of influenza virus type A [32] or type B [31] can produce a severe diffuse myopathy with rhabdomyolysis and myoglobinuria. In a 1918 outbreak of influenza in the United States and Great Britain, myositis was noted in 10–20 % of patients. Acute viral myositis in adults tends to be more severe than in children. The onset of symptoms is usually abrupt. Myoglobinuria, fever, myalgia, and swelling of muscles are common. Severe myalgia and myoglobinuria may develop during the acute phase of the illness [33, 34] or as the respiratory and gastrointestinal phases of the illness are resolving. Respiratory complications, acute renal failure, and myocarditis can occur in severe cases. Recovery from weakness usually occurs within 2–3 weeks.

Laboratory tests reveal elevated serum CK level, which is highest in the patient with myoglobinuria. Elevated ESR occurs in approximately half of cases. Elevated blood urea nitrogen and creatinine are also seen in association with myoglobinuria. Muscle biopsy reveals either diffuse or patchy area of myositis characterized by muscle cell necrosis and a perivascular and interstitial inflammatory infiltrate [31, 35]. Pathologic changes in acute viral myositis are focal and pathologic changes may be missed by muscle biopsy sample. Orthomyxovirus-like particles were found in the muscle from patients with influenza A-associated myositis [35]. Influenza B virus was isolated from the muscle of a patient with acute myositis with myoglobinuria about 2 weeks after the onset of symptoms. The viral particles were found within the membrane-bound vacuoles near the sarcolemma. Viral particles occasionally could be seen budding

from the limiting membrane of subsarcolemmal vacuole to the lumen of the vacuoles [31].

Treatment consists of supportive treatment with bed rest and adequate hydration to prevent renal complications. Antiviral agents such as amantadine have not been specifically evaluated for the treatment of acute myositis.

Other viruses may also produce acute diffuse myopathy. These include parainfluenza virus [36, 37] and respiratory syncytial virus [38], which causes myalgia and muscle weakness associated with respiratory tract infection as in influenza. Coxsackievirus also causes myoglobinuric polymyositis in newborn infants [39, 40] and adults [41]. Diffuse myalgia, muscle weakness, and myoglobinuria may occur with acute infection of adenovirus [42, 43], Epstein-Barr virus [44–47], respiratory syncytial virus [38], cytomegalovirus [48], herpes simplex [44], and herpes zoster [49, 50] . Echovirus infection can lead to acute myositis with rhabdomyolysis [51, 52]. Dengue virus has been reported to be associated with myositis and rhabdomyolysis in severe cases [53].

Epidemic Benign Myalgia of the Neck

Epidemic benign myalgia of the neck is characterized by severe occipital and neck pain, fever, headache, and occasionally nausea and vomiting, lasting approximately 4–5 days [54–56]. The syndrome most frequently affects young adults and is usually associated with epidemic influenza [26].

Although the clinical presentation may resemble aseptic meningitis, the cerebrospinal fluid (CSF) is normal and photophobia is absent. Positive serology for influenza virus type A and B may be detected in patients with epidemic benign myalgia of the neck. There are no reports of electrodiagnostic (EDX) studies or muscle pathology in this syndrome. Treatment consists mainly of supportive measures. Myalgia of the neck usually spontaneously resolves in 4–5 days.

Retrovirus-Associated Myositis

Myopathy Associated with Human Immunodeficiency Virus (HIV)

HIV-related muscular complications were first recognized and were more prevalent during the early phase after the initial description of acquired immunodeficiency syndrome (AIDS) between the late 1970s and 1980s. After the development of newer antiretroviral agents, the prevalence of HIV-associated myopathies has decreased but may be still seen in developing countries or in patients with inadequate treatment. The myopathies related to HIV infection need to be differentiated from the other muscular conditions found in HIV-infected patients, which mainly include muscular complication of antiretroviral therapy and myopathies related to opportunistic infections.

Subacute progressive inflammatory myopathy is probably the most common type of muscle manifestation related to human immunodeficiency virus (HIV) infection. This type of myopathy may occur early in the course of the infection but is more common with advanced disease.

Etiology and Pathogenesis

The pathogenesis of HIV-associated myopathy is unclear. The primary pathogenic mechanism responsible for muscle fiber injury appears to be similar in HIV-associated polymyositis and idiopathic polymyositis, which is through antigen-directed cytotoxicity mediated by CD8+ cytotoxic T cells [57, 58]. Although HIV can be detected by polymerase chain reaction (PCR) from muscle biopsy specimens in some patients, an electron microscopic study found viral particles only occasionally in the endomysial lymphoid cells [59]. From current evidences, it is more likely that the myopathy is caused by a cell-mediated autoimmune response triggered by HIV rather than by the direct HIV infection of the muscle.

Clinical Manifestations

HIV infection may cause several types of muscle pathology ranging from myopathy and polymyositis to rhabdomyolysis. Patients with HIV infection may develop subacute or slowly progressive inflammatory myopathy during the course of the disease. Myopathy usually occurs in patients with advanced HIV infection but sometimes occurs in early stages of HIV infection [60]. Also, myopathy may present together with other neurologic manifestation of HIV including peripheral neuropathy and dementia syndrome.

Patients present in similar fashion as adult onset acquired polymyositis, with subacute or slowly progressive muscle weakness and myalgia involving proximal muscles symmetrically [60–64]. Acute onset of severe weakness with myocardial involvement or dysphagia may also occur [65]. The myopathy associated with HIV infection needs to be differentiated from other causes of myopathy that can also occur in HIV patients including drug-induced myopathy (zidovudine and didanosine), HIV wasting syndrome, and opportunistic infections [66–68].

Diagnosis and Evaluation

Laboratory findings reveal elevated serum CK, which is often up to 10–15 times of normal ranges. Myoglobinuria is uncommon. Needle EMG findings show increased spontaneous activity with fibrillation potentials and low amplitude, brief duration MUAPs [61]. Muscle biopsy shows inflammatory cell infiltrates, which are mostly CD8+ cytotoxic lymphocytes and macrophages, in perivascular, perimysial, or endomysial locations, with invasion of necrotic and nonnecrotic muscle fibers [59]. Frank necrotizing vasculitis is not seen, but perivascular inflammatory cells are common.

Necrotizing myopathies without inflammatory cells infiltration have been described [69]. There were also rare case reports of granulomatous myositis with multinucleated giant cells in HIV-infected patients [57, 70]. In some cases, nemaline rods, which originate from contractile proteins in the Z disc, may be found in muscle fibers [71], although they are more commonly described in association with AZT-associated myopathy. This evidence suggests that HIV or reaction from inflammatory cells may be damaging to structural or contractile element in the muscle.

Treatment

Treatment of HIV myopathy depends on the severity of muscle weakness and stage of HIV infection. There are no controlled studies assessing the efficacy of medication treatments for HIV myositis. Generally, if the patient is not already on antiretroviral medications, they should be instituted. Oral corticosteroid shows clear benefit and is often used as first-line treatment, but there is always the risk of further immunosuppression and opportunistic infections. Treatment with other immunosuppressive agents that include azathioprine, methotrexate, and cyclosporine was reported [72]. Intravenous immunoglobulin (IVIG) may be useful. In mild cases, who presented with myalgia without clear proximal muscle weakness, nonsteroidal anti-inflammatory drugs can be used [73].

Other HIV-Related Muscle Conditions

Other Types of HIV-Associated Myopathies

Nemaline myopathy has been described in patients with HIV infection. The patients present during the early stage of HIV infection with painless, progressive muscle wasting, weakness, and elevated muscle enzymes. Muscle biopsy showed the presence of nemaline rods from the electron microscope findings. Although usually there were no inflammatory cells or necrotic fibers in muscle biopsy of these cases, some patients in the reports have shown response to steroid treatment [71, 74, 75].

Similar to patients with HTLV-1 infection (see below), cases with inclusion body myositis also were reported in HIV-infected individuals with clinical manifestation, and muscle pathology resembles the sporadic inclusion body myositis [57, 76]. The role of virus in the pathogenesis of HIV-associated inclusion body myositis appears to only be the trigger for autoimmune response more than to directly infect the muscles [57, 64, 76].

Opportunistic Infections Involving Muscle in HIV Patients

HIV infection is associated with progressive immunosuppression and development of multiple systemic opportunistic infections. Musculoskeletal infections from various opportunistic infections were reported in the patients with HIV infection which include pyomyositis from bacteria, cytomegalovirus, *Toxoplasma gondii, Mycobacterium tuberculosis, Mycobacterium avium intracellulare*, and rarely *Cryptococcus*. Pyomyositis had been a disease that occurred primarily in tropical countries but has been increasingly encountered in western countries because of the HIV pandemic [77–83]. *Staphylococcus aureus* is the most common organism that causes pyomyositis in HIV patients. Salmonella and Streptococcus are responsible for approximately10 and 4 % of the cases, respectively [84, 85]. *Mycobacterium tuberculosis* and atypical mycobacteria are rare causes of pyomyositis.

Pyomyositis affects mostly patients with advanced HIV infections (median CD4 count of 24). Risk factors for pyomyositis include underlying muscle abnormalities, exercise-induced trauma, and hematogenous spreading of the infection. Patients usually present with localized pain and swelling in large muscle groups, with or without elevation of serum CK. Fever and leukocytosis may not be prominent [80, 86]. Multiple abscesses also occur [63]. Imaging studies of muscles with ultrasound, magnetic resonance imaging, or computed tomography with contrast reveal enhancing lesions in the affected muscles [83]. Treatment with systemic antibiotics and aspiration or drainage of the abscess results in resolution of the infection in the majority of patients [63, 84].

Human T Cell Leukemia Virus Type 1 (HTLV-1)-Associated Myositis

Human T cell leukemia virus type 1 (HTLV-1) is a cause of T cell leukemia in adults and HTLV-1-associated myelopathy (HAM) or tropical spastic paraparesis. HTLV-1 virus is found worldwide, but is endemic in southwest Japan, Caribbean Islands, Central Africa, and South America. The majority of the patients infected with HTLV-1 will remain asymptomatic chronic carrier and only 1–5 % will develop T cell leukemia or HAM in their lifetime [87–89]. The virus is transmitted through blood products, breast feeding, and sexual contact. Evidence of myopathy and inflammatory myopathy has been demonstrated in several case reports of HAM patients. However, there are no distinguishing clinical manifestation and pathologic features that can differentiate myopathies in HTLV-1 patients from myopathies seen in noninfected patients. These findings suggest that the presence of virus may trigger the pathogenesis of myopathy in HTLV-1 patients but is not the direct cause of muscle pathology [90]. HTLV-1-related polymyositis may occur in isolation or in association with HAM. HTLV-1-related myositis is reported in Jamaicans, in Haitians, and rarely in native Americans [91, 92]. Although tropical spastic paraparesis

from HTLV-1 is quite common in Japan, polymyositis is less prevalent there which suggests that other factors may play roles in the development of myositis.

Etiology and Pathogenesis

Similar to HIV-associated myositis, the true pathogenesis of HTLV-1-associated myositis is unclear. In vitro experiments demonstrate that HTLV-1 virus can infect CD8 and T4 cells but does not directly infect the human myotubule cells in tissue culture. In vivo, antibody to HTLV-1 virus can be demonstrated in inflammatory cells from muscle biopsies but is not found in the muscle fiber itself [93, 94]. T cell-mediated inflammatory reaction and major histocompatibility complex (MHC) type 1-restricted cytotoxic process are likely responsible for creating inflammatory reaction in the patient with HTLV-1-associated myositis [90, 93].

Clinical Manifestations

The clinical presentation of HTLV-1-associated myositis includes progressive muscle weakness and elevated serum CK indistinguishable from HIV-related myositis or idiopathic polymyositis. HTLV-1-related polymyositis may occur in isolation or in association with HAM or T cell leukemia [95, 96]. HTLV-1-associated myositis should be suspected in patients with HAM, who develop proximal muscle weakness or neck weakness. Patients with idiopathic inflammatory myositis who live in the endemic area should be screened for HTLV-1 infection, although the result may not really change the plan of management [62, 92, 97].

Other type of muscle pathology was also described in patients with HTLV-1 infection, although the evidence that supports correlation with the virus is less strong compared to patients with myositis. These include reports of inclusion body myositis in HTLV-1-infected individuals [98–100].

Diagnosis and Evaluation

Serum CK level and HTLV-1 antibody titer are elevated. Needle EMG findings show myopathic MUAPs with presence of fibrillation consistent with inflammatory myopathy. Muscle biopsy reveals similar findings as in idiopathic inflammatory myositis and HIV-associated myositis [91, 92, 101]. HTLV-1 is found in the inflammatory cells but not in muscle fibers. There are reports describing inclusion bodies in the muscle of patients with HIV and HTLV-1-associated myositis [99].

Treatment and Prognosis

A few reports indicated that oral prednisone improved HTLV-1-associated myositis and reduces serum CK levels, although the clinical response was not consistent as most of the idiopathic polymyositis cases [97, 102, 103].

Bacterial Pyomyositis

Pyomyositis is a bacterial infection of skeletal muscle often with abscess formation. This disorder is also referred to as "tropical pyomyositis" due to its common geographic distribution [104, 105]. Cases of pyomyositis in the United States and Europe were considered rare in the 1970s [106]. However, after the 1980s, the incidence of pyomyositis in the western countries has then increased, which was likely related to the discovery of the HIV in late the 1970s [79, 80, 86]. Pyomyositis in western countries is currently seen in HIV-infected patients, oncology patients receiving chemotherapy, patients with autoimmune diseases on immunosuppressive therapy, and patients with diabetes [107–109].

Etiology and Pathogenesis

Pyomyositis occurs by extension of infection from adjacent tissues or by hematologic spread. Hematogenous infection usually develops when there is a primary source of infection elsewhere, which causes transient bacteremia in a setting of minor muscle injury at the site of pyomyositis. The most common organism that causes pyomyositis is *Staphylococcus aureus*, accounting for over 90 % of the cases in tropical countries [110] and approximately 70 % in the United States [79, 107]. Other organisms responsible for pyomyositis include group A and B hemolytic streptococci, *Escherichia coli, Streptococcus pneumoniae*, and *Yersinia* and *Legionella* species [111, 112]. Group B streptococci (*Streptococcus agalactiae*) are one of the new emerging organisms that cause soft tissue infection, pyomyositis, necrotizing fasciitis, and sepsis in patients with diabetes and multiple medical conditions [109, 113, 114]. There are also a few reports of pyomyositis caused by *Neisseria gonorrhoeae*, *Staphylococcus epidermidis, Proteus mirabilis*, *Aeromonas* species, *Salmonella* species, and anaerobic bacteria such as *Bacteroides* species [115–123]. Microscopically, intramuscular abscesses consist of a central area of necrotic tissue containing inflammatory cells, which are predominantly neutrophils. Macrophages, lymphocytes, and occasionally eosinophils and variable degrees of granulation tissue can be seen surrounding the area of necrotic tissue.

Clinical Manifestations

Staphylococcal pyomyositis commonly presents with fever and local swelling and tenderness in the affected muscles [124–127]. The evolution of pyomyositis may take 10–20 days to progress from the stage of local swelling of the muscle to the suppurative stage with prominent fever, tenderness, and purulent collection within the muscle [126]. Muscle

abscesses are usually small and do not result in acute swelling. History of local muscle trauma may precede the development of abscess in some cases [117, 128, 129]. Risk factors for the development of pyomyositis include HIV infection, intravenous drug use, diabetes, and steroid use [130–133]. The most common sites of involvement are the quadriceps, glutei, and deltoid muscles [126]. Pyomyositis of the paraspinal muscles may present with severe back pain [134].

Spontaneous streptococcal pyomyositis is less common than Staphylococcal pyomyositis. Pyomyositis due to group A beta-hemolytic streptococci may be virulent and associated with severe septicemia and a rapidly fatal outcome [110, 135–137]. Streptococcal pyomyositis also can occur in a more protracted clinical course or causes localized abscess in the muscle as in Staphylococcal infection [130, 138, 139].

Clostridial myositis (gas gangrene) is the most lethal type of infectious myositis. The infection is caused by large gram-positive spore-forming anaerobic rod organisms with *Clostridium perfringens* being the most common species isolated from wounds. Prior trauma, ischemia, pyogenic infection, and the presence of foreign body are risk factors that cause conversion of the clostridial spores into vegetative forms that can produce toxins. The clostridial toxins are responsible for producing multiple systemic manifestations such as septic shock and disseminated intravascular coagulation. The incubation period before the development of clostridial myonecrosis is often 2–4 days. The onset is acute and tense edema and local tenderness may be the only prominent findings very early in the course. Later on, the serosanguinous discharge with unpleasant foul odor together with the development of dark hemorrhagic blebs and areas of green black cutaneous necrosis appears and crepitus is detectable. High fever, hypotension, and disseminated intravascular coagulation then rapidly occur [110, 140–142].

Diagnosis and Evaluation

Diagnosis of pyomyositis is based on clinical manifestation of fever and local tenderness in specific muscles. Differential diagnosis of pyomyositis includes other soft tissue infection or conditions that can cause local swelling, pain, and tenderness such as intramuscular hematoma, deep soft tissue infection, septic arthritis, and venous thrombosis. Laboratory investigations reveal neutrophilic pleocytosis and elevated ESR. In patients with HIV infection, the absence of elevation of white blood cell count can be seen [107]. Serum CK is normal or elevated. Blood culture may be negative in up to 60 % of cases, since the bacteremia is often transient except in the cases that patients become septic [107]. Establishing the diagnosis of pyomyositis can be difficult in the patients with subtle local swelling and muscle tenderness. Ultrasound, CT scan, and MRI of muscles are useful in localizing the pyogenic abscess for diagnosis and needle aspiration [143–147]. Soft tissue X-ray is helpful in demonstrating interfascial gas in the case of clostridial myonecrosis.

Establishing the causal organism is important for the selection of the effective antimicrobrial agents. Gram stain and culture of the purulent discharge from surgical drainage or radiologically guided aspiration should be performed. Special stains and culture for other organisms such as Mycobacterium and fungus should also be performed when there is clinical suspicion of infection by other organisms, especially in immunocompromised patients.

Treatment and Prognosis

Before the abscess formation occurs, the infection may respond to antibiotics without surgical drainage. Well-formed abscesses require prompt incision and drainage together with intravenous antibiotics. The initial choice of antibiotics should provide good coverage for gram-positive organism especially for *S. aureus*. In immunocompromised patients, the choice of antibiotics should be broad spectrum before the identification of the causative organisms in gram stain or culture. Total duration of antibiotics usually needs to be at least 3–6 weeks [129]. In the cases of clostridial gas gangrene, excision of all involved muscles and adjacent tissue, as well as fasciotomy to decompress and drain the swollen fascial compartments, is required together with antibiotic treatment. Mortality rate of pyomyositis ranges from 1 to 4 %, despite treatment [107].

Fungal Myositis

Fungal infection of muscle is uncommon and usually occurs in immunosuppressed patients. Candida species is the most common fungus to cause myositis. Other fungi that produce myositis are *Cryptococcus neoformans* [148], *Aspergillus* spp. [149], *Pneumocystis jiroveci, Coccidioides* spp., *Sporothrix schenckii* [150], *Actinomyces* spp., and *Histoplasma capsulatum* [151, 152]. These organisms cause myositis in the setting of disseminated infection.

Candida myositis usually occurs in the setting of disseminated candida infection in an immunocompromised host or with a prolonged use of broad-spectrum antibiotics [153]. The patients present with high fever, diffuse erythematous skin rash, progressive myalgia, and muscle tenderness [154, 155]. Muscle tenderness is often severe and affects lower extremities predominantly [155].

Muscle biopsy shows areas of multiple microabscesses, hemorrhagic necrosis, and infiltration of the muscle by budding yeast, pseudohyphae, and inflammatory cells [153, 156]. Hemoculture may be positive in the setting of disseminated

candidiasis. The most common candida species causing muscle infection is *Candida tropicalis* but other candida species have also been reported [153, 155, 156].

Despite the treatment with intravenous amphotericin B for disseminated candida infection, the prognosis in general for the patient with systemic candida infection is poor and mortality rate is high [154].

Tuberculous Myositis

Granulomatous myositis caused by *Mycobacterium tuberculosis* and atypical mycobacterium species is uncommon. Other organisms in the mycobacterium species that cause soft tissue and muscle infections, in addition to Mycobacterium tuberculosis, are *M. ulcerans, M. marinum, M. fortuitum, M. chelonae, M. haemophilum, and M. xenopi* [157, 158].

Clinical Manifestations

Tuberculous myositis is seen in both normal and immunocompromised hosts [159, 160]. The infection often extends from adjacent primary foci of infection such as lung, pleura, joints, abdominal abscesses, or cutaneous lesions [161, 162]. This causes single or multiple muscle abscesses. Hematogenous spreading of infection also occurs [163]. One of the most common sites for tuberculous myositis occurs from direct extension of infection from vertebral osteomyelitis causing tuberculous psoas abscess. The clinical presentation is usually more indolent compared to cases of bacterial pyomyositis [159, 164–166]. Single or multiple masses of different sizes can be found on palpation of the involved muscles. Enlarged regional lymph nodes may occur [163]. Local trauma at the time of disseminated infection may contribute to the abscess formation [164].

Diagnosis and Evaluation

Diagnosis is based on clinical history of tuberculous infection, history of contacting tuberculosis, and indolent presentation of the intramuscular abscesses. CT scan and MRI of the affected muscles are helpful in identifying the site of intramuscular abscesses [167, 168]. Needle aspiration or surgical drainage of the mass is often required, and the final diagnosis is made based on the pathologic findings and acid-fast stain or culture for *Mycobacterium tuberculosis* [159, 164].

Histopathological study of infected muscle reveals granulomatous inflammation, consisting of histiocytes and macrophages surrounding the area of necrosis and caseation. The acid-fast bacilli are found in the inflammatory cells and in the necrotic tissue within the lesion [165]. Culture for mycobacteria may take weeks but is important for the identification of the organism and its sensitivity to antituberculosis agents.

Treatment and Prognosis

Treatment for tuberculous myositis consists of surgical drainage and administration of antituberculous drugs [159, 164, 165].

Sarcoid Myopathy

Sarcoidosis is a systemic granulomatous inflammatory disease of unknown etiology that involves multiple organs, primarily the pulmonary and lymphatic systems. The initial manifestation involves bilateral hilar adenopathy, pulmonary infiltrates, skin lesions (such as erythema nodosum), uveitis, and arthritis. Sarcoidosis is more prevalent in the African-American population and in women compared to men. The disorder is uncommon in childhood [169]. Incidence of myopathy ranges from 1 to 60 % of patients with sarcoidosis based on different series in literature. The majority of patients with myopathy are asymptomatic [169, 170].

Clinical Manifestations

Muscle weakness in sarcoidosis may present as acute myositis, chronic myositis, or neurogenic atrophy due to peripheral neuropathy or muscle involvement may be asymptomatic [171–177]. Acute or chronic myositis is the most common clinical presentation causing weakness, pain, and tenderness affecting proximal more than distal muscles [170, 178–181]. Muscle cramps and contracture also are described [182]. Dysphagia presumably from esophageal dysfunction and respiratory and extraocular muscle involvement is reported [183–186]. On examination, the nodular lesions in the muscle can be palpated in some patients [187]. Rarely, sarcoidosis can present with a tumorlike lesion in the muscle [187–189]. The myopathy may occur accompanied with peripheral neuropathy. Chronic sarcoid myopathy may cause significant muscle atrophy and wasting.

Diagnosis and Evaluation

The diagnosis of sarcoid myopathy is usually based on history of progressive proximal muscle weakness in a patient with clinical suspicion of systemic sarcoidosis. Systemic sarcoidosis has varied clinical presentations. Acute sarcoidosis usually develops over few weeks and presents with mild

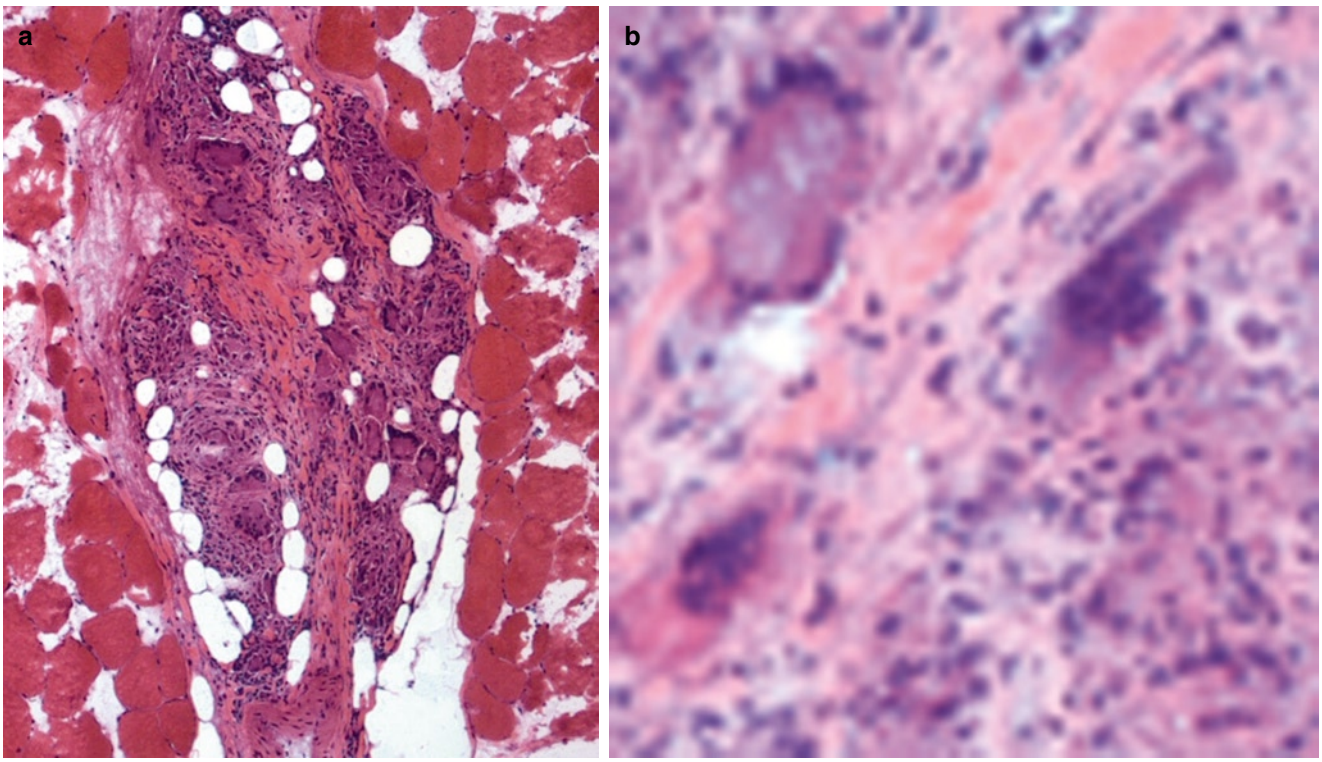

Fig. 69.1 Muscle biopsy from patient with sarcoid myopathy showing a large granuloma with clusters of epithelioid cells, lymphocytes, and giant cells (**a**: lower magnification; **b**: higher magnification) (H and E stain)

constitutional symptoms such as fever, fatigue, malaise, anorexia, or weight loss together with respiratory symptoms. The insidious form of the disease develops over several months with respiratory symptoms without constitutional symptoms [190]. The asymptomatic form, which represents approximately 10–20 % of cases, is detected mostly by routine chest X-ray. Skin lesions and eye involvement are also seen in 25 % of the cases. When neurosarcoidosis is the only manifestation of the disease, the diagnosis is difficult and often requires histopathological confirmation [181, 191].

About 90 % of patients with sarcoidosis have abnormalities on chest X-ray at some time during the course of the disease. Chest X-ray in systemic sarcoidosis often reveals hilar lymphadenopathy and interstitial infiltration of the lungs. Serum angiotensin-converting enzyme (ACE) is usually elevated in sarcoidosis. Although not always specific for the disease, serum ACE can be helpful in differentiating sarcoidosis from other granulomatous inflammatory diseases. Gallium scan is used in locating the specific sites of inflammation in the patient with clinical manifestations suggestive of systemic sarcoidosis [192–194]. Whole body fluorodeoxyglucose proton emission tomography (FDG-PET) has also been reported useful in some cases for locating the specific sites of inflammatory tissues for biopsy [195, 196]. MRI of the muscle in nodular type of muscular sarcoidosis sometimes shows distinctive star-shaped central structure of decreased signal intensity in the axial MRI images with peripheral enhancement with gadolinium [194, 197]. However, the MRI often reveals normal or nonspecific findings in the myopathic type of muscular sarcoidosis without intramuscular nodules [194]. EDX studies in sarcoid myopathy reveal findings consistent with myopathic or myopathic and neuropathic features in patients with concomitant peripheral nerve involvement. Muscle biopsy shows granulomatous inflammation in the connective tissue surrounding the muscle fascicles. The pathologic changes are focal and serial sections of muscles may be required to establish the diagnosis. The granuloma consists of clusters of epithelioid cells, lymphocytes, and giant cells (Fig. 69.1a, b) [198–200]. Large granulomas tend to compress and destroy the adjacent muscle fibers but muscle fiber necrosis is not common. There are no specific criteria to definitely distinguish pathologic changes in sarcoidosis from other granulomatous inflammatory disorders [201–203].

Treatment and Prognosis

Sarcoid myopathy and systemic sarcoidosis usually respond well to treatment with corticosteroids with significant improvement of muscle strength and systemic symptoms.

However, patients with very chronic myopathic manifestation may not response well to corticosteroid and may remain disabled [204, 205]. In some patients, treatment with nonsteroidal anti-inflammatory medications results in improvement of systemic symptoms [170, 171, 178, 179, 181, 206]. Treatment with other immunosuppressive agents, such as methotrexate or azathioprine, may be used in cases unresponsive to steroid treatment [188, 207]. Spontaneous remission may occur in a small portion of patients.

Lyme Myositis

Lyme disease is a systemic infection caused by the spirochete *Borrelia burgdorferi*, which is transmitted by tick bite [208].

Clinical Manifestations

The initial presentation includes characteristic rash (erythema migran), accompanied by flu-like symptoms, followed several weeks or months later by migratory arthritis, musculoskeletal pain, and neurologic and cardiac abnormalities [208–210]. Muscle weakness and myalgia is one of the presenting clinical manifestations of the disease, and chronic musculoskeletal pain usually occurs in the chronic phase of the disease [211–215]. Myocardial involvement may also occur [215, 216]. Orbital myositis associated with Lyme disease is reported [217, 218].

Diagnosis and Evaluation

Diagnosis of myopathy in Lyme disease is based on the presence of muscle weakness and myalgia in the setting of Lyme infection. Serology is often useful in making the diagnosis of Lyme disease after the first 3–6 weeks of infection. However, the serologic results need to be interpreted with caution since the presence of infection by other spirochete may create false-positive results [208, 210, 211]. Muscle biopsy in patients with musculoskeletal involvement often reveals infiltration of the muscle by lymphocytes and other mononuclear inflammatory cells [215, 219]. Using special stains for spirochetes, the organism can be identified in the muscle fibers [220].

Treatment and Prognosis

Treatment of myopathy related to Lyme disease is similar to the treatment of systemic disease with appropriate antibiotics such as tetracycline, penicillin, and cephalosporin. A prolonged course of treatment may be required in the patient with a long clinical course [208, 210, 211].

Myositis Secondary to Parasites

Trichinosis

Trichinosis occurs secondary to infection by the nematode *Trichinella spiralis*. The other parasites in the Trichinella species can also cause muscle infection but are uncommon. The infection involves multiple organs with predilection to the muscles. The transmission often occurs through ingestion of undercooked pork, bear, or walrus meat containing Trichinella pseudocysts (Fig. 69.2) [221, 222]. Trichinosis is found in nearly every region of the world, except Australia.

Etiology and Pathogenesis

Following ingestion of the meat containing pseudocysts, the gastric enzyme digests the cystic enclosure leaving the larvae to inhabit in the gastrointestinal system. After fertilization in the intestine, the male parasite dies while the female parasite penetrates the deep layer of the intestine. The young larvae pass through the intestinal mucosa into the bloodstream and to the muscles, where they then enter the muscle fibers and transform to the encysted form. The pseudocyst wall consists of connective tissue and cellular components from reaction of the host [223, 224]. Inflammatory cells in the early stage of inflammation are mainly polymorphonuclear leukocytes and eosinophils. In the chronic stages, calcification of the pseudocyst occurs, and mononuclear inflammatory cells replace the polymorphonuclear leukocytes [225].

During the period that the larvae encyst in the muscles, there is evidence of muscle degeneration and regeneration. Elevation of muscle's alkaline phosphatase is detected in the muscle fiber invaded with Trichinella in the acute stage of infection [226]. Between 2 and 4 weeks after the infection, the capsule surrounding the parasite gradually thickens, and in the chronic infection, the capsule will start to become calcified with no further destruction of muscle fibers [227].

Clinical Manifestations

The usual incubation period after ingesting meat with pseudocysts is between 2 and 12 days. The prodromal manifestations consist of abdominal pain and diarrhea. This is followed in the second week by fever, subconjunctival hemorrhage, periorbital edema, and myalgia, which predominately affects proximal muscles [228–232]. Trichinosis presenting as an acute severe myositis mimicking polymyositis can occur [233, 234]. The severity of clinical symptoms appears to be related to the number of Trichinella larva per gram of muscle [235]. Clinical examination reveals weakness and tenderness of the muscles, which may also involve the extraocular, intercostal, and diaphragmatic muscles [228]. Skin manifestations mimicking dermatomyositis rash, periorbital edema, and subconjunctival hemorrhage may occur [236]. Myocarditis may be seen although rare resulting

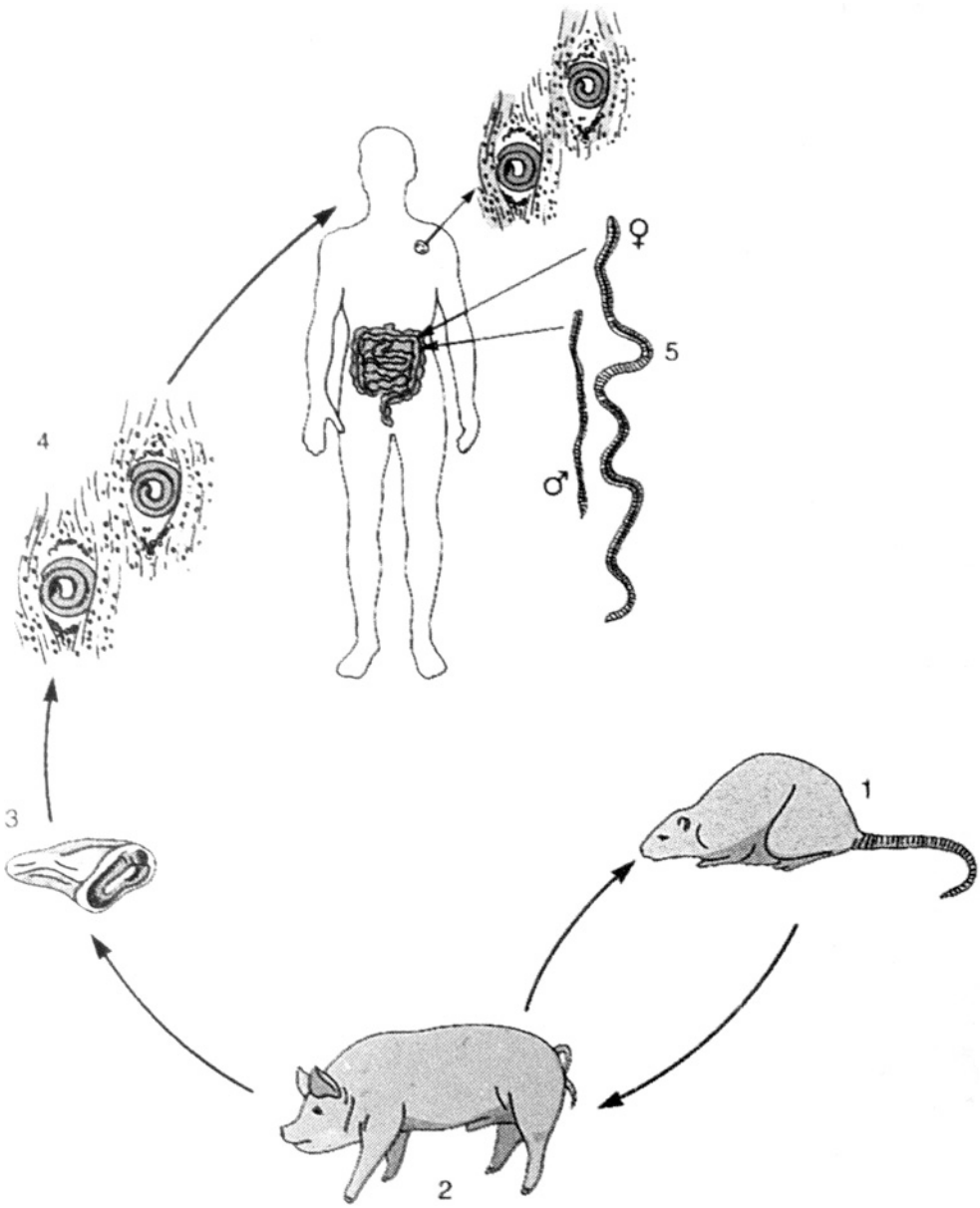

Fig. 69.2 Life cycle of Trichinella spiralis. This nematode causes a zoonotic infection that circulates between rats (*1*) and various carnivores. Trichinosis in human commonly results from eating raw or inadequately cooked pork or pork products such as sausages. Domestic pigs (*2*) and wild boar usually acquire the infection by eating infected rats (1). Infection is acquired by eating muscle (*3*) containing the encysted larvae (*4*). These excyst in the small intestine and develop into minute adults (*5*) in the mucosa. About 5 days after infection, the females, now mature, deposit larvae that migrate through the tissues to reach skeletal muscles in which they again encyst. Larvae deposition into muscle may continue for a week or more. Finally, the larvae become calcified. (Reproduced with permission from W Peter, HM Gilles. Color Atlas of Tropical Medicine and Parasitology, [4th ed]. St. Louis: Mosby-Year Book, 1995)

in tachycardia and may lead to cardiac failure. Headache, altered mental status, and nuchal rigidity occur in severe cases associated with central nervous system involvement [237, 238]. Myalgia from trichinosis may last for several months without treatment. Symptoms from myositis often start to improve when the parasitic larvae are encapsulated and calcified.

Diagnosis and Evaluation

Diagnosis of trichinosis is based on clinical presentation of acute weakness and myalgia in the patient with prior history of ingesting undercooked meat. Laboratory investigation shows increased eosinophil in the blood. Serum CK is elevated acutely. Needle EMG reveals fibrillation potentials and myopathic MUAPs [229]. Serology test for Trichinella antibodies becomes positive in 3–4 weeks after acute infection [229, 239, 240]. The definite diagnosis is obtained by muscle biopsy, which shows pseudocyst containing Trichinella larvae [241].

Treatment and Prognosis

Treatment with antiparasitic agents such as thiabendazole, mebendazole, and albendazole is effective against the larvae in gastrointestinal tract and may be effective against encysted larvae [230, 232, 242, 243]. A Herxheimer-like reaction can occur from simultaneous destruction of larvae from different sites and additional treatment with corticosteroids may be required [232]. Myalgia secondary to Trichinosis may persist for several months but serious complication or death rarely occurs [242].

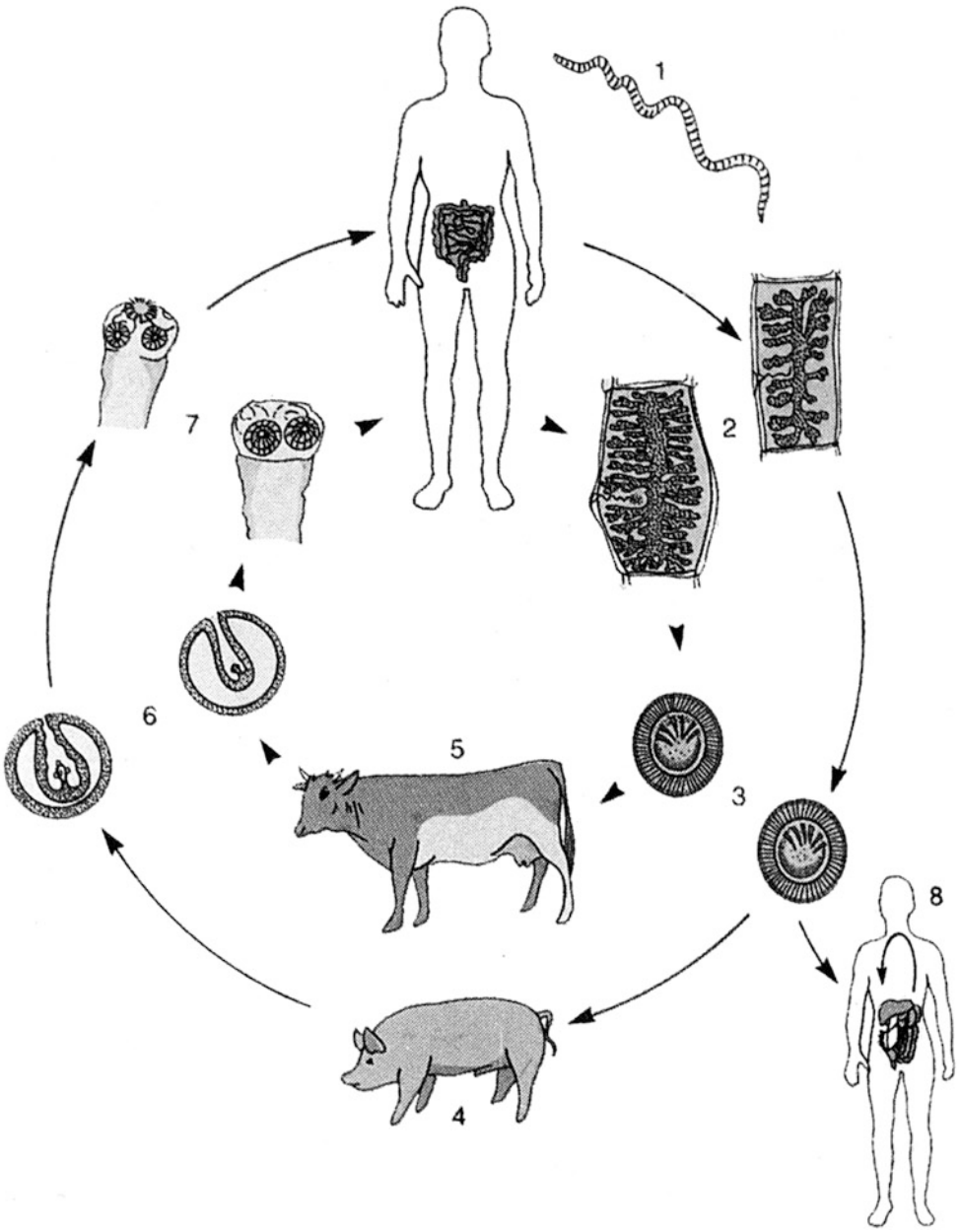

Fig. 69.3 Life cycle of Taenia solium and *Taenia saginata*. The adults (*1*) of both species live in the small intestine of human, the definitive host. The gravid segments (*2*) are very active and escape through the anus, releasing large numbers of eggs (*3*) in the perianal region or on the ground, where they can survive for long periods. When ingested by pigs (*4*) (Taenia solium) or cattle (*5*) (Taenia saginata), the eggs hatch, each releasing an oncosphere which migrates through the intestinal wall and blood vessels to reach striated muscle within which it encysts, forming cysticerci (*6*). When an inadequately cooked meat containing the cysts is eaten by man, the oncosphere excysts (*7*), settles in the small intestine, and develops into adult cestodes (1) over the next 3 months or so. If the eggs in the Taenia solium segments are released in the upper intestine (by contaminated food or water), they can invade the host (autoinfection) (*8*), setting potentially dangerous larval infection, known as cysticercosis, in muscle, brain, or any other tissues. (Reproduced with permission from W Peter, HM Gilles. Color Atlas of Tropical Medicine and Parasitology, [4th ed]. St. Louis: Mosby-Year Book, 1995)

Cysticercosis

Cysticercosis results from infection by *Taenia solium*, which occurs after ingesting undercooked meat especially pork. Ingesting fecal-contaminated food and water is another route of infection. Cysticercosis occurs in all parts of the world especially in Central and South America, Asia, Africa, Eastern Europe, and Spain, where there is poor sanitation of the water supply and sewage.

Etiology and Pathogenesis

Cysticercosis occurs from infection by a tapeworm, *Taenia solium*. The most frequent mode of transmission to humans is through fecal-oral contamination by ingestion of *T. solium* eggs excreted in the feces of intermediate hosts such as pigs or human. Ingesting the cysticercus in the undercooked pork meat does not directly lead to encysted larvae within the host, unless the host then again ingests the ova-contaminated food or water later.

When human ingested the undercooked pork meat with *T. solium* cysticerci, which contains mature larvae, the mature larvae hatch from the cysticercus and attach to the intestinal mucosa, which they inhabit for several years and where fertilization occurs. The ova are excreted in the feces and are ingested by the intermediate host such as pigs or are ingested by humans through fecal-contaminated food or water (Fig. 69.3). The embryo is released from the ova in the stomach by gastric enzymes and then

penetrates the intestinal mucosa into the lymphatic and bloodstreams to various organs. The larvae, then, grow rapidly in the tissue and develop scolex with hooks and suckers. The larvae often reach, in 2–3 months, its mature stage (cysticercus), which measure 5–6 mm in length and 8–10 mm in width. When humans ingest the undercooked pork, the mature larvae hatch from the cysticercus, attach itself to the intestinal mucosa, and begin another cycle [242, 244, 245].

Clinical Manifestation

Cysticercosis mainly affects the central nervous system and muscle. The involvement of the central nervous system is secondary to cysticercus cyst in the brain parenchyma resulting in an inflammatory reaction in the surrounding tissue leading to focal neurologic deficits. Seizures, obstruction of CSF pathways, and meningoencephalitis may occur in the central nervous system cysticercosis.

Muscle involvement in cysticercosis is not uncommon and is well described. Muscle involvement by cysticercosis is often asymptomatic. Calcified cysts in muscles sometimes are incidentally noted on the X-rays of the extremities. Weakness, muscle enlargement, and muscle tenderness are the main clinical manifestations that are described in symptomatic cases [246–249]. Muscle pseudohypertrophy has been reported, which often is symmetrical and occurs in limb girdle muscles [246, 250–252]. Nodular changes in the muscle may be found on deep palpation of the involved muscles. Involvement of extraocular muscles causing proptosis and ophthalmoparesis occurs [253–255]. Skin manifestations, such as subcutaneous nodules, sometimes accompany the skeletal muscle involvement.

Diagnosis and Evaluation

The diagnosis of cysticercosis is often based on clinical history and the presence of focal neurologic deficits, muscle weakness, and muscle pain in the patients from areas with poor sanitation. The presence of *T. solium* ova, which cannot be differentiated from *T. saginata* ova, in the feces alone is not sufficient for diagnosis of cysticercosis. Serologic testing of blood or CSF by enzyme-linked immunosorbent assays can be used to confirm the evidence of infection by *T. solium* [256]. Radiologic imaging such as CT or MRI or even plain X-ray revealing calcified cysts in the brain or muscles is helpful in judging for the extent of the disease [257–259]. Muscle biopsy may be required for definite diagnosis of skeletal muscle involvement. The cysticerci can be seen by gross examination of the muscle biopsy specimen as oval-shaped, milky white cysts of approximately 1 cm in size, containing fluid and a single scolex. Microscopically, the different components of the larvae are seen [242, 246, 247, 252].

Treatment and Prognosis

The antiparasitic agent, praziquantel and niclosamide, is the drug of choice for treating the adult form of *T. solium* in the intestine. Albendazole and steroid are used to treat central nervous system cysticercosis, and treatment results in a reduction of the number and size of the cysts [260]. The effectiveness of the antiparasite in the treatment of cysticercosis in muscles is established [244, 245, 261, 262]. The intramuscular viable cysts usually were treated with albendazole or praziquantel. Surgical removal of large intramuscular cysts may be required in some cases [263].

Myositis Secondary to Other Cestodes or Nematodes

Cestodes that can cause infection in muscles include the tapeworm in the *Spirometra* species and tapeworms in the genus *Echinococcus*. *Spirometra mansonoides* infects dogs and cats and, sometimes, causes infection in humans as accidental intermediate hosts. The infective stage of the parasite, which is the second-stage larva called sparganum, enters the human host through the oral route or open wounds and then encysts mainly in the subcutaneous tissue and muscles, but can also involve the eyes, brain, spinal cord, or viscera [264–267]. Most patients in the United States acquire infection through drinking water that is contaminated with first-stage larvae from a shallow pool or well [268]. In Asia, the parasites are usually acquired by eating undercooked snake or frog meat [269]. The patients present with slow-growing subcutaneous nodules or nodules in the muscles, which increase in size over several months and occasionally migrate distally. Excisional biopsy of the nodule is required for diagnosis. Pathology reveals presence of the sparganum in the nodule [270–272]. Surgical removal of the nodule is the treatment of choice.

Tapeworms in the genus Echinococcus include *Echinococcus granulosus* and *Echinococcus multilocularis*, which cause infections in dogs and wolves, as the definitive host, and human as an intermediate host. Cases of Echinococcus infections are found in the Middle East, parts of Europe, and Central and South America. The infection in humans (hydatidosis) is acquired through ingestion of food that has been contaminated by feces of the definitive hosts. The patients present with lobular cyst (hydatid cyst) in the muscle [273, 274] and in other visceral organs [275, 276], which slowly grows over several years and often calcifies. Thigh muscles are the most common location for muscle involvement. The nodule is usually not painful but the cyst may become infected by bacteria and result in abscess formation. Diagnosis requires surgical removal of the cyst. X-ray, ultrasound, or CT scan of the muscle may be helpful in identifying the cyst location [277]. Serology testing for serum

antibody to Echinococcus is also helpful for diagnosis. Definite treatment is surgical removal of the hydatid cysts [242]. Medical treatment with albendazole or praziquantel may be needed before surgery in cases that leakage of the cyst content may occur [278].

Other nematodes that cause muscle infection include *Toxocara canis* and *Toxocara cati*, *Ancylostoma caninum*, and dracunculiasis. *Toxocara* species usually cause visceral larva migrans in children, who acquire the infection by ingesting the soil contaminated with ova from infected dogs and cats. Clinical manifestations vary from asymptomatic with persistent eosinophilia to severe systemic infection with fever, hepatosplenomegaly, pneumonitis, and myalgia [279, 280]. Ocular and central nervous system involvement also occurs [279, 281, 282]. The invasion of muscle by *Toxocara* species usually causes granulomatous changes in the muscle. Pathologic finding reveals necrotic zone of the muscle centrally surrounded by granulomatous inflammatory reaction. Treatment with antiparasitic agents, such as albendazole, may be beneficial in cases of visceral larva migran [242].

Ancylostoma caninum normally causes cutaneous larva migrans and enters the host by directly penetrating the skin. Muscle infection from Ancylostoma is rare. The patient reported with muscle infection had severe cutaneous and visceral larva migran and developed tenderness and enlargement of the thigh muscle several months after the onset of the systemic infection [283]. The muscle biopsy revealed a nonencapsulated hookworm larva within the muscle fiber with inflammation surrounding the degenerative muscle fibers [242, 283].

Dracunculiasis, a common disease in Africa, India, and the Middle East, results from the nematode *Dracunculus medinensis*. The infection occurs after ingestion of the infected intermediate host, which is a crustacean called cyclops. The parasite then slowly migrates to the skin within a duration of 1 year causing focal induration in the subcutaneous tissue, fever, erythema, or periorbital edema. The mature parasites also create tracks in the connective tissue between the muscle and cause inflammatory reaction along the wall of the tracks and sometimes pyomyositis [284]. Some parasites usually die along the tracks and cause chronic calcifications. Treatment is by surgical removal of those parasites that come to the subcutaneous tissue or penetrate the skin. Treatment with antiparasitic agents helps to suppress the symptoms but usually cannot successfully eradicate the parasites [242, 285].

Myositis Secondary to Infection with Protozoa

Myositis secondary to infection from protozoa is relatively rare. The infection in human is usually acquired by ingesting the infected or contaminated meat or by living in close association with the definitive host. The protozoa reported to cause myositis are *Toxoplasma* species, Sarcocystis, *Trypanosoma* species [286, 287], and Microsporidium [288]. Malaria is reported to be associated with necrosis of the skeletal muscle and rhabdomyolysis [289, 290].

Toxoplasmosis

Toxoplasmosis is a systemic infection that occurs from coccidia, *Toxoplasma gondii*. Infection is more common in the immunocompromised hosts. A congenital form of toxoplasmosis also occurs. The patient presents with fever lymphadenopathy, hepatosplenomegaly, pericarditis, myocarditis, pneumonia, or meningoencephalitis. Myositis usually occurs with the systemic infection but may also occur in isolation [291, 292].

Etiology and Pathogenesis

Toxoplasmosis is found worldwide. Goats, cats, hogs, dogs, sheep, and cattle are affected by the protozoan *Toxoplasma gondii.* The most common mode of transmission to human is contact with cat feces or ingesting infected undercooked pork or lamb meat. Reactivation of the infection may occur in the chronic asymptomatic host, who becomes immunocompromised. Toxoplasmosis can also be transmitted through the placenta and blood products [242].

The most common mode of transmission is ingestion of infected meat, which contains Toxoplasma cysts. Ingesting oocyst-contaminated food may also transmit the disease. The oocyst, which contains the sporozoite form of toxoplasmosis, is excreted only in cats. Bradyzoites are then released from the cysts in the gastrointestinal tract and multiply. The tachyzoites then penetrate the nearby cells and leukocytes, which leads to disseminated infection through the bloodstream. The proliferation of the tachyzoites within the cells leads to necrosis of the cells. Tachyzoites eventually are destroyed by the host immune system, but the cysts containing bradyzoites persist for a long time in their host [242].

Clinical Manifestation

Polymyositis from toxoplasma infection often has a subacute presentation [291, 292]. Patients present with subacute progressive fever, myalgia, and muscle weakness similar to idiopathic polymyositis [293–299]. Lymphadenopathy and other signs of systemic toxoplasma infection are helpful in distinguishing toxoplasma-associated polymyositis from idiopathic polymyositis. Immunocompromised patients may also have clinical manifestations of infection involving other systems such as the central nervous system [300].

Diagnosis and Evaluation

Myositis secondary from toxoplasma infection should be considered in the immunocompromised patient with or without systemic manifestation of toxoplasmosis. Muscle

enzymes are usually elevated when muscle involvement occurs. Needle EMG examination reveals findings consistent with subacute polymyositis. Serology testing for toxoplasmosis may be helpful. A high titer of IgM antibody or a rise in IgG antibody titer testing over 3–4 weeks suggests the diagnosis [301, 302]. However, a single positive serology testing for toxoplasmosis can be a result from a remote chronic infection [242]. Demonstration of cysts or toxoplasma trophozoites from histopathological sections or isolation of toxoplasma from body fluid provides definitive diagnosis of toxoplasmosis. Muscle biopsy in toxoplasma-associated myositis reveals inflammatory cells, which are composed of histiocytes and lymphocytes in the perimysium and endomysium. Giant cells are sometimes present in inflammatory aggregates [293, 303, 304]. Toxoplasma tachyzoites are seen in the intracellular vacuoles as a crescentric or oval-shaped organism, stained with Wright and Giemsa stain. Toxoplasma cyst, which contains Toxoplasma bradyzoites, is easier to identify around or within the inflammatory cells and within the muscle fibers and usually stained well with the periodic acid Schiff (PAS) stain [305].

Treatment and Prognosis

The treatment of choice is with a combination of pyrimethamine and sulfadiazine, which eliminates the trophozoites in the acute stage of infection but is not as effective against the cyst form [242, 306].

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Part IX

Neuromuscular Disorders: Miscellaneous Neuromuscular Disorders and Syndromes

Myokymia and Neuromyotonia

70

Anne F. Josiah and Laurie Gutmann

Introduction

Myokymia and neuromyotonia are terms used to refer to specific clinical presentations and electrophysiologic findings associated with hyperexcitability of the peripheral axon [1, 2]. Myokymia is recognized as a spontaneous, continuous, undulating, vermicular movement of muscle. Focal clinical myokymia was first described in the legs in 1894 by Schultze and in the face in 1902 by Bernhart. The first description of generalized myokymia was by Denny-Brown and Foley in 1948 [3]. Neuromyotonia is also a continuous movement of muscle but is more generalized and results in muscular contractions and stiffness. The term, neuromyotonia, was first used by Mertens and Zschocke in 1965 [4]. Many terms have been used to describe this clinical phenomenon, including neuromyotonia [4], continuous muscle fiber activity [5], Isaacs' syndrome [5], neurotonia [6], Morvan's fibrillary chorea [7], and Morvan's syndrome [8]. In the literature, the clinical disorders of neuromyotonia and myokymia are sometimes difficult to distinguish, as the terms are not used in a consistent fashion. Both are associated with the same electrophysiologic accompaniments of myokymic discharges and, occasionally, neuromyotonic discharges. Some authors consider these two types of discharges to be a continuum [9]. In this chapter, the similar etiologies, clinical picture, and electrophysiologic studies will be reviewed. The more recent association with channel disorders will be highlighted.

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Etiology and Pathogenesis

Myokymia and neuromyotonia may be focal as well as generalized. The etiology of both types of myokymia and neuromyotonia is generally felt to be from a channel abnormality. A hereditary form of myokymia has been described as well as an autoimmune form of neuromyotonia [10–12]. Chromosome 12p13 has been identified as the gene for episodic ataxia and myokymia [10, 11, 13]. Potassium channel genes and a calcium channel gene map close to this locus. Antibodies to potassium channels have been identified in patients with Isaacs' and Morvan's syndrome [12]. Up to 50 % of patients with acquired neuromyotonia have antibodies to voltage-gated potassium channels [4, 7, 8]. Association with myasthenia gravis, thymoma, malignancy, amyloidosis, paraproteinemia, inflammatory demyelinating polyneuropathies, chronic graft-versus-host disease, penicillamine use, and lymphoma, along with response to plasma exchange and immunosuppression, has also been noted [11, 14–21]. Transient neuromyotonia has been recorded following oxaliplatin infusions, accompanied by paresthesias and dysesthesias with jaw and neck tightness, worsened with cold [22, 23]. The transient nature of symptoms implies a channelopathy, and a recent study implies a calcium-dependent potassium channel [24].

Myokymia and neuromyotonia may occur in mass lesions such as brainstem tumors and cysticercosis [25, 26], multiple sclerosis, timber rattlesnake bites, and a delayed effect after radiation therapy [21, 26–29]. The authors have also observed myokymia and neuromyotonia as a transient finding after severe anoxic injury. The clinical presentation is identical to the presentation in those with immunologic associations.

Myokymic discharges refer to the underlying electrophysiological abnormality in both clinical myokymia and neuromyotonia. The discharges are single motor unit action potentials which fire at rates of 5–150 Hz in bursts (Fig. 70.1). They may be doublets, triplets, or multiplets, firing at regular or slightly irregular intervals. The generator for these discharges is felt to be at some point along the motor axon. Ephaptic transmission from axon to axon may cause the multiple

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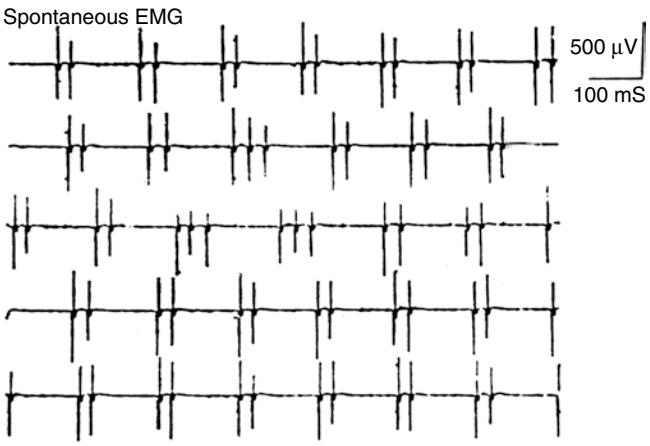

Fig. 70.1 Myokymic discharges firing at a rate of 7 Hz. Note the regular firing of bursts. Doublets predominate with occasional triplets

discharges linked together, but its exact role is not clear. These may be seen in a variety of disorders, including all those listed above. In addition, rare bursts of myokymic discharges may be seen in some focal neuropathies such as carpal tunnel syndrome or radiculopathies [27]. These latter are, however, not associated with clinically evident myokymia.

Neuromyotonic discharges fire at high frequencies (i.e., 150–300 Hz), last a few seconds, and may begin and end abruptly. They are not necessarily recurring and may have some slight waning of amplitude and frequency. The discharges may occur spontaneously or be initiated by needle movement, voluntary effort, or nerve percussion. They often occur intermixed with myokymic discharges.

With the discovery of the genetic abnormality of a potassium channel in episodic ataxia/myokymia and antibodies to voltage-gated potassium channels in acquired neuromyotonia, the pathogenesis of myokymia and neuromyotonia is felt to be an axonal channelopathy [9, 11, 12, 30]. This presumably results in abnormal firing of axons with the resulting clinical and electrophysiological picture. Development of abnormal transmission from the application of plasma from patients with neuromyotonia and potassium channel antibodies to in vitro mouse nerves implicates this further [18, 31].

The most common finding in muscle biopsies is mild denervation with some fiber-type grouping [18, 32, 33]. One report of predominance of type 1 myofibers proposed the possible conversion of fiber types through continuous stimulation by the neuromyotonic discharges [15]. In nerve biopsy specimens, loss of myelinated fibers has been described as well as marked decreased numbers of unmyelinated fibers [34].

Clinical Presentation

Clinical neuromyotonia is best described in patients with continuous muscle fiber activity or Isaacs' syndrome. It has been described in infants [35], but more commonly in adults. There is usually an insidious onset of persistent muscle contractions involving the distal extremities most severely, but also involving proximal extremities, trunk, and facial muscles. There may be hyperhidrosis and reddening of the skin. Persistent contraction often occurs following exercise. Often, a rippling of the continuously contracting muscles can be seen. Electrophysiologic recordings in the contracted muscles reveal myokymic discharges intermixed with occasional neuromyotonic discharges.

Morvan's syndrome is a form of neuromyotonia in which the above symptoms and findings are accompanied by encephalopathy with insomnia, hallucinations, and confusion [8]. The syndrome was first described by Morvan in 1890 and was referred to as Morvan's fibrillary chorea.

Neuromyotonia may be intensified after voluntary muscle contraction and persists for several seconds after attempted relaxation similar to myotonia of muscle origin. Unlike myotonia, however, neuromyotonia does not occur following muscle percussion. When it occurs only after voluntary contraction, it has been termed neurotonia [6]. A brief persistent muscle contraction is seen and is associated with bursts of motor unit potentials. There are no spontaneous discharges at rest. It is not clear whether neurotonia is a distinct clinical entity or a variation of neuromyotonia.

Clinical myokymia may occur focally, most commonly in the face or limbs. Patients with multiple sclerosis, pontine gliomas, or status-post irradiation have described persistent contraction of facial muscles. Focal myokymia of the face, when seen in patients with multiple sclerosis, is transient and usually indicates a new lesion. Facial myokymia has also been described in vestibular schwannomas and pontine neurocysticercosis and associated with an inherited disorder, familial dyskinesia with facial myokymia [21, 34, 36, 37]. Clinically, it may be seen as vermicular movements under the skin or a persistent contraction/distortion of the facial muscles, which has been referred to as clinical myokymia or focal neuromyotonia. Due to the persistent contraction, it is probably more appropriately called focal neuromyotonia. Electrophysiologic discharges in affected muscles are myokymic with occasional neuromyotonic discharges [25, 27, 28, 38]. Ocular neuromyotonia may cause episodic diplopia. The majority of patients with this disorder have received radiation therapy to the sellar and parasellar regions [39]. Isolated laryngeal myokymia, a rare entity described in relation to an ectatic vessel displacing the medulla, may cause a hoarseness or quivering quality of the voice [40].

Focal myokymia can also affect an extremity, as may occur following radiation. Patients may present with complaints of focal movement or an uncomfortable sensation in the extremity. The spontaneous wavelike movements under the skin occur while awake or asleep, the same as clinical neuromyotonia [27].

Generalized myokymia may occur in the setting of an immune-mediated disorder, either isolated or as part of an

autoimmune disease, or more rarely can be a part of a genetic disorder. Generalized myokymia has been described with toxins (rattlesnake venom) which may be related to their effect on the potassium channel [29, 41, 42]. The authors have also observed and recorded generalized myokymia as a transient phenomenon among patients with severe anoxic injury, usually within the first 48 h.

The most common inherited cause is episodic ataxia with myokymia [11, 27]. The myokymia in these disorders may well be just a less severe form of neuromyotonia without persistent muscle contraction. Episodic ataxia with myokymia is a rare familial disorder that presents with brief episodes of ataxia and dysarthria, lasting seconds to minutes with associated clinical myokymia in distal muscles during attacks. Some patients develop contractures in their Achilles tendons due to persistent myokymia/neuromyotonia. This genetic disorder has been mapped to chromosome 12p13, with a missense point mutation of the potassium channel gene, KCNA1 [11]. A highly varied phenotype has been observed in patients with gene mutations involving KCNA1, as severe neuromyotonia without prominent episodic ataxia has been described [43]. Inherited neuromyotonia has been linked to other mutations of the potassium channel. Dedek et al. described a syndrome of benign familial neonatal seizures and myokymia linked to KCNQ2, which encodes a voltage-gated potassium M subunit [44]. Rare generalized myokymia has been described in the setting of spinocerebellar ataxia and paramyotonia congenital [13, 45].

Differential Diagnosis

The presenting complaints in a patient with Isaacs' and Morvan's syndromes are usually muscle discomfort and persistent contraction, delay in muscle relaxation, and, in some cases, hyperhidrosis. The differential diagnosis includes drug intoxication, snake envenomation, hypocalcemic state with tetany, chronic inflammatory demyelinating polyneuropathy, myotonic disorders, and stiff-man's syndrome (see Chapter 71). For focal clinical myokymia/neuromyotonia, the differential is all of the disorders noted above, in addition to multiple sclerosis, pontine tumor, ectatic vessel or other mass lesion, amyloidosis, and postirradiation effects. Clinical myokymia may also occur following denervation with profuse fasciculation potentials. Differentiation is made on needle electromyography demonstrating fasciculation potentials instead of myokymic discharges.

Evaluation and Diagnosis

Electrophysiologic studies, including standard nerve conduction studies as well as needle electromyography, must be done to determine if the patient has myokymic and/or neuromyotonic discharges. The presence of these spontaneous electrical discharges in a patient clinically suspected to have neuromyotonia is confirmatory, in the absence of significant nerve conduction study abnormalities. Repetitive discharges after voluntary action or after single shock have also been described [6, 28]. Laboratory studies, such as serum protein electrophoresis and voltage-gated potassium channels, which are now available commercially, may help in planning treatment. Genetic testing may be considered in patients with generalized neuromyotonia when clinically appropriate.

The presence of slowed conduction with or without conduction block in the presence of myokymic discharges should lead one to pursue the diagnosis of acute or chronic inflammatory demyelinating polyneuropathy.

Patients with focal neuromyotonia/myokymia of the face warrant an imaging study of the brain, preferably an MRI scan, looking for a pontine lesion from either tumor or multiple sclerosis. At times, a muscle biopsy may be helpful, such as in a patient who may have a chronic denervation syndrome or a systemic disorder as seen in amyloidosis manifesting with focal muscular symptoms [15].

Treatment and Management

The treatment of Isaacs' and Morvan's syndromes is predominantly symptomatic. Isaac initially used phenytoin with success, which continues to be a useful treatment (Fig. 70.2). Carbamazepine has also been used [5, 17, 34]. Effective drugs most likely work by altering channel properties in nerves and reducing spontaneous discharges.

In acquired neuromyotonia, presumably of autoimmune origin, plasmapheresis and IV immunoglobulin treatment have been successful in relieving symptoms in patients with severe symptoms who have failed symptomatic medicines [17, 31, 46]. Whether or not recurrent treatments with plasmapheresis or IV immunoglobulin are necessary is not evident from the literature. The role of prednisone and other immunosuppressive agents has not been fully evaluated [47].

Prognosis

In Isaacs' original patients as well as other patients, response to medication and reduction in symptoms were noted [5, 33]. Resolution or reduction of electrophysiologic abnormalities has also been documented. A 14 year follow-up of Isaacs' original patients showed continued response to phenytoin with eventual remission [32]. When medications needed to be reduced or changed, due to side effects, the patients' symptoms returned. However, studies with follow-up periods longer than of Isaacs' patients do not exist.

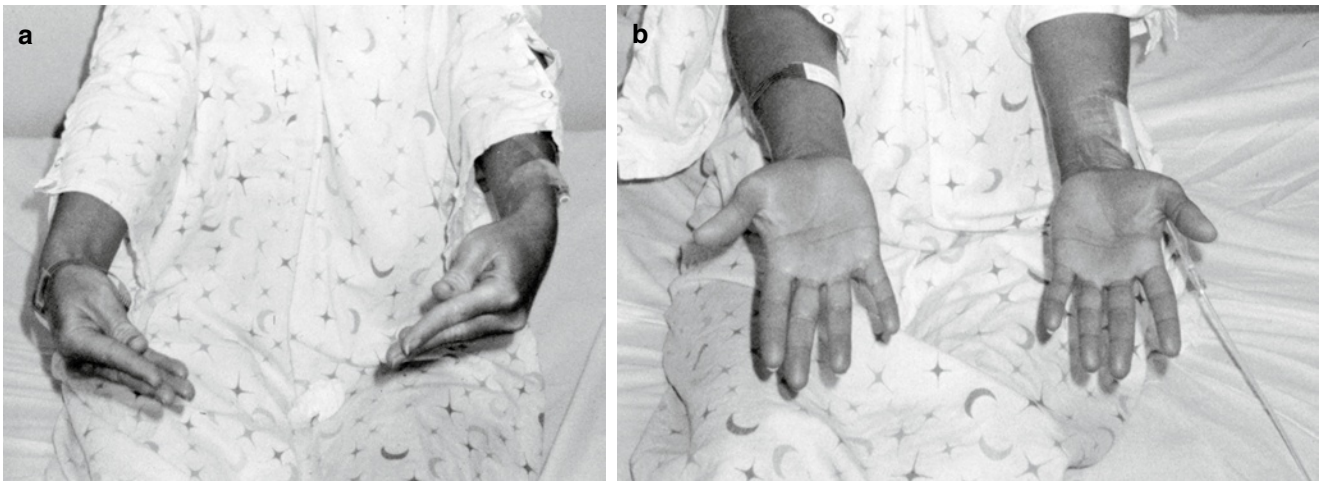

Fig. 70.2 (**a**) Patient with Isaacs' syndrome before treatment. Note the contractions in the hands. (**b**) Same patient after treatment with intravenous fosphenytoin and resolution of contractions

Overall, the prognosis for patients with generalized neuromyotonia (Isaacs' or Morvan's syndrome) is fair to good for resolution of symptoms. In other patients with myokymia/neuromyotonia, the underlying disease process will determine the prognosis.

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Muscle Cramps and Fasciculations

71

James B. Caress and Bandhu Paudyal

Introduction

Muscle cramps and fasciculations commonly affect healthy individuals, particularly in the setting of exercise, but also frequently occur in diseases of the peripheral nerves. Disturbances of metabolism including renal and liver failure also predispose to cramps and fasciculations. The physiology of the lower motor neuron accounts for most of the observed behavior of cramps and fasciculations, and there is emerging evidence that these neuromuscular phenomena are manifestations of peripheral nerve hyperexcitability. There are many proposed treatments for muscle cramps but most have not been evaluated rigorously.

Muscle Cramps

Muscle cramps are a nearly universal phenomenon [1], with a prevalence of around 50 % in people over 65 years old [2]. Cramps are a common complaint in general medical practice but are an unusual chief complaint in a neurologist's office. There are several common neurological conditions associated with frequent cramps, but the primary complaint is usually weakness or paresthesias. More rarely, muscle cramps occurring in apparent isolation present to the neurologist for consideration of the common benign etiologies as well as more serious conditions where cramps are a primary feature. Muscle cramps most frequently occur during exercise or during sleep and usually in the intrinsic foot or leg muscles. The exact pathophysiology of cramps is debated but most experimental and empiric evidence demonstrates that pathology of the lower motor neuron is of critical importance. A key point in the clinical assessment is to clarify that the patient's complaint of "cramps" meets that clinical definition and does not signify claudication, myalgia, dystonia, or spasticity. Treatments may be effective but there is little in the way of evidence-based medicine to guide clinicians in their therapy decisions.

Definition

A muscle cramp is defined as a sudden onset, painful, palpable, involuntary muscle contraction that can be terminated by passive stretching of muscle (Table 71.1) [3]. True muscle cramps, sometimes called "ordinary" cramps, need to be distinguished from other painful muscle conditions that do not follow the electromyographic (EMG) or clinical description of cramps (Table 71.2). These include electrical contractures, myotonic and neuromyotonic conditions, focal dystonias (e.g., writer's cramp), and vascular claudication. Patients with metabolic myopathy may experience painful involuntary muscular contractions following exercise that satisfy most of the clinical criteria for muscle cramps but do not respond to stretching and may resolve over longer periods of time. These painful contractions are termed "electrically silent contractures" because they are associated with electrical silence on needle EMG rather than the profuse motor unit activity recorded during a true cramp. Silent contractures may coexist with true cramps in some patients. Muscle tightness and pain related to exercise can occur in myotonic and neuromyotonic disorders, but these conditions have strikingly different EMG signatures that cannot be confused easily with true cramps. Claudication, due to vascular insufficiency, is often mistaken for cramps because it is similarly painful and occurs in calf muscles. However, a palpable "knot" of contraction is not present and

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the pain is ameliorated by rest rather than stretching. Writer's cramp and other focal dystonias are task specific rather than exercise induced and have slower onset and resolution than muscle cramps. Pain associated with dystonia is gradual in onset, unlike the explosive and severe pain that occurs with a cramp.

Table 71.1 Definitions of cramps

Clinical cramp
Sudden onset
Palpable muscle contraction
Gradual resolution
Unilateral
Residual soreness
Relieved by stretching
Electrophysiologic cramp
Single or multiple motor units
Most individual units firing within voluntary range
Associated with fasciculations
True cramp = clinical + electrophysiologic criteria
Nocturnal cramps
Exercise/heat-related cramps
Dialysis/cirrhosis/pregnancy
Neuropathic cramps

Table 71.2 Differential diagnosis of true cramps

Claudication
Electrical contracture
Myotonia
Neuromyotonia
Stiff person syndrome
Dystonia
Spasms associated with upper motor neuron lesions

Etiology of Cramps

While the clinical description of cramps is clear, the pathophysiology of cramps is more controversial. The EMG appearance of a cramp is either single or multiple motor unit action potentials firing at high frequencies (>10–30 Hz) [1] (Fig. 71.1). By EMG alone, it can be difficult to distinguish a cramp from a forceful voluntary contraction, although in some instances the firing frequency of individual motor units during a cramp is faster (>50 Hz) than can be achieved even with maximal voluntary effort. These direct observations indicate that cramps are initiated and sustained by repetitive firing of lower motor neurons and not generated at the muscle fiber membrane or the upper motor neurons. This corresponds with the clinical experience that cramps occur frequently in motor neuron disease and other neuropathic disorders. While the localization to the lower motor neuron seems clear, the exact mechanism of how cramps are generated and sustained is still debated. Proposed theories implicate either a "central" source, denoting events at the level of anterior horn cell, or a "peripheral" cause whereby the cramp is generated in the terminal axons of motor neurons. It is possible that both central and peripheral conditions are necessary to explain the complex neurophysiology of cramps in healthy and diseased states.

Denny-Brown's description of the EMG of spontaneous cramps concluded that cramps originate in the distal motor neuron [4]. The crucial observation was that cramps were associated with frequent fasciculation potentials that changed in morphology. The varying shape suggested that each fasciculation originated in a different branch of the terminal arborization of the motor neuron. Norris et al. [1] confirmed that motor units rather than muscle fiber discharges caused the observed EMG activity during a cramp; however, other

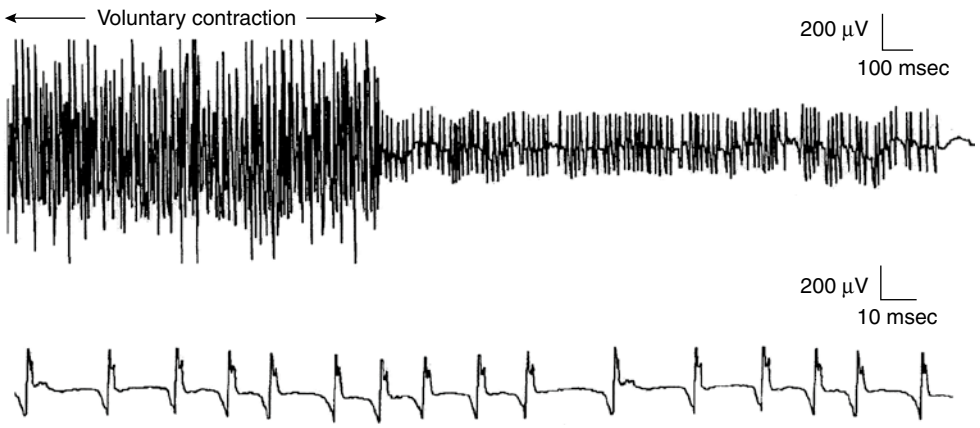

Fig. 71.1 Cramp discharge. In this example, the patient is first forcibly contracting his gastrocnemius muscle with an EMG needle electrode placed in the muscle. Following relaxation, a cramp discharge is seen (latter part of top waveform, expanded view – bottom waveform). In a cramp discharge, EMG shows either a full interference pattern of motor unit action potentials or one or several motor units firing repetitively and sometimes irregularly at high frequencies (usually 40–60 Hz), as in this example (Reproduced from Preston and Shapiro [110], with permission from Butterworth Heinemann)

observations led him to conclude that cramps have a central origin. Norris cited synchronous motor unit activation during a cramp and a reduction in cramp intensity following contraction of the appropriate antagonist muscle as evidence that cramps originate at the level of anterior horn cells. There is additional evidence for a central origin of cramps including studies that describe cramp cessation following sensory nerve stimulation [5, 6]. Further support of the "central" theory comes from the proposal that the membrane of the motor neuron soma has two equilibrium states, one at a resting potential and the second at a higher suprathreshold potential. This "bistability" allows for self-sustained high-frequency semi-rhythmic firing. Under the right conditions, in various animal preparations, a brief depolarization will switch the membrane from the resting value to the suprathreshold value [7–9]. The similarities between these experiments in animals and the features of muscle cramps in humans led Baldissera and coworkers to induce cramps by repetitive stimulation in three patients with frequent spasms of varying etiologies. By selectively stimulating the IA afferents at the popliteal fossa at intensities below the motor threshold, they were able to generate spontaneous sustained contractions in the soleus, suggestive of a cramp. The investigators theorized that hyperpolarizing the motor neuron soma would terminate the cramp and demonstrated this by supramaximally stimulating the tibial nerve and noting attenuation of the ongoing EMG activity. Stimulating the skin overlying the intrinsic foot muscles terminated cramps perhaps due to inhibition of spinal motor neurons. This study provides some evidence that experimental cramps may be produced from a central generator in individuals who suffer from unusual cramp syndromes.

Bertolasi et al. [10] expanded upon experiments first performed by Lambert [11] to provide support for a "peripheral" cause of muscle cramps. In a healthy subjects, repetitive supramaximal electrical stimulation of the tibial nerve at the ankle reliably produced cramps in intrinsic foot muscles. This stimulation could generate a cramp distal to a complete nerve block and resolved with stretching despite the nerve block prohibiting any afferent information from reaching the spinal cord. Cramps could not be induced when the muscle was passively stretched during the same stimulation. These experiments demonstrate that muscle cramps can be produced, maintained, and manually terminated in the absence of afferent input to the central nervous system or anterior horn cell. In fact, the study indicates that the physiology of the distal motor neuron is sufficient to account for the key clinical observations of cramps.

Ross and Thomas performed a variety of experiments that offer some evidence for a combined central and peripheral mechanism of cramps [12]. They induced cramps in the gastrocnemius and soleus muscles of seven subjects by forceful plantar flexion and observed the pattern of motor unit firing with a unique array of surface and intramuscular electrodes. At the onset of cramp in the medial gastrocnemius, motor unit activity ceased in the other muscles of the posterior calf. This selective activation of the medial gastrocnemius was not possible voluntarily, suggesting the involuntary nature of the observed contraction. This observation quantitatively confirmed earlier observations that cramps are localized to a specific muscle and, often, a discrete part of that muscle [1, 13].

The individual motor unit firing rate was significantly faster during a cramp (up to 89 Hz) than during maximal voluntary activation. Firing rates of individual motor units slowed gradually rather than by a quantal jump to a slower frequency as might be expected if "bistability" (see above) of motor neuron discharge rates were the operative factor in sustaining the cramp. These points favor a peripheral etiology of cramps, but further observations from this experiment suggest a possible central influence. The decay in motor unit firing rates during these provoked cramps is similar to that observed in sustained voluntary maximal contractions [14], and terminating the cramp by passive, forceful dorsiflexion of the foot typically generated a surge of motor unit activity in all of the calf muscles. The authors suggest that the stretch provokes a surge of Ia afferent activity generating the burst of motor units that is followed by Golgi tendon organ generated Ib activity, inhibiting the anterior horn cells and terminating the cramp. Reduction of the tonic vibration reflex and enhancement of the H-reflex following a cramp but not after voluntary contraction indicates that motor neuron excitability is increased after a cramp but does not prove that central excitation is present at the moment of cramp initiation. The investigators concluded that changes in synaptic input to motor neurons play a role in the generation of exertional cramps and speculated that a positive feedback loop exists following strong contraction that leads to a self-sustained involuntary contraction or cramp [12].

Layzer has theorized that unmyelinated branches of the terminal arborization are susceptible to the excitatory influences of extracellular ions, muscle metabolites, and neurotransmitters such as acetylcholine [15]. In neuropathic situations, immature collateral nerve sprouts might have reduced membrane stability and fire spontaneously during mechanical deformation. He speculated that muscle in the shortened position was "crumpled" and might generate spontaneous electrical activity in the terminal branches in response to the mechanical deformation. Once a local discharge developed, the contraction might then deform adjacent areas of muscle, allowing the cramp to shift and spread as is observed clinically [12, 13]. Fluid loss and ion imbalance from dehydration would promote this chain reaction through a mechanical effect of a contracted extracellular space in the vicinity of nerve terminals.

In summary, the pathophysiology of cramps is still controversial. The finding that the chief clinical phenomena of muscle cramps including improvement with stretching can be reproduced distal to a nerve block and so without apparent participation of the anterior horn cell bodies or synaptic input strongly suggests of a peripheral mechanism [16]. Yet, the development of a muscle cramp may be influenced by events in the spinal cord under physiologic conditions.

Clinical Evaluation of Muscle Cramps

When cramps become frequent, they may interfere with working and sleeping and can rarely become disabling [17]. Healthy individuals commonly suffer cramps during exercise or sleep, but cramps may also signify a variety of neuromuscular and metabolic conditions (Table 71.3). When evaluating the patient with problematic muscle "cramps," the initial task is to differentiate muscle cramps from other common disorders such as vascular claudication, muscle strain, and neuropathic pain, and usually, the history and neurological exam are sufficient to distinguish between these conditions. Attention should be paid to events surrounding the onset of the cramp, including provoking factors such as exercise, cold temperature, and sensory or emotional stimuli. Special note should be made if cramps are reported in muscles outside of the legs as this is unusual and may suggest an alternative condition such as myalgia or a serious neuropathic process like motor neuron disease. If the "cramp" involves multiple muscles in a limb, especially an agonist/antagonist pair, or more than one limb simultaneously, the movement is more likely to be an upper motor neuron-generated spasm (e.g., flexor spasms) or dystonia rather than a true cramp which is generally limited to one muscle. This distinction can also be useful when malingering or conversion disorder is suspected. As with most neuropsychiatric disease, these patients will gladly provoke their tremendous "cramps" which typically involve simultaneous contraction of agonist/antagonist pairs and involve the entire limb. In contrast, motor neuron disease patients plagued with frequent cramps may refrain from manual exercise testing for fear of provoking a painful cramp. Patients with frequent exercise-induced cramps, benign nocturnal cramps, benign fasciculation syndrome (BFS), and cramp-fasciculation syndrome have normal neurological exams.

Blood tests in the evaluation of muscle cramps include serum electrolytes test (including calcium and magnesium), thyroid studies, and creatine kinase and liver function tests (Table 71.4). Antibodies directed against voltage-gated potassium channels can be measured in those with disabling cramps or whenever an immune-mediated or paraneoplastic syndrome is suspected [18]. Standard EMG will identify patients with motor neuron disease and radiculopathy and may be helpful in identifying benign fasciculation syndrome patients and those with muscle contractures due to metabolic myopathy. Ischemic exercise testing should also be considered to identify metabolic myopathies if electrical contractures are suspected. Repetitive electrical stimulation may identify persons with an abnormally high propensity to suffer cramps [17, 19]. Cramps resulting from supramaximal repetitive electrical stimulation of the distal peroneal and tibial nerves at frequencies at or below 10 Hz indicate peripheral nerve hyperexcitability with an increased tendency toward cramping [20].

Table 71.3 True cramp types and their proposed therapies

True cramp type	Proposed therapy
Exercise/heat	Intravenous saline, salt tablets, oral rehydration
Nocturnal	Stretching, quinine, verapamil, phenytoin, carbamazepine
Dialysis	Salt tablets, sodium-enriched dialysate, quinine, L-carnitine, nifedipine, vitamin E
Pregnancy	Magnesium, B complex vitamins
Cirrhosis	IV albumin, taurine, branched chain amino acids, vitamin E
Neuropathic conditions	Phenytoin, carbamazepine, levetiracetam, gabapentin, quinine

Table 71.4 Lab evaluation for muscle cramps

Electrolytes (sodium, potassium, calcium, magnesium)
Thyroid studies
Liver function studies
Creatine kinase
NCS/EMG evaluation
Ischemic exercise test (selected cases)
Paraneoplastic antibodies (selected cases)

Clinical Syndromes and Treatment

Heat and Exercise Cramps

These occur in healthy individuals participating in extreme physical exercise with variable degrees of muscle fatigue, dehydration, and electrolyte depletion. While heat and exercise cramps are sometimes referred to as separate entities, it may be that they have the same physiological basis with heat merely increasing the risk of hypovolemia. Profuse sweating followed by rehydration with pure water leads to hyponatremia and subsequent severe cramps in the muscles most heavily stressed. In the 1935, Talbott chronicled the experiences of miners and factory workers performing heavy labor under conditions of extreme heat [21]. He described extremely painful and widespread cramp "attacks" that would start in the distal arm muscles followed by leg and abdominal cramps. He reported that "feeble twitchings," perhaps fasciculations, of a muscle would herald a cramp

and that the attack could last for hours without treatment. Hyponatremia occurred in these workers, and the cramps would resolve as normal levels of serum sodium were established via intravenous saline infusions presumably by correcting hyponatremia and hypovolemia. Salt tablets were effective in preventing heat cramps [21]. Dextrose solutions did not relieve heat cramps, suggesting that hyponatremia is critical for the initiation of heat cramps. Heat cramps did not occur unless hyponatremia was accompanied by a loss of total body sodium or hypovolemia. This finding is supported by the clinical observation that cramps do not occur in the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) or with water intoxication where total body sodium is normal [22].

Exercise cramps are common in athletes undergoing extreme physical exercise with variable degrees of muscle fatigue, dehydration, and perhaps electrolyte depletion. They can occur during exercise or for some hours following exercise [23]. Several small studies have evaluated athletes following intense exercise and found a relative hyponatremia in the cramp group [24–26], but other studies have not found a difference [27]. Of course, the metabolic state of the intercellular milieu surrounding the muscle and innervating fibers during cramping is unknown and may not reflect conditions as measured in the serum. Another potential explanation for exercise cramps is that with muscle fatigue, there is an alteration of neuromuscular control resulting in peripheral nerve hyperexcitability and cramps, but there is no direct evidence at this time [27].

Cramps Associated with Other Medical Conditions

Cramps commonly complicate hemodialysis and usually occur toward the end of the session when fluid loss is maximal [28]. Both intravenous hypertonic dextrose [29] and saline may promptly alleviate these cramps [30]. Performing dialysis with a sodium-enriched dialysate reduces the incidence of muscle cramps [31], and salt tablets are efficacious in prevention [32]. Other proposed therapies for dialysis patients with cramps include quinine sulfate [33], L-carnitine [34], nifedipine [35], and 400 IU per day of vitamin E [36].

About half of cirrhotic patients experience painful cramp episodes several times per month and nearly one-third suffer cramps three or more times per week [37]. The incidence of cramps appears to be independent of the mechanism of liver failure but correlates with worsening liver function [38]. Ascites, lower mean arterial blood pressure, and higher plasma renin activity predict the development of cramps [37], suggesting that reduced effective circulatory volume is the underlying risk factor for cramps in cirrhotics. However, in a study of 100 nonalcoholic cirrhotic patients, there was no correlation of the presence of cramps with serum electrolytes, creatinine, glucose, bilirubin, or albumin levels. Muscle biopsies from cirrhotic patients show depletion of ATP which may prevent muscle relaxation, predisposing to cramps [39]. There are clinical trials demonstrating a reduction in cramps following weekly infusions of intravenous albumin [37] and 3–6 g/day of taurine, an amino acid that reduces myotonic discharges [40] with no major side effects [41, 42]. Similarly, an open-label study of branched chain amino acid supplements in the late evening dramatically decreased nocturnal cramp in a small group of advanced cirrhosis patients [43]. Vitamin E levels in cirrhotics with cramps are reduced compared to those without cramps perhaps due to a higher degree of fat malabsorption, and oral replacement of vitamin E decreased cramps in this group in a small, uncontrolled trial [44].

Severe hypothyroidism [45, 46] and hyperthyroidism [47] may cause painful muscle contractions which may be electrically silent contractures rather than true cramps.

Nifedipine [48, 49], clofibrate [50, 51], cyclosporine [52], and beta-agonists [53, 54] are associated with cramps. Although diuretics have been implicated in muscle cramps, a study performed in general medical patients did not reveal an association between cramps and diuretic use [2]. Excessive alcohol consumption may cause muscle spasms due to persistent motor unit discharges [55] or exacerbate an underlying metabolic myopathy, resulting in either cramps or electrical contractures [56]. There is no evidence that moderate alcohol intake predisposes to nocturnal cramps or exercise-induced cramps.

Leg cramps of pregnancy typically occur at night beginning in the second trimester. They occur in up to 30 % of pregnant women and are a daily event in 28 % of pregnant women who report cramps. A randomized, double-blind, placebo-controlled trial demonstrated that oral magnesium supplementation diminished cramp frequency and severity without changing serum magnesium levels [57]. The supplemental magnesium may have boosted intracellular magnesium levels. Hypomagnesemia may cause motor neuron irritability similar to tetany from hypocalcemia. B vitamins may also be effective in the treatment of cramps during pregnancy [58].

Lower motor neuron disorders including polyneuropathy, radiculopathy, and, especially, amyotrophic lateral sclerosis (ALS) are frequently punctuated with cramps [22]. Muscle cramps afflict 62 % of ALS patients [59] and are the most frequent cause of discomfort in ALS patients occurring in 55 % of those reporting pain [60]. Many drug therapies including quinine sulfate, clonazepam, magnesium, gabapentin, lioresal, dantrolene, and diphenylhydantoin have been suggested for the treatment of cramps in ALS, but few have been rigorously examined. A randomized and blinded trial of tetrahydrocannabinol failed to show any benefit [61]. An open-label study of levetiracetam showed reduced cramp frequency and severity [62]. In a study examining the efficacy of vitamin E to slow the progression of ALS, vitamin E did not affect cramps over the course of a year [63].

There may be inherited conditions where muscle cramps are the chief complaint. The reported cases show dominant inheritance and the conditions appear to be neuropathic, but no gene has been identified [64, 65]. Other neurologic disorders which are particularly characterized by cramps include Machado-Joseph disease [66], hereditary angiopathy, nephropathy, aneurysms, and muscle cramps due to COL4A1 gene mutations [67] and Satoyoshi syndrome, a rare condition characterized by a constellation of findings including painful muscle spasms, alopecia, amenorrhea, skeletal deformities, and diarrhea [68]. The onset is usually in childhood, although adult cases sharing many of the features are described. There is emerging evidence for an autoimmune etiology in these cases, but other reports suggest a recessive inheritance [69, 70]. The scarcity of the disorder and lack of consistent clinical findings or biomarkers hinder efforts to clearly define Satoyoshi syndrome.

A study of 50 cancer patients complaining of new muscle cramps revealed associations with a variety of neurogenic conditions, most commonly peripheral neuropathy from chemotherapy. Cramps also indicated direct cancerous invasion or radiation injury of peripheral nerves and were frequently an early sign of unrecognized neurologic dysfunction [71].

Benign Nocturnal Cramps

These sudden onset and extremely painful cramps usually occur in calf muscles and awaken patients from sleep. They are common in the healthy, elderly population yet are also observed with neuropathy and with peripheral vascular disease [72]. These cramps occur typically within the first few hours of sleep and may be extremely disruptive if they become recurrent during the night [73]. Familial cases of nocturnal cramps have also been reported [74].

Muscle stretching three times daily has been advised to prevent nocturnal cramps [75], but a randomized study comparing calf stretching versus a sham non-stretching exercise failed to show benefit [76]. Other investigators proposed that sleeping with the feet in a passively plantar-flexed position predispose persons toward calf cramps [77], consistent with the well-established relationship between muscle shortening and cramps [10]. Theoretically, cramps would be reduced if the patient wore an ankle-foot orthotic to bed.

Until the 1990s, the mainstay of nocturnal cramp treatment was quinine sulfate. Quinine is purported to prevent muscle cramps by reducing motor end-plate excitability or by increasing the muscle membrane refractory period [78]. Over the ensuing years, several small, controlled clinical trials showed mixed results for the efficacy of quinine [79–84]. A meta-analysis of six randomized, double-blind, placebo-controlled trials of quinine sulfate utilizing crossover designs with 107 non-dialysis patients revealed a 27 % decrease in nocturnal cramps during a 4-week period [85]. Severity and duration of the cramps were not altered. While this meta-analysis may confirm the efficacy of quinine, the weak clinical effect may not offset the small but definite risk of serious adverse reactions. While tolerated by most people, quinine can cause nausea, vomiting, blurred vision, tinnitus, vertigo, and hearing loss. Severe visual side effects include night blindness, scotomata, loss of color vision, and permanent blindness [86]. Life-threatening thrombocytopenia occurs in one in 1,000 to 3,500 patients [87]. Patients with renal failure or hepatic cirrhosis are at greater risk of developing serious toxicity.

Due to the lack of clear efficacy and quinine's dangerous potential toxicities, the US Food and Drug Administration (FDA) banned over-the-counter quinine for cramps in 1995. In 2006, the FDA cautioned consumers about their off-label use and ordered unapproved quinine drugs to be removed from the market stating 665 reports of serious adverse events and 93 deaths due to quinine since 1969 [87–89]. Quinine-containing preparations should be avoided in all patients except those with truly disabling cramps who have provided clear understanding of the marginal benefits and significant risks with informed consent and careful monitoring when no other agents relieve symptoms [89].

Other drugs that could be considered for the treatment of nocturnal leg cramps include vitamin E, verapamil, phenytoin, carbamazepine, gabapentin, magnesium, baclofen, vitamin B complex, tonic water containing quinine, nifedipine, botulinum toxin injections, and levetiracetam [16, 35, 90–93]. However, the purported efficacy of these drugs frequently rests on small, uncontrolled studies or anecdotal reports.

Fasciculations

Fasciculations are easily recognized in the clinic as the spontaneous, involuntary, irregular, and painless twitching of part of one muscle. On needle EMG, fasciculations are defined as a discharge of a single motor unit and typically fire in an irregular and relatively slow (0.1–10 Hz) pattern [94]. Fasciculations generate concern in the clinic because of their ominous association with motor neuron disease. "Benign" fasciculations tend to fire faster than "malignant" fasciculations [95] but are not distinguishable on the basis of EMG waveform as highly complex fasciculation potentials can be seen in both conditions [96]. The presence of atrophy, weakness, other EMG abnormalities, or tendon reflex abnormalities in association with fasciculations is the most reliable way to make the distinction. Caffeine, beta-agonists, D-penicillamine, overcorrection with synthetic thyroid preparations, and stress [97–99] have been associated with frequent fasciculations.

The pathogenesis of fasciculations is less controversial than that of muscle cramps. Early studies demonstrated the

neural origin of fasciculations [100] with impulses generated in the peripheral nerve rather than the spinal cord or motor cortex [101, 102]. Collision experiments have demonstrated that most fasciculations are generated in the terminal portion of the axon [101, 103]. Roth [104] studied the F-wave responses from spontaneous fasciculations. The morphology of the fasciculations changed, but the shape of F-wave responses was identical, suggesting that fasciculations are generated in the terminal arborization of the motor neuron. The situation may be more complex in some ALS patients where analysis of the firing pattern of fasciculations suggested both peripheral and spinal sources could generate fasciculations in the same muscle [105]. Stretching of the affected muscle reduced fasciculation frequency in ALS [106], suggesting that mechanical changes in the distal arborization of the motor neuron play an important role in the generation of fasciculations as well as cramps.

Benign Fasciculation Syndrome

While an occasional fasciculation is reported by 70 % of healthy people, only 2 % report daily fasciculations [107], and those with frequent fasciculations are often diagnosed with benign fasciculation syndrome (BFS). Blexrud and colleagues reported that patients diagnosed with BFS have frequent fasciculations beyond what is normally experienced by most people [99]. In a retrospective study, 121 persons were interviewed an average of 7 years after receiving the diagnosis of BFS. Almost all patients had complaints of muscle twitching, and many others had additional complaints such as fatigue, muscle cramps, transient migratory paresthesias, and generalized myalgias. One-third of the group worked in the medical profession and 14 % listed concern about ALS as a chief complaint. Several BFS patients had family members with ALS or multiple sclerosis. In the study, all had normal neurological exams and standard nerve conduction and EMG studies with the exception of fasciculations. Although the examining neurologist noted only sparse fasciculations on neurologic exam, excessive fasciculations were noted by EMG in at least one muscle in 68 % of the group. The investigators concluded that BFS is not simply an increased awareness of occasional fasciculations experienced by most people, although a heightened awareness of the potential ominous significance of fasciculations may spur presentation to a neurologist. During a follow-up period of 2–32 years, none of these patients developed ALS or any other significant neurological disorder. Half of the group reported spontaneous improvement in their condition, and less than 5 % worsened. A minority of patients reported a viral upper respiratory or gastrointestinal infection within the month prior to the development of fasciculations. This observation combined with the frequent occurrence of transient paresthesias in the BFS group led the investigators to speculate that some patients develop BFS following a mild, acute generalized polyradiculopathy [99]. There are very infrequent case reports of patients with evident fasciculations but normal neurologic and EMG exams who go on to develop motor neuron disease within several years so it may not be accurate to label fasciculations "benign" until 4–5 years have passed [108].

BFS may be diagnosed in patients with the chief complaint of painless muscle twitching and minor symptoms of cramping, paresthesias, myalgia, or fatigue who have normal neurological and electrophysiological examinations, with the exception of excessive fasciculations. These patients may be reassured that it is highly unlikely that they will develop motor neuron disease.

Cramp-Fasciculation Syndrome

The diagnosis of cramp-fasciculation syndrome (CFS) should be considered in patients with disabling cramps not provoked by exercise or heat, and normal neurologic and EDX examinations. CFS may overlap with BFS where non-disabling cramps are frequently noted, and some authors have included this group within a wider category of peripheral nerve hyperexcitability that includes patient with non-disabling symptoms [20]. Tahmoush et al. described CFS patients as plagued by frequent, disabling muscle cramps but normal neurological exams except for visible fasciculations or clinical myokymia. CBC, electrolytes, thyroid studies, serum protein electrophoresis, and ischemic exercise tests were normal, but creatine kinase levels were sometimes mildly elevated. EMG examination revealed fasciculations without other abnormal spontaneous activity or motor unit abnormalities. Repetitive nerve stimulation (up to 5 Hz) of distal motor nerves provoked afterdischarges of involuntary motor units in all patients. These afterdischarges, which may have been cramp potentials, were greatest in the intrinsic foot muscles and were not attenuated by ischemia or by proximal nerve block. Regional curarization abolished the abnormal discharges. Carbamazepine was often dramatically effective in relieving the cramps, and efficacy persisted after the medicine had been discontinued [17]. In a larger sample of patients with symptoms of peripheral nerve hyperexcitability, repetitive stimulation was helpful in identifying those with CFS and other conditions along the spectrum of hyperexcitable nerve disorders [109].

BFS and CFS appear to have some clinical overlap and might be the most benign of hyperexcitable nerve disorders. The syndrome of acquired neuromyotonia may represent the other end of the spectrum where there is an immune-mediated attack on potassium channels [18]. The effectiveness of a sodium channel blocker, carbamazepine, in CFS suggests that CFS and BFS may be milder versions of a peripheral nerve ion channel disorder.

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Stiff-Man Syndrome

72

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Introduction

Stiff-man syndrome (SMS) is a rare disorder of the central nervous system, characterized by progressive and fluctuating muscle rigidity with superimposed painful spasms; at rest the latter may occur spontaneously or be precipitated by sensory stimuli. The disease involves the muscles of the limbs, trunk, and neck, sometimes asymmetrically [1, 2]. The diagnosis is established by the finding of a characteristic electromyographic pattern indicating continuous normal motor-unit activity at rest. Such activity is abolished by sleep, general or spinal anesthesia, peripheral nerve blockade, curare, and intravenous diazepam [2].

Ornsteen described a patient with clinical features suggestive of SMS in 1935, calling it "chronic generalized fibromyositis" [3]. Moersch and Woltman described the syndrome in 1956 and coined the term "stiff-man syndrome," which they found to be more frequent in males [1]. However, current evidence shows the disease to be slightly more common in women [1, 3–9]. Additional reports of SMS soon appeared [10–19], and an association with diabetes mellitus, hyper- and hypothyroidism, and epilepsy was diagnosed in 10 % of patients [3, 4, 8, 13, 18, 20–26].

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Etiology and Pathogenesis

Stiff-man syndrome associated with type 1 diabetes mellitus and organ-specific autoimmune diseases.

The pathogenesis of SMS is a matter of active investigation with a variety of clinical, pharmacological, and laboratory evidence pointing to a functional impairment of the γ-aminobutyric acid (GABA) inhibitory system. Moersch and Woltman found no significant pathological changes at autopsy [1]. This finding has since been confirmed with few exceptions, which suggest loss of GABA-ergic cells in the cerebellar cortex or anterior motor horns [12, 26–30]. In addition to causing muscular rigidity, disruption of the GABA systems could explain the frequent association of epilepsy, autonomic instability, and psychiatric manifestations among SMS patients [2, 20, 27–41].

A report in 1986 of a 48-year-old woman with SMS and epilepsy and the abrupt onset of diabetic ketoacidotic coma lead to the search for a possible pathogenic link between SMS and type 1 diabetes mellitus [42]. The patient had complement-fixing islet cell (ICA), gastric parietal cell, and thyroid autoantibodies. The patient had a human leukocyte antigen (HLA) phenotype A 1/28, B 8/44, Cw5/x, and DR3/4. These data suggested an autoimmune pathogenesis of diabetes in the patient. The onset of signs of autoimmunity in a patient affected by a rare and elusive disorder of the central nervous system prompted the search for signs of autoimmunity against the central nervous system [25]. The serum and the cerebrospinal fluid (CSF) of the patient were used for immunohistochemical analysis of rat brain and produced specific immunostaining in all brain regions in a distribution corresponding to the known distribution of GABA-ergic nerve terminals (Fig. 72.1) [25, 43–45]. A less intense immunoreactivity

†Deceased Dec. 25, 2012

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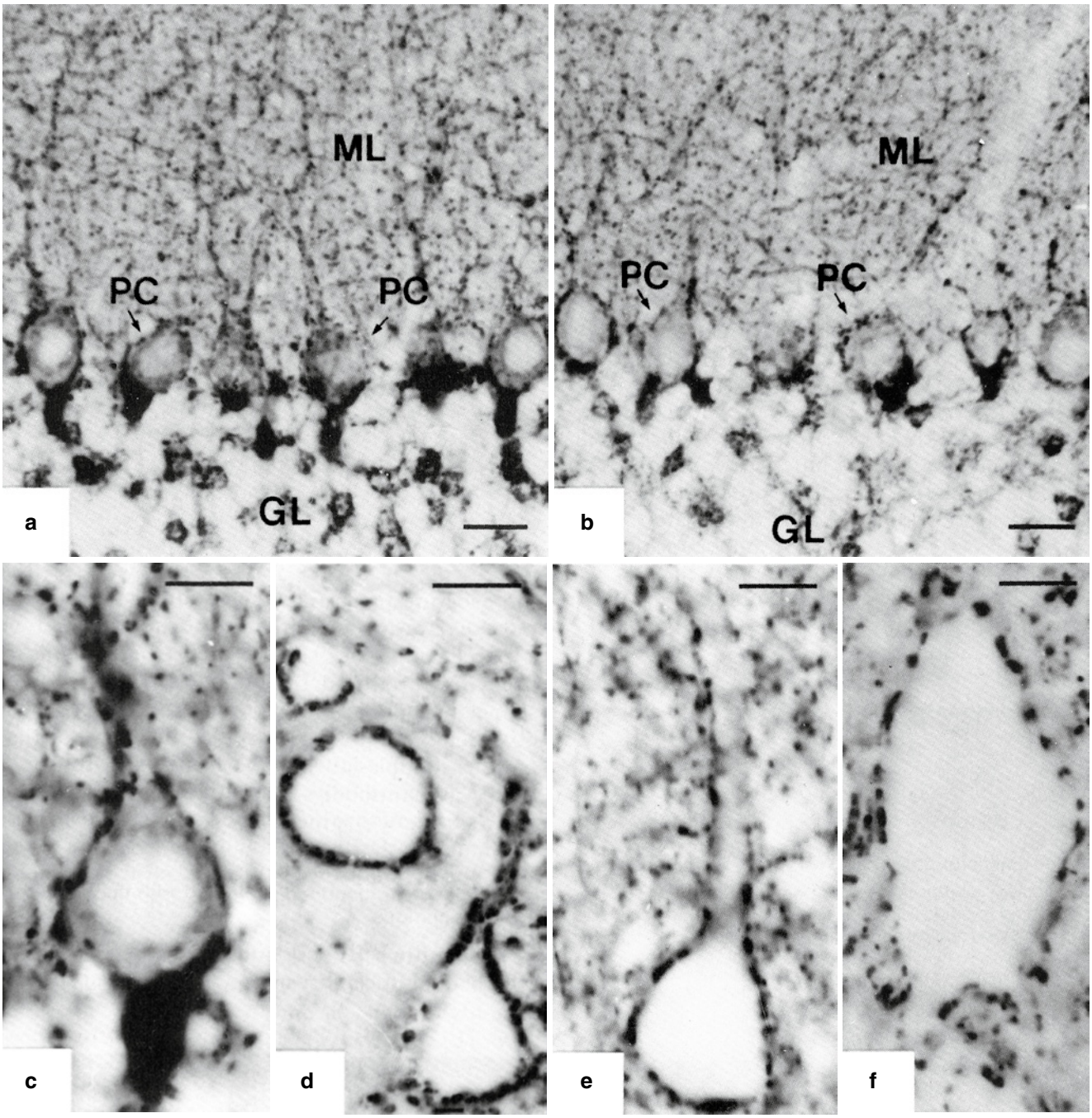


Fig. 72.1 Immunoperoxidase staining of rat brain regions by cerebrospinal fluid (CSF) (**a**, **c**–**f**) and serum (**b**) of a patient with stiff-man syndrome. Immunoreactivity is represented by the *dark areas*. Panels **a** and **b** show similar fields of the cerebellar cortex immunostained with CSF and serum, respectively; the identity of both patterns is striking. Panel **c** shows a higher magnification of a Purkinje cell. Note the dense accumulation of immunoreactivity at the axon hillock and the abundance of the immunoreactive puncta that outline the perikaryon and the proximal portion of its dendritic tree. Note also the weak immunoreactivity of the Purkinje cell cytoplasm. Panel **d** shows two large neurons of the deep cerebellar nuclei. Their surface is outlined by densely apposed immunoreactive puncta. Panel **e** shows a layer of V pyramidal cells of the cerebral cortex, and panel **f** shows a brain stem motor neuron. These cells are also outlined by immunoreactive dots. Scattered puncta are visible in a surrounding neuropil. No immunoreactivity is visible in the cytoplasm of the cells shown in panels **d**–**f** (compare with the cytoplasm of Purkinje cells visible in **c**) (*PC* Purkinje cells, *ML* molecular layer, *GL* granule cell layer) (*Bars* in panels **a** and **b** denote 20 μm, and those in **c**–**f**, 10 μm) (Reprinted with permission from Solimena et al. [25])

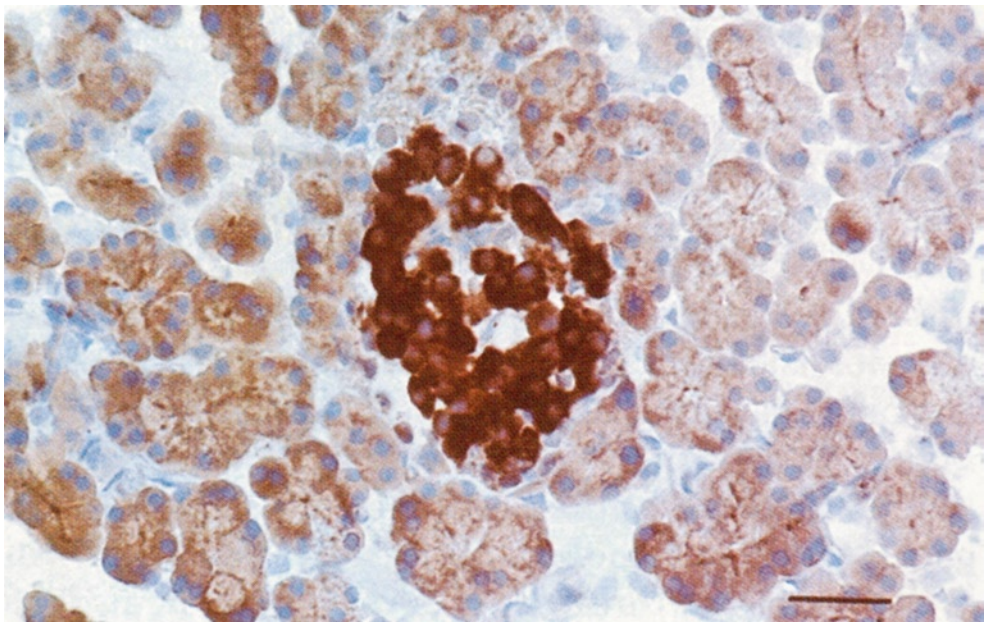


Fig. 72.2 Immunoperoxidase staining of rat pancreas with the serum of a patient with stiff-man syndrome (SMS). The histological section of rat pancreas was counterstained with hematoxylin and immunostained SMS patient sera and detected with peroxidase. β-cells of Langerhans islets are heavily stained (Reproduced with permission from Solimena et al. [4]. Copyright 1990 Massachusetts Medical Society. All rights reserved)

was detectable in the cytoplasm of the perikarya of known GABA-ergic neurons (i.e., Purkinje cells; Fig. 72.1c), while the cytoplasm of non-GABA-ergic neurons was not immunoreactive (Fig. 72.1d–f). The staining patterns produced in all of the brain regions were reminiscent of the patterns produced by antibodies directed against glutamic acid decarboxylase (GAD), the enzyme responsible for the biosynthesis of GABA including localization to nerve terminals [43, 44, 46–48].

Outside the central nervous system, GAD and GABA are found in pancreatic β-cells, male germ cells, the oviduct, and the ovary [48–51]. Accordingly, the serum and CSF of patients with SMS react with rat pancreatic β-cells (Fig. 72.2) [4]. Immunoprecipitation and western blotting experiments conducted on a large series of patients demonstrated that 60 % of patient sera reacted with GAD 65kD/GAD 67kD isoforms [3]. In this series of patients, 30 % of patients positive for anti-GAD antibodies were also affected by type 1 diabetes mellitus, and almost all patients in the anti-GAD positive group had clinical or serological evidence of other organ-specific autoimmune diseases (Fig. 72.3, panels a and b) [3]. Other investigators confirmed these observations [8, 40, 52–56].

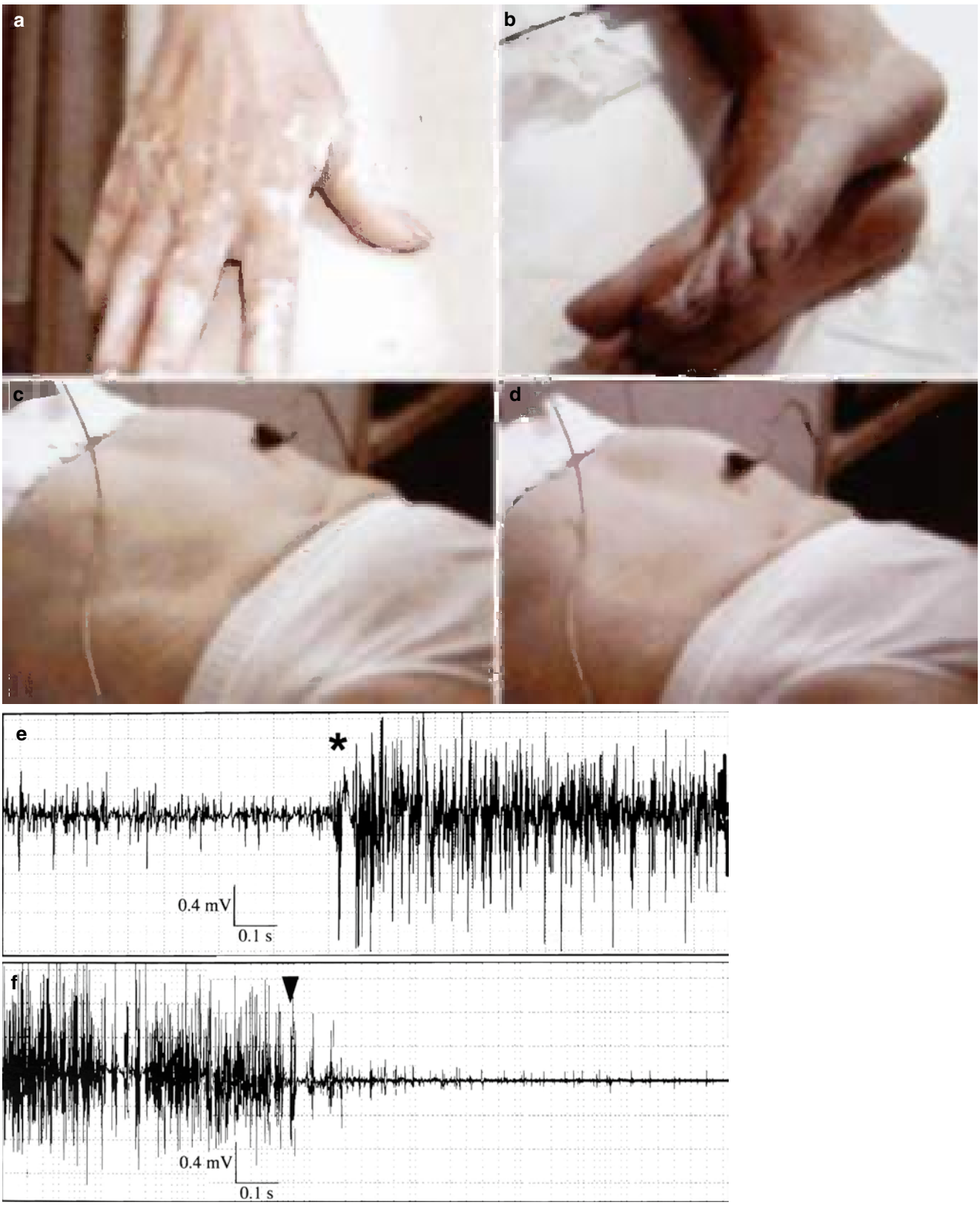
The demonstration that GAD is a major autoantigen in SMS also led to the demonstration that the 64 kD protein, identified as a major autoantigen in type 1 diabetics, was in fact GAD [57]. SMS is associated with HLA phenotypes predisposing to type 1 diabetes and organ-specific autoimmunity [25, 58, 59]. Anti-GAD immunoreactivity identifies patients at risk for developing type 1 diabetes mellitus, years before the development of clinical symptoms [60, 61]. Autoantibodies directed against GAD are also found in late-onset cerebellar degeneration associated with endocrine disorders and palatal myoclonus [62, 63].

In vivo confirmation of the involvement of the inhibitory GABA-ergic pathways in the SMS pathogenesis came out from MR spectroscopy studies that reported decrease in GABA levels in several brain regions of patients with disease compared with control subjects [64].

Moreover in vivo evidence of central GABA-A receptors dysfunction in SMS has emerged by studies conducted with a [^{11}C]flumazenil (FMZ) positron emission tomography (PET) [65, 66]. FMZ is a radioligand to the postsynaptic central benzodiazepine receptor which is co-localized with the GABA-A receptor, and its derangements in SMS patients may be related to the motor symptoms. In the first study with PET conducted in two patients with SMS, the authors demonstrated a reduction of FMZ binding potential in motor-premotor cortex and increased FMZ binding potential in the cerebellar nuclei [65]. As reported above, this is consistent with MRI spectroscopy data [64]. These data were confirmed by another study that has demonstrated a global reduction of cortical FMZ binding in a female patient with SMS compared to nine healthy individuals [66].

Stiff-Man Syndrome Associated with Breast Cancer

In some patients, SMS is associated with cancer, in particular breast cancer [7, 8, 67–72]. Immunohistochemistry employing serum and CSF of these patients demonstrates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immunoreactivity co-localization with synaptic-vesicle-associated proteins (Fig. 72.4) [7, 73, 74]. The serum and CSF antibodies of these patients recognized a non-intrinsic membrane protein of 128 kD, which is expressed at high levels in the central nervous system and at lower levels in the testis and endocrine tissues [7]. The 128 kD autoantigen proved to be amphiphysin [75]. Autoantibodies directed against amphiphysin I and amphiphysin II are also present in other paraneoplastic nervous system disorders [75–79].

Psychiatric Disorders Associated with Stiff-Man Syndrome

Anxious symptoms and other psychiatric manifestations are found frequently in patients with SMS [35–37, 80, 81]. Evidence suggests that anxiety disorders are related to disturbances in the GABA-ergic system in cortico-limbic pathways and disruption of the GABA systems could explain the frequent association of SMS with psychiatric manifestations [81, 82]. A woman with SMS and profound anxiety underwent a PET scan analysis showing reduced ^{11}C-FMZ binding potential in the limbic region, amygdale, and hippocampus, and these findings were supported by previous reports of decreased GABA levels in the amygdale region measured with MRI spectroscopy [41, 64, 65] (Fig. 72.5).

Moreover to explore the pathogenic role of antibodies against GAD 65 on psychiatric symptoms of SMS, the authors passively transferred the patient IgG fraction intrathecally into rats and demonstrated that anxiety can be reproduced in rat, suggesting a probable pathogenic action of IgG autoantibodies (Fig. 72.6). Furthermore, rat sections of CNS incubated with purified SMS patient IgG displayed a pronounced immunoreactivity in particular in structures associated with emotional control, such as amygdale, hippocampus, and frontal cortex, and similar staining patterns were observed in the human autopsy CNS material [41].

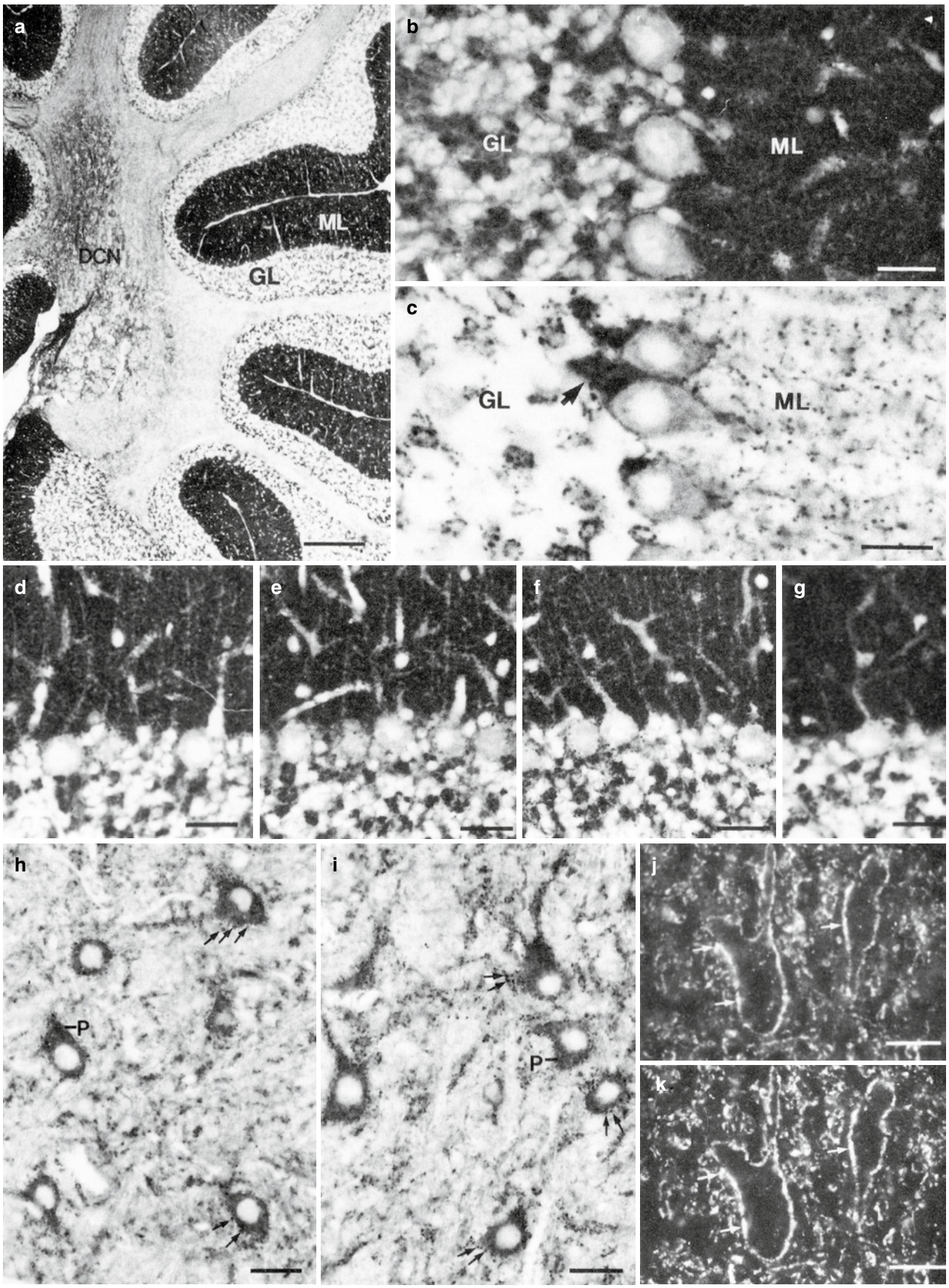
Clinical Presentation

SMS is a rare disorder characterized by fluctuating, progressive muscle stiffness, and painful spasms of the trunk [1, 2, 23, 40, 54, 83–85]. The onset is insidious usually in the fourth and fifth decades. The incidence of SMS is slightly greater in women than men; however, the exact incidence and prevalence of SMS are unknown.

The initial complaints are usually muscular tightness, stiffness, rigidity, and painful spasms of the lower back [1, 2, 53, 83]. Patients describe the pain as a dull, cramping feeling with severe muscle fatigue. Muscle rigidity first presents as symmetrically predominantly affecting the axial muscles, such as the neck, lumbar paraspinal, and abdominal muscles (Fig. 72.3, panels c and d). Axial rigidity progresses slowly over months or years causing a characteristic hyperlordosis of the lumbar region. Proximal limb muscles are involved later and the lower extremities are affected greater than the upper leading to difficulty in walking. In severely symptomatic cases, the distal musculature may be affected. SMS has a slow progression of manifestations associated with impairment of walking. Respiratory, swallowing, and facial muscles may be involved in advanced patients. The disease has usually a chronic course, but patients tend to stabilize after months or years. Neurological examination reveals normal strength and sensation. Deep tendon reflexes are often increased. The affected muscles are tight and rock-hard with a board-like consistency. Muscles supplied by the cranial nerves are rarely involved, and trismus does not occur. Examination shows truncal rigidity and there is a characteristic lumbar hyperlordosis in established cases. The gait is slow, laborious, and stiff. Passive or voluntary movement precipitates severely painful spasms of all involved musculature [1, 2, 23, 54, 83, 86–88].

SMS is usually an acquired condition; however, a hereditary form of SMS is described in several families

Fig. 72.3 Clinical characteristics of a typical stiff-man syndrome (SMS) patient with autoantibodies against glutamic acid decarboxylase (GAD). A 53-year-old woman with a past medical history notable for onset of vitiligo at age 33 (panels **a** and **b**), Graves' disease at age 38, and type 1 diabetes mellitus at age 51 was treated with thyroid hormone replacement and insulin. She complained of muscle rigidity, cramps, and painful spasms of 1-year duration. These symptoms involved mainly the axial musculature (panels **c** and **d**) but also the proximal portion of lower and upper limbs. She also noticed that these symptoms were partially ameliorated by low doses of diazepam. On the basis of clinical examination, a diagnosis of probable SMS was made. The patient underwent laboratory and electromyographic investigations. HLA phenotype was A3/30(19), B8/13, BW4/BW6, CW6, DR7/17(3), DR52/53, DQ2. An organ-specific autoimmunity screening of the serum demonstrated the following: thyroid-stimulating hormone receptor autoantibodies 97 U/L (normal value, 0–10), thyroid microsomal autoantibodies 1:102,400 dilution (normal value, absent), islet cell antibodies weakly positive (normal value, negative), GAD autoantibodies 63.1 U (normal value, 0–3 U), and autoantibodies directed against GABA-ergic synapses by immunohistochemistry on rat cerebellar sections. Autoantibodies directed against GAD were also present in the CSF. Needle electromyography demonstrated continuous motor unit activity at rest (rectus abdominis), which was exacerbated by hand clapping (* in panel **e**) and abolished by 10 mg intravenous diazepam (*arrow* in panel **f**). A diagnosis of SMS was made and the patient treated with diazepam 20 mg/day, with partial remission of muscular stiffness and painful cramps (Folli F, Galardi G, unpublished observations, 2000)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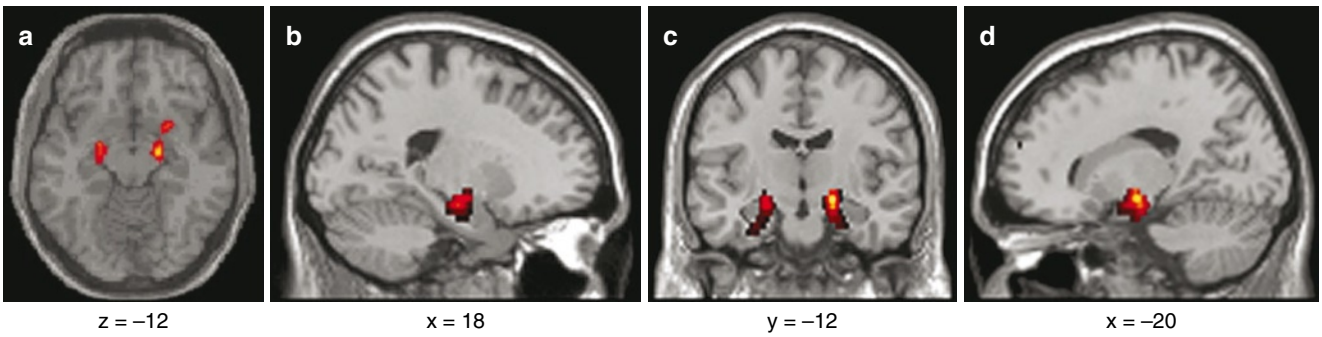

Fig. 72.5 Bilateral reductions of (11)C-FMZ binding potential in amygdala regions in the SMS patient. This figure shows the results of the PET scan analysis with statistical parametric mapping (SPM) with voxel-based analysis and thus the comparison of GABA-A receptor binding potential in a 53-year-old woman with SMS and anxiety. The (11)C-FMZ binding potential is significantly reduced bilaterally in the patient's limbic region when compared to normal controls (Reproduced with permission from Geis et al. [41])

[84, 85]. Hereditary SMS differs from acquired forms with stiffness present at birth but resolving by 3 years of age. Stiffness reappears at adolescence, often precipitated by sudden movement or cold, but remains mild when compared with the sporadic condition. The pattern of inheritance appears autosomal dominant, but X-linkage cannot be excluded in some families.

Differential Diagnosis

Conditions that cause continuous motor-unit activity at rest, rigidity, reflex, and action-induced spasms should be considered in the differential diagnosis of SMS. Focal lesions of the spinal cord, encephalomyelitis, corticobasal degeneration, or tetanus may at times be confused with SMS.

Variants of SMS are described and, on clinical and electrophysiological grounds, are divided into five groups of patients (Table 72.1). The first is typical SMS. The second variant is progressive encephalomyelitis with rigidity: a very rare rapidly deteriorating condition that may present with clinical features similar to those of the SMS. The clinical course is severe and progressive, often resulting in death within a few months [89–96]. The third variant is stiff-limb syndrome characterized by rigidity, abnormal fixed posturing, and painful spasms, usually of the distal lower limb. About half of the patients go on to develop sphincter or brainstem involvement. Half of patients become wheelchair bound. The patients partially respond to GABA-ergic drugs [97–100]. The fourth variant is SMS associated with antibodies to the synaptic vesicle protein amphiphysin II. This is a form of paraneoplastic SMS described in a small number of women with breast and lung cancer, characterized by different clinical features, partially responsive to benzodiazepines at high dose and with a significant response to tumor excision and chemotherapy [65, 73, 78, 101, 102]. The fifth variant is jerking stiff-man syndrome, in which myoclonic jerking is a prominent additional feature [103–105].

Fig. 72.4 Immunoreactivity of serum from a patient with stiff-man syndrome (SMS) against rat cerebellum and brain stem. Patients 1, 2, and 3 were affected by SMS and breast cancer, and a control patient was affected by SMS with autoantibodies against glutamic acid decarboxylase. In panels **a**–**i**, immunoperoxidase staining was used (immunoreactive areas are *black*), and in panels **j** and **k**, immunofluorescence staining was used (immunoreactive areas are *white*). (**a**) Sagittal section of cerebellum stained with serum from patient 1 shows staining of all regions containing synapses in the cerebellar cortex and the deep cerebellar nuclei (*DCN*). The dense staining of the molecular layer (*ML*) and the patchy staining of the granular layer (*GL*) correspond to the known distribution of the synapses in the two layers. (**b**) Cerebellar cortex stained with serum from patient 3 shows widespread immunoreactivity on synapses. (**c**) Cerebellar cortex stained with serum from the control patient shows only a few immunoreactive synapses, corresponding to "γ-aminobutyric acidergic synapses". These include synapses made by basket cell axons around the axon hillocks of Purkinje cells (*arrow*). (**d**–**f**) Adjacent sections of cerebellar cortex stained with serum samples from patients 1, 2, and 3, respectively, have identical patterns of immunoreactivity. This pattern is very similar to that produced by rabbit antibodies directed against a nerve-terminal marker, synapsin I (**g**). (**h**, **i**) Adjacent sections of deep cerebellar nuclei stained with serum samples from patients 1 and 3, respectively, show localized immunoreactivity in the cytoplasm of neuronal perikarya (*P*) and dendrites, as well as in the nerve terminals that form synapses at their surfaces (*arrows*). (**j**) Double immunofluorescence labeling of a brain stem section with serum from patient 3 and (**k**) antibodies directed against synaptophysin, a synaptic vesicle marker, shows nerve terminals filled with synaptic vesicles (with puncta). The profiles of neuronal perikarya and dendrites (*arrows*) are apparent. The *scale bar* measures 0.25 μm in **a**, 25 μm in **b** and **c**, 50 μm in **d–g**, and 25 μm in **h**–**k** (Reprinted with permission from Folli et al. [7])

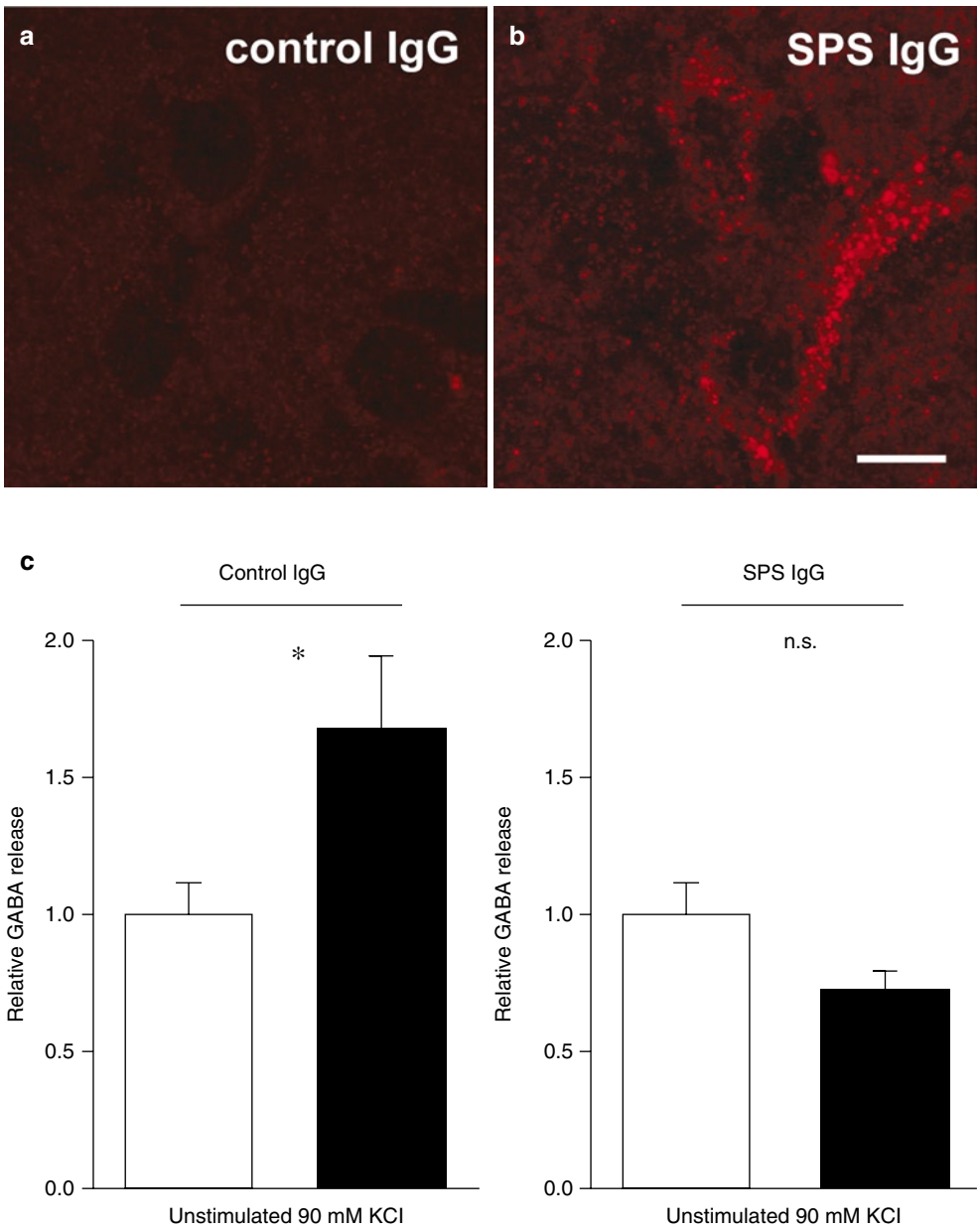

Fig. 72.6 SMS IgG accumulates in interneurons of rat amygdala complex and reduces GABA release from hippocampal neurons. In rats treated intrathecally with SMS IgG (**a**) but not in those treated with control IgG (**b**), immunoreaction against human IgG showed positive staining of neurons in the amygdala complex (*scale bar*, 10 mm). (**c**) Dissociated hippocampal neurons from E18 mouse embryos were incubated with SMS or control IgG. The increase of GABA release into the supernatants induced by stimulation with 90 mmol KCl was absent in SMS IgG-treated neuronal cell cultures as demonstrated by HPLC analysis (*p, 0.05, student's t-test) (Reproduced with permission from Geis et al. [41])

Evaluation and Diagnosis

Electromyography and muscle examination are critical to make a clear diagnosis and to understand pathophysiological mechanisms underlying SMS [2, 33, 34, 39, 40, 106]. Routine nerve conduction studies for both sensory and motor nerves are normal. The needle electromyographic pattern, although not unique to the disease, is present in virtually all patients with SMS with evidence of continuous motor-unit activity, especially in the paraspinal and abdominal muscles. The activity is continuous during wakefulness, diminished during sleep, exacerbated by sensory stimuli, and abolished by intravenously administered diazepam (Fig. 72.3, panels e and f) [2]. It is detectable, with needle or surface electrodes, particularly in abdominal and thoracolumbar muscles. Limb muscles are involved too but less severely than truncal muscles. Motor-unit activity is more prominent in lower limbs than upper limbs, and the severity of muscle involvement decreases with a proximo-distal gradient.

Electromyographic activity in SMS resembles the electromyographic pattern observed in voluntary muscle contraction. It is composed by motor-unit action potentials (MUAPs) of normal morphology, which fire tonically at rest. The number of MUAPs and the firing rate are higher in the thoracolumbar than in the limb muscles producing different electromyographic patterns, ranging from full interference pattern to single MUAPs, corresponding to the severity of involuntary muscle contraction. Although not specific for

Table 72.1 Clinical characteristics and laboratory findings of stiff-man syndrome (SMS) and its variants

	SMS	Progressive encephalomyelitis with rigidity	Stiff-limb syndrome	Paraneoplastic SMS/stiff-limb syndrome	Jerking SMS
Trunk stiffness	Yes	Yes	Yes/no	Yes	Yes
Limb stiffness	Yes/no	Yes	Yes	Yes	Yes
Myoclonus	No	Yes/no	No	No	Yes
Electromyography: continuous motor unit activity at rest	Yes	Yes	Yes/no	Yes	Yes
Response to GABA-ergic drugs	Yes	Yes/no	Yes/no	Yes/no	Yes/no
Response to plasmapheresis/IV IgG	Yes	No	No	No	No
Associated type 1 diabetes mellitus and/or other autoimmune endocrine diseases	Yes	No	Yes/no	No	No
Associated breast/lung cancer	No	Yes/no	Yes/no	Yes	No
GAD autoantibodies	Yes	Yes/no	Yes/no	No	No
Amphiphysin autoantibodies	No	Yes/no	Yes	Yes	No

SMS, measurement of the silent period may be helpful. The physiology of the silent period is complex [107, 108]. After a brief latency following a painful cutaneous stimulus, motor-unit activity is suppressed for a short period (i.e., the silent period). This reflex is mediated via spinal intraneural inhibition. The silent period can be useful in differentiating motor-unit activity of lower motor neuron or peripheral origin (e.g., tetanus, where the silent period is short or absent) from an upper motor neuron or central origin (e.g., SMS, where the silent period is normal) [108].

The continuous motor-unit activity of SMS is responsible for the abnormal lordotic posture and the gait abnormalities. It affects both agonists and antagonists muscles without asymmetry, and it is unresolved by attempts of voluntary relaxation or by stretching the stiff muscles.

The presence of superimposed episodic spasms on continuous motor-unit activity is another fundamental aspect of the final diagnosis of SMS. Muscle spasms might be spontaneous or induced by acoustic, somatosensory, or emotional inputs. They are electromyographically characterized by a sudden increment of the tonic motor-unit firing and a progressive return to the basal continuous motor activity.

Recent studies point to the possibility that hyperexcitability of the motor cortex in SMS plays a role in the pathogenesis. This could be explained by impairment of supraspinal GABA-ergic neurons leading to impaired balance between inhibitory and excitatory circuitry [98, 109].

There are no specific clinical laboratory findings in SMS, i.e., routine laboratory investigations are usually normal. GAD antibodies are present in serum in up to 80 % of patients with non-paraneoplastic form of SMS and are present in CSF as well. A high proportion of patients (>80 %) have other autoimmune diseases including insulin-dependent diabetes mellitus [110, 111]. Autoimmune thyroid disease, pernicious anemia, and vitiligo are also common. Epilepsy in the stiff-man syndrome occurs in about 10 % of patients (see Fig. 72.3) [3, 8, 25, 53, 112]. Five percent of patients have autoantibodies against amphiphysin and have an associated breast cancer [7, 8, 75].

Clinical and Laboratory Criteria

Diagnostic criteria for the SMS are the following [1, 2, 23]:

1. Stiffness and rigidity in axial muscle, progression of the stiffness to the proximal limb muscles, making volitional movements including walking difficult.
2. Abnormal axial posture, most often lordosis, resulting from continuous contraction of paraspinal and abdominal muscles.
3. Superimposed spasms precipitated by voluntary movement, noise, emotional upsets, and unexpected auditory and somatosensory stimuli.
4. Normal muscle strength and sensory examination.
5. Absence of brainstem; pyramidal, extrapyramidal, and lower motor neuron signs; and sphincter disturbance.
6. Normal intellect (epilepsy may occur).
7. Continuous motor-unit activity in at least one axial muscle with typical EMG findings.
8. Favorable response to the oral or intravenous administration of diazepam.
9. Diagnosis is supported by the finding, in association with the above clinical and electrophysiological criteria, of anti-GAD antibodies (65–67 kD doublet in western blot

on total brain homogenate or GABA-ergic synaptic pattern by indirect immunohistochemistry on rat cerebellar sections). They are found in 70 % of patients in blood and CSF. In about 5 % of patients, anti-amphiphysin II antibodies in blood and CSF are found by western blot using total brain homogenate. A substantial proportion of patients have oligoclonal bands in the CNS or abnormal Link/Tourtellote index, which is further indication of immune system activation in the CNS [3, 7, 113, 114].

Treatment

Therapy for stiff-man syndrome is based on knowledge of the pathophysiology of the disease: (1) drug-potentiating GABA-ergic transmission and (2) immunosuppressive agents.

Drug-Potentiating GABA-ergic Transmission

Diazepam is the initial treatment for SMS patients. High dosages of up to 100 mg/day are usually required. The majority of patients respond to diazepam to a certain extent, and the dramatic clinical improvement after administration of the drug helps to confirm the diagnosis [2, 20, 27, 31]. However, the high doses of diazepam are not easily tolerated, and other agents are often necessary to control manifestations. Clonazepam may be employed as an alternative to diazepam (up to 6 mg/day) [31]. Other drugs affecting GABA transmission, such as vigabatrin (which decreases GABA catabolism, up to 3,000 mg/day), tiagabin (which interferes with GABA uptake), and sodium valproate (up to 2,000 mg/day) may be helpful [32, 115–117]. Baclofen (up to 60 mg/day) increases GABA activity and may be helpful [21]. In a double-blind, placebo-controlled trial of three patients, 50 μg intrathecal baclofen improved electrophysiologic findings more than placebo; however, there is only slightly improved physical symptoms of one patient [118]. Most recent case reports confirm treatment improves symptoms and quality of life [119, 120].

Immunosuppressive Agents

There is evidence from expert opinion, nonrandomized historical controls, and case reports that plasmapheresis is beneficial in the treatment of SMS, although it is not uniformly effective [59, 121–125]. Plasma exchange for SMS is considered investigational by the Therapeutic and Technology Assessment Subcommittee of the American Academy of Neurology [125]. Prednisone, high-dose intravenous immunoglobulin, and cyclosporine are reported to be effective for some patients [121, 126–130]. Based on one randomized placebo-controlled trial [131], noncontrolled studies [132, 133], and several case reports [134], in patients with SMS and a poor response to initial GABA-potentiating therapy, the use of intravenous immunoglobulin at a total dose of 2 g/ kg is recommended [135].

Support for use of immunosuppressive therapies comes from the demonstration of high titers of GAD autoantibodies among SMS patients and that these autoantibodies inhibit GABA synthesis in vitro, suppress cerebellar GABA-ergic transmission, and are directed against the enzymatic active site of the protein [12, 41, 136, 137].

Prognosis

The prognosis of SMS in association with autoantibodies against GAD is usually good for long-term survival and maintenance of independence in activities of daily living. However, five percent of patients may develop frequent attacks of muscle spasms with severe paroxysmal autonomic dysfunction resulting in sudden death [1, 6, 38, 53–55, 72, 100]. The prognosis of patients affected by stiff-limb syndrome differs. The disease is chronic (decades), but at variance with SMS, approximately half of patients become wheelchair bound [97]. Encephalomyelitis with rigidity follows a subacute course leading to death within 3 years [55, 92, 94–96, 100]. The prognosis of the patients affected by the paraneoplastic forms of SMS is dependent on cure of the underlying cancer.

Acknowledgements This chapter is dedicated to my beloved cousins, Maria Cristina Folli MD and Marcello Folli.

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Tetanus

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Jayashri Srinivasan and Thomas D. Sabin

Introduction

Tetanus is a neurological disorder caused by a potent neurotoxin, tetanus toxin (tetanospasmin), elaborated by *Clostridium tetani*, a gram-positive, spore-forming obligate-anaerobic bacillus found normally in the mammalian gut as well as soil and animal excrement. Reported cases of tetanus have declined greater than 95 %, and mortality has declined by greater than 99 % in the USA since 1947 with a case fatality rate of 13.2 % [1]. Incidence is higher among persons over 65 years of age, Hispanics, intravenous drug users, and diabetics. Tetanus toxin abolishes inhibitory spinal reflex arcs, allowing excitatory reflexes to predominate, thus resulting in increased muscle tone and spasms that are the cardinal manifestations of the disease. Tetanus is predominantly seen in neonates and children in the developing world, where immunization programs remain inadequate. In the Western world, where immunization with tetanus toxoid is universal, tetanus is most often encountered in patients over 65 years of age, often after a trivial injury acquired outdoors, and in drug addicts. Tetanus occurs in several distinct clinical forms including localized, generalized (including neonatal), and cephalic disease.

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Etiology

Clostridium tetani are gram-positive, spore-forming, motile, obligate anaerobes that are found worldwide; the spores are formed terminally, giving the organism a distinctive drumstick-like appearance. The spores are relatively resistant to drying and various disinfectants. Phenol (5 %), formaldehyde (3 %), and chloramine (1 %) generally require more than 15 h to kill the spores, while autoclaving, aqueous iodine and 2 % glutaraldehyde at pH 7.5–8.5 are lethal. The spores of *C. tetani* are ubiquitous and survive many years, especially in soil cultivated by manure. Spores may also be found in animal and human feces and in house and operating room dust.

Under appropriate anaerobic conditions, particularly in wounds associated with necrosis and foreign bodies, the spores germinate into the vegetative form that elaborates two exotoxins, tetanolysin and tetanospasmin. Tetanolysin is an oxygen-sensitive hemolysin that may have some role in establishing infection, but is not otherwise thought to be involved in the pathogenesis of tetanus. Tetanospasmin, a zinc metalloprotease, is formed under plasmid control as a single 1315-amino acid 150 kD polypeptide chain. It is cleaved by bacterial protease, papain, resulting in a nontoxic C fragment (carboxy terminal of heavy chain) and an A–B fragment (light chain and amino terminal of the heavy chain) to form a heterodimer joined by a disulfide bond [2, 3]. The heavy chain is responsible for specific binding to neuronal cells and for cell penetration of the light chain which blocks transmitter release. When tetanospasmin is released in infected wounds, the C fragment binds to specific axonal membrane gangliosides (GD1b and GT) at the neuromuscular junction predominantly at the terminals of alpha motor and to lesser extent autonomic neurons [4, 5]. The C-terminal H (CC)-domain interacts with complex polysialo-gangliosides, such as GT1b and a synaptic vesicle protein receptor via two neighboring binding sites, resulting in highly specific uptake of the neurotoxins at synapses of cholinergic motor neurons [6–8]. The toxin is internalized inside the lumen of synaptic vesicles following vesicle reuptake and is translocated from the endosomes to the

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cytosol [6, 7]. Their multistep mode of mechanism can be ascribed to their multidomain three-dimensional structure. It is then transported by retrograde transsynaptic axonal transport to the cell bodies of inhibitory interneurons in the spinal cord and brainstem [8, 9]. In the inhibitory neurons in the spinal cord, the light chain fragment causes proteolytic cleavage of the SNARE (synaptosomal-associated protein receptor) complexes, particularly the synaptobrevin/vesicle-associated membrane protein, and prevents neurotransmitter release (glycine in the spinal cord and gamma-aminobutyric acid [GABA] in the brain) [9]. This disinhibition results in uncontrolled excessive efferent discharge of motor and autonomic neurons resulting in muscle rigidity, spasms, and autonomic dysfunction characteristic of tetanus. The amino acid structures of the two most powerful toxins known, botulinum and tetanospasmin, are partially homologous; the estimated human lethal dose of tetanospasmin is less than 2.5 ng/kg [10].

Epidemiology

Tetanus is a sporadic disease which only affects non-immunized and partially immunized persons or immunized individuals who fail to maintain adequate immunity with booster doses of vaccine. Tetanus causes substantial morbidity and mortality in developing countries. The World Health Organization estimated that about 277,400 deaths from neonatal tetanus alone occurred in 1997 [11]. Improved hygiene and childbirth practices, improvements in wound care, and active immunization have led to substantial reductions in tetanus in developed countries.

Tetanus surveillance in the USA between 1995 and 1997 yielded a total of 124 cases, giving an annual incidence of 0.15 cases per 1,000,000 population. Sixty percent of patients were aged 20–59 years, 35 % were aged ≥ 60 years, and 5 % were aged <20 years, including one case of neonatal tetanus. Tetanus among intravenous drug users compromised 11 % of all cases [12].

Of 67 cases of tetanus reported in California during 1987–1997, a total of 27 (40 %) occurred in injecting drug users (IDUs); injection technique information was available in 14 persons, all of whom had used the subcutaneous route ("skin popping"), and specific drug use information in ten persons revealed heroin use in all [13].

There is evidence that following natural disasters such as earthquakes and tsunamis in Haiti, Indonesia, and Kashmir, there have been clusters of outbreaks of tetanus. In a population where immunization is inadequate, following crush injuries, there is contamination of wounds by spore-containing soil resulting in tetanus [14].

Rarely, tetanus may be seen in spite of adequate immunization; the reason for this not known [15].

Pathogenesis

Spores of *C. tetani* usually gain access to the body by wound inoculation and the spores are converted to the toxin-producing vegetative forms. An anaerobic milieu or a local reduction in oxidation-reduction potential, as in wounds with devitalized tissue, foreign bodies, or active infection, causes vegetative organisms to produce the toxins tetanospasmin and tetanolysin. Calcium appears to increase local necrosis and may enhance germination in wounds contaminated with soil. *C. tetani* by itself does not provoke a significant inflammatory response so the infection may remain localized and inconspicuous.

The transport of tetanospasmin, released at the site of injury, to the central nervous system is complex. Although the toxin gains access to the systemic circulation and enters the central nervous system (CNS) with the highest efficiency of any known protein, tetanospasmin does not appear to cross the blood-brain barrier. The portal of entry appears to be through binding of the toxin to peripheral alpha motor neuron terminals. Binding to a specific ganglioside-containing receptor is followed by internalization of the toxin by endocytosis and retrograde axonal transport to cell bodies in the brainstem and spinal cord [16]. The toxin then migrates across the synapse to presynaptic terminals, where it blocks release of the inhibitory neurotransmitters glycine and GABA. The resultant disinhibition of the spinal reflex arcs leads to an increase in the resting firing rate of the alpha motor neuron, producing rigidity. Agonists and antagonists may be recruited rather than inhibited, thereby producing tetanospasms. The clinical picture is similar to strychnine poisoning, which acts by competitively binding to postsynaptic glycine receptors at the motor neurons. Loss of inhibition may also affect preganglionic sympathetic neurons in the lateral gray matter of the spinal cord mediated by protease activity of the light chain on synaptobrevin [17], producing sympathetic hyperactivity and high circulating catecholamine levels.

In localized tetanus, only the nerves supplying the affected muscles are involved. Generalized tetanus occurs when toxin released in the wound enters the bloodstream and is spread to other nerve terminals; if intra-axonal transport time, approximately 75–250 mm/day, is assumed to be equal for all nerves, short nerves are likely to be affected before long nerves. This may explain the sequential involvement of nerves of the head, axial trunk, and extremities in generalized tetanus [4].

Clinical Manifestations

The incubation period for tetanus varies from 3 days to 3 weeks and is usually 8 days after an acute injury. The incubation period varies directly with the distance of the injury

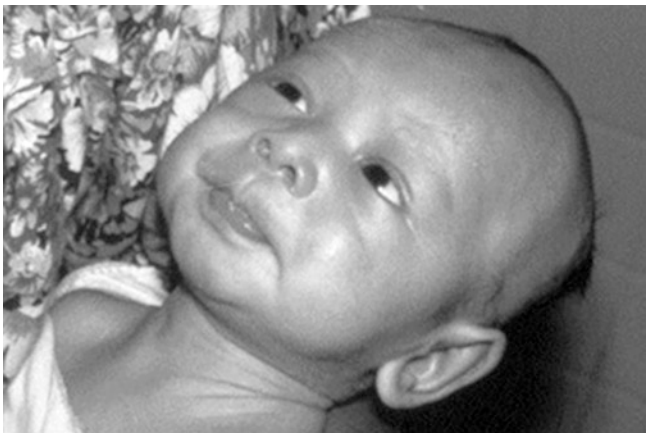

Fig. 73.1 Risus sardonicus. Note the spasm of the facial muscles, producing a grimace or sneer on the baby's face (Photo courtesy of the World Health Organization)

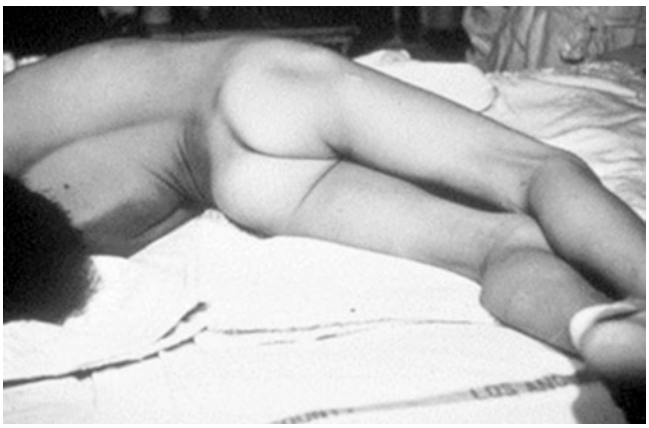

Fig. 73.2 Opisthotonus. Note the severe contraction of the extensor back muscles (Photo courtesy of the Centers for Disease Control)

from the CNS. Injuries to the lower extremities are likely to be associated with longer incubation periods than injuries to the head and neck; the shorter the incubation period, the greater the possibility of death. Some 15–25 % of patients with tetanus have no evidence of a recent wound.

Tetanus may take one of three clinical forms: localized, generalized, and cephalic. *Localized tetanus* is limited to painful muscular spasms in a confined area close to the site of injury. These contractions may persist for weeks to months before spontaneously subsiding. Localized tetanus is uncommon in humans and is generally mild, with death-to-case ratios of less than 1 %. However, it may be the first manifestation of generalized tetanus, which portends a more dire outcome. Most patients have *generalized tetanus* with widespread signs and symptoms. In approximately 50 % of patients, the illness starts with spasm of the muscles of mastication – the classical *trismus* or *lockjaw*. Dysphagia, stiffness, and pain in the neck, shoulder, and back muscles appear soon thereafter. Symptoms progress to involve the abdominal muscles producing a rigid abdomen and proximal limb muscles; the hands and feet are relatively spared. Sustained contraction of the facial muscles produces a grimace or sneer (*risus sardonicus*) (Fig. 73.1) and contraction of the extensor back muscles produces an arched back (*opisthotonos*) (Fig. 73.2). Some patients develop *tetanospasms* – paroxysmal, generalized, painful, tonic muscle contractions that occur repetitively and are spontaneous or provoked by even minor stimulation. Distention of the bowel or bladder, mucus plugs in the bronchi, or slight noises may trigger tetanospasms.

A constant threat during generalized spasms is reduced ventilation or apnea secondary to laryngospasm. Tetanospasms occur intermittently, irregularly, and unpredictably, persisting from a few seconds to minutes. Initially mild and separated by periods of relaxation, the paroxysms tend to become more frequent, severe, painful, and exhausting as they continue. Dysphagia or ileus may preclude oral feeding. The degree of illness may be mild (muscle rigidity and few or no spasms), moderate (trismus, dysphagia, rigidity, and spasms), or severe (frequent explosive spasms). The patient may have a mild fever; cognitive testing and sensory examination are usually normal; deep tendon reflexes may be increased.

Autonomic dysfunction commonly complicates severe cases and is characterized by labile or sustained hypertension, tachycardia, arrhythmias, hyperpyrexia, profuse sweating, peripheral vasoconstriction, and increased plasma and urinary catecholamine levels. Periods of bradycardia and hypotension may also occur and may require pacemaker insertion. "Autonomic storms", characterized by episodes of sinus tachycardia and severe hypertension followed within hours by profound bradycardia and hypotension, may occur. These are often a harbinger of cardiac arrest, which remains the single most dreaded complication of tetanus. It usually occurs under conditions of marked cardiovascular instability secondary to wildly fluctuating sympathetic and parasympathetic activity. Cardiac arrest may also be secondary to excessive vagal activity during suctioning of the pharynx and trachea, severe hypoxia due to prolonged muscular and laryngeal spasm, hyperpyrexia causing cardiovascular collapse, or massive pulmonary embolism.

Maternal and neonatal tetanus are important causes of morbidity and mortality, claiming 187,000 lives every year mostly in Asia and Africa [18]. Neonatal tetanus occurs as a generalized form and has a high mortality. It develops in the first 2 weeks of life in children born to inadequately immunized mothers, frequently after non-sterile treatment of the umbilical cord stump. Infants present with poor feeding, rigidity, and spasms.

Cephalic tetanus is rare and follows lesions of the head and face (e.g., otitis media), especially in the distribution of the facial nerve. It is characterized by unilateral facial paralysis, trismus, facial stiffness on the nonparalyzed side, nuchal

rigidity, pharyngeal spasms causing dysphagia, and frequent laryngeal spasms with risk of death from asphyxia. Cephalic tetanus may be associated with paresis involving the glossopharyngeal, vagus, and rarely the oculomotor nerves. The disease has a short incubation period and may graduate to generalized tetanus.

Other complications include rhabdomyolysis, fractures, muscle rupture, deep venous thromboses, pulmonary emboli, atelectasis and pneumonia, sepsis, decubitus ulcers, gastric ulcers, fecal impaction, and urinary retention.

Differential Diagnosis

The differential diagnosis of tetanus depends on the clinical pattern of presentation. Spasm of the masseter (trismus) may be seen in patients with dental caries, tonsillitis, peritonsillar abscess, temporomandibular joint dysfunction, and parotitis. Trismus and muscle spasms may occasionally be seen in purulent meningitis and encephalitis but are associated with characteristic clinical and cerebrospinal fluid (CSF) abnormalities. Rabies may cause muscle spasms, particularly in the muscles of respiration and deglutition. However, the accompanying encephalitis is characterized by hallucinations, hydrophobia, mania, stupor, and tonic-clonic seizures.

Hypocalcemic tetany may superficially resemble tetanus. However, it is accompanied by Chvostek's and Trousseau's signs, affects the extremities more than the trunk, and is not associated with trismus. Tetany is confirmed by low serum calcium levels.

Drug-induced dystonia such as those due to dopaminergic blocking agents such as phenothiazines may produce oculogyric movements, characterized by eye deviation and head and neck movements; this usually responds to benztropine unlike tetanus. Malignant neuroleptic syndrome may also mimic tetanus, but the history of medication use and the presence of altered mental status differentiate this condition from tetanus.

Strychnine poisoning produces an almost identical clinical presentation to tetanus. However, trismus is either absent or appears late in strychnine poisoning and is impersistent. Also, body temperature is normal, muscle rigidity between spasms is absent, and symptoms and signs usually develop much more rapidly than with tetanus. A history suggestive of poisoning may be obtained and the diagnosis can be confirmed by detecting strychnine in the gastric contents or urine.

Stiff person syndrome has an insidious onset, tends to cause minimal symptoms in facial and jaw muscles, does not have the characteristic loss of the silent period in the electromyography (EMG), and may be associated with antibodies to glutamic acid decarboxylase (GAD) or, in rare cases, to amphiphysin, glycine receptor or gephyrin.

Conversion reactions may also mimic tetanus, but patients with hysteria are more likely to relax when distracted, and the EMG shows no loss of the silent period.

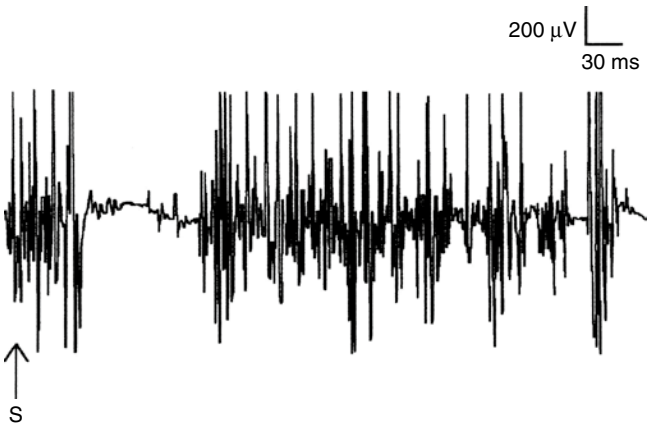

Fig. 73.3 Normal silent period. During sustained voluntary contraction or spontaneous motor unit activity from a central origin, a supramaximal mixed nerve or cutaneous stimulus (*S*) will inhibit motor unit activity, resulting in the silent period. The silent period normally occurs 50–100 ms after a supramaximal stimulus and is most pronounced with a painful stimulus. The silent period is absent in tetanus

Cephalic tetanus may be confused with Bell's palsy or trigeminal neuralgia; however, cephalic tetanus is frequently associated with multiple cranial nerve palsies, trismus, and nuchal rigidity.

Evaluation and Diagnosis

The diagnosis of tetanus is largely made on the basis of clinical findings. The absence of a wound does not exclude tetanus. Tetanus is less likely if a reliable history of primary immunization with appropriate booster doses is obtained or if serum antitoxin levels are 0.01 unit/ml or higher. However, there are reports of tetanus developing in fully immunized patients [15]. Anaerobic cultures of wound specimens should be done although *C. tetani* is isolated only in approximately a third of cases. A positive wound culture is not diagnostic of tetanus as the organism may be grown from wounds of patients who do not have tetanus. Laboratory tests are of little value; the leukocyte count may be mildly elevated and serum creatine kinase may be moderately elevated in generalized tetanus. Cerebrospinal fluid (CSF) examination is usually normal though in severe cases, CSF protein and immunoglobulins may be elevated.

Electrodiagnostic studies in cephalic tetanus may show abnormal blink reflex [19]. Needle EMG recording from muscles in spasm may show continuous discharges of motor unit action potentials, like those recorded during forceful voluntary contraction. A characteristic feature of tetanus on EMG is shortening or absence of the silent period normally seen 50–100 ms after supramaximal nerve stimulation (Fig. 73.3). The silent period is mediated partially through recurrent inhibition of the alpha motor neurons by the Renshaw cells, the inhibitory neurons in the spinal cord.

Neurotransmitter release from these inhibitory neurons is blocked by tetanus toxin. The loss of the silent period may be demonstrated in an affected muscle in localized tetanus and in the masseter in generalized tetanus [20]. After discharges following F waves have been observed in mild tetanus [21]. Single-fiber EMG of the affected muscle may show increased jitter and blocking in a significant proportion of the recorded units [22].

Treatment

Treatment strategies are directed toward the following goals: elimination of the source of toxin; neutralization of circulating, unbound toxin before it reaches the nervous system by the early administration of specific antitoxin; exploration, careful cleansing, and thorough debridement of wounds; and adequate immunization to prevent infection.

General Measures

General supportive measures include expert intensive medical and nursing care in a dimly lit room where environmental stimuli are minimized, ideally in an intensive care, where adequate cardiopulmonary, caloric, fluid, and electrolyte balance monitoring can be maintained. In addition, patients usually require prophylaxis against venous thrombosis and stress gastric ulcers, adequate treatment of fevers, stool softeners to prevent fecal impaction, and urinary catheterization if retention develops. Since tetanus is a catabolic illness, caloric intake of 3,500 cal with at least 100 g of protein is essential and is often given by nasogastric feeding. Physical therapy should be initiated as soon as the spasms are controlled to prevent contractures from prolonged immobility.

Antitoxin

Human tetanus immunoglobulin (TIG) should be given immediately at the time of diagnosis to prevent further spread of the circulating unbound toxin. The dose is 3,000–6,000 units injected intramuscularly; part of the dose may be infiltrated around the wound for the theoretical, but unproven, objective of neutralizing the toxin at the site of its production. Tetanus antitoxin does not cross the blood-brain barrier and has no effect on toxin already bound to nervous tissue. Intrathecal antitoxin administration is not recommended in the United States. However, a study done in Brazil suggested that intrathecal tetanus immunoglobulin may be of benefit; the duration of spasm, hospital stay, and period of respiratory assistance was shorter [23] and a meta-analyses from Kenya also confirmed that intrathecal tetanus immunoglobulin may be beneficial [24].

Wound Care and Antibiotics

After administration of antitoxin, the wound should be debrided, necrotic tissue must be excised, and foreign objects removed. The wound should be bathed and irrigated with 3 % hydrogen peroxide at least three times a day. Antibacterial therapy is routinely used to prevent the growth and multiplication of bacteria in the wound, though there are no controlled trials to show that antibacterial therapy is clearly beneficial. Metronidazole 500 mg is given intravenously every 6–8 h in adults and 20–30 mg/kg/day in three divided doses in children. Crystalline penicillin G 100,000 units/kg/day given in four divided doses is also widely used in developing countries. In mixed infections, intravenous cephalosporins such as a cefazolin, cefuroxime, or ceftriaxone may be used.

Sedatives and Muscle Relaxants

This is an important aspect of the treatment of tetanus and the aim is to reduce rigidity and control spasms. Diazepam is widely used in doses of 0.5–10 mg/kg/day given either as an infusion or in divided doses. Higher doses have been used but are invariably associated with respiratory depression. An alternative agent is midazolam 5–15 mg/h as an intravenous infusion. Chlorpromazine is also used though there is small risk of dystonic reactions and the malignant neuroleptic syndrome. Baclofen, a GABA B agonist, is a potent muscle relaxant that can be given by the intrathecal route with a bolus of 300–500 μg and continued at a steady rate of 500–1,000 μg/day [25]. Intrathecal baclofen has the advantage of treating spasms but preserving voluntary movement and respiration. Dantrolene, a direct muscle relaxant, has also been used to treat spasms [26]. Propofol, an intravenous sedative agent, is used in patients who are artificially ventilated. There has been a recent reemergence of the practice of using magnesium sulfate intravenously to reduce spasms without compromising respiratory function. However, studies suggest that although magnesium sulfate may reduce the medications used for cardiovascular instability, there is no definite evidence it reduces the need for mechanical ventilation [27].

Tracheostomy, Neuromuscular Blockade, and Ventilatory Support

Tracheostomy is mandatory in severe tetanus as prolonged laryngeal spasm can result in significant hypoxia and death; it is also recommended in mild to moderate cases where it may assist in artificial ventilation. The use of neuromuscular blockade with pancuronium or vecuronium is often necessary, particularly when spasms do not respond to conservative treatment with sedatives and muscle relaxants.

Table 73.1 Routine diphtheria, tetanus, and pertussis immunization schedule summary for children <7 years of age

Dose	Customary age	Age/interval	Product
Primary 1	2 months	6 weeks old or older	DTaP[a,b]
Primary 2	4 months	4–8 weeks after first dose[c]	DTaP[a,b]
Primary 3	6 months	4–8 weeks after second dose[c]	DTaP[a,b]
Primary 4	15–18 months	9–12 months after third dose[c]	DTaP[a,b]
Booster	4–6 years old, before entering kindergarten or elementary school (not necessary, if fourth primary immunizing dose administered after fourth birthday)		DTaP[a,b]
Additional boosters	Every 10 years after last dose		Td

[a]Whole-cell DTP is an acceptable alternative if DTaP is not readily available
[b]Use DT if pertussis vaccine is contraindicated. If the child is 1 year of age or older at the time that dose three is due, a third dose 6–12 months after the second completes primary immunization with DT
[c]Prolonging the interval does not require restarting series

Treatment of Autonomic Circulatory Derangement

Management of the complex autonomic disturbances seen in tetanus may be very difficult. Hypotension can be treated with fluid load and if needed inotropic support with dobutamine or dopamine. Hypertensive episodes can be treated with beta blockers such as an intravenous infusion of labetalol. Intravenous magnesium sulfate can also be used to treat autonomic dysfunction, and some authors recommend this as a first-line therapy for spasms [27]. Epidural bupivacaine may be useful to treat episodes of severe circulatory disturbances [28].

Prevention

Since tetanus spores cannot be removed from the environment, the goal of tetanus prevention consists of adequate immunization. The Maternal and Neonatal Tetanus Elimination Initiative of the World Health organization assists countries where tetanus has not been eliminated by providing immunization to expectant mothers. Immunization of pregnant women or women of childbearing age with at least two doses of tetanus toxoid is estimated to reduce mortality from neonatal tetanus by 94 % [29].

Active Immunization

Primary tetanus immunization, usually with combined DTaP (diphtheria and tetanus toxoid and acellular pertussis) or DTP (diphtheria and tetanus toxoid and pertussis) vaccine, is recommended for all children 6 weeks to 7 years of age without contraindications to vaccination (Table 73.1). A minimum of 4 weeks (typically 6–8 weeks) should separate the first, second, and third doses of tetanus toxoid. The fourth dose of the primary series should be given no less than 6 months after the third dose.

For active immunization of infants and children, the recommendation is to receive the first dose at 2 months of age, two further doses at 1–2 month intervals, the fourth dose at 15–18 months of age, and a fifth dose at 4–6 years of age. Thereafter, the adult formulation should be given every 10 years. Combined adsorbed tetanus and diphtheria toxoid for adult use (Td) rather than single-antigen tetanus toxoid is preferred for persons over 7 years of age. In addition to decennial booster doses of tetanus and diphtheria toxoids during adult life, the Advisory Committee on Immunization Practices (ACIP) recommends review of vaccination history for adolescents at age 11–12 years and for adults at age 50 years to enable health-care providers to administer any required vaccine.

All partially immunized and unimmunized adults should receive vaccine, as should those recovering from tetanus. The primary series for adults consists of three doses: the first and second doses are given 4–8 weeks apart, the third dose is given 6–12 months after the second, and a booster dose is required every 10 years.

Immunization After Wounds

Proper wound management requires consideration for passive immunization with TIG (tetanus immunoglobulin) and active immunization with vaccine. For active immunization, in children <7 years of age, DTaP (diphtheria, tetanus toxoid, and acellular pertussis) or DT, if pertussis vaccine is contraindicated, is preferred to tetanus toxoid alone. For children ≥7 years and adults, Td (tetanus toxoid, diphtheria) is preferred to tetanus toxoid alone; DTaP may be given if the patient has not previously been vaccinated with Tdap.

For clean, minor wounds, Td is administered to persons who have unknown tetanus immunization histories, received less than three doses of adsorbed tetanus toxoid, or received three or more doses of adsorbed vaccine but 10 years or more have elapsed since the last dose.

The recommendations for contaminated or severe wounds are identical, except that vaccine should be given if more than 5 years have elapsed since the last booster dose. TIG is not recommended for clean, minor wounds but is given for all other wounds if the immunization history indicates unknown or incomplete immunization. The dose of TIG for passive immunization is 250 units intramuscularly (deltoid or lateral thigh) in adults and children >7 years old; in children <7 years old, the dose is 4 units/kg. This is thought to produce a protective antibody level in the serum for at least 4–6 weeks. Vaccine and tetanus antitoxin should be administered at separate sites in separate syringes.

Preventive efforts of neonatal tetanus include maternal vaccination, including vaccination during pregnancy, measures to increase the number of in-hospital births, and training for nonmedical birth attendants.

Adverse Effects of Tetanus Toxoid

Tetanus toxoid is well tolerated. There is no evidence that tetanus toxoid use is associated with Guillain-Barre syndrome or any other significant adverse effect [30].

Prognosis

The prognosis is influenced by various factors, including age, immunization status, underlying illness, and quality of supportive care. The most important factor determining outcome is the quality of intensive care. Mortality rates are low in countries where good quality intensive care units are available. In developing countries, with poor access to supportive care mortality rates as high as 50 % may be seen [18]. The outcome is poor in neonatal tetanus, in the elderly, and in those with a short incubation or a short period from onset of symptoms to the first spasm. In the 124 cases reported in the USA between 1995 and 1997, fatalities ranged from 2.3 % for persons aged 20–39 years to 16 % for persons aged 40–59 years to 18 % for persons over 60 years [12].

The clinical course of tetanus extends over 4–6 weeks, and patients may require ventilatory and intensive care support for up to 3 weeks during this period. Increased tone and minor spasms can last for months, but recovery is usually complete. Most patients will benefit from physical therapy in a rehabilitation unit prior to discharge home.

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Neuroleptic Malignant Syndrome

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Introduction

Neuroleptic malignant syndrome (NMS) is a condition characterized by altered mental state, muscular rigidity, autonomic dysfunction, and hyperpyrexia occurring most often (but not invariably) during treatment with antipsychotic and other psychotropic medications [1–4]. NMS remains an enigmatic condition. Despite its decreasing frequency over the last two decades, it is still a cause for concern among psychiatrists and neurologists alike.

The first descriptions of the syndrome ("syndrome malin des neuroleptiques") originated in France [5, 6]. Building upon earlier observances in their clinic, Delay and Deniker described a constellation of signs (temperature elevation, rigidity, delirium) which were associated with a severe and life-threatening neurotoxicity to neuroleptic therapy [5]. Thereafter, reports of NMS appeared with increasing frequency in the literature, and the syndrome was described in relation to treatment with other psychotropic medications (e.g., antidepressants, lithium) and in other conditions such as postoperatively or with dehydration [4, 7–9]. The occurrence of NMS in patients with neuropsychiatric conditions associated with compromised dopamine function (e.g., Wilson's disease, Parkinson's disease, and Huntington's chorea) [9–11] provided impetus to the notion that NMS was due to acute hypodopaminergia. Also, these reports heightened concern that NMS could occur in a variety of pathological states and that NMS would not be limited in risk merely to persons with serious mental illness who are treated with antipsychotic medications (Table 74.1).

Epidemiology

The true incidence of NMS is unknown. Attempts to determine its frequency have been thwarted by diagnostic imprecision, shifts over time, and variance across several diagnostic criteria which have inevitably resulted in divergent formulations of this syndrome and a focus on distinct (psychiatric) patient populations rather than a broader, epidemiologically based approach which looks at drug use and adverse effects across diverse patient populations [1]. That said, it is certain that NMS is considerably less common now than the high incidence figures which were cited in earlier psychiatric

Table 74.1 Conditions in which NMS occurs in the absence of antipsychotic medications

L-DOPA withdrawal in Parkinson's disease
Tetrabenazine therapy in Parkinson's disease
Phenelzine
Tricyclic antidepressants
Metoclopramide
Following surgical procedures

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Table 74.2 Commonly prescribed antipsychotic medications

Agent	Trade name	Daily dosage range (mg)[a]
Typical		
Haloperidol	Haldol	1–30
Perphenazine	Trilafon	4–32
Thioridazine	Mellaril	25–1,800
Mesoridazine	Serentil	25–300
Chlorpromazine	Thorazine	25–800
Molindone	Moban	25–250
Thiothixene	Navane	5–30
Atypical		
Clozapine	Clozaril	12.5–900
Risperidone	Risperdal	1–6
Olanzapine	Zyprexa	2.5–20
Quetiapine	Seroquel	100–800

[a]Representative of the effective doses which are generally used in clinical practice for the treatment of psychotic, nonpsychotic, and neurological conditions

studies [1, 9, 12]. For example, in one of the first studies of the epidemiology of NMS, Pope and colleagues estimated a 1.4 % incidence of NMS in the psychiatric population [13]. Another study found a 12.2 % rate of NMS [14]. Subsequent studies cited a much lower incidence of NMS at 0.07–0.15 % [15–17]. Several factors, alone or in combination, are likely to account for the falling incidence of NMS. First, the diagnostic stringency has improved over time [1, 2]. Second, clinicians are wary of this condition and, consequently, are apt to discontinue antipsychotic medications and to institute supportive measures promptly so as to avert the full-blown syndrome. Third, prescribing practices with antipsychotic medications have changed: Doses have decreased over time, the practice of "rapid neuroleptization" is now obsolete, and the typical antipsychotics have been replaced by new, "atypical" antipsychotics in many psychiatric settings. Table 74.2 illustrates representative compounds in the typical (older) antipsychotic and atypical (newer) class. The atypical antipsychotics appear less likely to induce NMS [18, 19]. Finally, it cannot be discounted that some other factors of pathogenic importance (e.g., low serum iron or genetic predisposition to NMS) may have declined in frequency. While NMS is less common than in previous decades, it remains as one of the most acute and serious of the neurologic side effects of antipsychotic therapy.

Etiology and Pathogenesis

There remain large gaps in our understanding of the etiology and pathophysiology of NMS [20]. Various competing theories are postulated. Most of them are speculative without any robust evidence. Some theories try to integrate dysregulation among the various neurotransmitter systems, including γ-aminobutyric acid (GABA), acetylcholine (Ach), norepinephrine, and serotonin, as contributing to the development of NMS. There are also etiologic hypotheses related to endorphin dysregulation [21] and to prostaglandin receptor sensitivity [22]. Current theories, however, do not explain why NMS develops only in a small minority of patients exposed to the offending agents. Other cofactors need to be invoked to explain the idiosyncratic occurrence of NMS [9, 23, 24].

Genetic Factors

Family studies are difficult in NMS because they would involve treating family members with a drug which may not be medically indicated; however, without family studies of drug exposure, the possibility of a genetic basis for NMS cannot be ruled out. So far only few reports of familial NMS have appeared in the literature [25–27]. Deuschl and colleagues reported the occurrence of unrecognized NMS in the twin brother (concordant for schizophrenia) of an index case with schizophrenia and NMS [25]. The twin brother had at least one documented episode with otherwise unexplained fever, tachycardia, and rigidity, suggesting the occurrence of unrecognized NMS. Otani and colleagues described a Japanese family consisting of a mother and her two daughters, all of whom experienced NMS on therapeutic or subtherapeutic doses of neuroleptics [26]. The authors advise extreme caution in starting neuroleptic treatment in a patient with a family history of NMS. Manor and colleagues reported two Ashkenazi Jewish siblings suffering from GM2 gangliosidosis with similar neurological and psychiatric manifestation who developed NMS while on low to very low doses of neuroleptics [27]. Lazarus and colleagues diagnosed possible NMS without rigidity in a mentally retarded patient with an inverted duplication of chromosome 15 [28]. Association between NMS and polymorphisms in the 5HT1A and 5HT2A receptor genes was excluded in a recent study [29]. Analogous to Parkinson's disease, polymorphism of CYP2D6 has been suggested as a possible marker of susceptibility to the NMS [30].

NMS may show a genetic overlap with malignant hyperthermia (MH). However, data from family studies [31], from in vitro muscle contracture testing [32], and from association studies [33] indicate that NMS patients do not share a genetic defect with malignant hyperthermia patients. Six mutations in the skeletal muscle ryanodine receptor (RYR1) gene (associated with MH) were investigated in unrelated NMS patients by single strand conformation polymorphism, and none were detected [33]. Though MH and NMS are similar clinically, they are pharmacologically distinct, implying that cross-reactivity between triggering agents is unlikely to occur.

Dopamine-Blockade Hypothesis

Dopamine hypoactivity is perhaps the most widely favored as a plausible explanation for the occurrence of NMS [34]. There are several lines of evidence linking dopamine hypoactivity to key physical signs important for diagnosis of this complex syndrome.

Firstly, blockage of D2 receptors in the nigrostriatal and hypothalamic pathways is responsible for the clinical signs of muscular rigidity and impaired thermoregulation, respectively [35]. Jauss et al. reported a patient with NMS who underwent single-photon emission computed tomography scan (SPECT) that demonstrated no binding of iodobenzamide tracer to D2 receptors in the striatum during the acute phase of NMS [36], thereby providing experimental evidence highlighting the involvement of the nigrostriatal pathway. Secondly, clinical features of NMS have been seen not only with use of antipsychotics and antiemetics that have dopamine receptor antagonistic properties but also have been reported following withdrawal of dopaminergic medications [37, 38].

Studies measuring dopamine metabolites in cerebrospinal fluid (CSF) also add support to the dopamine hypoactivity hypothesis. Nisijima et al. studied monoamine metabolites of dopamine in the CSF [39] and demonstrated a decrease in homovanillic acid (HVA) levels and increased concentrations of norepinephrine in the CSF of NMS patients versus controls. The study by Nisijima supported not only the dopamine-blockade hypothesis but also hinted at a potential role of noradrenergic hyperactivity in the pathogenesis.

Genetic studies have identified a number of functional polymorphisms in the dopamine D2 receptor gene. A TaqI A genotype A1 allele identified by Suzuki et al. [40] is particularly important. A1 allele carriers have been shown to be prone to developing drug-induced NMS due to lower D2 receptor gene density in the basal ganglia and diminished dopaminergic activity [41]. Finally, favorable therapeutic response in NMS to dopaminergic agents, for example, bromocriptine and lisuride, lends further support to a primary role for dopaminergic mechanisms in the pathogenesis of NMS.

Dopamine–Serotonin Interactions

NMS has often been compared and contrasted with serotonin syndrome (SS) due to a considerable overlap in their clinical manifestations. In the past, these two clinical entities have been thought by some to represent "a spectrum of the same disorder," whereas others have called it "a common end point for two pathophysiological processes" [42, 43]. While NMS is caused by antipsychotic medications, resulting in dopamine hypofunction, SS is attributed to serotonin hyperfunction, due to ingestion of serotonin-enhancing agents [39, 44, 45]. Gomez-Esteban et al. reported a patient who developed NMS with haloperidol, followed by SS associated with fluoxetine use 6 years later [46]. They suggested a common fundamental pathogenic mechanism underlying the two disorders. DSM IV criteria, however, define NMS and SS differently. The American Psychiatry Association DSM IV criteria considered NMS an unpredictable idiosyncratic drug reaction, while SS a predictable consequence of excess serotonergic activity [47].

Serotonergic agents, such as lithium and clomipramine, have also been shown to result in the development of NMS in cases where multiple psychotropic medications are used simultaneously and by mechanisms other than dopamine blockade [48, 49]. There is also evidence to suggest that some of the atypical antipsychotics, that is, aripiprazole, ziprasidone, clozapine, and quetiapine, behave as partial agonists of the 5-HT1A receptor. This partial agonist action is suggestive of a serotonin-mediated pathway in the causation of NMS.

There is, however, a paucity of biochemical evidence to support this serotonin-mediated hypothesis, with only a handful of prospective studies available in literature.

Spivak et al. performed a small prospective study of eight patients with acute NMS and measured serum plasma levels of dopamine, serotonin, and norepinephrine. They demonstrated a statistically significant increase in serotonin/dopamine ratio ($p = 0.015$) in the acute phase of NMS, suggesting that this imbalance of neurotransmitters is crucial to the development of NMS [50]. In contrast, Nisijima et al. demonstrated no significant differences in CSF levels of serum 5-hydroxy indole acetic acid (5-HIAA) – a major metabolite of serotonin – between NMS patients and controls [51].

NMS and SS are thus perhaps best described as simultaneously discrete yet similar syndromes. There is a greater need for biochemical evidence to support the diagnosis of NMS, as the current observations differentiating it from SS are inconsistent [52].

Cholinergic Hyperactivity Hypothesis

Deuschl et al., in 1987, hypothesized that cholinergic hyperactivity is a mechanism for altered consciousness, as demonstrated by a patient with NMS experiencing prompt return to consciousness with utilization of biperiden, an anticholinergic agent [25]. There is however a paucity of subsequent literature that lends support to this mechanism. Tanii et al. reported a 43-year-old male who developed NMS 2 weeks after discontinuation of olanzapine and an anticholinergic agent and switching to perospirone [52]. Although the authors attributed the development of NMS to anticholinergic withdrawal, there is evidence to suggest that partial serotonergic agonists such as perospirone can also cause NMS [53].

In addition, cholinergic hyperactivity fails to account for the clinical symptoms and signs of NMS such as hyperthermia, tachycardia, and labile hypertension. The role of cholinergic excess in NMS is hence best described as controversial.

Opioid GABAergic and Glutamatergic Hypotheses: Slim Evidence for Implication in NMS

The role of the opioid system in NMS is speculative at best. Sandyk reviewed evidence of opioid system involvement in thermoregulation and how this might relate to other symptoms of NMS [21]. At present, opiate antagonists, naloxone, have no role in the management of hyperthermia or muscle rigidity in NMS.

Although not widely endorsed, it is possible that a relative GABAergic deficiency may have a primary pathogenic role in NMS or, alternatively, occur secondary to enhanced dopaminergic turnover reported during NMS [54]. Since diazepam is known to facilitate GABA transmission, it could potentially exert indirect dopaminergic effects mediated by GABAergic feedback loops within nigrostriatal and mesolimbic centers. Indeed, diazepam-responsive NMS has been suggested as a subtype of NMS, given the association of good response to diazepam [54, 55]. On the other hand, the temporal association between clonazepam withdrawal and the induction of NMS in one patient suggests that clonazepam withdrawal may have contributed to induction of NMS [56]. In another patient, the addition of zopiclone to the benzodiazepine nitrazepam produced an NMS-like picture [57].

Based on successful treatment of acute akinetic catatonic patients with intravenous infusion of amantadine, an N-methyl-D-aspartate (NMDA) receptor antagonist, Northoff and colleagues [58] have postulated glutamatergic dysfunction in catatonia as well. There is a paucity of studies showing glutamatergic abnormalities in NMS.

Sympathoadrenal Hyperactivity: A More Central Role?

In contrast to the neurotransmitters above, sympathetic hyperactivity has often been reported in NMS [59]. Increased levels of noradrenaline (NA) and adrenaline in urine and blood have been noted during the active phase of NMS [60, 61]. Schibuk and Schachter suggest that tricyclic antidepressants could predispose neuroleptic-treated patients to NMS by causing an excess of norepinephrine relative to dopamine [62]. Similarly, a tricyclic-induced hyperadrenergic state, compounded by neuroleptic-induced dopamine receptor blockade, has been proposed as a putative mechanism of NMS [60]. Urinary catecholamines and their metabolites are positively correlated with blood creatine kinase (CK) levels in acute phase of NMS, but other clinical features are not [61]. CSF levels of NA were significantly higher in NMS patients than those of controls and returned to normal after recovery [63]. Compared with control levels, CSF levels of 3-methoxy-4-hydroxy-phenylglycol (MHPG), a metabolite of NA, showed no significant change, either during the active phase or NMS or after recovery, although the values showed a tendency to be higher during the active phase than after recovery. These results support a secondary role for increased sympathetic activity during the acute phase of NMS [63].

Gurrera suggests that dysregulated sympathetic nervous system hyperactivity could be responsible for many features of NMS. A predisposition to more extreme sympathetic nervous system activation and/or dysfunction in response to emotional or psychological stress may even confer vulnerability for NMS [59]. Gurrera cogently articulates how a hyperadrenergic state, in combination with variables like dopamine receptor antagonism or psychological stress, would produce the clinical syndrome of NMS [59]. At the very least, the relative mutual independence of neural and adrenal segments of the sympathetic nervous system and the differential effects of norepinephrine and epinephrine at adrenoreceptors may contribute to the unpredictable course and fluctuating signs that characterize NMS. The therapeutic implications of this remain uncertain.

Hypoferremia and Acute Phase Reaction

Acute phase reaction in NMS is a complex physiological reaction involving activation of leukocytes and cytokine-mediated thermoregulatory, neuroendocrine, and metabolic changes. Hypoferremia, or low serum iron, was described by Rosebush et al. to be an epiphenomenon in the acute phase of NMS. Rosebush and Mazurek found that 95 % of patients who developed NMS had reduced iron levels. This seemed to accompany rather than precede the development of the syndrome, and the levels returned to normal upon resolution of NMS [64–66]. The exact mechanism for this serum iron reduction is not clear. Weiss et al. demonstrated that anti-inflammatory cytokines, such as IL-4 and IL-13, caused uptake of iron by activated macrophages [67, 68]. Others have suggested the role of hepcidin – an anti-inflammatory molecule induced by the liver during the acute phase that mediates iron homeostasis [69].

There is a body of evidence that implicates low serum iron levels in increasing risk for NMS. In a study from Australia, Lee et al. studied 55 patients with catatonia during a 3-year period. They measured serum iron in 39 patients and found it to be low in 44 %. Patients with low iron and normal serum iron were then retrospectively compared. Low serum iron levels were found to be associated with malignant catatonia, excited catatonia, and a poor response to benzodiazepines [55]. In their study, a total of five patients with malignant catatonia developed NMS and each of these had received neuroleptics. Patients with malignant catatonia, on neuroleptic medications with low serum iron levels, were at high risk of developing NMS. This study suggested that hypoferremia might predict development of NMS in patients on concurrent neuroleptics for catatonia.

Similarly, Peralta et al. reported 40 patients with catatonia compared with 40 non-catatonic patients. Catatonics had significantly lower mean serum iron than non-catatonics.

Serum iron <50 μg/dl was significantly more prevalent in the catatonic (35 %) than in the non-catatonic (7.5 %) group. Severity of catatonic symptoms was inversely correlated with level of serum iron ($r = -0.34$, $p = 0.002$) [70].

The observation that low serum iron occurs in NMS and non-NMS malignant catatonia, and the evolution of the latter into NMS following exposure to neuroleptics, provide support to the hypothesis that NMS could be a form of malignant catatonia and that the two conditions may share similar pathophysiology. Although low serum iron is found to be associated with catatonia and NMS, its role as a causative factor needs further investigation.

Postmortem Changes

There do not appear to be consistent pathologic changes of brain structures based on postmortem NMS reports. One autopsy study of NMS has implicated anterior and lateral hypothalamic nuclei in NMS, with preservation of remaining hypothalamic nuclei [71]. These findings, however, were not confirmed in other pathologic studies of NMS patients [72–75]. A finding in several postmortem studies was that of cerebellar degeneration, with particular involvement of the Purkinje cell layer. This finding was postulated by several investigators to reflect the effects of hyperthermia rather than any underlying pathophysiology of NMS [73, 75]. Slettedal et al. demonstrated similar findings in two patients with the serotonin syndrome [76]. Similar cerebellar changes have been demonstrated on autopsy in patients with severe hyperthermia from other causes [75].

Postmortem studies of three patients with NMS-like syndromes demonstrated decreased levels of norepinephrine, catechol-o-methyltransferase (COMT), and homovallinic acid (HVA) in all three patients [73]. The investigators used these findings to suggest that cholinergic depletion may have contributed to dopamine blockade in these patients. Gabellini et al. [72] reported a case of an AIDS patient with two clinical episodes of NMS induced by antipsychotics and antiemetics, respectively. In this patient, there was a marked loss of dopaminergic neurons in the substantia nigra. While this pathologic finding is typical of AIDS, the authors postulate that a relative dopaminergic loss made the patient more susceptible to dopamine blockade by pharmacologic agents. In a study of both brain and muscle tissues following a resolved case of NMS, investigators noted prominent myopathic changes in muscle tissue but normal brain tissue [74]. They used these findings to suggest that the primary effects of NMS may be exhibited in the muscle rather than the brain.

Animal Models

There have been a number of studies that investigated animal models of NMS. Swine susceptible to porcine stress syndrome, a genetic disorder of swine characterized by hyperthermia, muscle rigidity, and autonomic dysfunction, were identified as a possible animal model for NMS. The administration of both haloperidol and lithium produced the syndrome in two of three susceptible swine, but only one of three non-susceptible ones [77]. The syndrome was only induced by administering both agents simultaneously and was not prevented by pretreatment with bromocriptine. The swine animal model has also been used to support the role of serotonin in the development of NMS. When mutant and wild-type swine were exposed to the serotonin-2 agonist 1-(2,5 dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride (DOI), both groups developed NMS symptoms. The susceptibility of wild-type swine to DOI demonstrates the potential role of serotonin in the development of NMS [78].

Tanii et al. [79] demonstrated a model of an NMS-like syndrome in genetically normal rabbits that was reversible with the administration of dantrolene. Symptoms of fever, muscle rigidity, and elevated CK were induced in the rabbits after administration of haloperidol, atropine, and exposure to elevated ambient temperatures. The investigators used this model to propose the interaction between dopamine blockade, cholinergic deficiency, and exposure to risk factors as necessary to produce NMS symptoms. Another study demonstrated the importance of dopamine activity in the perifornical–lateral hypothalamus (pfLH) in thermoregulation in rats [80]. Based on their observations, the investigators proposed that dopamine activity in the pfLH plays a central role in NMS pathophysiology.

Etiology and Pathogenesis: Conclusions

As yet, no clear theory of etiology or a unified model of pathogenesis of NMS exists. Part of the problem lies in how the syndrome is defined, whether it is a unitary syndrome or a heterogeneous conglomeration of various iatrogenic conditions [1]. If the boundaries of the syndrome are broad and over-inclusive, it will be difficult to arrive at a single theory or model of etiopathogenesis. It is apparent that a dysregulation or imbalance of various neurotransmitter systems may be involved. Such imbalances may be aggravated by noradrenergic or serotonergic actions of drugs which are co-administered with neuroleptics or, alternatively, by physiologic changes involving these neurotransmitters associated with psychosis [20].

The dopaminergic theory needs to be revised in view of the recent advances in cloning of various dopaminergic receptors. Instead of focusing on D2 receptor blockade alone, we need to consider involvement of both D2/3/4 and D1/5 subfamilies of dopamine receptors and their interactions with other neurotransmitter receptor systems. Alterations in second messenger system functioning and state-dependent changes in receptor sensitivity and function also need to be taken into account. The availability of in vivo receptor imaging using positron emission tomography (PET) or SPECT may help elucidate the changes in receptor occupancies in

various CNS regions which may be involved in the pathogenesis of NMS.

Clinical Presentation

There has been a significant increase in recognition and management of NMS in the last decade due to the proliferation of literature in this field [81, 82]. The severe and potentially life-threatening nature of this idiosyncratic reaction makes it critical for physicians and nursing staff to recognize it early and appropriately direct clinical interventions. Clinical presentations vary from mild to severe and often present along a continuum. Woodbury and Woodbury described five stages of NMS spectrum-related symptoms that include (1) stage I, drug-induced parkinsonism; (2) stage II, drug-induced catatonia; (3) stage III, mild, early NMS; (4) stage IV, moderate NMS; and (5) stage V, severe NMS [83]. Treatments are determined based upon severity as well as duration and characteristics of symptoms present.

Drug-Induced Parkinsonism

The symptoms of NMS classically evolve over 24–72 h. Caroff et al. reported onset of NMS within 24 h in 16 % patients and within a week in 66 % of patients after initiation of antipsychotic medications [84, 85].

Due to the basal ganglia dopaminergic involvement, the first features to develop are tremor and cogwheeling rigidity. A case study by Addonizio [86] demonstrated that the development of rigidity preceded hyperthermia in 91 % of the patients. The subsequent development of bradykinesia results in progression to a parkinsonian phenotype. Withdrawal of the offending agent at this time results in regression of symptoms.

Drug-Induced Catatonia

Dystonia or abnormal posturing, mutism, dysarthria, and involuntary movements can occur in the parkinsonian subtype of NMS. This stage may be confused with a host of neurologic, psychiatric, or metabolic disorders. Thus, the differential presents a challenge for the treating clinician [87]. Acute lethal catatonia is a life-threatening neuropsychiatric emergency that mimics NMS and must be ruled out. Initial features such as psychosis, automatisms, and negativism often precede the onset of motor symptoms in patients with lethal catatonia. Posturing with waxy flexibility is also unique to acute lethal catatonia and is not seen in patients with NMS [88, 89].

Mild, Early NMS

The prodrome of drug-induced parkinsonism and catatonia progresses to full-blown NMS if neuroleptics are continued. Hyperthermia and autonomic changes follow the changed mental status and rigidity. Typically body temperature exceeds 39 °C; however, occasional case reports have been reported without fever [90]. This stage very quickly progresses to moderate or severe NMS if left untreated. In an analysis of 340 cases, mental status changes were followed by rigidity, hyperthermia, and autonomic dysfunction, respectively, in 70 % of patients [90].

Moderate to Severe NMS

Moderate and severe NMS are characterized by a variety of symptoms and sometimes can be differentiated only by fluctuations in severity. Severe rigidity, coma, hyperthermia, tachycardia, and blood pressure fluctuations are a hallmark of this disease process. Blood pressure typically shows increases in both systolic and diastolic pressures. Harsch [91] reported a mean systolic increase of 42 mmHg and a mean diastolic increase of 36 mmHg with a mean pulse of 136 (range 112–180) beat/min. Other autonomic abnormalities include diaphoresis, sialorrhea, and urinary incontinence.

Individuals with NMS have characteristic abnormalities on laboratory testing, most prominently elevated creatine kinase levels (CK). Mean CK elevation is usually in the range of 3700–5,000 units/l; however, levels are not consistently related to the degree or duration of rigidity [92].

In addition to abnormal CK, white blood cell count is also often elevated and peaks at 24–48 h, with a range of 10,000–40,000 cells/ml. Hyperthermia results in the development of severe dehydration that leads to abnormalities in serum electrolytes. Rigidity can cause accelerated rhabdomyolysis and renal failure. Myoglobinuria, proteinuria, hyaline casts, and white and red blood cells in the urine are often seen. Urine volume may drop to less than 500 ml/day, with a urine/plasma creatinine ratio of more than 40 or urine osmolality of higher than 500 mosmol/kg [24]. Other nonspecific abnormal laboratory values may include an increase in serum transaminases, lactic dehydrogenase, alkaline phosphatase, and aldolase.

Complications and Residual Symptoms

NMS is associated with a variety of medical complications. Muscle rigidity and rapid breakdown with rhabdomyolysis is one of the most frequently encountered complications and is an important predictor of mortality. Adequate hydration, urine alkalization, and monitoring serial renal function panels can prevent the development of renal failure.

Deep venous thrombi and pulmonary embolism often result from protracted immobility and severe rigidity that impair venous return. Respiratory failure may also occur due to decreased chest wall mobility and autonomic dysfunction. In addition, altered mental status may increase the risk for aspiration pneumonia in about 20 % of patients [93]. Autonomic dysfunction can also predispose to cardiac arrhythmias and myocardial ischemia that might be lethal [94].

Early recognition and treatment of NMS is critical in preventing long-term and residual symptoms. Patients with underlying structural brain disease are particularly susceptible to residual catatonic and parkinsonian symptoms [95].

Follow-up studies (of sufficient sample and duration of observation), to accurately determine the occurrence and pattern of residual symptoms after NMS, are lacking. Hyperthermia, which is a cardinal feature of NMS, may lead to cerebellar neuronal degeneration and permanent cerebellar ataxia [3]. Individuals who are on concomitant lithium therapy when NMS occurs may be particularly prone to risk of pancerebellar damage [96]. This may occur even at lithium levels that are within "therapeutic range." A variety of chronic neurological abnormalities persist after resolution of NMS, including mutism and cognitive impairments [97]. Generally, cases of residual cognitive impairment are also associated with elevated temperature as a component of NMS.

Diagnosis and Evaluation

NMS was first described by Delay and Deniker [98] as a syndrome of pallor and hyperthermia. They described three main groups of symptoms: (1) hyperpyrexia with temperature of between 38 and 40 °C within 24–48 h; (2) akinesia, stupor, hypertonicity, or dyskinesias; and (3) pulmonary symptoms, for example, congestion or infarcts accompanied by dyspnea and signs of asphyxia. NMS continues to be a descriptive syndrome, and the absence of concrete criteria has led to its misdiagnosis and confounding by other syndromes which are of a superficially similar clinical profile.

There currently exists no "gold standard" technique to diagnose NMS. Several diagnostic criteria have been established over the years by formal consensus and expert review which include classifications by Kurlan et al. [99], Levenson [100], Sachdev et al. [24], and Adityanjee et al. [1], and the DSM IV consensus [47]. The most prominent and widely accepted of these until recently were the DSM IV criteria that required the presence of severe muscle rigidity and hyperthermia, and two or more associated symptoms which include impaired consciousness, mutism, tremor, dysphagia, incontinence, diaphoresis, elevated blood pressure, increased white count, and raised CK levels [47].

Most recently a study by Gurrera et al. [81] established an international NMS consensus regarding diagnostic criteria using the Delphi technique. Their 2011 study assigned scores to each diagnostic feature in order of its importance relative to others. In contrast to prior scores, these criteria provided critical cutoffs for temperature, CK elevation, blood pressure elevation and fluctuation, hypermetabolism, and changes in respiratory rate.

Although these criteria require validation prior to application in clinical settings, they do reflect a step forward in the field, as they highlight the relative importance of individual elements, include critical values that provide more objective guidelines for evaluation of these patients, and represent a consensus of worldwide experts in the field.

A high index of suspicion should always be maintained for NMS, particularly in patients on neuroleptics and those in whom dopaminergic medications were recently tapered. Evaluation must be prompt and aimed at excluding other neurologic, toxic, infectious, or metabolic conditions that can masquerade as NMS (see section on Differential Diagnosis). A medical evaluation also helps to identify concurrent medical illnesses and complications of NMS. A thorough physical examination, including a detailed neurological evaluation, should guide the clinical evaluation. For the sake of uniformity, extrapyramidal symptoms should be serially assessed on standardized extrapyramidal symptom rating scales such as the Simpson–Angus neurological rating scale [101], catatonic symptoms on the Francis–Bush catatonia scale [82, 102], and altered consciousness should be assessed on the Glasgow coma scale [103]. Careful vital signs monitoring and telemetry is essential to detect any autonomic instability.

Laboratory evaluation must include complete blood counts, serum electrolytes, CK levels, urine microscopy, protein, and myoglobin testing. A lumbar puncture and brain imaging, such as non-contrast CT and MRI, are often necessary to exclude infection and structural brain disease. Electroencephalography (EEG) is often performed in keeping with the presence of altered mental status and demonstrates mild to moderate diffuse encephalopathy. Whenever indicated, other optional tests such as toxicology screen, lithium levels, arterial blood gases, and coagulation studies should be ordered. SPECT or PET scan for receptor occupancy is not indicated but may be performed in the research setting.

Differential Diagnosis

While NMS has a classic tetrad of symptoms of altered mental status, rigidity, hyperthermia, and autonomic instability, a wide array of disorders can present with similar symptoms. As NMS is considered a diagnosis of exclusion [37], it is essential to consider a broad array of diagnostic possibilities prior to arriving at a diagnosis of NMS. As noted in Table 74.3, various categories of disease can lead to an NMS-like picture. Other medication-induced disorders may mimic

NMS. These include malignant hyperthermia, neuroleptic heat stroke, serotonin syndrome, parkinsonism-hyperpyrexia syndrome, and either abuse or withdrawal of several drugs.

Table 74.3 Differential diagnoses of neuroleptic malignant syndrome

Infection
Central nervous system
Encephalitis, meningitis, rabies, tetanus
Systemic
Sepsis secondary to localized infection
Drug-Induced States
Adverse effects of psychotropic drugs
Neuroleptic heat stroke, serotonin syndrome, central anticholinergic syndrome
Other medication effects
Malignant hyperthermia
Medication withdrawal
Parkinsonism-hyperpyrexia syndrome, baclofen withdrawal
Drugs of abuse and toxins
Ecstasy, strychnine toxicity (heroin, pesticides)
Autoimmune
Encephalitis lethargica
Stiff man syndrome
Metabolic conditions
Mitochondrial disease
Inherited disorders of catecholamine production
Psychiatric conditions
Acute psychosis, with agitation
Catatonia

Table 74.4 illustrates clinical and laboratory differences that might be anticipated with NMS versus serotonin syndrome.

A variety of infectious causes may present with an NMS-like syndrome, including systemic sepsis and central nervous system infection such as meningoencephalitis, rabies, and tetanus. Autoimmune encephalitis and nonconvulsive status epilepticus are other neurological diagnoses to consider in such patients. Finally, metabolic conditions such as Leigh's disease, mitochondrial disorders, and inherited disorders of catecholamine production may lead to acute dystonias that resemble NMS [104]. Given the broad range of potential diagnoses, critical features of the history, physical exam, laboratory, and imaging studies must be sought to corroborate the diagnosis. Nonetheless, considerable uncertainty may remain regarding the final diagnosis in a patient with NMS features and exposure to neuroleptic medications. Consideration is given here to conditions that are life threatening, common, and bear the most resemblance to NMS.

Infections

When assessing a patient with the classic features of fever, rigidity, altered mental status, and autonomic instability, one of the most important diagnoses to rule out is that of acute infection [37, 104]. Both central nervous system infection and other localized sources of infection with associated sepsis can present with fever and altered mental status. Patients presenting with these symptoms in the setting of neuroleptic medication use may present a diagnostic dilemma to the clinician [64]. A careful survey of the patient for common sources of infection, such as pneumonia, urinary tract

Table 74.4 Clinical and laboratory test features that help to distinguish NMS from serotonin syndrome

Features	Neuroleptic malignant syndrome	Serotonin syndrome
Inciting agents	Typical and atypical antipsychotics	SSRI's, MAO inhibitors, tricyclic antidepressants, meperidine
Time to development	1–3 days	<12 h
Clinical features		
(a) Neuromuscular symptoms	Tremor and rigidity	Tremor, rigidity, shivering, ataxia, myoclonus, hyperreflexia, ankle clonus
(b) Gastrointestinal symptoms	Typically not seen	Nausea, vomiting, diarrhea
(c) Mental status changes and autonomic dysfunction	Hyperthermia, labile blood pressure	Mild hyperthermia (not as severe as in NMS)
Laboratory studies – general	Leukocytosis, metabolic acidosis, elevated CK, myoglobinuria, electrolyte imbalances, rhabdomyolysis	Similar laboratory abnormalities but not as severe as in NMS
Laboratory studies – urine metabolite levels	Elevated urine dopamine, epinephrine, norepinephrine, metanephrine, and nonmetanephrine	No elevation in urine levels of 5-hydroxy indole acetic acid (5-HIAA)
Prognosis and recovery	Higher mortality, recovery can take up to 3–4 weeks after withdrawal of offending agent	Benign and patients recover 1–7 days after withdrawal of offending agent

infection, catheter-associated infections, and abdominal cavity infections, must be undertaken.

The initial evaluation should include a careful history and physical examination searching for signs and symptoms of infection. Physical examination should focus on identifying signs of localized infection, such as skin and soft tissue swelling, changes in breath sounds, abdominal tenderness, suprapubic tenderness, or abnormal appearance of indwelling lines and catheters. Detailed neurological examination is essential to evaluate for focal neurologic deficits indicative of a central nervous system (CNS) infection. Additionally, signs of meningeal irritation, such as nuchal rigidity or photophobia, should be elicited. Laboratory evaluations should include complete blood count, blood cultures, and serum lactate, in addition to serum CK. Additional investigations such as specific cultures, chest and abdominal radiographs, lumbar puncture, and neurological imaging should be obtained based on clinical suspicion. If CNS infection is suspected based on history and physical exam, a lumbar puncture is essential to evaluate for inflammatory cells in the cerebrospinal fluid and identify the nature of infection. In NMS, CSF studies may show elevated protein with normal cell counts and glucose [64], and neurological imaging is usually normal [64, 100]. While hypoxia and resulting metabolic acidosis may be present in severe cases of NMS, the only consistently elevated laboratory values are serum CK and white blood cell count which are present in most, but not all, cases [64, 100]. Such elevations may also occur in the setting of sepsis, which may lead to confusion in establishing the diagnosis.

In addition to sepsis and meningoencephalitis, other less common forms of CNS infection may present with an NMS-like picture. Tetanus, the clinical syndrome caused by infection with the bacterium *C. tetani,* causes patients to have tetanic spasms of both axial and appendicular muscles. In late stages of the disease, the tetanic activity is sustained and therefore may resemble NMS [104]. As treatment of tetanus is different from that of NMS, prompt recognition is important in order to improve patient outcome. Similarly, rabies infection may mimic NMS in its early stages with the common symptoms of fever, rigidity, autonomic instability, and altered mental status [104]. Distinguishing features of rabies include a history of animal bite, insidious onset, and the presence of hallucinations. Finally, encephalitis lethargica, a noninfectious, autoimmune form of encephalitis, presents with dyskinesias and neuropsychiatric features that may mimic NMS [104, 105]. This syndrome is responsive to high-dose intravenous steroids and therefore must be distinguished from NMS [106].

Drug–Drug Interactions

While NMS should be considered in patients on antipsychotics medications who present with fever and muscle rigidity, there are other drug-induced neurotoxicities and drug–drug interactions which should also be taken into account as part of the differential diagnosis. This becomes especially important for patients with serious mental illness, treated with multiple psychotropic medications, who are particularly vulnerable to neurological adverse effects. Also, patients with schizophrenia or other serious mental illnesses may be on other systemic medications for comorbid physical ailments, and the high rates of polypharmacy across different drug classes predisposes to drug–drug interactions and toxicities.

Given the broad features of current NMS diagnostic criteria, it is conceivable that some published case reports may have been misattributed to NMS. Hasan and Buckley analyzed published reports of NMS due to the atypical antipsychotic medications (risperidone and clozapine) and found that, not only was NMS misdiagnosed in 50 % of the cases, the rates varied when different diagnostic criteria were applied [18]. Differential diagnoses included known adverse effects of the atypical antipsychotics, drug–drug interactions, drug withdrawal syndromes, seizures, and systemic infections. Strict diagnostic criteria like the ones proposed by Gurrera and colleagues might help to decrease the inconsistencies and misdiagnoses of NMS [81].

Adverse Effect of Atypical Antipsychotics

As a class, the atypical antipsychotics have been characterized by lower rates of extrapyramidal symptoms and muscle rigidity that are commonly associated with the older, typical antipsychotics [107]. This has contributed to some case reports of clozapine-induced NMS to be diagnosed without the cardinal NMS feature of muscle rigidity, though clozapine is virtually without extrapyramidal side effects. It is still unknown if the clinical presentation of NMS differs with atypical antipsychotic medications; however, it is our position that the stringent diagnostic criteria for NMS be maintained to decrease incidences of misdiagnosis or overdiagnosis of the syndrome. For patients on atypical antipsychotics where characteristics of NMS are present, the diagnosis of NMS should only be considered if the complete criteria are met.

Another reason for retaining the established NMS diagnostic criteria is that the side effects profile of the atypical antipsychotics can overlap with many features of NMS. For example, approximately 3 % of patients on clozapine develop a benign hyperthermia during the first 10 days of treatment. Approximately 20 % of patients starting therapy with an atypical antipsychotic will show some signs of autonomic instability, that is, tachycardia, postural hypotension, and instability of vital signs. Thus, clinicians should be conservative in diagnosing NMS when atypical antipsychotics are prescribed.

Contributing to the divergence on NMS criteria may be the overemphasis on CK elevation as a diagnostic criterion. CK elevation is seen in many psychiatric conditions and contexts, including acute psychosis, agitation, following seclu-

sion or restraint, and with the use of intramuscular psychotropic (antipsychotic and other) medications. There have also been reports of isolated CK elevation during treatment with atypical antipsychotics medications, including clozapine, olanzapine, risperidone, and quetiapine, without the development of NMS. In some cases, the CK elevation has been of the magnitude of 13,000 U/L without pathological sequelae of NMS or ill outcome; thus, the increase in CK seen after the initiation of atypical antipsychotic treatment may be benign. Currently, the mechanism and significance of this effect and its frequency with each new drug is undetermined.

Catatonia and Malignant Hyperthermia

There are overlaps in clinical presentations between NMS and catatonia, as well as NMS and malignant hyperthermia (MH). Catatonia is a rare form of psychosis, which presents as a subtype of schizophrenia. When catatonia is diagnosed, it is usually associated with underlying CNS lesion. Characteristics unique to catatonia include a past history of similar presentations, a gradual onset of illness, a predominance of motor signs, the presence of features typical of catatonia (flexibilities cera, ambitendency), and the presence of other clinical signs which are associated with an underlying organic pathology. Unlike NMS, fever is a late effect of catatonia.

MH is a disorder of skeletal muscle calcium regulation. It occurs usually in genetically susceptible patients receiving halogenated inhalation anesthetics or depolarizing muscle relaxants (see Chap. 54). NMS and MH share many clinical features and were once thought to have a common pathophysiological basis; however, research has shown this to be unlikely (see Etiology and Pathogenesis section). In MH, the calcium channel dysfunction in the sarcoplasmic reticulum has been attributed to abnormalities in the ryanodine receptor complex, a receptor system that has been linked to ryanodine receptor gene on chromosome 19. There has not been any significance of this receptor gene for NMS in previous animal studies. There is also no associated increase in anesthetic complications either in patients with NMS or any of their first degree relatives. Furthermore, electroconvulsive therapy (ECT) has been given as a form of treatment to patients with NMS without either the development of MH or exacerbation of NMS.

Treatment and Management

Treatment of NMS or suspected NMS is based upon symptom severity, character, and duration. Both Woodbury and Woodbury [83] and Velamoor and colleagues [108] suggested guidelines for management of NMS, based on a hierarchy of symptom severity. This approach has merit, considering the oftentimes nonspecific presentation of NMS particularly in its early stages. This remains a major challenge for the field [109]. Accurate diagnosis is another challenge [81]. Given the serious and potentially rapidly progressing course of NMS, all individuals with suspected NMS should be monitored in closely supervised settings, usually in a hospital. Individuals who meet criteria for full-blown NMS should be treated in a medical intensive care unit for initial care [3].

Prodromal Phase

Individuals who are being treated for acute psychosis and who exhibit agitation, catatonia, or disorganization should be closely observed, as is good practice for all acutely ill patients. Regular monitoring of vital signs, including temperature (which is not consistently done in some psychiatric settings) should occur. This becomes particularly important in situations where restraints are utilized or when the patient receives injectable antipsychotic medication. Disorganized or catatonic patients may have reduced fluid intake, and this should be closely monitored, encouraging oral fluids and initiating intravenous fluids if the patient becomes dehydrated and is unable to drink. Blood pressure measurements should evaluate for orthostasis. Dosing of antipsychotic medications should be moderate, with adjunctive benzodiazepines utilized for sedation or the management of acute agitation, if possible.

Early/Mild NMS

The most critical intervention in the treatment of early NMS is discontinuation of antipsychotic agents [108, 110]. Benzodiazepines, for example, lorazepam 1–2 mg, may be substituted to manage agitation, and good fluid intake should be assured. The notion that benzodiazepines may prevent NMS from occurring, or may treat mild NMS, has been suggested by some investigators [94], although controlled studies of risk factors have not consistently supported this hypothesis [64]. Discontinuation of lithium is also generally recommended. Lithium has been implicated in the re-induction of NMS among patients with a prior history of NMS [3], although a case-controlled study by Keck and colleagues did not show that the use of lithium was associated with development of NMS [23]. Dopamine agonist medications, such as amantadine, should be continued if already in use, as withdrawal of these agents may worsen NMS [3]. In addition to physical examination and routine laboratory studies, sequential serum CK and CBC with differential should be performed, as well as urinalysis.

Management of full-blown NMS consists of supportive measures and active, specific treatments.

Supportive Measures

Patients should be treated in an intensive care unit with continued vital sign and cardiac monitoring. General measures, such as the use of cooling blankets and antipyretics, may reduce hyperthermia [111]. This is an important objective in the acute care of patients with NMS. Intravenous fluids should be instituted if dehydration has occurred or is imminent [112]. In cases of severe hypertension, short-acting antihypertensive agents such as nifedepine may be utilized [3]. Intensive, skilled nursing care for patients confined to bed, with attendant physical therapy, will prevent the development of decubitus ulcers, which may delay recovery from NMS. Where gag reflex is absent or swallowing is impaired, patients should receive parenteral nutrition to prevent aspiration pneumonia until swallowing improves [3, 92]. Respiratory failure may occur due to decreased chest wall compliance. These patients may require oxygen or intubation and mechanical ventilation in severe cases [92]. Subcutaneous heparin should be initiated to prevent pulmonary embolism and deep venous thrombosis triggered by prolonged immobility. Caroff reviewed 60 cases of NMS and found that supportive therapy was the predominant treatment modality with a mortality rate of 20 % [113]. Later reviews have suggested that improved outcome may be obtained with the addition of specific treatments for NMS [92, 114, 115].

Specific Treatments

In patients who do not appear to be responding adequately to supportive treatment, specific medications should be considered. Clinical conditions that would suggest that specific treatment should be implemented include refractory hyperthermia, persistent rigidity, and rising CK levels. The decision to start specific therapies is usually made after 1–3 days of observation and support [3]. There are a number of treatment options available [115]. Because of the rarity of NMS, the literature on effectiveness of various somatic treatments is not based on prospective, controlled trials but is generally from case series.

Dopamine agonists such as *bromocriptine* and *amantadine* have been utilized effectively to treat NMS [92, 115]. It has been suggested that neuroleptic-induced dopamine antagonism is the primary cause of NMS, and thus dopamine agonists may reverse this effect in the brain [20]. Bromocriptine is one of the most often utilized dopamine agonists for NMS and may be the dopamine agonist of choice [4]. Dosing should be initiated at 2.5 mg bid or tid and increased by up to 7.5 mg/day with no serious side effects [3, 92]. Rosenberg and Green reported that bromocriptine decreased response to treatment time from 6.8 days with supportive treatment alone to 1.03 days with bromocriptine ($p<0.0005$) [92]. Time to complete resolution of NMS was 10 days with bromocriptine, compared to 15.8 days with supportive therapy alone, although this did not reach statistical significance ($p=0.09$). Sakkas reviewed over 700 published cases of NMS and found that mortality was 21 % for supportive treatment alone and decreased to 10 % with bromocriptine [116]. Amantadine is another dopamine agonist that is fairly commonly utilized for treatment of NMS. Sakkas reported that the use of amantadine reduced mortality in NMS from 21 % with supportive treatment alone to 3 % with amantadine.

Based on clinical similarity of NMS to malignant hyperthermia, *dantrolene* has been utilized for the treatment of NMS. Dantrolene can be given intravenously or orally. Tsutsumi and colleagues used a mean dose of dantrolene of 0.97 mg/kg/day for a mean duration of 8.3 days [117]. Rosenberg and Green reported that use of dantrolene reduced treatment response time to 1.72 days with dantrolene, compared to 6.8 days with supportive treatment [92]. Sakkas reported that mortality from NMS treated with dantrolene was reduced to 10 % compared to 21 % with supportive care alone [116]. Greenberg and Gorelick [118] recommend the concomitant use of dantrolene with bromocriptine for some patients. Their protocol includes giving dantrolene 0.25 mg/kg intravenously tid, until rigidity and hyperthermia resolve, and bromocriptine tid for 10 days, which is gradually withdrawn over the next week.

Benzodiazepines may also be used with other agents to treat NMS and are beneficial for the treatment of agitation during NMS [115]. Other more speculative drug treatments that have been utilized for NMS include pancuronium [119], levodopa [100], apomorphine and lisuride [3], and vitamin E [120]. Iron supplementation is proposed as having a protective effect; however, this has not been well supported [3].
Finally, electroconvulsive therapy (ECT) is reported to be an effective treatment for NMS where pharmacotherapy fails [121–123]. Fink proposed that ECT should be utilized as second-line therapy for NMS, after failure of benzodiazepines [121]. Davis and colleagues reported that mortality rates for NMS with ECT were half that of supportive treatment alone [122]. When ECT is utilized, multiple seizures may be required for best response [123]. On the other hand, the use of succinylcholine during the ECT procedure is implicated in causing hyperkalemia and cardiac arrhythmias in patients with rhabdomyolysis or autonomic abnormality [124]. Thus, other muscle relaxants during ECT should be used if rhabdomyolysis is severe.

Post NMS

After the resolution of an episode of NMS, patients often continue to have severe psychiatric illness and are in need of continued pharmacologic care. These patients present a

challenge to the treating clinician, in that recurrence of NMS is a continued risk. Wells and colleagues reported that the risk of reoccurrence of NMS diminishes if at least 5 days had elapsed from recovery from NMS to neuroleptic rechallenge [125]. Rosebush and colleagues recommend a waiting period of 2 weeks between NMS recovery and neuroleptic rechallenge [126]. Harsch [91] recommended that guidelines for restarting neuroleptic drugs include (1) normal CK, (2) state of good hydration, and (3) inpatient monitoring. Use of adjunctive agents such as benzodiazepines, valproate, carbamazepine, and verapamil may help manage behavioral manifestations and allow for lower dosages of antipsychotic medication [23]. For patients who show resolution of the hypermetabolic state, but remain catatonic, ECT may be a useful option. The use of an atypical antipsychotic is preferred for individuals with a history of NMS who require antipsychotic therapy. While atypical antipsychotics have the potential to induce NMS, clozapine may be a strong choice when rechallenging patients with an NMS history. This remains one area of great therapeutic uncertainty, and clinicians should proceed cautiously. A second opinion can be helpful in such circumstances.

Prognosis

In accordance with its title [6], NMS was once considered to carry an ominous prognosis. In adults, early reports cited a mortality rate of 15–25 % [110, 127]. Subsequent reports provide a more favorable outcome with a mortality rate of below 5 % [3]. The decline in mortality reflects more judicious prescribing practices, heightened awareness, prompt diagnosis of NMS, and the success in managing this condition aggressively with supportive measures and with pharmacotherapy [115]. Outcome is better with atypical compared to typical antipsychotics [128].

In general, the prospect of a favorable outcome is greatly enhanced by early diagnosis and prompt management. There are isolated reports of persistent cognitive impairment following an episode of NMS [129, 130]. This adverse effect appears uncommon but has not been systematically studied. It appears that most patients recover from NMS without complications.

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Paraneoplastic Neuromuscular Disorders

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Introduction

Neuromuscular dysfunction in a cancer patient usually represents the side effect of neurotoxic therapy, infiltration of nerves or spinal roots by the tumor, or metabolic or nutritional deficits. Paraneoplastic disorders (PND) may also lead to neuromuscular dysfunction. These cancer-associated syndromes are largely mediated by immune mechanisms. Many PND of the central nervous system are associated with the presence of specific anti-neuronal antibodies in cerebrospinal fluid and serum that serve as markers of the paraneoplastic origin of the disorder (Table 75.1) [1]. For neuromuscular syndromes, the only two antibodies that define a disorder as paraneoplastic are anti-Hu and anti-CRMP5. Patients with Lambert–Eaton myasthenic syndrome (LEMS), myasthenia gravis, neuromyotonia, and stiff-person syndrome may have antibodies against voltage-gated calcium channels (VGCC), the acetylcholine receptor (AChR), Caspr2, or amphiphysin, respectively; however, these antibodies are also found in the non-paraneoplastic forms of these disorders. Identification of these antibodies confirms the neurologic diagnosis but not that of a cancer association. Therefore, the diagnosis of a paraneoplastic neuromuscular disorder is strongly based on clinical history and findings. In patients with a known cancer, the major differential diagnoses must always include the more common mechanisms noted above. For example, mononeuropathies and plexopathies in cancer patients are most often secondary to compression of nerves by tumor or hemorrhage, and infarction secondary to infiltration by leukemia. Tumors that express neuroendocrine proteins such as small-cell lung cancer (SCLC) or that effect immunoregulatory organs (e.g., thymus) or immunoglobulin-producing cells (plasma or B cells) are more commonly associated with PND, and thus, the development of neurologic dysfunction in a patient with one of these disorders should alert one to the possibility of a PND. In patients without a known tumor, one should suspect that a neuromuscular disorder might be paraneoplastic when there is the acute to subacute development of symptoms, when the patient presents with a syndrome known to be frequently associated with cancer or if a specific anti-neuronal antibody is found in serum or cerebrospinal fluid.

In general, the approach to treatment for paraneoplastic neuromuscular dysfunction is the same as for the non-cancer-associated disorder. In all cases, identification and treatment of the associated tumor should be the first concern [2]. For disorders such as LEMS in which the antibodies are pathogenic, therapy to remove the antibodies is often successful. In disorders with stiffness or cramping, pharmacological interventions can be useful. Immunosuppressive interventions are largely empiric with their use based on the presumed immune-mediated pathogenesis and clinical trials with non-paraneoplastic disorders.

Paraneoplastic Sensory Neuronopathy

In contrast to sensory neuropathies, sensory neuronopathies are rare with the two most common causes being paraneoplastic and Sjögren's syndrome. Rather than the distally predominant pattern of symptoms seen in a length-dependent neuropathy, paraneoplastic sensory neuronopathy (PSN) patients have patchy and asymmetric presentation which may mimic a radiculopathy or multiple mononeuropathies. Onset of symptoms is subacute, and frequently, the upper extremity is the site of initial involvement; over weeks or months, symptoms spread and may involve all limbs as well

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Table 75.1 Paraneoplastic neuromuscular disorders: immune and cancer associations

Disorder	Antibody association	Cancer when associated	Comments
Sensory neuronopathy	Anti-Hu	SCLC, others	Often in association with PEM
Motor neuron disease	None	Breast (upper motor neuron syndrome) Hodgkin's, non-Hodgkin's, SCLC (lower motor syndrome)	About 20 % of patients with PEM have predominant motor neuron dysfunction
Stiff-person syndrome	Anti-amphiphysin, anti-GAD	SCLC, thymoma, breast	Anti-GAD antibodies are mostly associated with non-paraneoplastic cases
Acute necrotizing myelopathy	Anti-amphiphysin, CRMP5, Hu	Lung, breast	
Polyradiculoneuropathy	None	Hodgkin's, non-Hodgkin's	
Chronic sensorimotor neuropathy	CRMP5, Hu None	Lung, others Plasma cell dyscrasia	
Sensorimotor neuropathy associated with malignant monoclonal gammopathies	Autoantibodies targeting peripheral nerve antigens	MGUS, Waldenström's macroglobulinemia, amyloidosis, multiple myeloma, osteosclerotic myeloma, POEMS, Castleman's, any disorder with a paraproteinemia	Includes anti-MAG in 50 % of patients with IgM MGUS
Vasculitic neuropathy	None	Lymphoma, leukemia, SCLC	May be part of PEM
Peripheral nerve hyperexcitability	Anti-Caspr2, likely others	SCLC, thymoma	Morvan's syndrome when there is additional CNS involvement
Myasthenia gravis	AChR, titin, RyR, MuSK	Thymoma	MuSK antibodies rarely associate with thymoma
Lambert–Eaton myasthenic syndrome	VGCC, Sox1	SCLC	Sox1 antibodies strongly support the presence of SCLC
Dermatomyositis	Anti-synthetase, signal recognition particle, anti-translation factor, anti-Jo-1	Ovarian, breast, pancreatic, lymphoma, others	
Necrotizing myopathy	None	Solid tumors	

SCLC small-cell lung cancer, *PEM* paraneoplastic encephalomyelitis, *GAD* glutamic acid decarboxylase, *CRMP5* collapsin response mediator protein, *MGUS* monoclonal gammopathy with undetermined significance, *Caspr2* contactin-associated protein-like 2, *AChR* acetylcholine receptor, *RyR* ryanodine receptor, *MuSK* muscle-specific kinase, *VGCC* voltage-gated calcium channel

as the trunk and face [3]. Pain and/or paresthesias are reported, but the most disabling feature is often proprioceptive loss, resulting in a sensory ataxia [4]. When the loss is severe, patients may have choreiform movements of the hands and feet and may become wheelchair bound from profound proprioceptive loss in the legs. On examination, patients also have impaired vibration sensation; there may be loss of pain or temperature, though typically not as severe as proprioceptive and vibratory loss. Reflexes are depressed or absent [5]. Poor proprioception may make it difficult to fully evaluate strength. However, some patients may also have involvement of not only the dorsal root ganglia but also the ventral horns or the sensory and motor peripheral nerves [6, 7]. Cranial neuropathies which may result in signs and symptoms such as facial paresthesias, impaired taste or hearing, and tonic pupils are felt to be associated with concurrent PEM involving the brainstem [8, 9].

Symptoms of PSN may occur in isolation or as part of paraneoplastic encephalomyelitis (PEM). Additional clinical features may include cognitive impairment, psychiatric symptoms, seizures, cerebellar ataxia, opsoclonus, myoclonus, and dysautonomia of the gut [3, 6, 10].

Anti-Hu antibodies in the serum of a patient with subacute sensory neuronopathy are highly suggestive of a paraneoplastic disorder. In a study of such patients with prolonged follow-up, only 3 % did not have an underlying malignancy identified. There were no clinical features predictive of patients more or less likely to have a cancer [11]. In contrast to the PSN picture associated with Hu antibodies, anti-CRMP5 antibodies and anti-amphiphysin are more likely to be associated with a sensory motor neuropathy [12, 13].

The CSF may show increased proteins and a mononuclear pleocytosis at the onset of PSN or only increased proteins at later stages. Oligoclonal bands and intrathecal synthesis of IgG or anti-Hu antibodies are common findings. Other laboratory studies are usually normal or nondiagnostic.

In a true isolated sensory neuronopathy, one expects to see small or absent sensory nerve action potentials with normal motor nerve conduction studies (NCS) and electromyography in a non-length-dependent pattern. Though clinically apparent motor involvement in patients with PSN is infrequent, electrophysiologic studies in patients with Hu antibodies have found changes not only on sensory NCS but also on abnormal motor NCS, albeit less frequently. Rarely, pure

motor or motor-predominant abnormalities are found. Reduced amplitudes supporting axonal and/or neuronal loss are typical, but mild slowing of conduction velocities in addition to amplitude loss in some suggests there may also occasionally be a mixed axonal/demyelinating process at play [14, 15].

The most commonly associated tumor is SCLC [3]. Other associated tumors include cancer of the breast, cancer of the ovary, non-SCLC, and Hodgkin's and non-Hodgkin's lymphoma, but almost any type of malignancy has been reported. Symptoms usually precede the diagnosis of the tumor by several months to 2 years, although longer periods may occur.

Since dorsal root ganglia cannot regenerate, treatment tends to be ineffective once these cells have been lost. Therefore, early recognition of the syndrome, leading to identification and treatment of the underlying cancer, is the best therapy. Studies of patients with SCLC and anti-Hu-associated PSN and PEM demonstrated that patients whose tumors completely responded to therapy were more likely to have neurologic stabilization or improvement compared to patients whose tumors were untreated or that did not respond to therapy [6, 16].

Other non-cancer-related causes of a sensory neuronopathy include exposure to toxins (chlorobiphenyl), pyridoxine overdose, antibiotics, and immune-mediated disorders, including primary biliary cirrhosis, chronic active hepatitis, anti-ganglioside antibodies, and Sjögren's syndrome [17]. Chemotherapeutic agents, such as paclitaxel, docetaxel, cisplatin, and oxaliplatin, can result in a predominant or pure sensory neuropathy [18, 19]. Thalidomide used to treat multiple myeloma also results in a length-dependent sensory more so than motor axonal neuropathy [20]. An idiopathic form of sensory neuronopathy has been described, which may respond to treatment with immunoglobulins. Chronic sensory ataxic neuropathy associated with IgM anti-disialosyl ganglioside antibodies against GD1b, GQ1b, GT1c, and GD3 should also be considered in the differential diagnosis. Because of its association with eye movement abnormalities, the acronym CANOMAD, or chronic ataxic neuropathy ophthalmoplegia M protein agglutination disialosyl antibodies, has been suggested [21]. Other features may include bulbar signs, facial weakness and paresthesias, and optic neuropathy; both demyelinating and axonal features have been described on electrophysiologic studies [5, 21, 22].

Motor Neuron Disease

Motor neuron disorders (MND) have been reported in some patients with cancer, but for many this is most likely a coincidental finding. Most population-based studies have failed to show any increase incidence in cancer in those with amyotrophic lateral sclerosis (ALS) [23, 24], though a recent report found a slightly higher incidence of cancer, predominantly breast and lung, in patients with ALS than expected [25]. Reports of stabilization or remission of motor neuron symptoms in some patients, and unusual pathological findings such as inflammatory changes in others, also suggest that some cases may have a paraneoplastic origin.

Predominant motor neuron dysfunction, sometimes resembling ALS, occurs in about 20 % of patients with anti-Hu-associated PEM, although with time other areas of the nervous system will become involved. Pure lower motor neuron syndromes which have at least in part improved following treatment of the associated cancer have been reported in patients with renal cell carcinoma and breast cancer [26–28]. Breast cancer has also been found in women with primary lateral sclerosis, a pure upper motor neuron disorder [29]. Improvement of signs and symptoms of MND has been reported following resection of a parathyroid adenoma in some but not all patients [30–32]; patients with typical ALS may not improve and in most the relationship is likely coincidental [32, 33].

Since patients with primary hyperparathyroidism can develop weakness in a pattern similar to ALS, it is possible that some cases were misdiagnosed [34]. Feature that distinguishes PHP-related weakness includes distal loss of pain and vibration senses and the association with changes in mentation and personality [32].

Stiff-Person Syndrome

The stiff-person syndrome (SPS) is characterized by the development of progressive rigidity of the skeletal muscles with superimposed painful spasms. The spasms are severe and can lead to limb deformities and bone fractures. Three subtypes have been described: (1) stiff-limb syndrome with symptoms limited to a limb, typically the distal leg; (2) stiff-person syndrome with stiffness in the trunk and proximal legs; and (3) rapidly progressive and fatal encephalomyelitis associated with rigidity [35]. Both antibodies to glutamic acid decarboxylase (GAD) and amphiphysin have been described in SPS. GAD antibodies can be seen in type 1 diabetes mellitus and may be associated with other neurological manifestations including cerebellar ataxia, limbic encephalitis, epilepsy, and encephalomyelitis [36]. Rarely, paraneoplastic SPS with GAD antibodies has been described in patients with breast cancer, multiple myeloma, and thymoma [37–39]. Amphiphysin antibodies are not uniquely associated with SPS; other neurological symptoms may occur including neuropathy, encephalopathy, myelopathy, and a cerebellar syndrome; when the antibody is present, there is a high rate of cancer found, particularly small-cell lung and breast cancer [40]. In women with SPS and amphiphysin

antibodies, there was a high rate of breast cancer (10/11) and stiffness in the cervical region. There was good response to treatment with high-dose benzodiazepine, steroids, and cancer-specific therapy [41].

Nerve conduction studies in patients with SPS are normal, and EMG may show either continuously firing normal-appearing motor units or grouped units firing in bursts [35].

Response to symptomatic and immunosuppressive therapy is mixed for SPS patients with or without cancer. Paraneoplastic SPS may respond to treatment of the tumor and steroids [37, 40]. Benzodiazepines, baclofen, gabapentin, and levetiracetam may offer symptomatic relief [35, 42, 43]. Intravenous immunoglobulins (IVIg) is useful in patients with non-paraneoplastic SPS and may be effective in the paraneoplastic form of the disorder though perhaps less so when amphiphysin antibodies are present [44, 45].

Acute Necrotizing Myelopathy

Paraneoplastic myelopathy usually occurs in association with dysfunction at other level of the nervous system as in encephalomyelitis or cerebellar degeneration. Isolated paraneoplastic myelopathy is rare and most often described in association with lung or breast cancer. The more commonly associated antibodies are anti-amphiphysin, CRMP5, and Hu. The onset is insidious or subacute and, in more than half of patients, precedes the cancer diagnosis. In one series, CSF abnormalities including lymphocytic pleocytosis and elevated protein and oligoclonal bands were found in many cases [46]. In this series, 23 % of patients were initially diagnosed with primary progressive multiple sclerosis, in part due to the presence of these CSF abnormalities. These authors also found that the presence of symmetric longitudinally extensive tract or gray matter-specific changes on spinal MRI was characteristic of paraneoplastic myelopathy.

Tumor treatment and immunotherapy may provide mild improvement or temporary stabilization, but the majority of patients fail to respond and become wheelchair dependent within 1 year of onset.

The Peripheral Neuropathies

Polyradiculoneuropathy

An acute to subacute polyradiculoneuropathy indistinguishable from the Guillain–Barré syndrome (GBS) appears to occur at a higher-than-expected frequency in patients with cancer, most commonly Hodgkin's and non-Hodgkin's lymphoma. Patients present with the acute onset of a rapidly progressive sensorimotor or pure motor neuropathy. The protein and one pathologic study demonstrated perivascular lymphocytic infiltration of the peripheral nerves and inflammatory infiltrates in Schwann cells [47, 48]. Electrophysiological studies most commonly demonstrate an acquired demyelinating sensorimotor neuropathy typical for GBS, but acute motor axonal neuropathy and acute motor and sensory axonal neuropathy may also be seen. The disorder may occur during active disease, remission, or prior to tumor relapse, and the course of the neuropathy is independent of the lymphoma. Similar to GBS, some patients with paraneoplastic polyradiculoneuropathy respond to plasmapheresis or IVIg, though mortality in patients with cancer and GBS is higher than seen in isolated GBS [48]. Rarely, patients develop weakness and sensory symptoms secondary to motor and sensory neuronopathy that mimics axonal Guillain–Barré syndrome (GBS) [49].

In patients with cancer, the differential diagnosis of acute or subacute polyradiculoneuropathy should include leptomeningeal carcinomatosis, or infiltration of nerve roots and peripheral nerves by leukemia or lymphoma (neurolymphomatosis). In most metastatic infiltrations of leptomeninges and nerves, symptoms are asymmetric, usually associated with pain, and do not evolve acutely.

Chronic Sensorimotor Neuropathy

In many cases, when patients with cancer develop a chronic neuropathy, it occurs after the cancer diagnosis and is more likely related to the side effects of chemotherapy, metabolic dysfunction (such as from failing liver or kidneys), or poor nutrition. Patients present with symmetric, distal paresthesias, sometimes associated with pain. There is loss of deep tendon reflexes and, with time, atrophy of the distal musculature. Cranial nerves are usually spared [50]. In most patients, symptoms will be slowly progressive with weakness developing late. More rarely, some patients may have remitting and relapsing symptoms. There is no associated antibody, and the relationship to the underlying cancer is uncertain.

Electrodiagnostic and pathologic studies demonstrate axonal degeneration, segmental demyelination, and, less commonly, a combination of both. The diagnosis of chronic sensorimotor neuropathies in patients with cancer is usually complicated by superimposed neuropathies secondary to treatment.

A length-dependent sensorimotor axonal neuropathy may precede the identification of cancer in patients with CRMP5 antibodies. Some of these patients have not only a neuropathy but also cerebellar dysfunction [13]. Small-cell lung carcinoma and thymomas are the common associated tumors; time to find a tumor may be longer in patients with CRMP5 antibodies and neuropathy compared to those with anti-Hu-associated neuropathy. Despite this,

patients with CRMP5 antibodies have longer median survival compared to Hu patients [12].

A chronic demyelinating sensory motor neuropathy (similar to CIDP) has been reported in conjunction with breast cancer and CRMP5 antibodies. The neuropathy preceded the cancer diagnosis by 2 years and improved after the breast cancer was treated with wide local excision, chemotherapy, and radiation therapy [51].

Sensorimotor Neuropathy Associated with Malignant Monoclonal Gammopathies

Approximately 10 % of patients with a chronic sensorimotor neuropathy of unknown etiology will have a paraproteinemia including benign monoclonal gammopathy, multiple myeloma, Waldenström's macroglobulinemia (WM), primary systemic amyloidosis, and POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M spike, and skin changes).

Although the exact pathogenetic mechanism is not known, neuropathy can be secondary to the monoclonal proteins targeting neural antigens as in the case of IgM antibodies binding to myelin-associated glycoprotein in nerves. The relationship of the IgG or IgA monoclonal gammopathy with polyneuropathy is less clear. The neuropathy subtype can have variable clinical and electrophysiologic presentations depending on the associated serum paraproteins and the underlying hematologic process.

Treatment for the neuropathies associated with malignant monoclonal gammopathies is not standardized. Due to the slow progression of many of the neuropathies, older age of the patients, lack of randomized trials to determine efficacy, and adverse events associated with different therapies, many reserve treatment for those patients with progressive functional impairment. In general treatment is aimed at the underlying disorder, thus removing the cells that produce the paraprotein or by directly removing the paraprotein from the circulation.

Monoclonal Gammopathy with Undetermined Significance (MGUS)

MGUS is the most common hematologic disorder associated with a peripheral neuropathy. It is a premalignant condition that affects more than 3 % of the general population over the age of 50 and carries a 1 % per year persistent risk of malignant transformation [52]. The most common neuropathy is described as "distal acquired demyelinating symmetric" (DADS) sensory and motor neuropathy. It is very slowly progressive, with the prominence of sensory loss and ataxia, little or no weakness initially, and frequent tremor [53]. In about 50 % of patients with IgM MGUS, the monoclonal protein binds to myelin-associated glycoprotein (MAG), a constituent of normal peripheral nerve myelin. This results in a characteristic change in peripheral nerve myelin, consisting of widening of myelin lamellae demonstrated in electron microscopy, and is likely responsible for the nerve damage [54–56]. The neuropathy with anti-MAG antibodies typically affects older men in their 60s–70s, who develop insidious paresthesias of the distal lower extremities that gradually extend proximally over a period of 10–20 years [57]. Gait ataxia, tremor, and loss of vibratory and position sense are also frequently present. Overall prognosis is good but half of patients will become disabled by 15 years after onset [58].

Electrophysiologically, the findings are consistent with a primarily demyelinating process with absent or markedly reduced sensory nerve action potentials. Motor nerve conduction velocities are significantly slowed, but the degree of distal slowing, and hence prolongation of the distal motor latency, is much greater.

Less commonly, patients with IgM MGUS have antibodies to other peripheral nerve antigens such as ganglioside GM1, chondroitin sulfate, and sulfatide. The phenotype of the neuropathy varies with the antibody. High titers of anti-GM1 IgM are associated with a pure lower motor neuron syndrome with multifocal motor conduction block, while anti-chondroitin sulfate or sulfatide IgM associates with a predominantly sensory neuropathy [59]. Anti-GM1 IgM antibodies are not associated with underlying plasma cell dyscrasia. In the subgroup of patients with IgM MGUS without anti-MAG or other antibody activity, the neuropathy has features of a chronic inflammatory demyelinating polyneuropathy [60].

Waldenström's Macroglobulinemia

Waldenström's macroglobulinemia (WM) is a rare disease defined as having an IgM paraproteinemia and bone marrow (BM) infiltrated by lymphoplasmacytic lymphoma. Associated clinical features are anemia, hepatosplenomegaly, lymphadenopathy, and hyperviscosity, but these are not required for diagnosis [61, 62]. Older series suggested a low occurrence of neuropathy in WM; however, when targeted evaluations are done, a neuropathy is found in almost 50 % of patients [63, 64]. Clinical signs and symptoms suggest small- and large-fiber sensory involvement; on examination, patients may have trouble with tandem walking even with relatively good strength and proprioception. The electrophysiology may demonstrate a sensory axonal neuropathy or a sensorimotor demyelinating neuropathy with associated axonal loss. The former may be associated with anti-sulfatide antibodies and the latter with anti-MAG antibodies. Patients

with the demyelinating features on nerve conduction study tend to have more significant findings on exam [64]. Amyloid and cryoglobulinemia associated with WM may also produce neuropathy in some patients.

Primary Systemic Amyloidosis

Primary systemic amyloidosis is due to the overproduction and organ deposition of immunoglobulin light chains (predominantly lambda). It is also known as immunoglobulin light chain amyloidosis (AL). Clinical features vary according to the organs affected and can include macroglossia, organomegaly (hepatomegaly and/or splenomegaly), cardiomyopathy, or nephrotic syndrome [65]. About 20 % of patients with AL present with a peripheral neuropathy [66]. The neuropathy is predominantly sensory, symmetric, and slowly progressive and more commonly affects the distal lower extremities. There is often prominent involvement of small fibers that results in autonomic dysfunction and pain [67]. Uncommon presentations have been reported such as a multifocal, large-fiber process affecting the upper limbs [68].

Electrophysiologic studies usually show a primarily axonal sensorimotor neuropathy, with decreased compound muscle action potential amplitudes, decreased to absent sensory nerve action potentialss, and normal or mild decreases in conduction velocities with signs of denervation on EMG.

The diagnosis can be confirmed by nerve biopsy is positive for amyloid deposition in most cases with a clinically symptomatic sensory neuropathy. The prognosis of amyloidosis has improved from a median survival of less than 18 months in the 1990s to a 2-year survival of 82 % with autologous stem cell transplant [69, 70].

Multiple Myeloma

One-third of patients with multiple myeloma have electrophysiologic signs of peripheral neuropathy, but only 5–10 % develop clinical symptoms that usually precede the diagnosis of myeloma. The neuropathy is heterogeneous and attributed to perineural or perivascular immunoglobulin deposition, specifically IgM or IgG kappa, with or without associated amyloid infiltration. Patients may develop a mild sensorimotor axonal neuropathy, a pure sensory neuropathy, or a subacute monophasic or relapsing and remitting neuropathy with evidence of demyelination on electrophysiologic and morphologic studies. For the evaluating neurologist, it is important to keep in mind that treatment-related peripheral neuropathies are currently the most frequent cause of symptomatic polyneuropathy in patients with multiple myeloma [71].

Osteosclerotic Myeloma and POEMS Syndrome

The term osteosclerotic myeloma has been used for many years to describe an unusual form of myeloma characterized by single or multiple plasmacytomas that manifest as sclerotic bone lesions. The lesions involve ribs, vertebrae, pelvic bones, and proximal long bones and usually spare skull and distal extremities. The serum M protein is IgG or IgA subtype and almost always lambda light chain restricted. POEMS syndrome is a syndrome defined by the presence of polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes and has also been called Crow–Fukase or Takatsuki syndrome. Almost all patients with POEMS have sclerotic bone lesions, and whether there is a true distinction between osteosclerotic myeloma and POEMS is under debate, and the clinical course of patients with osteosclerotic myeloma is similar whether they meet some or all POEMS criteria [72]. Additionally, almost all patients defined as having POEMS will have coexisting Castleman's disease (see below).

In all cases, peripheral neuropathy is the dominant symptom**.** In contrast to the neuropathy associated with multiple myeloma, the neuropathy in osteosclerotic myeloma/POEMS is fairly homogeneous and recognizable as a chronic, distal, and large-fiber sensorimotor neuropathy, with symmetric proximal spread. The disorder resembles a chronic demyelinating polyneuropathy (CIDP) but has less marked prolongation of the motor distal latencies, has more marked motor amplitude loss in the lower extremities, and is less likely to have conduction block [73]. Nerve biopsy shows mixed primary demyelination and axonal degeneration and uncompacted myelin lamellae [74].

For those patients with single or a few osteosclerotic lesions, a limited field radiation can be effective. For those with widespread lesions, systemic therapy is necessary, although there are no standardized approaches to therapy. Autologous peripheral blood stem cell transplant has become the treatment of choice, particularly in younger patients. Other treatment options include high-dose melphalan, lenalidomide, thalidomide, anti-VEGF monoclonal antibody, and cyclophosphamide [75].

Castleman's Disease

There are several subtypes of this disorder including an asymptomatic localized (unicentric) mediastinal lymphadenopathy as originally described by Castleman [76]. Plasmablastic multicentric Castleman's disease is an aggressive variant that is associated with immunosuppression and HHV-8 infection and is increasingly being described in persons living with HIV infection [77].

Patients may develop several types of neuropathies, including painful sensorimotor deficits, a chronic relapsing

sensorimotor neuropathy, and a predominantly motor neuropathy. Nerve biopsy may show demyelination and axonal loss. The finding of capillary proliferation and endothelial hypertrophy in the epineurium and endoneurium supports the concept that a diffuse vasculopathy may contribute to the neuropathy [78].

Vasculitic Neuropathy

Paraneoplastic systemic vasculitis is a nonsystemic vasculitis that involves small vessels of the skin and, rarely, the nerve. Skin rash or a necrotic skin ulcer may provide a clue to the underlying vasculitis. It is most often but not exclusively described in association with lymphomas, leukemias, and SCLC. Symptoms may precede the cancer diagnosis and often start as a painful, asymmetric sensorimotor neuropathy or as multiple mononeuropathies [79]. Nerve biopsy shows Wallerian degeneration with perivascular infiltrates of the epineurium or endoneurium. Muscle biopsy reveals neurogenic changes and rarely demonstrates microvasculitis as well [80, 81].

Electrophysiological studies may demonstrate a diffuse axonal sensorimotor axonal neuropathy or multiple mononeuropathies [80, 82]. The CSF frequently shows an elevated protein with mild pleocytosis but negative cytology [80, 83].

Paraneoplastic vasculitis of nerve and muscle can develop in association with other paraneoplastic syndromes, such as PEM with or without PSN [80]. There are reports of responses to treatment of the tumor and immunosuppressants (steroids, cyclophosphamide) [83, 84].

Peripheral Nerve Hyperexcitability (PNH)

PNH is a heterogeneous disorder with a constellation of symptoms that may include cramps, fasciculations, spasms, myokymia, neuromyotonia paresthesias, muscle atrophy, and weakness [85, 86]. It is also called Isaacs' syndrome [87], and when neuropsychiatric and autonomic symptoms are present, it carries the eponym Morvan's syndrome [88]. The disorder is characterized by spontaneous and continuous muscle fiber activity of peripheral nerve origin, which can be triggered by voluntary muscle contraction (Fig. 75.1). In approximately half of the patients with PNH, an axonopathy is present. In one-third of these, there is a known inherited or acquired disorder of the motor neuron or axon, while in the remainder no recognizable cause for the axonopathy is found. Electrophysiology shows that the axonopathy may be a pure motor or sensorimotor axonal neuropathy or multiple mononeuropathies [89].

A minority of patients with PNH have an associated cancer (11–13 %) with SCLC and thymoma most commonly found [86, 89]. Patients with paraneoplastic PNH are older, less likely to have sensory complaints, more likely to have proximal muscle weakness, less likely to have muscle atrophy, and are less likely to have an axonal neuropathy on nerve conduction studies and have abundant myokymia [89].

Antibodies erroneously described as targeting voltage-gated potassium channels have been described in 5–54 % of patients with PNH [86, 89, 90]. Recent studies have shown that the potassium channel is not the target antigen but rather an antigen that interacts with the potassium channel including contactin-associated protein-like 2 (Caspr2) [91]. Caspr2

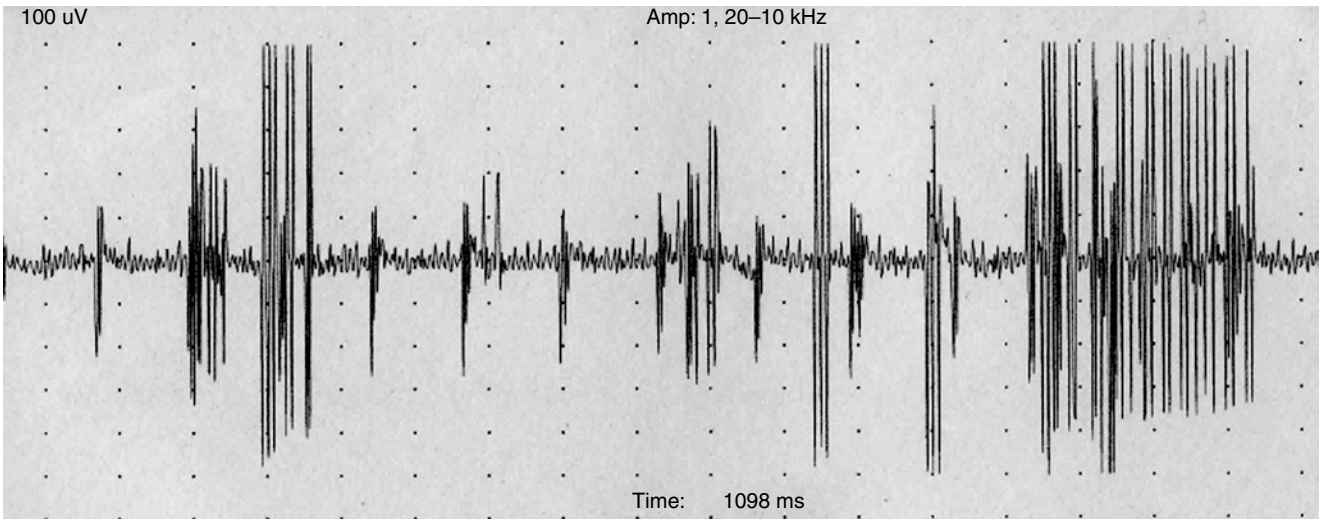

Fig. 75.1 A 34-year-old woman with a recent diagnosis of thymoma develops seizures, hallucinations, and difficulties with short-term memory. Her examination reveals limb stiffness with muscle twitching. EMG of the frontalis muscle demonstrates neuromyotonia with bursts of spontaneous high-frequency discharges. The combination of neuromyotonia and central nervous system dysfunction in encephalitis is known as Morvan's syndrome. Serology evaluation revealed the presence of anti-Caspr2 antibodies

antibodies have been found in patients with thymoma but are also found in patients without cancer. Some patients with Caspr2 antibodies have additional central nervous system dysfunction representing Morvan's syndrome [91, 92]. Patients with Caspr2-associated symptoms are likely to have other immune-mediated disorders such as myasthenia gravis. The combination of symptoms related to the PNH and those due to other autoimmunities such as fasciculations and muscle atrophy has resulted in some patient with Caspr2-associated symptoms being misdiagnosed as having motor neuron disease. The detection of Caspr2 antibodies helps identify a disease that may respond to immunotherapy [91].

In PNH, the spectrum of motor symptoms may range from cramps and fasciculations to neuromyotonia (NMT) with the latter defined by specific electromyographic features. These include bursts of doublets, triplets, and multiplets with maximum intraburst frequency between 40 and 350 Hz. Fasciculations are frequently seen, but fibrillations and positive sharp waves are not. NMT discharges can arise spontaneously or be provoked by nerve stimulation and are more commonly found distally than proximally [93]. Motor nerve conduction studies may show repetitive discharges following the expected compound muscle action potential with waning amplitude following a single stimulus [94, 95]. In contrast to neuromyotonia, myotonic discharges wax and wane in amplitude and have a characteristic dive bomber or revving motorcycle sound. Myotonia is only rarely reported as paraneoplastic in patients with lung cancer; before making this diagnosis, patients should be examined carefully for signs of myotonic dystrophy, myotonia congenita, or paramyotonia congenita [96].

Myasthenia Gravis (MG)

Myasthenia gravis (MG) is an autoimmune disorder characterized by fatigable weakness of skeletal muscles due to antibodies directed against components of the neuromuscular junction, frequently the acetylcholine receptor (AChR) and less often against muscle-specific kinase (MuSK), a surface membrane muscle enzyme. The clinical manifestations may be highly variable in patients; some have purely ocular symptoms (ptosis and diplopia), while others will have generalized disease. Patients with generalized disease may have not only the ocular symptoms but also proximal greater than distal extremity weakness, nasal voice or dysarthria, dysphagia, and shortness of breath. Symptoms may become more apparent with use of the muscle involved; for example, with sustained up gaze, a lid may become droopy or an eye may come down [97].

When MG is suspected, acetylcholine receptor antibodies (AChR) are obtained, and electrophysiologic testing performed. AChR antibodies are found in up to 59 % of patients with ocular only symptoms and in up to 82 % of patients with generalized disease [98]. Routine nerve conduction studies are normal, and with slow rates of stimulation, a decremental response exacerbated by exercise is found. Single-fiber EMG demonstrates increased jitter and blocking [99, 100].

Patients diagnosed as having MG need to have chest imaging as 10–15 % of patients with MG have a thymoma. In addition, MG occurs in up to 45 % of patients with thymoma [101, 102]. MG patients with a thymoma nearly always have detectable AChR antibodies in serum and tend to be less responsive to treatment than those without thymoma [103].

Striational antibodies, which react with epitopes on the muscle proteins titin and ryanodine receptor (RyR), are frequently found in MG patients with thymoma [104]. The presence of titin and RyR antibodies is associated with more severe disease in thymoma-associated MG and in late-onset MG [105]. Muscle-specific kinase (MuSK) antibodies may be found in up to half of the patients with MG without AChR antibodies, and these patients rarely have an associated thymoma [106].

When the diagnosis of a thymoma in a MG patient is established, the neoplasm should be removed. Thymectomy can be performed transternally or through a video-assisted thoracoscopic approach, usually with similar outcome [107]. Almost all patients will have some response to anticholinesterase drugs, but this is rarely complete. Additional immunosuppressive and immunomodulatory therapies are often required with corticosteroids the most commonly used. Steroid-sparing immunosuppressant therapies used to treat MG include azathioprine, cyclophosphamide, and cyclosporine as well as several novel strategies such as the use of antisense oligonucleotides that affect the efficacy of AChR activation [108, 109].

Lambert–Eaton Myasthenic Syndrome

Lambert–Eaton myasthenic syndrome (LEMS) is a presynaptic disorder of neuromuscular transmission. Proximal leg muscle weakness is usually the first symptom reported by patients followed by weakness of the arms. The symptoms usually are insidious progressing over months or years before the diagnosis is made. Ptosis and diplopia are seen in about 25 % of patients. The oropharyngeal and ocular muscles are affected but usually not to the same extent or severity as in myasthenia gravis. About 80–90 % of LEMS patients have some degree of autonomic dysfunction, usually characterized by dry mouth that may be the initial presenting symptom. Other symptoms of autonomic dysfunction include constipation, urinary retention, pupillary constriction, sweating, dry eyes, and postural hypotension. Respiratory muscle weakness is uncommon but may be present in patients with generalized weakness and rarely may be the presenting symptom [110]. Reflexes usually are reduced or absent in LEMS. They can be elicited by the patient actively contracting the muscle group in question for 10 s prior to reflex

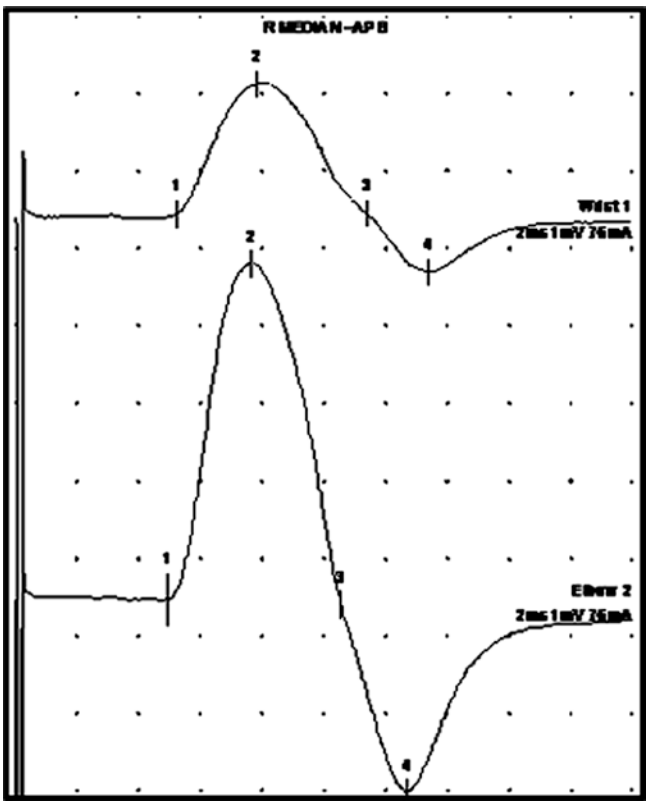

Fig. 75.2 A 57-year-old man is being evaluated for complaints of generalized weakness and difficulty walking for several months. He reports dizziness upon standing and has had several near syncopal episodes. His examination reveals proximal weakness of all extremities and areflexia. *Top tracing*: Right median compound muscle action potential (Compound muscle action potential) at rest which is small in amplitude. *Bottom tracing*: The Compound muscle action potential following 10 s of exercise, demonstrating greater than 100 % increment that is diagnostic for a presynaptic neuromuscular junction defect. The patient was an active smoker and CT of the chest was abnormal. Bronchoscopy revealed SCLC

testing. This increase in reflex activity or muscle strength for a short term after muscle contraction is a characteristic phenomenon called postexercise facilitation.

Repetitive nerve stimulation is the electrophysiological study of choice to diagnose LEMS. The first compound muscle action potential (Compound muscle action potential) amplitude is typically low in these patients; however, high-frequency stimulation (50 Hz) or, preferably, stimulation after brief (10 s) exercise can induce an increase in Compound muscle action potential amplitude (increment) greater than 100 % (Fig. 75.2). Ten-second postexercise stimulation has a sensitivity of 84–96 % and is 100 % specific for LEMS [111]. High-frequency stimulation has comparable sensitivity but is very painful and should be avoided if possible.

Most reports estimate that between 50 and 60 % of patients with LEMS have an associated cancer, most commonly SCLC. However, other malignancies have been reported including prostate carcinoma, thymoma, and lymphoproliferative disorders [112–114]. In most patients the symptoms

Table 75.2 LEMS tumor association prediction score

	Present	Absent
Dysarthria, dysphagia, masticatory, bulbar, or neck muscle weakness	1	0
Erectile dysfunction (women score 0)	1	0
Loss of weight ≥ 5 %	1	0
Active tobacco use	1	0
Age ≥ 50	1	0
Karnofsky Performance Status ≤ 60	1	0

Adapted from [120]
Patient scores directly correlate with increasing risk of having an associated SCLC. Patients with scores of 0–1 have little to no risk, while those with a score of 6 have close to 100 % risk

of LEMS develop before or coincident with the cancer diagnosis. In tumor-associated cases of LEMS, the most common age for the appearance of symptoms is 60 years and 65 % of patients are men. Non-tumor-associated cases can be seen in all ages, more commonly after 35 years with almost an equal frequency in men and women [115].

Patients with older age, male sex, weight loss, and smoking history should be screened with thoracic CT and 18F-fluorodeoxyglucose (FDG)-PET. Screening detected 91 % of SCLC within 3 months and 96 % within 1 year of diagnosis of LEMS. If negative, subsequent screenings with thoracic CT or FDG-PET should be done every 3–6 months, until 2 years after the diagnosis [116].

Antibodies to P-/Q-type voltage-gated calcium channel (VGCC) are responsible for the clinical symptoms of LEMS. These antibodies have been detected in 85–90 % of patients with LEMS, and some studies report a percentage close to 100 % in LEMS patients with SCLC [117, 118]. The antibodies impair the calcium entry to motor nerve terminals and, therefore, decrease the number of quanta released by a nerve impulse. Similarly, the antibodies result in a reduction in the density and distribution of active zone particles, thought to be the morphological representation of the VGCC. Parasympathetic, sympathetic, and enteric neurons are all affected.

In addition to VGCC antibodies, almost two-thirds of patients with LEMS and SCLC have antibodies to SOX1, a developmental transcription factor [119]. SOX1 antibodies are found in less than 5 % of those without SCLC, and thus, their presence is useful in alerting the physician to an underlying tumor in a patient with LEMS. Taking the presence or absence of SOX1 antibodies into consideration, along with several clinical and demographic features such as age of LEMS onset and smoking history, a LEMS tumor association prediction score has been developed that accurately discriminates LEMS with and without SCLC with high accuracy (Table 75.2) [120].

In addition to treatment of the associated cancer, the first choice for symptomatic treatment of patients with LEMS is 3,4-diaminopyridine. The results of four randomized controlled trials reported a significant improvement in muscle strength score or Compound muscle action potential

amplitude after treatment [121]. The drug blocks voltage-gated potassium channels, prolonging the action potential at the motor nerve terminals and lengthening the opening time of the VGCC. In general, 3,4-diaminopyridine is well tolerated; the common side effects reported are perioral tingling and digital paresthesias and gastrointestinal symptoms. The most frequent serious adverse events are seizures; this risk seems to be dose dependent and is described at doses of around 100 mg/day. Supraventricular tachycardia and prolongation of the QT interval are other possible adverse effects of the drug. Some patients with LEMS reported benefits from adding pyridostigmine to 3,4-diaminopyridine [122–124]. If symptoms remain, long-term treatment with prednisone and azathioprine should be considered. Prednisone, given most often in combination with azathioprine, was found to be effective in a retrospective study but its use is supported by the positive results of the combined treatment in myasthenia gravis [125, 126]. Acute treatment with IVIg, plasmapheresis, or additional immunosuppressive agents is rarely needed [127]. One crossover trial reported significant improvement in limb strength after treatment with IVIg [128]. Rituximab was effective in three LEMS patients with severe weakness [129, 130].

Dermatomyositis

About 20–25 % of patients with dermatomyositis develop cancer that is usually diagnosed shortly before the onset of neurological symptoms. The clinical symptoms of dermatomyositis are similar in patients with and without cancer, and except for older age, there are no symptoms or laboratory markers that indicate a paraneoplastic origin. In patients with dermatomyositis, a characteristic reddish or purplish skin rash often precedes the appearance of proximal muscle weakness. The pharyngeal muscles, neck flexors, and respiratory muscles may be involved, leading to dysphagia and rarely ventilatory failure. Reflexes and sensation are unaffected. Other manifestations include arthralgias and contractures, myocardial inflammation leading to congestive heart failure, and interstitial lung disease. Electrophysiological studies show features of myopathy, including motor unit action potentials of brief duration and low amplitude that are often polyphasic. Typically, the levels of serum creatine kinase are elevated and may change with disease activity; normal serum creatine kinase does not rule out dermatomyositis.

About 20-40 % of patients with dermatomyositis have anti-synthetase, anti-signal recognition particle, and anti-translation factor antibodies. An antibody against histidyl-tRNA synthetase (anti-Jo-1) is present in about 80 % of adult patients with dermatomyositis who have associated interstitial lung disease [131, 132].

The most common cancers are ovarian, breast, pancreatic, lung, gastrointestinal, and lymphomas. In one review, the risk for lymphoma was only raised the first year after diagnosis of dermatomyositis, while for the other tumors, the risk of developing cancer was the highest within the first year of follow-up and then dropped substantially in subsequent years but still remaining higher than expected. It has been recommended that patients with a new diagnosis of dermatomyositis undergo cancer screening annually for the first 3 years after diagnosis and then as required for new signs or symptoms suggesting a possible cancer.

Treatment of dermatomyositis is the same for patients with or without cancer. It often responds to corticosteroids and, if refractory, to IVIg.

Paraneoplastic Necrotizing Myopathy

Myopathies with little or no inflammatory infiltrate but extensive muscle fiber necrosis have also been associated with malignancies. Since its first description by Smith in 1969, no systemic studies have been done to assess the overall risk of cancer in patients with this condition [133]. Necrotizing myopathy has been more commonly associated with gastrointestinal tumors, small-cell lung cancer, and breast cancer. The myopathy can precede the diagnosis of myopathy or be discovered within 3 years of the diagnosis [134]. Histopathological findings in paraneoplastic necrotizing myopathies have been reported to be heterogeneous, with a picture ranging from sparse, segmental necrotic lesions to massive necrosis [135, 136]. The hallmark histological feature of a necrotizing myopathy in contrast to an inflammatory one, however, is sparse inflammatory cells confined to damaged, necrotic muscle fibers. Clinically, patients develop a subacute, progressive, and symmetric weakness of proximal muscles. The reported outcomes vary considerably from fast progression with no remission to complete recovery [137]. The severity of the condition does not always parallel tumor progression. Since the pathophysiology of the disease is not well established, treatment of the underlying cancer seems to be the mainstay of therapy. Additional treatment with corticosteroids, IVIg, or other immune modulators may be of benefit to some patients. More studies on the pathophysiology and treatment of paraneoplastic necrotizing myopathy are warranted, as the condition is severe and outcome differs dramatically among patients.

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Acute Neuromuscular Weakness in the Intensive Care Unit

76

David Lacomis and Ahmed El-Dokla

Introduction

Over the last three decades, the following scenario has become increasingly common: a patient is noted to have generalized flaccid limb weakness with – and sometimes without – diaphragm weakness while undergoing treatment of a non-neurologic critical illness [1]. The onset of weakness is usually difficult to pinpoint because of prior sedation, pharmacologic paralysis, or encephalopathy. Furthermore, the weakness or failure to wean from the ventilator usually does not become a concern until the underlying critical illness improves. Rarely, it is determined that the weakness is due to "unmasking" of an underlying neuromuscular disorder such as myasthenia gravis or motor neuron disease. Occasionally, the patient may have a new disorder, such as Guillain–Barré syndrome, that typically presents outside the ICU. Much more frequently, the patient is manifesting features of an acute, ICU-acquired, neuromuscular disorder that is related to either the critical illness, its treatment, or both. Indeed, in most hospitals, it is now much more common for patients to develop newly acquired neuromuscular weakness while in the ICU than it is for patients to be admitted to the ICU for treatment of a neuromuscular disorder [2].

Since ICU patients with newly acquired neuromuscular weakness all tend to have attenuated tendon reflexes and unreliable sensory examinations due to sedation, encephalopathy, or both, it is usually difficult to totally delineate whether the weakness is due to a disorder of anterior horn cells, nerves, muscles, or neuromuscular junctions without ancillary testing. In many patients, several of these components of the motor unit, especially muscle and nerve, may be injured simultaneously [3, 4]; and, in others, central nervous system disorders may coexist with the neuromuscular weakness making diagnosis even more challenging.

Utilizing electrodiagnostic techniques in the ICU in spite of the electrically unfriendly environment has led to better characterization of these processes, and subsequent histopathologic studies of muscle and nerve as well as analysis of animal models have also enhanced our understanding of the major ICU-acquired neuromuscular disorders. These disorders are somewhat broadly categorized as *critical illness polyneuropathy* (CIP), *critical illness myopathy* (CIM), and *prolonged neuromuscular junction* (NMJ) *blockade*. Prolonged NMJ blockade has become less common, likely due to the reduced use of paralytic agents in ICUs, while reports of combined CIM and CIP have increased. These three disorders will be the focal points of this chapter which will relate their clinical, electrodiagnostic, and pathologic features as well as discuss pathogenesis and controversies. However, potential subgroups of the three major disorders and the differential diagnosis of weakness in the ICU patient will also be discussed.

The Spectrum of Weakness in the ICU

It is very difficult to assemble a large prospective study of the various causes of neuromuscular weakness that lead to admission to the ICU or arise while in the ICU. In a retrospective study of 92 ICU patients who underwent EMG from our center, newly acquired disorders were more than twice as common as disorders such as Guillain–Barré syndrome that led to ICU admission. Acute myopathy (mostly CIM) was found to be three times as common as acute axonal sensorimotor polyneuropathy (mainly CIP) [2]. In that study,

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prolonged NMJ blockade was seen only in one patient who also had CIM. On the other hand, there are a large number of studies that prospectively evaluate neuromuscular disorders arising in the ICU. Methodologies vary, but in general, it is known that 25–34 % of patients treated for critical illness develop neuromuscular weakness due to myopathy, neuropathy, or both. Electrodiagnostic studies are abnormal in up to 80 % in some studies [5–10].

The proportions of patients having critical illness myopathy and neuropathy also vary in these studies, possibly due to the types of disorders treated and an overrepresentation of CIP alone if comprehensive electrodiagnostic testing and judicious use of muscle biopsy were not utilized as diagnostic tools in differentiating CIP from CIM or in identifying CIM in addition to CIP.

Etiology and Pathogenesis: Epidemiology

Critical Illness Polyneuropathy

"Sepsis," a clinical response to infection that is also termed the systemic inflammatory response syndrome (SIRS), and multiple organ dysfunction syndrome (MODS) are common problems in the ICU [11]. Bolton and colleagues noted that up to 70 % of prospectively studied ICU patients treated for SIRS or MODS have electrophysiologic evidence of an acute axonal sensorimotor polyneuropathy (PN) they termed CIP, and half of these have clinical evidence of PN [12]. The neuropathy ranges from mild to severe and tends to occur in ICU patients who are hospitalized for at least one and usually more than 2 weeks. The neuropathy occurs as a preexisting "septic" encephalopathy is often resolving [13]. Although there is an association with hypoalbuminemia and hyperglycemia, these metabolic changes could simply reflect the presence and severity of SIRS or MODS [14, 15]. However, hyperglycemia could be a true risk factor, since its intensive treatment in the ICU may be associated with a decreased incidence in newly acquired neuromuscular disorders (discussed again later) [16–20].

CIP may also be triggered by mechanical or thermal injury as well as infection [21].

Critical Illness Myopathy

Patients with CIM, also previously called acute necrotizing myopathy of intensive care, thick filament myopathy, acute myopathy with myosin loss, acute quadriplegic myopathy, and critical care myopathy, are often exposed to high doses of intravenous corticosteroids (IVCS) sometimes in combination with neuromuscular junction blocking agents (NMBAs) [22]. The disorder was first reported in 1977 in a patient treated for status asthmaticus [23], and many subsequent studies involved status asthmaticus patients [24–44]. Thereafter, other critically ill patients, such as organ transplant recipients, and patients with acute respiratory distress syndrome, pneumonia, and chronic obstructive pulmonary disease were commonly noted to develop CIM [45–52]. Children as well as adults may be affected.

There has been an evolution regarding consideration of risk factors. First, it was noted that occasional patients were exposed to NMBAs without IVCS [47]. In fact, there may be a correlation with the dose of NMBA and likelihood of developing CIM [38]. It had also been noted that patients who had received IVCS got high doses, at least a total dose of 1,000 mg of methylprednisolone or its equivalent [22, 32], but some patients had lower corticosteroid exposures. It was then noted that few patients also have coexisting SIRS or MODS, although many status asthmaticus patients who develop CIM do not [44]. Propofol administration [53], severe disuse, and myasthenia gravis [54] in combination with IVCS have also been associated with CIM. Increasingly over the past decade, patients with SIRS or MODS who are not exposed to either corticosteroids or NMBAs were noted to develop the syndrome [55, 56].

One of the more recent larger prospective studies of both CIP and CIM found that there was increased risk for corticosteroids as well as females, duration of ventilation, and organ dysfunction [6]. Other studies of mixed CIM and CIP populations that generally included patients with SIRS or MODS did not clearly identify corticosteroids as a risk factor [7–9, 57, 58]. Risk factors included the severity of illness and the presence of SIRS [8]. Of note, muscle biopsies were either not performed or did not demonstrate myosin loss.

A more recent prospective study utilizing muscle membrane inexcitability as a diagnostic tool in screening 40 patients for CIM during the early course of critical illness also concluded that systemic inflammation appears to be the main risk factor in developing CIM. Risk factors did not include either adjunctive hydrocortisone treatment in septic shock or administration of neuromuscular blocking agents or aminoglycosides [59]. Muscle histopathology was not examined.

There are only several other prospective studies of CIM alone. Up to two-thirds of patients treated for status asthmaticus develop elevations in serum creatine kinase, and one-third have clinical features of myopathy [38]. There was a 34.6 % incidence of CIM in patients with severe chronic obstructive pulmonary disease exacerbations. Biopsies in a subset confirmed CIM. Risk factors included total corticosteroid dose and illness severity as well as sepsis [52]. Approximately 7 % of liver transplant patients develop severe CIM after transplantation [48]. In the liver transplant patients, associated risk factors include higher severity index of critical illness according to APACHE-II (acute physiology

and chronic health evaluation) [60] scores, presence of renal failure, and higher corticosteroid doses [48]. Retrospective studies noted 19–44 % incidences in status asthmaticus patients [32, 41, 44].

Some patients with suspected CIM may actually have *rhabdomyolysis* from infection or pharmacologic agents other than IVCS or NMBAs [61–69]. Rarely, an underlying inherited metabolic myopathy [70] could present in the ICU with rhabdomyolysis. Rhabdomyolysis can also occur in ICU patients or lead to ICU admission following illicit drug use, extreme overexertion, or limb ischemia [58–62, 71–75] with compartment syndrome; these disorders can be differentiated clinically and by toxicology screening. It is uncertain whether rhabdomyolysis or muscle necrosis histologically in association with NMBAs should be categorized separately from CIM. We do not consider it as a separate entity in this chapter. Differentiating rhabdomyolysis from CIM with thick filament loss may be impossible without muscle histologic examination, and even the pathologies may overlap. In patients with presumed rhabdomyolysis, we recommend waiting for at least a month from onset of the attack to obtain a muscle biopsy because early histologic examination will show necrosis regardless of the etiology of the rhabdomyolysis, and selective loss of thick filaments, which may be seen with CIM, may not be seen prior to 2 weeks of onset anyway [22].

A catabolic or *cachectic myopathy* may also manifest in the ICU in some chronically ill patients. The incidence is unknown. This disorder is discussed later in this chapter.

Prolonged Neuromuscular Junction Blockade

Prolonged neuromuscular junction (NMJ) blockade is a very rare cause of prolonged weakness; it tends to occur in patients treated with high doses of vecuronium or pancuronium [49, 76–78]. Affected patients usually also have renal failure. Although these drugs are deacetylated in the liver, they are secreted in the urine [79], and their active metabolites (e.g., 3-desacetyl-vecuronium) accumulate in the setting of renal dysfunction [76]. The first reported patient with prolonged NMJ blockade received gallamine, and that patient also had renal failure [80]. Female sex, acidosis, and hypermagnesemia were also associated risk factors in one study [76]. Hepatic failure [49] and medications with neuromuscular junction blocking properties may also increase susceptibility. The roles of associated sepsis and corticosteroid use in affected patients are unresolved. Some affected patients also have superimposed CIM [47, 49]. Since electrophysiologic and pathologic studies in some reported cases are limited, it is unclear how often these superimposed processes are present and, if so, if they are the actual primary cause of weakness.

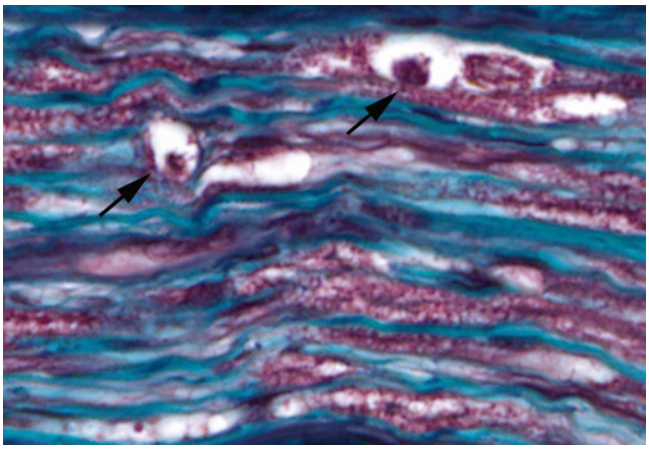

Fig. 76.1 Critical illness polyneuropathy. This sural nerve specimen was obtained at autopsy from a 43-year-old woman who succumbed from anaerobic septicemia and renal and hepatic failure after 34 days in the ICU. She had new-onset weakness, respiratory failure, and a remote history of multiple myeloma. The specimen reveals myelin ovoids (*arrows*) which are indicative of acute axonal degeneration. Elastic trichrome

Pathology and Pathogenesis

The pathogenesis of *critical illness polyneuropathy* is uncertain. Autopsy and surgical pathologic studies reveal (noninflammatory) acute degeneration of sensory and motor axons [15, 81] (Fig. 76.1). It is controversial whether CIP can be a pure motor neuropathy [82]. Careful exclusion of CIM is necessary in such cases. Muscle necrosis is also occasionally noted histologically in some patients with CIP. However, muscle necrosis may be an incidental finding in many ICU patients [83]. Typically, muscle histopathology in CIP reveals angulated atrophic fibers of both fiber types, whereas, in CIM, the atrophy is usually worse in type 2 fibers, and one must look carefully for evidence of myosin loss (described below); otherwise histopathologic features of CIM could be misdiagnosed as neurogenic atrophy.

If CIM is a consideration, biopsy of a proximal muscle might have a higher yield than a distal muscle biopsy as is typically performed along with a nerve when both tissues are biopsied. In our opinion, electrophysiologic and muscle histopathologic findings are complementary in establishing a diagnosis of combined critical illness myopathy and polyneuropathy, but they are not often performed together in clinical practice. In patients who cannot activate motor units, EMG may not differentiate myopathy from axonal neuropathy or if there is motor axonal regeneration with small "nascent" motor unit potentials simulating myopathy. In these situations, muscle biopsy may be particularly useful in determining the presence of myopathy rather than or in addition to CIP. Clinical judgment is needed to determine whether the prognostic implications are useful, since CIM usually improves faster than CIP (discussed later).

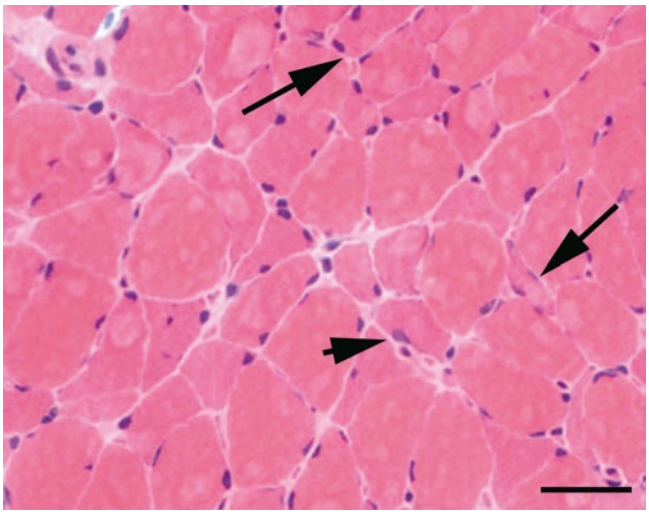

Fig. 76.2 Critical illness myopathy. A hematoxylin and eosin-stained cryostat section of skeletal muscle reveals atrophic myofibers that have abnormal basophilic stippling (see *long arrows*). The lighter *pink* regions in the sarcoplasm of many fibers correspond to myofibrillar disruption. The *short arrow* depicts an atrophic myofiber with an enlarged nucleus (bar = 50 μ)

In CIP, it has been postulated that cytokines and free radicals associated with the SIRS or MODS may adversely affect the microcirculation and ultimately cause endoneurial hypoxia and axonal degeneration [13, 21]. The central nervous system is usually affected as well. Numerous possible causes of axonal dysfunction are yet to be investigated. Malnutrition associated with SIRS and MODS may have a role, but no specific nutritional deficiencies have been identified. Hyperglycemia may play a role, and its treatment reduces the incidence of polyneuropathy and possibly myopathy in the ICU, but the reported risk reduction is likely to be an overestimation of the treatment effect due to the limited diagnostic methods used [84].

A humoral factor (identity undetermined) has also been noted in CIP patients and shown to be toxic to rat spinal cord neurons, but its significance is unknown [85, 86].

Although the cause of *critical illness myopathy* is also uncertain, a number of pathologic changes and "triggering factors" are now well known. Histologically, there is a spectrum of abnormalities [87]. Myofiber atrophy, especially involving type 2 fibers, is very common, and myofiber necrosis and regeneration are present in varying degrees [28, 37, 47]. However, necrosis may be absent. On cryostat sections, the atrophic fibers may have a stippled basophilic appearance (probably reflecting myofibrillar disorganization) with hematoxylin and eosin. Nuclei may be enlarged in some atrophic fibers (Fig. 76.2). The atrophic fibers also tend to stain darkly (purplish) with Gomori trichrome (Fig. 76.3). The intermyofibrillar network often also appears disrupted with the NADH-TR reaction (Fig. 76.4). These features should alert the muscle pathologist that the atrophy is not "neurogenic." Gutman et al. also reported a variant of CIM associated with acute atrophy and regeneration of only type 2 fibers [88]. *The histopathologic hallmark is loss of myosin.* It is most easily detected on the myosin-ATPase stain, but it can be subtle. Myosin-ATPase reactivity is usually patchy, sometimes core-like, or completely absent in some to many non-necrotic fibers studied at alkaline and acid pHs especially if the biopsy is obtained more than 12 days after the likely onset of weakness [34, 37, 56] (Figs. 76.3, 76.5, and 76.6). There may be a subpopulation of fibers that stain less intensely than the lighter normal type 1 fibers at an alkaline pH in which the type 2 fibers are usually dark and type 1 fibers are of medium intensity (Fig. 76.6). The loss of myosin may be confirmed immunohistochemically (Fig. 76.5), biochemically [89], or ultrastructurally (loss of thick filaments with preservation of thin filaments and Z bands) (Fig. 76.7). Myosin loss may preferentially affect type 2 fibers or atrophic fibers [90] in some cases, but both fiber types and atrophic and non-atrophic are usually affected. Loss of thick filaments, although characteristic, is not specific to CIM and has been noted focally in other disorders such as dermatomyositis, thrombotic thrombocytopenia purpura, human immunodeficiency virus infection, and congenital myopathy. Furthermore, in CIM, other structural proteins, such as titin, nebulin, and actin, are also reduced but to a lesser degree than myosin [56].

Myosin loss may be related to a decreased transcription rate or loss of myosin mRNA [91]. In addition, the atrophic fibers of CIM often express fetal myosin and desmin consistent with regeneration [56]. There is also evidence of increased expression of calpain, a calcium-activated protease [56] suggesting that changes in cellular calcium homeostasis play a role in pathogenesis, and calpain may degrade myosin [56]. The calpain expression was noted predominantly in atrophic fibers. Calpain expression was also noted in a dermatomyositis disease control in perifascicular fibers [56]. There is also increased apoptosis [92] as well as upregulation of the transforming growth factor-b/mitogen-activated protein kinase pathway [93]. It is unclear whether or not the ubiquitin–proteasome pathway is upregulated [56, 92].

Intravenous corticosteroids, especially in conjunction with either pharmacologic (NMBA-mediated) or structural denervation, seem to precipitate the process of myosin thick filament loss [22]. In disuse states (including ICU hospitalizations), glucocorticoid receptors are upregulated [94], perhaps rendering critically ill patients more vulnerable to corticosteroid myotoxicity. Likewise, nicotinic acetylcholine receptors are increased in patients receiving NMBAs as they are with denervation perhaps rendering such patients more vulnerable to NMBA toxicity [95]. Interestingly, a mouse neuropathy model suggests that the state of innervation regulates myosin isoforms [96]. Activity levels also influence myosin isoform expression [97], and disuse may also cause end-plate alterations. Single-fiber EMG demonstrates

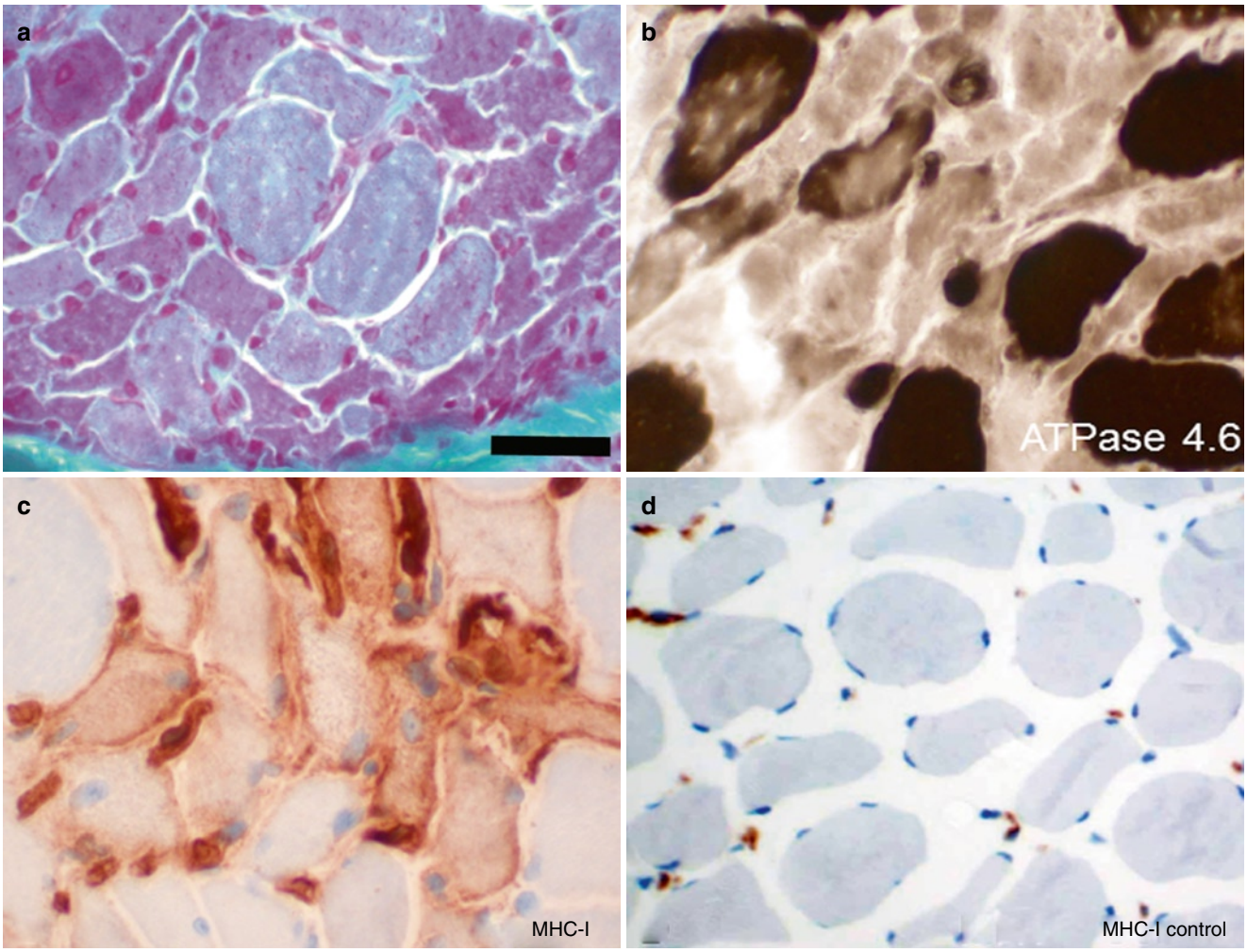

Fig. 76.3 Additional histopathologic features that may be seen in critical illness myopathy. (**a**). Atrophic myofibers often stain abnormally *purple* with Gomori trichrome (bar = 50 μ). (**b**). Typical patchy and homogenous reductions in myosin-ATPase reactivity are also shown in this patient. (**c**). In addition, there is upregulation of major histocompatibility complex type 1 seen as the brown reaction product mainly in the sarcolemmal membranes. Normally, myofibers are nonreactive, but capillaries stain as seen in the normal control (panel **d**)

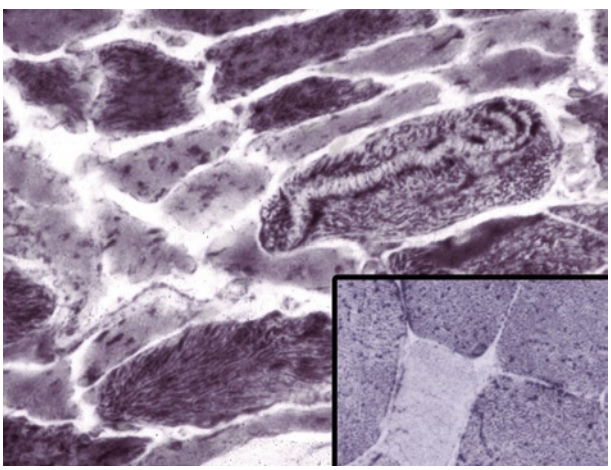

Fig. 76.4 Critical illness myopathy. This NADH-TR-reacted cryostat section illustrates, abnormal, nonhomogeneous staining due to disruptions in the myofibrillar architecture. In particular, the light, atrophic fibers have abnormal clumping of NADH-TR reactivity. The inset reveals normal homogeneous NADH-TR reactivity

a transient increase in mean consecutive differences in muscles subjected to disuse [98].

The roles of SIRS and MODS which often accompany CIM are unclear. Some asthma patients with CIM do not have SIRS or MODS; on the other hand, other patients with CIM have SIRS or MODS without either IVCS or NMBA exposure and develop CIM with thick filament loss [55, 56]. It is uncertain how SIRS or MODS (with disuse) precipitates myopathy in these patients. Sepsis alone may produce a hypercatabolic state resulting in loss of muscle energy stores [99], but it is difficult to explain a relatively selective loss of thick filaments [55, 56]. In patients with SIRS or MODS who receive IVCS with or without NMBAs, these toxins (IVCS and NMBAs) may have enhanced effects due to increased capillary permeability caused by SIRS or MODS [21].

Evidence of inflammation in the form of inflammatory cells is not seen in biopsy specimens, but abnormal upregulation of major histocompatibility complex type 1 is

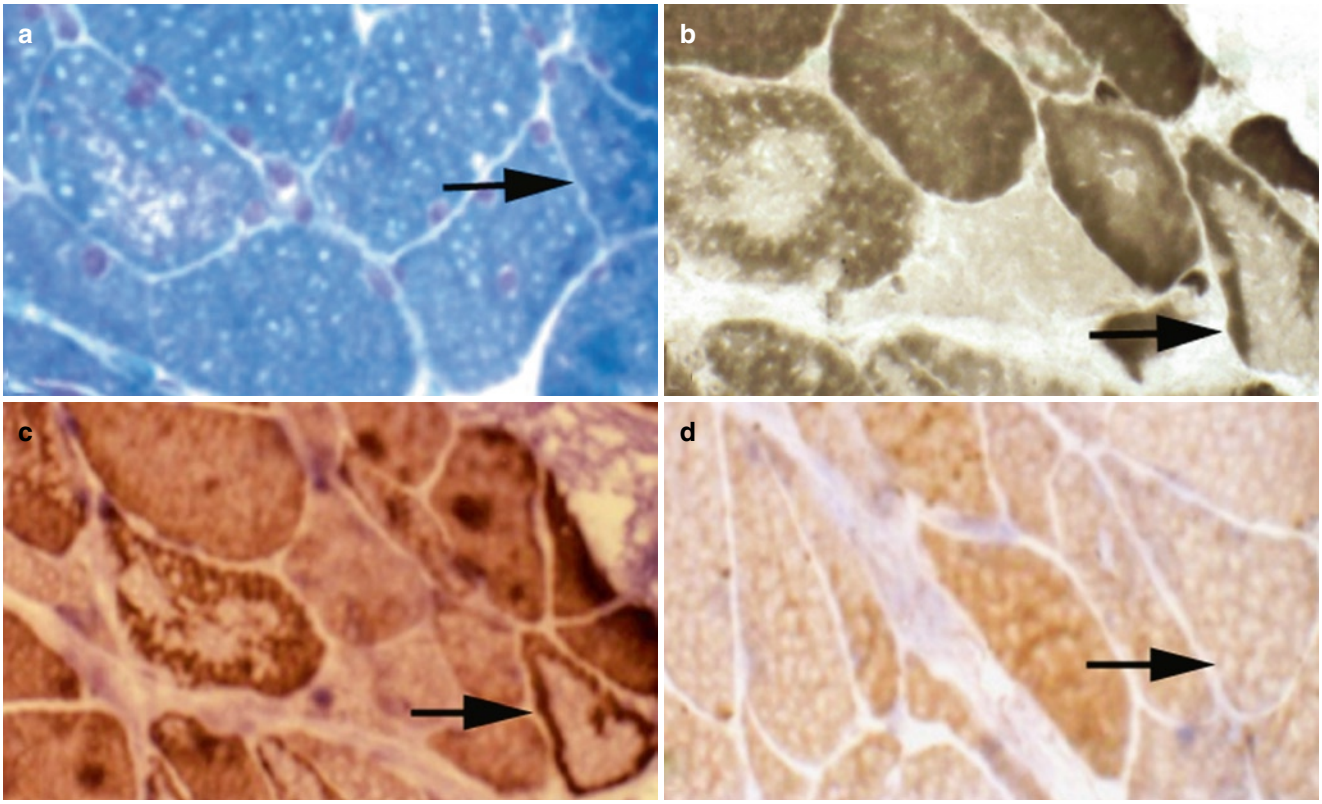

Fig. 76.5 Histologic features of critical illness myopathy from serial cryostat sections. Follow the *arrows* to see the same myofiber in each panel. (**a**). There is an abnormal variation in myofiber sizes without necrosis (Gomori trichrome). (**b**). A myosin-ATPase-reacted section (pH 4.6) reveals reduced or absent central staining in several myofibers and completely absent staining in the fiber at the back of the *arrow*. The abnormal reactivity was also present at pHs 9.4 and 4.3. (**c**). Pan-myosin heavy chain immunoreactivity is absent or reduced in a pattern similar to that illustrated in b. (**d**). Actin immunoreactivity is preserved in this deeper section (bar = 50 μ)

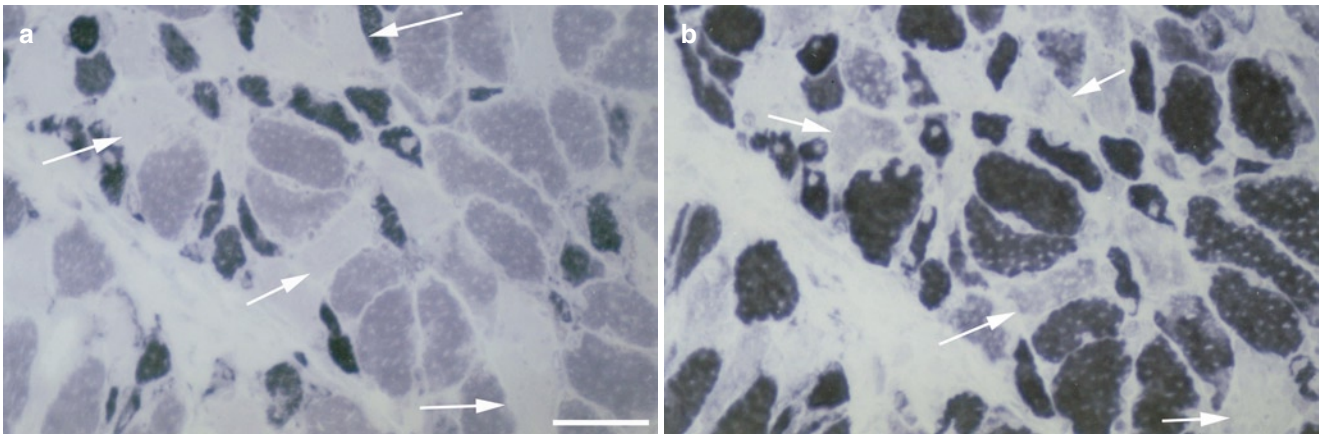

Fig. 76.6 Serial ATPase-reacted sections illustrate myofibers with reduced or absent reactivity at pH 9.4 (**a**) and 4.6 (**b**). At pH 9.4, the abnormal myofibers stain less intensely than the normal light type 1 fibers (see *arrows* for examples of fibers with reduced ATPase reactivity in both panels). Bar = 40 μ

occasionally noted (Fig. 76.3). However, the effects of systemic inflammation on muscle may not be apparent structurally. There is clear evidence of reduced or absent muscle membrane excitability in CIM [100–103]. Perhaps the early effects are on the muscle membrane and involve cytokines and factors such as interleukin-6, insulin-like growth factor (IGF), and IGF-binding protein-1 (IGFBP-I) with impairment of growth-factor-mediated insulin sensitivity [59], and later effects lead to myosin loss. Evidence from animal models points toward abnormal sodium current as the cause of inexcitability [102]. There is relatively increased chloride conductance associated with changes in chloride channel

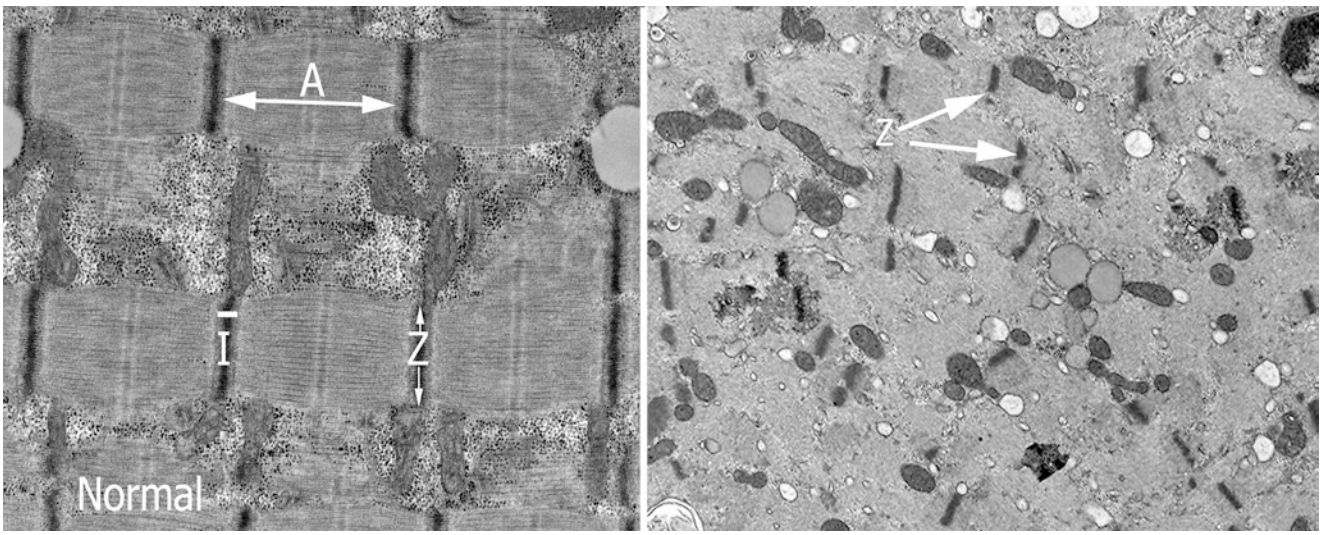

Fig. 76.7 An electron photomicrograph from a patient with critical illness myopathy (*right*) illustrates relatively selective loss of myosin thick filaments and *A* bands with preservation of *Z* lines and *I* bands compared to the normal control on the *left*

mRNA expression. Thus, there is decreased sarcolemmal depolarization when sodium channels open. Sodium current is also reduced, but sodium channel mRNA is increased rather than decreased suggesting that the changes in sodium current are secondary or posttranscriptional and not due to reduced upregulation of Na channels. Others have suggested that calcium ions have a role, but data are conflicting [104, 105]. Oxidative stress may also play a role. It has been hypothesized that loss of sarcolemmal nitric oxide synthase 1 leads to muscle fiber inexcitability by reducing nitric oxide release at the muscle membrane [106]. In septic patients, an increase in muscle nitric oxide synthase 2 mRNA and protein has been associated with peroxynitrate formation and reduced contractile strength [107].

The animal model mentioned above utilizes traumatic soleus denervation and treatment with corticosteroids [108, 109]. After about 7 days of CS exposure, the denervated soleus develops myosin loss. (The animals are otherwise healthy.) If the sciatic nerve is only crushed and allowed to regenerate, the myopathy reverses. Thus, only denervation and CS are required to cause myosin loss as well as sodium channelopathy in this model [91, 102, 108, 109]. Another model using rabbits also provides evidence of negative effects of high doses of intramuscular methylprednisolone on diaphragm muscle function. In the animals, there was a decline in diaphragm maximum muscle tension, myofibrillar disarray, suppression of insulin growth factor type 1, and overexpression of muscle atrophy F-box mRNA as well as activation of the ubiquitin–proteasome pathway [110].

Thus, membrane proteins as well as thick myofilaments and other structural proteins are altered in CIM. Although controversial, it seems that IVCS, functional or structural denervation (NMBAs, denervation-IVCS animal model), critical illness, systemic inflammation, cytokines, possibly disuse, and calpain overexpression have roles in CIM; it is not certain exactly how they trigger myosin loss or incite the pathologic cascade which also involves sarcolemmal ion channels and other structural proteins. Furthermore, it is possible that there are two categories of critical illness myopathy, one with myosin loss triggered by IVCS and one with muscle necrosis only, and that the risk factors differ.

In addition to a thick filament myopathy, the syndrome of CIM may overlap with acute myopathies from *rhabdomyolysis* and with a "catabolic" or *cachectic myopathy* related to chronic illnesses. These disorders warrant separate discussion since they can present in ICU patients. Toxic myopathies that do not result in rhabdomyolysis rarely present in the ICU and are discussed briefly in the "Differential Diagnosis" section of this chapter and extensively in Chap. 68.

The pathogenesis of *rhabdomyolysis* from illicit or pharmacologic drugs, such as cocaine, heroin, and amphetamines [69], is usually unknown. Part of the final common pathway of myocyte injury appears to involve an increase in free sarcoplasmic or mitochondrial calcium with activation of proteolytic enzymes that damage the sarcolemmal membrane [64]. Calcium-related abnormalities may also be shared with CIM and hypermetabolic syndromes associated with rhabdomyolysis (see "Differential Diagnosis" section). Secondary mitochondrial injury could also lead to oxidative cellular damage [65]. Similarly, carbon dioxide gas, when used as an arteriography contrast agent, can also cause rhabdomyolysis, presumably due to tissue hypoxia [111].

Importantly, one particular sedative drug, propofol, that is used in the ICU may cause rhabdomyolysis and has been reported to do so especially in the setting of treatment of nonconvulsive status epilepticus [62]. The pathogenesis is uncertain, but it is important to mention this occurrence, because CIM, prolonged NMBA blockade, and other problems with nondepolarizing NMBAs have led to reduced use of NMBAs and increased use of propofol sedation. Propofol has desirable pharmacokinetic properties (short half-life) and a relatively low incidence of side effects, but at least some physicians recommend that it not be first-line therapy in the pediatric population [62]. In addition to rhabdomyolysis, other reported adverse events include cardiac toxicity, anaphylaxis, movement disorders, seizures, metabolic acidosis, hypoxia, and hypotension. However, it may be difficult to determine if propofol alone or other drugs or associated illnesses cause such adverse events in complicated ICU patients. Nevertheless, it is important to keep in mind that ICU patients receiving propofol who develop weakness may have propofol-induced rhabdomyolysis and not CIM with thick filament loss with which it is also associated [53]. Although the mechanisms of these myopathies may differ, they may be difficult to differentiate without muscle histologic evaluation.

Rhabdomyolysis may also develop in patients with an underlying undiagnosed or known inherited glycogen or lipid storage myopathies in the ICU during stress or fasting. The mechanism of rhabdomyolysis in these disorders is also incompletely understood, but ultimately increased calcium sensitivity of contractile proteins and elevated intracellular calcium lead to muscle injury [112, 113].

As mentioned, rhabdomyolysis may also be caused by viral or bacterial infections. Infections may account for about 5 % of cases of rhabdomyolysis [63], and they certainly may present in the ICU patient. The cause is again uncertain, but lymphocytic or viral invasion of myofibers and cytokine-induced damage (via tumor necrosis factor alpha and interleukin-1 (IL-1)) are possible mechanisms [64].

The mechanism of rhabdomyolysis from vascular compromise and compartment syndrome, which can also occur in the ICU, appears to be "pressure-related." However, some authors noted that patients may retain their pulses and postulated that the compartment pressure may not have to be high enough to completely compromise arterial supply yet it still can cause muscle necrosis [71].

Regardless of the cause, the pathologic changes in rhabdomyolysis range from subtle, scattered myofiber necrosis to severe panfascicular necrosis without selective thick filament loss.

Cachectic myopathy, a vague and poorly described entity, has received more study in medical disciplines other than neurology. Although it is a chronic condition, patients with cachectic myopathy are usually medically fragile and may end up in the ICU with the mildest intercurrent illness. Cachectic myopathy is a known complication of cancer and cardiovascular disease that usually has a component of severe congestive heart failure [114]. It also occurs with severe chronic obstructive lung disease and infections like human immunodeficiency virus. Usually the severe associated medical conditions overshadow any functional limitations due to the myopathy, but sometimes the weakness is the rate-limiting step in discharging the patient from the hospital.

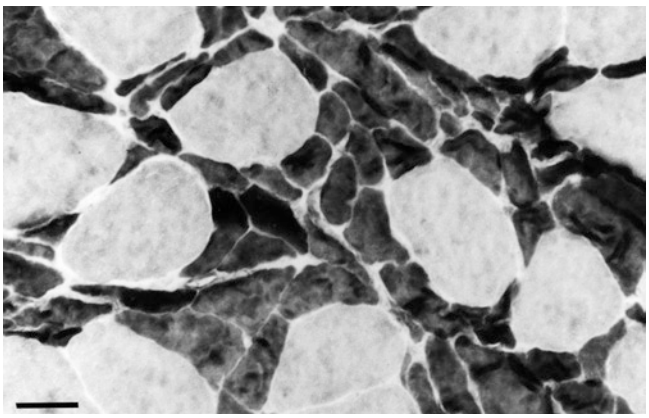

Fig. 76.8 A myosin-ATPase-reacted cryostat section (pH 9.4) reveals prominent atrophy of the dark type 2 fibers in this congestive heart failure patient who was in the intensive care unit for months and was diagnosed with cachectic myopathy (bar = 25 μ)

The exact etiology of cachectic myopathy is unknown. Like many of the entities discussed in this chapter, some authors advocated that cytokines are important precipitating factors. There are also animal models in which cachectic myopathy could be induced by cachectin or IL-1 [115]. In addition, some tumors are reported to secrete cachectin, and both cachectin and IL-1 elevations are thought to lead to cachectic myopathy in humans with malignancies. Myogenic differentiation factor D, which plays an important role in regulating muscle differentiation, may be involved in cachectic as well as in CIM. Myogenic differentiation factor D and other myogenic regulatory factors influence the activity of a number of muscle-specific genes [116].

Even though the mechanisms proposed to cause cachectic myopathy are similar to those proposed to cause CIP and CIM, cachectic myopathy can usually be differentiated from CIM pathologically. In cachectic myopathy, there is no loss of thick filaments and only type II fiber atrophy is seen (Fig. 76.8). In addition, cachectic myopathy is a chronic condition and, therefore, likely has a unique yet incompletely understood etiology. However, until the true pathogenesis of both CIM and cachectic myopathy are delineated, the distinction becomes arbitrary.

The pathophysiology of *prolonged neuromuscular junction blockade* from vecuronium or pancuronium is related to prolongation of circulating drug metabolites usually in the

setting of renal failure [76]. In most cases, it is controversial and unproven as to whether patients with very prolonged weakness (lasting weeks) develop a terminal motor axonopathy or end-plate disorder as the cause of prolonged weakness or whether they have superimposed critical illness polyneuropathy or myopathy. There are few pathologic studies of motor end plates in humans with this disorder. Subtle changes (regeneration) have been noted [117]. Animals with prolonged NMBA exposure may develop subtle end-plate damage with regeneration [118]. In addition, acetylcholine sensitivity may be increased after prolonged NMBA administration [119], and AChR number increases (upregulation) akin to denervation [95].

Clinical Presentation

Patients with *critical illness polyneuropathy* usually present after 1–2 weeks of SIRS or MODS with failure to wean from mechanical ventilation or with diffuse limb weakness, or both [12–14, 47, 120–122]. The exact onset may be difficult to pinpoint given the common associations of encephalopathy and sedation. The disorder is often overlooked unless clinical suspicion is high. Occasionally, the weakness is more pronounced distally. The face is rarely weak, and extraocular muscle weakness is not expected. Tendon reflexes are usually attenuated or lost, but sometimes they are preserved [21]. Distal sensation may be impaired, but sensation is often difficult to assess in the ICU patient. Patients may grimace with painful stimulation but not withdraw limbs. Muscle atrophy, especially in the distal extremities, commonly occurs over weeks.

Patients with *critical illness myopathy* usually also present with failure to wean, flaccid generalized weakness, or both [22]. The disorder is usually recognized days to weeks after exposure to IVCS with or without NMBAs. Sometimes proximal and rarely distal muscles are predominantly affected. The degree of weakness varies from mild to severe. Only with rare exception is the weakness asymmetric [123]. Neck flexor, facial, and diaphragm muscles are also commonly affected, and rarely extraocular muscles are involved [36, 45, 47]. Tendon reflexes are usually reduced or lost, but they may be normal. Sensation is normal if it can be assessed. Encephalopathic patients with CIM usually only grimace to pain since they are too weak to withdraw noxiously stimulated limbs. In addition, muscle wasting is sometimes present [24, 55].

Patients with *rhabdomyolysis* usually have proximal more often than diffuse weakness, but weakness can be diffuse. About 50 % have muscle swelling and myalgias that may be the predominant symptoms. Focal pain and swelling from compartment syndromes may be present. Tendon reflexes and sensation are normal. Other symptoms and signs can be protean and include hyperthermia, bleeding from coagulopathy, malaise, fever, tachycardia, abdominal pain, nausea, vomiting, and encephalopathy from the high levels of urea. Inadequate ventilation, hypoxemia, and respiratory acidosis may also occur. There may be metabolic acidosis from the release of sulfate and phosphate ions from muscle cells. Potential major complications include cardiac conduction abnormalities and arrest, compartment syndrome, and acute renal failure.

Cachectic myopathy may present in a chronically ill appearing patient. There may be acute to subacute progressive proximal weakness and a history of more chronic painless proximal weakness with associated diffuse muscle atrophy.

Prolonged *neuromuscular junction blockade* also presents as flaccid generalized weakness with failure to wean and areflexia that persists (usually for days) after NMBAs are discontinued [76, 77]. Cranial muscles may be affected, and the presence of significant extraocular muscle involvement should alert the clinician to this diagnosis since it is uncommon in CIM and not reported in CIP [124]. Patients recover over hours to days unless there is an associated terminal motor axonopathy, CIM, or CIP.

Differential Diagnosis of Weakness in the Intensive Care Unit (Table 76.1)

In the ICU patient, both prolonged ventilator dependence (in the absence of pulmonary disease [125–127] or phrenic nerve trauma) and acute flaccid generalized weakness are usually of peripheral nervous system origin, but central nervous system processes such as septic or toxic encephalopathy, an ischemic or hemorrhagic brainstem stroke, or central pontine myelinolysis should be considered as causes or contributors to weakness. Acutely, upper motor neuron signs may or may not be present. We have also found, however, that it is not uncommon for patients to have concurrent encephalopathy and weakness, the latter being of neuromuscular origin. In such instances, neuromuscular weakness may be overlooked. It is unlikely for septic or toxic encephalopathy alone to cause severe flaccid weakness.

Cervical myelopathy from tumor, trauma, inflammation, or ischemia may also produce flaccid quadriplegia acutely usually with sphincter dysfunction and a sensory "level." Nerve conduction studies are normal in such patients. Needle electrode findings may be normal except for reduced recruitment; however, fibrillation potential activity may be present simulating a lower motor neuron disorder [128].

In addition to CIP, other acute polyneuropathies to consider include Guillain–Barré syndrome (GBS) and rarely porphyric, toxic, vasculitic, paraneoplastic, and nutritional neuropathies. Axonal GBS (acute motor sensory axonal

Table 76.1 Other causes of generalized weakness in the ICU

Brain
Septic or toxic encephalopathy
Brainstem stroke
Central pontine myelinolysis
Spinal cord/anterior horn cell disorders
Cervical myelopathy
Amyotrophic lateral sclerosis
Peripheral neuropathies
Guillain–Barré syndrome
Acute inflammatory demyelinating polyneuropathy
Acute motor sensory axonal neuropathy
Acute motor axonal neuropathy
Porphyria
Paraneoplastic
Vasculitis
Nutritional
Neuromuscular junction disorders
Myasthenia gravis
Lambert–Eaton myasthenic syndrome
Botulism
Myopathies
Polymyositis, dermatomyositis
Viral myositis
Pyomyositis
Toxic
Muscular dystrophies
Acid maltase deficiency
Mitochondrial
Hypokalemic
Hypermetabolic syndromes with rhabdomyolysis
Neuroleptic malignant syndrome
Malignant hyperthermia
Heat stroke
Serotonergic syndrome
Central anticholinergic syndrome

neuropathy or AMSAN) may be particularly difficult to differentiate from CIP, but axonal GBS is unlikely to present while the patient is in the ICU for treatment of another disorder. In addition, many patients with axonal GBS have an antecedent, usually diarrheal, illness from *Campylobacter jejuni*; and, as opposed to CIP, they tend to lack spontaneous activity on EMG at the time of initial diagnosis [120]. Acute motor axonal neuropathy (AMAN) often follows Campylobacter infection also and presents like AMSAN but without sensory involvement.

A motor axonal neuropathy or terminal motor axonopathy from NMBAs has been reported; however, it has not been proven that this entity is a separate disorder because some of these patients may have actually had CIM – no muscle pathology reviewed – or CIP. An experimental model is needed to determine if this condition exists. Limited animal data (frog) only reveal subtle changes at the motor end plate after long-term curare exposure [118].

Motor neuron diseases (amyotrophic lateral sclerosis or viral poliomyelitis including West Nile virus) can present with respiratory failure precipitating ICU admission; however, such processes only very rarely present during an ICU admission for another disorder. It is thought that patients may also rarely develop diffuse anterior horn cell injury acutely after hypoperfusion or hypotension [129].

Neuromuscular transmission defects can be precipitated by aminoglycosides, lithium, anesthetic drugs, and hypermagnesemia and can unmask myasthenia gravis. Lambert–Eaton myasthenic syndrome can also result in respiratory failure requiring ICU treatment. Lastly, botulism, especially wound botulism, can occur in the ICU patient.

Myopathies other than CIM and rhabdomyolysis are rarely diagnosed in the ICU and are usually responsible for respiratory failure or aspiration which results in ICU admission. They include polymyositis, dermatomyositis, viral myositis, acid maltase deficiency, mitochondrial myopathy, and muscular dystrophies. Pyomyositis rarely develops in "septic" patients. It is also conceivable that trichinosis or sarcoid myopathy could be severe enough to lead to ICU admission. Hypophosphatemic and hypokalemic myopathies may also develop in the ICU [99].

Nonsteroidal toxic myopathies that do not cause overt rhabdomyolysis may rarely present in the ICU and may be difficult to identify in the setting of multiple medical problems or multiorgan dysfunction. These disorders may cause some muscle necrosis and present in either an acute or subacute fashion with proximal more often than diffuse weakness and sometimes with myalgias and muscle tenderness. As causes of ICU weakness, their true incidence is uncertain, but it is probably low [61]. Therefore, the neurologist consulted for evaluation of proximal weakness in the setting of MODS or SIRS would probably consider CIM as the first diagnostic choice, but toxic myopathy should be considered if the patient is receiving a potentially myotoxic medication especially in the setting of MODS or changes in medications which can slow drug metabolism.

Two toxic drugs that warrant specific mention are colchicine and hydroxychloroquine. Colchicine can affect transplant patients who are often in the ICU [130]. We specifically noted colchicine neuromyotoxicity in heart transplant patients taking multiple drugs including cyclosporin and with renal insufficiency [130]. Cholesterol-lowering drugs may also increase the risk of colchicine myotoxicity in addition to causing myopathy by themselves. The ultimate cause of most toxic myopathies is usually unknown, but colchicine toxicity is probably due to disruption of microtubules involved in lysosomal processing. Hydroxychloroquine can cause a vacuolar myopathy that causes ventilatory failure as well as limb weakness, leading to an ICU admission [131].

As discussed earlier in this chapter, rhabdomyolysis can also cause ICU weakness. In addition to the aforementioned

drugs and infections, there are also several specific hypermetabolic states that cause rhabdomyolysis. They may occur in the ICU or lead to ICU admission. These syndromes are rare and are not easily confused with other causes of ICU weakness because they usually also affect the central nervous system. These hypermetabolic or hyperexcitable syndromes include malignant hyperthermia (MH), neuroleptic malignant syndrome (NMS), central anticholinergic syndrome, heat stroke, and serotonergic syndrome [132, 133]. The illicit drug "ecstasy" can also cause a hyperthermia syndrome with seizures, tachycardia, and rhabdomyolysis [134]. Malignant hyperthermia is reviewed in Chap. 54. Neuroleptic malignant syndrome is thought to occur due to a central disorder of dopaminergic blockade affecting hypothalamic thermal regulation. It is also associated with hyperthermia, encephalopathy, muscle rigidity, tachycardia, leukocytosis, and autonomic dysregulation and usually evolves hours to days after initiation or increased doses of neuroleptic medication or rarely during withdrawal of dopaminergic medications used to treat Parkinson's disease. It can occur in treated Parkinson's disease patients who are admitted to the ICU and have their oral medications discontinued.

Central anticholinergic syndrome (from anticholinergic toxicity) can be associated with rhabdomyolysis and also consists of dry mouth, dilated pupils, urinary retention, and increased body temperature. It can overlap with heat stroke which is due to thermoregulatory failure in spite of a normal set point for temperature. Exertional heat stroke occurs in normal individuals after significant exercise, possibly in extreme conditions such as warm humidity. While this condition might be in the differential weakness in the ICU, classic heat stroke is more common and occurs in patients who develop a usually acquired inability to dissipate heat due to medical problems such as obesity, alcohol, illicit drugs (amphetamines), or medications, such as anticholinergics, that reduce sweating [133]. There can be an associated mild leukocytosis and dehydration with hyponatremia. In addition to rhabdomyolysis, renal failure, liver damage, and disseminated intravascular coagulation can also occur. Interestingly, cold temperatures can also produce rhabdomyolysis, perhaps from vasoconstriction and excessive energy demands.

Serotonergic syndrome, which is associated with the use of serotonergic reuptake inhibitors and Eldepryl, includes agitation, disorientation, confusion, and occasionally coma. Frequently, there are autonomic instability and leukocytosis in addition to rhabdomyolysis. This syndrome is felt to progress more rapidly and with less rigidity and myoclonus than NMS although there is overlap. There is also overlap in the supported pathogenetic mechanisms of these syndromes, and some appear to share a final common pathway.

Patients with these hypermetabolic syndromes all tend to have associated encephalopathy and rhabdomyolysis along with the features noted above; thus, they could easily be confused with septicemia or SIRS, and the patient could be diagnosed with associated CIM. It should be noted that elevated cytokines (like in so many of these disorders) have been reported to be the mechanism of muscle cell injury in these patients.

Evaluation and Diagnosis

Laboratory and Electrophysiologic Studies (Table 76.2)

In critical illness polyneuropathy, the cerebrospinal fluid and the serum creatine kinase (CK) are usually normal [47]. Electrophysiologic studies are consistent with a diffuse sensorimotor axonal polyneuropathy manifest as reduced sensory and motor amplitudes with no or minimal conduction slowing. The findings are usually noted in a week or two after ICU admission, but they may occur earlier. In a population of septic patients with CIP and CIM, low motor

Table 76.2 Summary of features and diagnostic criteria for CIM and CIP

Both CIM and CIP
Following onset of critical illness, the patient develops generalized, flaccid weakness with or without difficulty weaning from mechanical ventilation in the absence of another neuromuscular disorder
Absence of decremental response with 2–3 Hz repetitive stimulation
CIM[a]
Normal or minimally reduced sensory nerve amplitudes
Low motor responses with broad, long-duration CMAPS *or* low-amplitude CMAPs and early recruitment of short-duration motor unit potentials on EMG with or without fibrillation potentials, *or* low CMAP amplitudes and direct muscle stimulation consistent with reduced muscle membrane excitability (nerve-evoked to muscle-evoked CMAP ratio >0.5) *or* muscle biopsy demonstrating myosin loss
CIP
Low-amplitude CMAPS *and* sensory responses *or* low-amplitude CMAPS responses and the lack of myosin loss on muscle biopsy or direct muscle stimulation findings consistent with neuropathy (nerve to muscle ratio <0.5)
Absence of prolonged F-waves, conduction block, and substantial slowing of conduction velocities
EMG revealing reduced recruitment of normal MUPs and fibrillation potentials early in the course or high-amplitude long-duration MUPs later

[a]Elevated serum creatine kinase level is a supportive feature

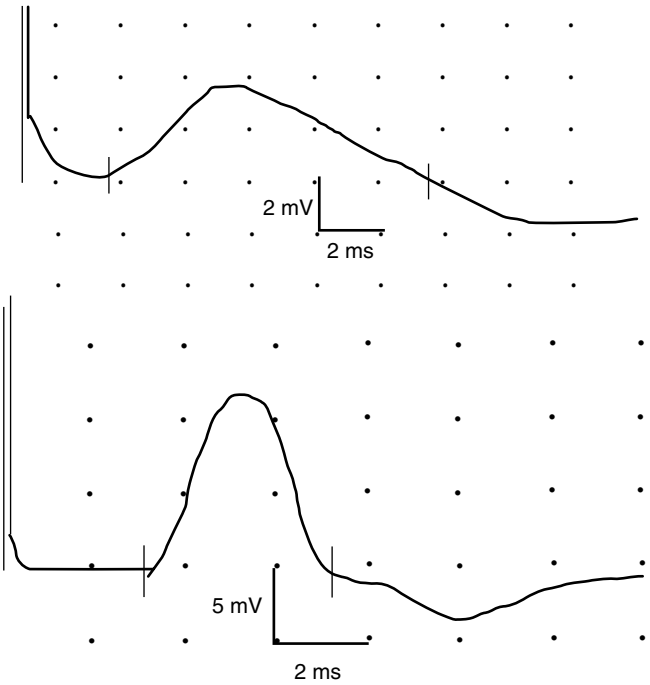

Fig. 76.9 The *top panel* illustrates a low-amplitude, broad, long-duration CMAP from a patient with CIM. The *bottom panel* is a normal for comparison

responses were seen within 72 h of admission in 63 %, and the findings were predictive of mortality. Twenty-one percent went on to have mostly mixed CIP and CIM [7].

Needle electrode examination usually reveals widespread spontaneous activity (positive waves and fibrillation potentials) [12, 14, 47, 120, 135]. Voluntary motor unit potentials (MUPs) are reduced in number and may be small and polyphasic during early reinnervation [15]. If studied, the phrenic nerve amplitudes are often reduced, and the diaphragm needle examination may reveal fibrillation potentials [127].

It is controversial as to whether CIP patients can have normal sensory responses [82, 135, 136]. Careful correlation with histopathologic examinations that at least exclude myopathy is necessary to resolve this issue. In particular, myosin loss should be excluded. Serial electrophysiologic studies or direct needle stimulation (discussed below) may also be useful. Sophisticated electrophysiologic studies have shown a predominance of myopathy in mixed cases of critical illness myopathy and neuropathy [137]. Additionally, a more recent study of 33 ICU patients with marked weakness prospectively assessed by electrodiagnostic testing and percutaneous muscle biopsy also showed that myopathy was highly predominant over the neuropathic impairment [138]. Therefore, some authors suggest that muscle biopsy should be performed more frequently as it establishes the diagnosis of at least a component of CIM in many patients especially since EMG can be technically difficult in ICU setting [139]. In our experience, CIP alone is uncommon, and most of the cases are associated with CIM.

In at least half of patients with *critical illness myopathy,* the creatine kinase is elevated especially early in the course. Usually, the elevation is less than 50-fold, but some patients have higher elevations. CK is usually normal later in the course of the disease. Prospectively studied and one group of retrospectively studied status asthmaticus patients with CIM all had an elevated CK [38, 44]. Thus, it is possible that the CK elevations may be missed in some patients because the CK has fallen by the time the diagnosis is suspected. This occurrence relates to the fact that patients become weak while they are sedated or pharmacologically paralyzed. In fact, Douglass et al. prospectively noted that the CK peaks at 3.6 ± 1.5 days and the elevation lasts 9.8 ± 6 days [38]. This elevation pattern is similar to that seen with rhabdomyolysis. We often see patients not diagnosed with CIM until weeks after probable onset of weakness, and their CK is usually normal.

In CIM, magnetic resonance imaging of skeletal muscle may demonstrate nonspecific, diffuse high-intensity signals on both T2-weighted images and the short-tau inversion recovery (STIR) sequence with isointense signals on T1-weighted images in both proximal and distal muscles [140].

Nerve conduction studies in CIM frequently reveal low motor amplitudes with normal conduction velocities. Occasionally, motor amplitudes are normal. CMAP durations may also be increased in multiple nerves in varying degrees due to slow conduction through the muscle membrane [103, 141–143] (Fig. 76.9). Sensory amplitudes are usually normal or mildly reduced compared to motor responses [47]. (Patients with low sensory responses may have superimposed CIP, a preexisting PN, or edema at recording sites.) Only rarely is there a transient decremental response with 2–3 Hz repetitive stimulation of motor nerves consistent with superimposed neuromuscular junction blockade [49]. Serial studies showed an increase in motor and sometimes sensory amplitudes during recovery [47]. Needle electrode examination reveals widespread positive waves and fibrillation potentials in 56–100 % of patients [22, 38, 44, 46–48, 53]. The fibrillation potential activity is variable in degree. Complex repetitive discharges [42, 44] and rarely myotonia [48] may be present. Abnormal spontaneous activity can be seen as early as 7 days after treatment with IVCS and NMBAs [42]. Motor unit potentials may not be recruited in very weak patients. Occasionally, only a few MUPs may be transiently recruited. In milder cases, there may be normal to more often, early recruitment of short-duration, often low-amplitude, and polyphasic MUPs. These "myopathic" motor unit potential changes become more apparent during recovery while spontaneous activity disappears [42]. In patients who cannot recruit MUPs well, it may not be possible to differentiate a motor axonopathy (possible variant of CIP)

from CIM without a muscle biopsy. In these patients especially, there is utility for the technique of direct muscle stimulation (DMS).

Rich et al. noted that some muscles in patients with CIM were inexcitable to direct electrical stimulation, whereas denervated muscles maintained normal excitability despite atrophy [100, 101]. These investigators then noted that needle-evoked (nerve-stimulated) compound muscle action potential (neCMAP) amplitudes were reduced in both myopathy and neuropathy but that the compound muscle action potentials obtained with direct needle stimulation of muscle (dmCMAP) were lower in myopathy patients [101]. Thus, a nerve/muscle ratio of the neCMAP/dmCMAP is close to 0 or at least <0.5 in patients with neuropathy and close to 1 if the patient has myopathy. (Both absent responses equal a ratio of 1.) They also noted that a patient undergoing vecuronium neuromuscular junction blockade had a preserved dmCMAP despite an absent neCMAP excluding acute neuromuscular junction blockade as a cause of the high neCMAP/dmCMAP ratio in CIM. Furthermore, a patient with periodic paralysis (membrane inexcitability) had findings similar to those of patients with CIM supporting the contention of membrane inexcitability in CIM [101]. Others have confirmed these results and also used DMS to demonstrate slowing of muscle fiber conduction as well as reduced muscle fiber excitability by DMS and by using paired stimuli [103]. In addition, velocity recovery cycles of muscle action potentials have also been used for assessment of muscle membrane properties in CIM. In ten patients, velocity recovery cycles were recorded from the brachioradialis muscle by DMS. Muscle fibers were depolarized likely because sodium channel inactivation was increased [144].

Utilizing all the known clinical, laboratory, and electrodiagnostic features described above, clinicians and researchers have proposed diagnostic criteria for CIM and CIP [145–147] (modified in Table 76.2). Differentiating these entities is critical for research studies that especially address risk factors and pathogenesis. In clinical practice, differentiation may be less critical, but it does provide prognostic as well as diagnostic information. (Patients with CIM tend improve faster than those with CIP as discussed below.)

Laboratory abnormalities associated with *rhabdomyolysis* include a highly elevated CK, increased or reduced potassium, reduced phosphate, increased creatine, and reduced calcium. Blood urea nitrogen and creatinine will be elevated if there is secondary renal injury. However, visible myoglobinuria is not always present; renal failure may or may not occur. A rise in serum myoglobin precedes the increase in CK, and CK peaks within 1–3 days and can decline by 3–5 days; therefore, if a CK is not assessed during this interval, rhabdomyolysis cannot be excluded by a normal CK obtained later. Urine chemistries may reveal hyperuricemia, myoglobinuria, or pigmented granular casts. Nerve conduction studies are usually normal, and fibrillation potentials of varying degrees may be present in a patchy or generalized fashion. However, EMG findings may be normal [148].

In *cachectic myopathy*, the CK is normal. The electromyogram may reveal motor unit potential changes consistent with myopathy but usually without associated significant spontaneous activity.

Reported electrophysiologic studies in patients with *prolonged neuromuscular junction blockade* are often limited to train of four (TOF) stimulation which shows a reduction or absence of twitches. In a few cases, 2–3 Hz repetitive nerve stimulation also revealed a decremental response [47, 49, 50, 76]. Inexcitable nerves were reported in another patient [77]. The use of stimulated single-fiber EMG has not been reported. Needle electrode examinations in a few patients revealed spontaneous activity [76]. Short-duration motor unit potentials may also be present [50].

Treatment, Management, and Prognosis

General Principles

All critically ill patients, including those with neuromuscular weakness, require adequate nutritional intake, correction of underlying metabolic disorders such as hypokalemia and hypophosphatemia, and aggressive treatment of underlying infections since all of these metabolic abnormalities can aggravate weakness.

Since paralyzed limbs are susceptible to deep venous thrombosis, prophylaxis via either subcutaneous heparin or pneumatic devices is warranted. Frequent turning and padding of pressure points is important to avoid development of decubitus ulcers or nerve entrapments.

If the patient is not yet receiving mechanical ventilation, the risk of and likelihood of respiratory compromise must be assessed by serial assessment of vital capacity and negative inspiratory force and monitoring their clinical signs and symptoms to determine if and when tracheal intubation is required.

Patients with neuromuscular respiratory failure may require prolonged ventilatory support. If the clinical and electrodiagnostic findings are consistent with significant neuromuscular respiratory weakness, early tracheotomy is indicated to improve pulmonary toilet.

Initially, physiotherapy is generally limited to range of motion and bracing to prevent contractures (especially at the ankles). As patients recover, inpatient rehabilitation is often required [24]. A recent study showed that the majority of patients discharged from the ICU with critical illness polyneuropathy and myopathy and treated in a neuro-rehabilitation setting had a good functional outcome. The mean length of

inpatient rehabilitation stay was 76.2 ± 28.1 days. At discharge, 57.1 % of patients achieved good recovery [149]. A small minority required long-term care. Due to residual deficits in some, ankle foot orthoses may be required long term as well as other assistive devices for ambulation. Rehabilitation for patients with CIP/CIM should be started as soon as possible after diagnosis, because the improvement in function decreases as the time from established diagnosis to the start of rehabilitation increases [150].

Critical Illness Polyneuropathy

Aside from the general principles noted above, there are no proven specific therapies. The use of intravenous immunoglobulin (IVIG) has generated interest, but it has not been well studied. A small pilot study showed no obvious improvement in PN with IVIG [151]. A prospective, uncontrolled study of 33 patients with MODS (16 with gram-negative septicemia) suggested that 0.9 g/kg of IVIG given over 3 days may prevent CIP in patients with septicemia or SIRS [152], but a prospective controlled trial is necessary to make that determination.

In CIP, there is a high mortality rate (up to 50 %) due to the underlying disease [21]. However, survivors tend to recover partially (severe PN) or fully (mild to moderate PN) over months, and milder forms may "resolve" in weeks [21, 149]. About 22 % of patients with CIP have severe residual handicaps at 1 year [153], and, as with most axonopathies, distal leg weakness is the most common residual effect.

Critical Illness Myopathy

There is no specific treatment for CIM, but the general principles noted above apply. Prevention is ideal if possible. Limiting intravenous corticosteroids or paralytic agents in ICU patients is recommended in order to make occurrence less likely, and these agents should generally not be used without proof of utility. In particular, avoidance of continuous or high-dose recurrent NMBAs is suggested. The use of train of four monitoring and serial assessments of serum creatine kinase during use of paralytic agents may also help reduce the incidence of CIM theoretically. Some investigators recommend the use of non-aminosteroid NMBAs such as atracurium; however, atracurium is also clearly associated with CIM, and there is no proof that this more expensive agent leads to a lower incidence of CIM. Patients could also be monitored for CIM as well as CIP by serial peroneal motor responses. A unilateral peroneal CMAP reduction of more than two standard deviations of normal value was sensitive (100 %) and moderately specific (67 %) in diagnosing critical illness neuromuscular weakness in one study, and all patients developed the electrophysiological findings within 13 days of ICU admission [154].

Once CIM is identified, corticosteroids should be tapered or discontinued if possible. Rechallenge with IVCS should be avoided, if possible, since CIM may recur [28]. There is conflicting data about the beneficial effect of strict glucose control and the duration of mechanical ventilation in CIP and CIM [84]. In our opinion, the beneficial effect has not been fully proven, and more studies need to be done before we reach a final conclusion.

Patients with CIM who do not succumb to their underlying disorder usually recover over weeks to months, and most recover fully. However, there is considerable morbidity and increased medical costs associated with CIM. For example, the mean time to ambulation is about 8 weeks, and in one study of liver transplant patients with CIM, the time in the ICU was 49 ± 36 days (mean ± SD) vs. 14 ± 14 days for those without CIM [48]. Although patients with CIM are generally in poorer health overall, failure to wean from CIM is a major contributor to prolonged ICU stays.

Patients with *mixed CIM and CIP* tend to recover more like patients with CIP. In those patients, CIM tends to occur before CIP, and the addition of CIP likely prolongs ICU stays and delays the recovery [155].

In patients with *rhabdomyolysis*, intravenous hydration with alkaline diuresis is recommended to avoid renal failure [71]. Analgesics can be used for myalgias. Medical complications, such as hyperthermia, coagulopathy, hypoxemia, and acidosis, may also require treatment. Compartment syndromes require orthopedic evaluation for possible fasciotomy.

In patients with *cachectic myopathy*, there has been a treatment paradigm proposed using branched chain amino acids (BCAAs). BCAAs did not alter muscle protein catabolism, but they did increase intracellular amino acid nitrogen pools. The clinical significance of this finding is unknown [114]. The prognosis of cachectic myopathy is likely different than in CIM or CIP in that it almost entirely depends on treatment of the underlying condition so that normal activity can be resumed.

Prolonged Neuromuscular Junction Blockade

This disorder is self-limited; therefore, prevention is optimal. It is felt, but not proven, that the process can be avoided by paying careful attention to train of four monitoring. In general, avoidance of continuous infusions of NMBAs or recurrent boluses is advised, and one should consider alternative therapies such as propofol or other sedatives. However, propofol use has also been associated with rhabdomyolysis [62] and CIM (in association with IV corticosteroids) [53]. Once prolonged NMJ blockade is identified, administration

of neostigmine or edrophonium may transiently reverse the weakness; but, generally, it persists for days until the metabolites are excreted. Patients with prolonged weakness, which can be due to CIM, CIP, or end-plate myopathy, may then require rehabilitation.

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Floppy Infant

77

Bassam A. Bassam

The floppy infant syndrome (FIS) is characterized by prominent generalized hypotonia. Hypotonia manifests with diminished muscle tone and resistance to passive movements, excessive joint mobility, abnormal infant postures, and a variable degree of weakness. Hypotonia at birth, or during the first 6 months of life, is a nonspecific sign because it may be encountered with many illnesses.

The first step in the differential diagnosis is a detailed clinical history, including developmental milestones, and a physical examination, with careful observation for dysmorphic features that might suggest chromosomal abnormalities or syndromic patterns. Examination for hypotonia is usually carried out with the infant at rest, the head in midline position, and the limbs moved passively (Fig. 77.1). The truncal tone is assessed by suspending the infant with the abdomen held on the examiner's hand. A normal, full-term infant assumes a posture with straightened back, flexed limbs, and straight head; a hypotonic infant drapes over the examiner's hand "inverted U sign." The shoulder-girdle tone may be assessed by suspending the infant vertically while supporting the axillae. A full-term infant adducts the arms and fixes the shoulders, whereas a hypotonic infant tends to slip through the examiner's hands "scarf sign." Laboratory tests, including muscle enzymes, electrodiagnostic (EDX) studies, and muscle biopsy with histochemical stains and electron microscopy, are helpful in the diagnosis of peripheral neuromuscular disorders that may cause FIS.

The differential diagnosis of FIS includes a wide variety of causes that may be related to the central nervous system (CNS), anterior horn cell, peripheral nerve or muscle disorders, as well as connective tissue disorders, mitochondrial disorders, or systemic illness (Table 77.1 and Fig. 77.2) [1]. In some disorders, both the CNS and neuromuscular system are simultaneously involved. Analysis of three clinical series showed that chromosomal disorders accounted for 31 % of the elucidated diagnosis (CNS anomalies were present in 13 %, myopathies in 5 %, congenital myotonic dystrophy in 4 %, spinal muscular atrophy in 2 %, muscular dystrophy in 2 %, and inborn errors of metabolism in 3 %) [2]. When only one limb is affected, traumatic neuropathy, or more commonly brachial plexus palsy, should be considered.

Central Nervous System Disorders

Approximately 80 % of floppy infants have primary acute or chronic CNS diseases. Usually, the clinical diagnosis is readily recognized by the neurologist, and neither EDX studies nor muscle biopsy is necessary. Despite prominent hypotonia, these infants often have better muscle strength than tone and may have normal strength or only transient weakness early in life. Increased tendon reflexes, seizures, obtundation, or delayed intellectual and language milestones suggest a CNS disorder (Table 77.2).

Acute Central Nervous System Diseases

Acute CNS causes of FIS include perinatal hypoxia, sepsis and meningitis, birth trauma, intracranial hemorrhages, intoxication, drug withdrawal, inborn errors of metabolism, and acquired metabolic disturbances of glucose, calcium, and electrolytes. *Hypoxic-ischemic encephalopathy* is by far the most common cause of all hypotonia in newborns. Acute CNS diseases, such as birth trauma, intraventricular hemorrhage, or asphyxia, may have prominent hypotonia and decreased reflexes early in life, which change to hyperreflexia in early childhood.

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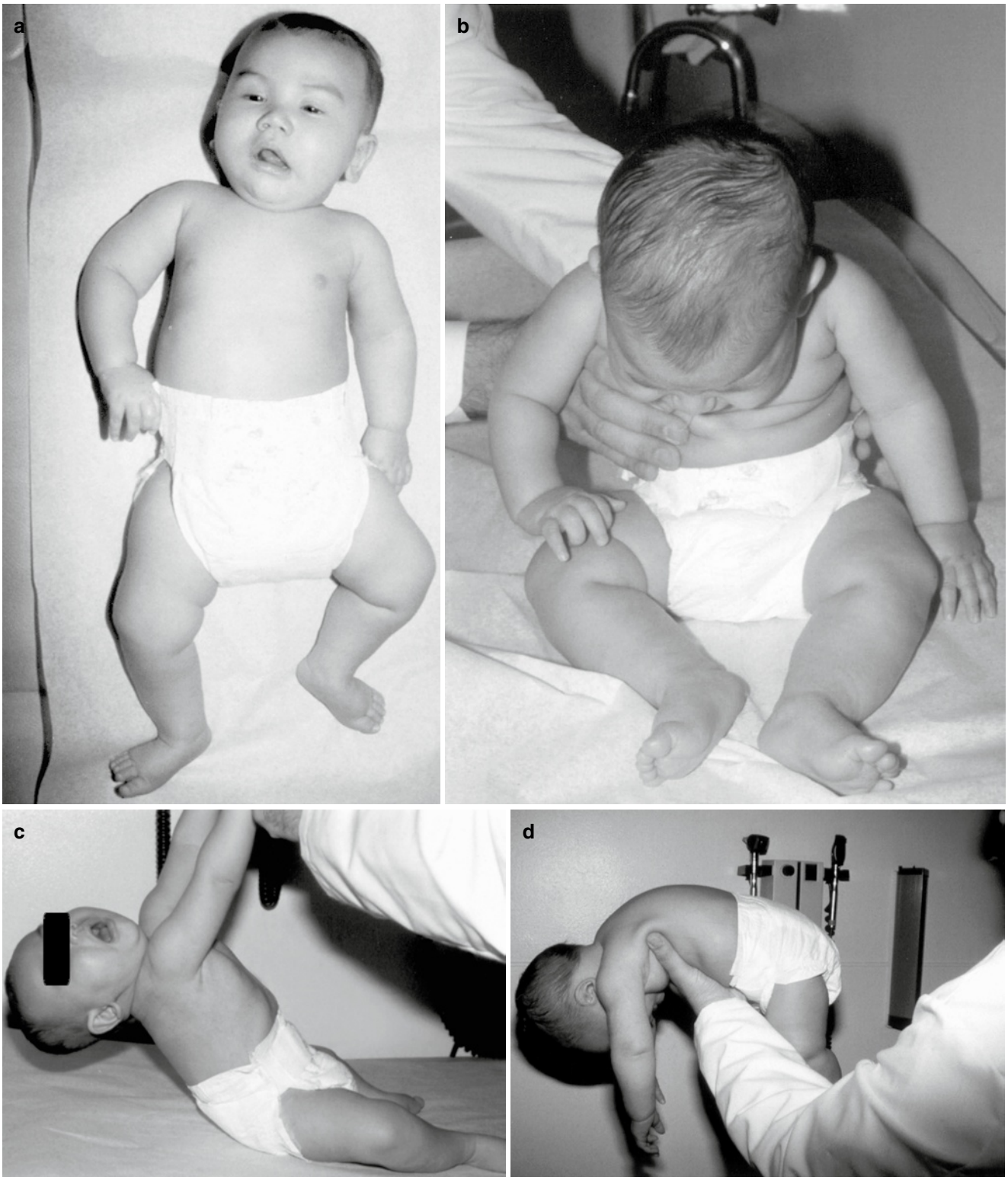

Fig. 77.1 An infant with infantile spinal muscular atrophy (SMA I, Werdnig-Hoffman disease) lies flat and floppy, with the legs spread in a "frog leg" position and the arms externally rotated with the elbows flexed (**a**). Note also the triangular mouth and facial expression consistent with bifacial weakness. On sitting, the infant cannot sustain his head upright (**b**), and the head falls back when he is pulled by the arms (**c**). While held supine, there is no active truncal tone and the head and limbs drop by force of gravity (**d**) (Reprinted from Bradley et al. [48])

Chronic Central Nervous System Diseases

Chronic CNS diseases associated with FIS include neural tube defects, microcephaly, cerebral and cerebellar malformations, congenital infections, cerebral lipidoses, chromosomal disorders, and dysmorphic syndromes. Long-term follow-up study showed that *cerebral palsy* and *mental retardation* are common chronic CNS causes of FIS [3]. Hypotonia associated with ataxia is often seen in disorders of the cerebellum and with choreoathetosis in basal ganglia dysfunction. Spinal cord malformations or injuries, such as those seen in a difficult breech delivery, may be associated with hypotonia, weakness, and a sensory level, with normal muscle strength and tone above the involved level. Among the dysmorphic syndromes known to be associated with hypotonia are Prader-Willi syndrome, Cohen syndrome, Zellweger

Table 77.1 Common causes of the floppy infant syndrome

Central nervous system disorders
Motor unit disorders
Connective tissue disorders
Systemic illnesses
Mitochondrial disorders
Maternal medications
Benign congenital hypotonia

Table 77.2 Clinical features of upper and lower motor neuron causes of the floppy infant syndrome

Upper motor neuron disorders	Lower motor neuron disorders
Hypotonia in infancy and spasticity in childhood	Hypotonia
Mild weakness or normal strength	Significant weakness
Increased tendon reflexes	Decreased or absent tendon reflexes
Abnormal reflexes (Babinski sign, ankle clonus)	No abnormal reflexes
No muscle atrophy	Muscle atrophy (may not be present early)
Delayed developmental milestones	Only motor skills delayed
Signs and symptoms of central nervous system involvement	No central nervous system involvement

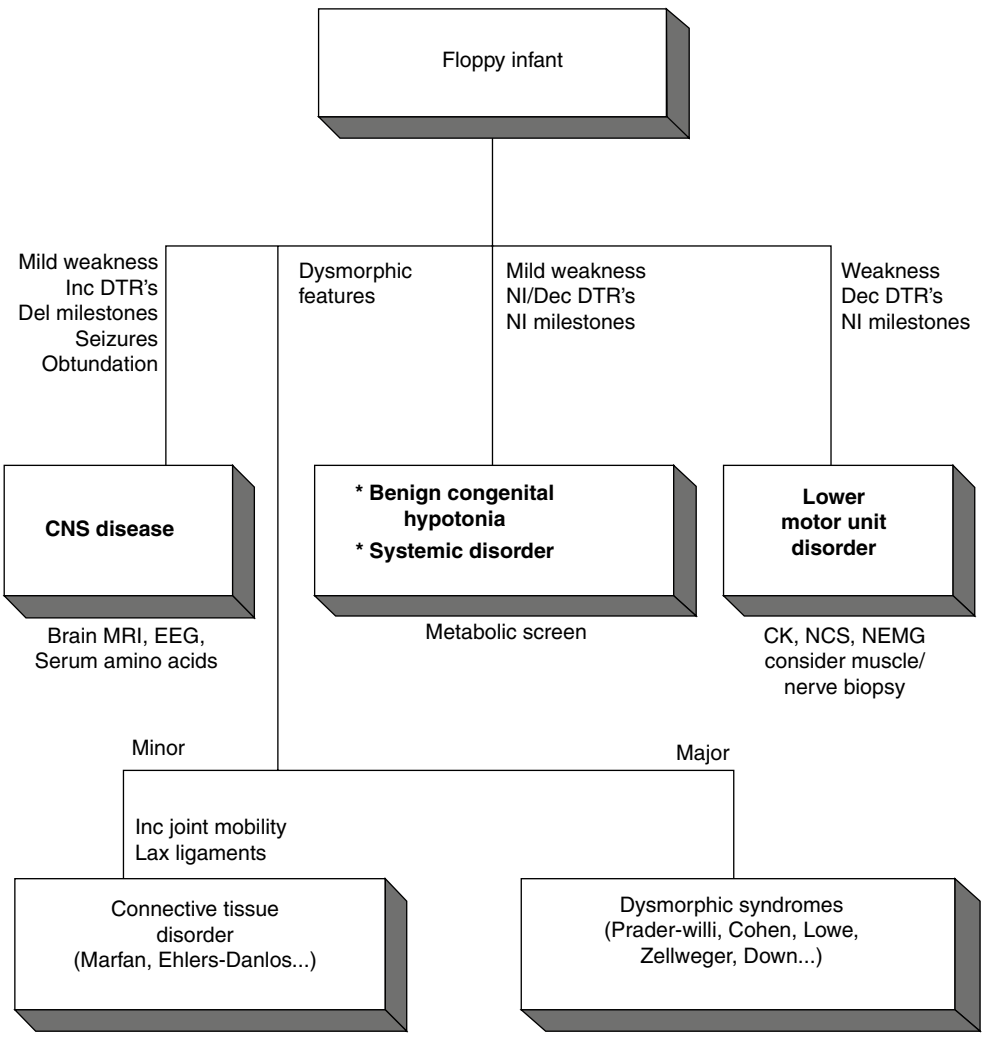

Fig. 77.2 Differential diagnosis algorithm of the floppy infant syndrome (*Inc* increased, *DTR* deep tendon reflexes, *Del* delayed, *Dec* decreased, *NL* normal, *CNS* central nervous system, *MRI* magnetic resonance Imaging, *EEG* electroencephalography, *CK* creatine kinase, *NCS* nerve conduction studies, *NEMG* needle electromyography)

syndrome, Lowe's syndrome, and Down syndrome. In many of these syndromes, hypotonia is an early manifestation at birth, and children develop the more classic signs of the syndrome over time. Chromosomal studies are confirmatory with a limited but ever-increasing number of conditions and are indicated in evaluating the hypotonic infant with dysmorphic features. In genetically determined conditions with a metabolic defect resulting in hypotonia and various physiologic and mental impairments, such as storage disorders and phenylketonuria, the diagnosis relies exclusively on laboratory analysis of certain enzymes or metabolic products. Additionally, the high-resolution imaging technology and unprecedented advances in genetic technology in the last decade have increased our abilities to establish a specific diagnosis for a significant number of genetic disorders.

Motor Unit Disorders

Approximately 20 % of patients with FIS have neuromuscular diseases, including anterior horn cell disorders, neuropathies, neuromuscular junction disorders, and myopathies (Table 77.3). Infants with lower motor neuron disorders usually have profound weakness proportional with the severity of hypotonia, decreased or absent tendon reflexes, and abnormalities on muscle enzymes, EDX studies, edrophonium (Tensilon®) test, or muscle biopsy. Examination of the child's mother in suspected neonatal myasthenia gravis or congenital myotonic dystrophy may render additional diagnostic evaluation unnecessary. The following is a brief discussion of motor unit disorders associated with FIS.

Table 77.3 Motor unit disorders associated with the floppy infant syndrome

Anterior horn cell disorders
Spinal muscular atrophy
Spinal muscular atrophy I (Werdnig-Hoffmann disease)
Spinal muscular atrophy II (intermediate form of SMA)
Glycogen storage type II (Pompe's disease)
Enterovirus infection (Coxsackie, ECHO, polio)
Organic aciduria (biotin-responsive carboxylase deficiency)
Peripheral neuropathies
Guillain-Barré syndrome
Toxic (heavy metals)
HMSN type III (Dejerine-Sottas disease)
Congenital hypomyelinating neuropathy
HMSN type I variant (rare)
Krabbe's disease,[a] metachromatic leukodystrophy[a]
Giant axonal neuropathy
Neuromuscular junction disorders
Infantile botulism
Neonatal myasthenia
Congenital myasthenic syndromes
Hypomagnesemia
Aminoglycoside antibiotics
Myopathies
Congenital myopathies
Central core
Nemaline
Myotubular
Congenital fiber-type disproportion
Metabolic myopathies
Infantile acid maltase deficiency
Infantile debranching enzyme deficiency (Cori-Forbes disease)
Myophosphorylase deficiency
Muscle phosphorylase-b-kinase deficiency
Branching enzyme deficiency
Carnitine deficiency
Cytochrome C oxidase (COX) deficiency
Muscular dystrophies
Myotonic dystrophy
Congenital muscular dystrophy

ECHO enteric cytopathogenic human orphan virus, *HMSN* hereditary motor and sensory neuropathy
[a]Affects the CNS and PNS

Anterior Horn Cell Disorders

Most neurogenic cases of severe weakness and hypotonia in infancy are secondary to spinal muscular atrophy (SMA) type I (acute infantile or Werdnig-Hoffmann disease). Rare cases are due to organic aciduria or glycogen storage type II (Pompe's disease) or are associated with enterovirus infections.

The SMAs are a group of heterogeneous disorders characterized by degeneration of motor neurons within the anterior horn of the spinal cord and in the motor nuclei of the brain stem (see Chap. 21). They may arise in the newborn, during childhood, adolescence, or adult life. The infantile form of SMA is the most severe among the group, but less severe chronic forms of infantile SMA are well known [4]. *Acute infantile SMA* (*type I*, *Werdnig-Hoffmann disease*) is an autosomal-recessive disease that usually presents at birth or during the first few months of life. The infant has hypotonia, areflexia, and severe generalized weakness, including bulbar and respiratory muscles. Facial expression, strength, and ocular movements are preserved, and the infant looks fully alert and is often smiling. Tongue fasciculations may be observed. EDX studies reveal normal motor conduction velocity for age, low-amplitude CMAPs, widespread fibrillations, diminished number of motor unit action potentials (MUAPs); some are of long duration and polyphasic potentials. However, early EDX studies may give ambiguous results. Muscle biopsy is essential for the diagnosis, often showing mixed atrophic with hypertrophic fascicles (Fig. 77.3). Most infants die within the first 2 years of life due to aspiration pneumonia and respiratory failure [5]. In the *chronic infantile form of SMA* (*type II*, *intermediate*), the infant looks normal at birth. Weakness and hypotonia usually appear between 6 and 18 months of age. The pelvic girdle is

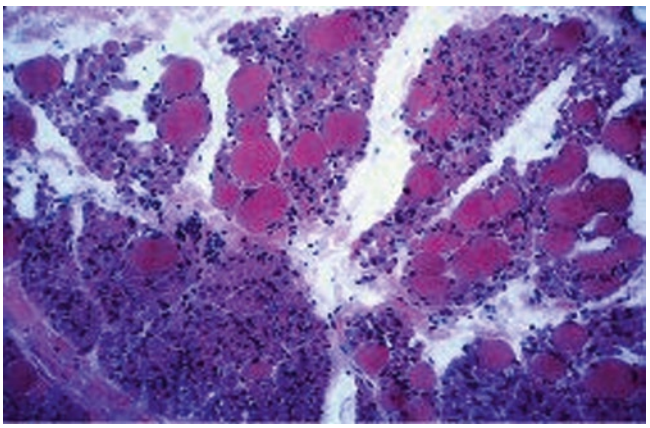

Fig. 77.3 Muscle biopsy in spinal muscular atrophy (SMA I, Werdnig-Hoffman disease). Typically, the severe form of SMA exhibits markedly hypertrophic fibers among atrophic fascicles of myofibers. While both fiber types undergo atrophy, the majority of hypertrophic fibers are type I fibers

often weaker than the shoulder girdle and the face and bulbar muscles are spared. The weakness may stabilize or in some cases may improve. Usually patients attain sitting ability; however, these children often are never able to achieve independent ambulation. Progressive respiratory insufficiency, joint contractures, and scoliosis are common complications. Life expectancy is variable, with some individuals surviving into early adulthood [5]. Muscle biopsy and EDX finding are similar to those seen in SMA I. Diagnosis of SMA can be adequately confirmed in the vast majority of SMA cases by a positive peripheral blood gene study for a DNA mutation of the motor neuron survival gene [6].

Infants with the *biotin-responsive carboxylase deficiency* present with weakness, hypotonia, areflexia, and lethargy and may be diagnosed by urine screening for organic acidurias. The classic form of *Pompe's disease* usually presents with hypotonia, accompanied by cardiomegaly and hepatomegaly, but variant forms with prominent hypotonia and no cardiac involvement are described. The diagnosis of suspected Pompe's disease can be established by muscle biopsy and deficient acid maltase activity in leukocyte or fibroblasts. Acute *acquired enterovirus infections*, including Coxsackie virus, enteric cytopathogenic human orphan virus, and, especially, poliomyelitis virus, may be associated with asymmetric flaccid paralysis. However, poliovirus infections have been nearly eradicated in Western societies with immunization programs (see Table 77.3).

Peripheral Neuropathies

Several neuropathies may present in very early life with weakness and hypotonia (see Table 77.3 and Fig. 77.4). The symptoms may be predominantly motor, sensory, autonomic, or a combination. Areflexia or hyporeflexia is found in most neuropathies. EDX studies confirm the diagnosis and characterize the neuropathy as axonal versus demyelinating. Nerve biopsy may provide a specific diagnosis in some cases. Examination of family members is important when hereditary neuropathies are suspected. The disease course may be acute, subacute, or chronic.

Acute inflammatory demyelinating polyneuropathy (*Guillain-Barré syndrome*) is probably the most common acute acquired neuropathy of childhood. It should be considered in young infants with subacute onset of hypotonia because the youngest reported case is 4.5 months old [7]. The weakness is symmetric and reaches a peak in 2 weeks, associated with a high cerebrospinal fluid protein level and slow nerve conduction velocities. A complete recovery is expected in the majority of these infants. Acute or subacute neuropathies due to heavy metal poisoning, toxins, or drugs may present with severe weakness, and a history of exposure should be investigated.

Hereditary neuropathies with symptom onset in infancy are rare. *Hereditary motor and sensory neuropathy type III* (*HMSN III*, *Dejerine-Sottas disease*) has an earlier onset and more profound weakness than HMSN type I. HMSN III usually presents during the first year of life with hypotonia, areflexia, and predominant distal severe weakness. Enlargement of the peripheral nerves, persistently elevated CSF protein level, and markedly decreased nerve conduction velocities are characteristic features (see Chap. 26) [8]. DNA-based molecular leukocyte testing for mutations in the PMP22, PO, and ERG2 genes are commercially available and may establish a specific diagnosis. A rare severe *congenital hypomyelinating neuropathy* (*CHN*) has been described, characterized by profound neonatal hypotonia, slow nerve conductions, thin myelin sheaths, and absence of onion-bulb formation, setting this disorder apart from HMSN III. These infants usually die within the first few months of life due to respiratory and bulbar dysfunction. Mutations of PO, PMP22, and ERG2 are all reported in CHN [9, 10]. *Krabbe's disease*, *metachromatic leukodystrophy*, and *giant axonal neuropathy* affect both the central and peripheral nervous systems (see Chap. 27). However, some infants with Krabbe's disease may present with polyneuropathy manifested by weakness and hypotonia instead of hypertonia. Leukocyte enzyme assay shows a reduced galactosylceramidase ß-galactosidase level. Patients with the infantile variant of metachromatic leukodystrophy develop normally for 1 or 2 years before developing hypotonia; however, some cases present before the age of 6 months, with neuropathic weakness as the dominant clinical feature and the diagnosis confirmed by arylsulfatase A assay of lymphocytes or fibroblasts [11]. Giant axonal neuropathy is an autosomal recessive disorder, localized to chromosome 16q24. The primary features of this disorder include rapidly progressive polyneuropathy, initial hypotonia before developing spasticity, kinky hair, and a variable CNS involvement. EDX studies show axonal

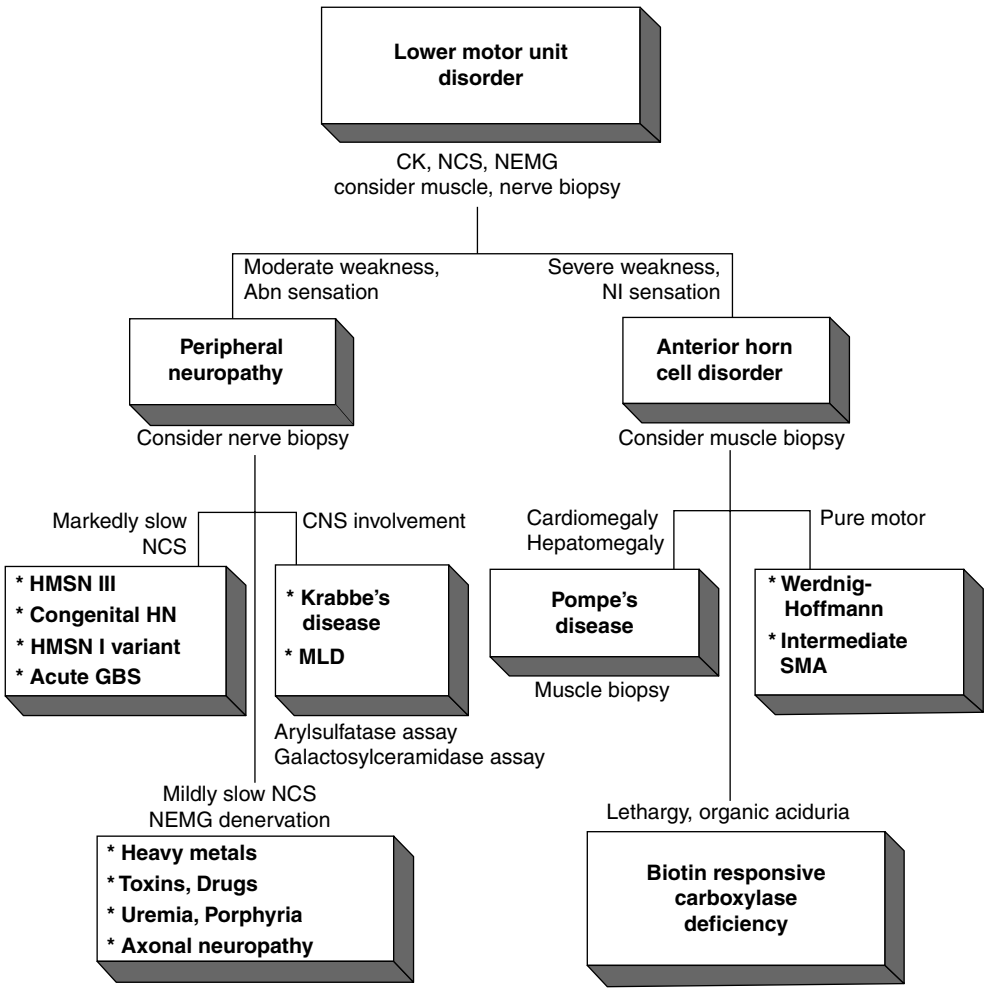

Fig. 77.4 Diagnostic approach algorithm of motor unit disorders associated with the floppy infant syndrome (part 1) (*CK* creatine kinase, *NCS* nerve conduction studies, *NEMG* needle electromyography, *Abn* abnormal, *NL* normal, *CNS* central nervous system, *HMSN III* hereditary motor sensory neuropathy type III (Dejerene-Sottas disease), *HN* hypomyelinating neuropathy, *HMSN I* hereditary motor sensory neuropathy type I (Charcot-Marie-Tooth disease type I), *GBS* Guillain-Barré syndrome, *MLD* metachromatic leukodystrophy, *SMA* spinal muscular atrophy)

neuropathy, and nerve biopsy demonstrates distended axons with filamentous inclusions and axonal loss [12].

Neuromuscular Junction Disorders

Neuromuscular junction disorders that may present in the newborn include neonatal myasthenia gravis, congenital myasthenic syndromes, and infantile botulism (see Table 77.3 and Fig. 77.5).

Neonatal myasthenia gravis occurs in approximately 10–15 % of infants born to women with seropositive myasthenia gravis. Infants develop transient myasthenia, which usually resolves completely in 3–6 weeks. Symptoms develop after birth, or within few days, and include feeding difficulty, weak cry, facial and generalized weakness, and hypotonia [13]. The disease is caused by passive transfer of acetylcholine receptor (AChR) antibodies from mother to child, and symptoms severity correlates with antibody concentration. The diagnosis is suspected by family history and supported by a Tensilon test and decrement response on repetitive motor nerve stimulation. Elevated serum AChR antibodies are detected in 80–85 % of these infants. When the disease is severe, treatment with neostigmine or pyridostigmine is indicated, along with supportive measures until recovery.

Congenital myasthenic syndromes (*CMS*) are a group of genetic disorders characterized by neuromuscular junction dysfunction. Engel described the clinical, ultrastructural, and neurophysiologic features of the congenital myasthenic syndrome subtypes, which comprise several discrete ultrastructural presynaptic, synaptic, and postsynaptic abnormalities [14]. The mother does not have myasthenia gravis, but there may be a family history of similarly affected siblings, consistent with autosomal-recessive inheritance. The clinical symptoms present at birth or within the first year of life, of variable severity, include hypotonia, muscle weakness, ptosis, ophthalmoparesis, and often dysphagia (see Chap. 51) [15]. Hypotonia at birth, respiratory difficulty, and episodes of apnea may occur in severe cases, whereas only intermittent hypotonia and increased fatigue are seen in mild cases. EDX studies demonstrate decremental response of the

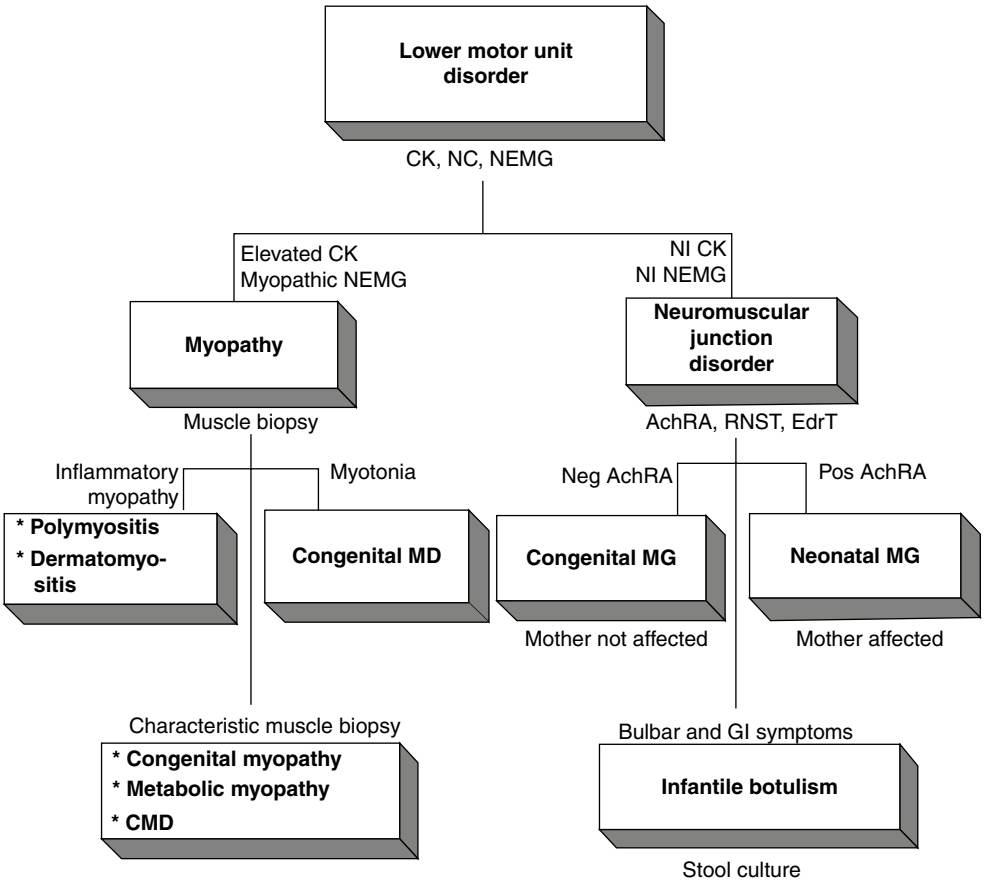

Fig. 77.5 Diagnostic approach algorithm of motor unit disorders associated with the floppy infant syndrome (part 2) (*CK* creatine kinase, *NCS* nerve conduction studies, *NEMG* needle electromyography, *Abn* abnormal, *AchRA* acetylcholine receptor antibodies, *RNST* repetitive nerve stimulation test, *EdrT* edrophonium test, *MG* myasthenia gravis, *CMD* congenital muscular dystrophy)

compound muscle action potential (CMAP) on repetitive motor nerve stimulation, but AChR antibodies are absent. Clinical symptoms improve with acetylcholinesterase inhibitor (AchE-I) drugs administration, however, not in CMS subtypes with AchE deficiency.

Infantile botulism manifesting as hypotonia is not uncommon presynaptic neuromuscular junction disorder. It is caused by absorption of *Clostridium botulinum* toxin from the intestine. Symptoms appear between 6 weeks and 9 months of age. Constipation is a common initial symptom, followed by a descending paralysis of cranial muscles, upper and then lower extremities. The infant has marked hypotonia, prominent facial weakness, ophthalmoplegia with pupillary abnormality, feeding difficulty, and limb weakness (see Chap. 52) [16]. Weakness may progress to respiratory failure requiring mechanical ventilation. Most laboratory tests are negative. Repetitive motor nerve stimulation is useful, showing an incremental response of the CMAP to rapid stimulation rates (20–40 Hz) ranging from 30 to 100 %. The initial CMAP has a small amplitude and short duration. The diagnosis is confirmed by isolation of the organism from stool samples. Treatment is supportive, including feeding and mechanical ventilation when necessary, and full recovery is common.

Myopathies

Myopathy, in a strict sense, refers to pathology primarily involving muscle fibers. Clinical examination, family history, needle electromyography (EMG), serum enzyme levels, and muscle biopsy usually define a specific diagnosis of myopathy. Infants with congenital myopathies, metabolic myopathies, congenital myotonic dystrophy, congenital muscular dystrophy, and a few other myopathies are hypotonic at birth and have weakness of limbs, trunk, or facial muscles (see Table 77.3 and Fig. 77.5).

Congenital myopathies are a group of primary muscle diseases, clinically and genetically heterogeneous, defined according to microscopic structural changes or, in some cases, abnormalities in the proportion or size of one fiber type (see Chap. 62). These disorders include central core disease, nemaline myopathy, myotubular myopathy, congenital fiber-type disproportion, and a few other less common conditions (Figs. 77.6 and 77.7). The clinical manifestations usually start in the neonatal period with hypotonia, limb and facial weakness, decreased movements, and poorly developed musculature. Associated skeletal abnormalities, such as elongated faces, hip dislocation, scoliosis, high arched palate, and pes cavus, are variably seen.

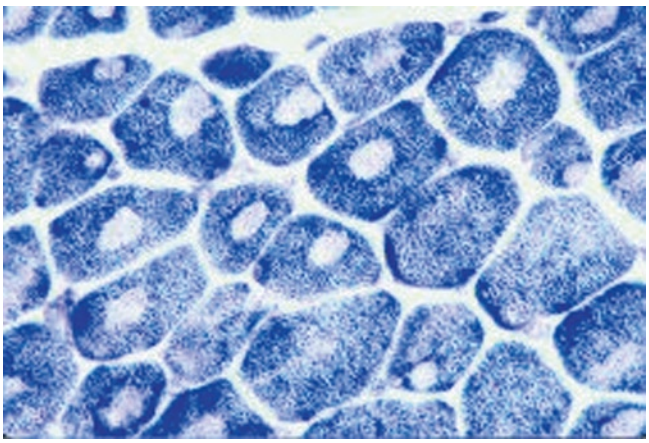

Fig. 77.6 Muscle biopsy in central core disease. Characteristic changes of central core disease are observed in this illustration. Roughly rounded regions with absent NADH diaphorase activity are seen toward the center of the affected myofibers. These features reflect disarray of cytoskeletal elements in the sarcomere

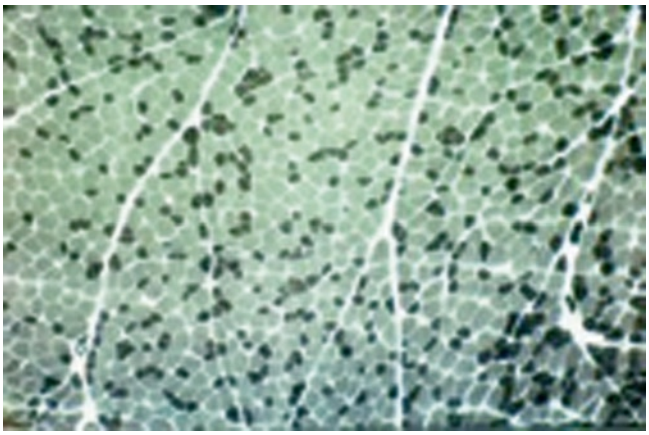

Fig. 77.7 Muscle biopsy in congenital fiber type disproportion. As shown in this typical case, most type I fibers are smaller than type II fibers. Frequently, these changes are a consequence of increased diameters of type II fibers

Serum CK is usually normal, but needle EMG often reveals short-duration, low-amplitude and polyphasic MUAPs in the hands of an electromyographer with experience in pediatric EMG. Specific diagnosis is made on the basis of the muscle biopsy histological findings. The disease course is usually nonprogressive or only slowly progressive; however, some individuals are severely weak and may die from respiratory failure [17, 18].

Metabolic myopathies usually present in childhood and, occasionally, in infancy. The diagnosis is made by muscle biopsy showing excess glycogen or lipid storage and, in some forms, by enzymatic analysis. Infantile acid maltase deficiency (Pompe's disease) is the most frequent metabolic myopathy presenting in infancy as FIS, with severe hypotonia, weakness, respiratory difficulty, cardiomegaly, hepatomegaly, and macroglossia. The enzyme deficiency is systemic, and the heart, liver, kidneys, and CNS are also involved. Needle EMG examination reveals short-duration, low-amplitude, and polyphasic MUAPs and, often, myotonia-like discharges. The diagnosis is best established by leukocytes, fibroblasts, or muscle enzyme assay. Enzyme replacement therapy with recombinant alpha-glucosidase intravenously is currently available [19].

Infantile phenotype of debranching enzyme deficiency (Cori-Forbes disease) presents early in life with hypoglycemia, hypotonia and weakness, and liver dysfunction. Diagnosis can be established by enzyme assay of erythrocytes, muscle, or liver biopsy [20]. Rare cases of myophosphorylase deficiency (McArdle's disease) may present as FIS and follows a rapidly progressive fatal course [21]. Isolated infantile muscle phosphorylase-b-kinase deficiency presenting with severe FIS and respiratory failure have been reported [22]. Glycogen storage disease type IV (branching enzyme deficiency) is a rare disease that can present at different ages, characterized by myopathy, alone or in combination with liver or heart involvement, and is increasingly being recognized as a cause of severe congenital hypotonia [23]. Carnitine deficiency rarely presents in infancy as FIS and is diagnosed by muscle biopsy [24]. A small number of patients with cytochrome C oxidase (COX) deficiency may present in infancy with hypotonia, muscle weakness, feeding and respiratory difficulty, and lactic acidosis and recover in few years [25]. However, the majority of COX deficiency cases have associated multiple CNS and ophthalmologic manifestations, and death often occurs within 2 years of onset.

Congenital myotonic dystrophy is among most common muscle diseases presenting with FIS. Approximately 20 % of infants with myotonic dystrophy have hypotonia in the neonatal period (see Chap. 59) [26]. In congenital cases, the disease is inherited from the mother, and the pregnancy is often complicated by polyhydramnios and prolonged labor. Often these children display inadequate diaphragm and respiratory muscle function and require assisted mechanical ventilation for several weeks. In addition to marked hypotonia, these infants have facial diplegia, feeding difficulty, gastrointestinal dysfunction, mental deficiency, and, often, joint contractures. A facial appearance with tented upper lip, drooping of the eyelids, and wasting of temporalis muscle is a characteristic appearance. Cardiomyopathy and cardiac arrhythmia are frequently encountered and may contribute to early death along with respiratory failure and aspiration. If the infant survives the respiratory failure and swallowing difficulty gradually resolves over a few years, then the disease follows the course of myotonic dystrophy, with delayed motor development and mental retardation. The diagnosis is achieved by neurologic and needle EMG examination of the mother, which reveals myotonic discharges, although the mother may be unaware of her disease, and confirmed by leukocytes analysis for unstable DNA trinucleotide repeat on chromosome 19. Myotonic discharges are usually absent in affected infants and become evident only later in childhood [27].

Congenital muscular dystrophies are a rare and heterogeneous group of muscular dystrophies with benign and severe types, most of which has autosomal-recessive inheritance. Infants present with hypotonia at birth and proximal muscle weakness. Joint contractures, delayed motor milestones, and a clinical picture of arthrogryposis are common. Needle EMG examination shows myopathic features, and serum CK level is variable. Diagnosis of congenital muscular dystrophy is usually achieved by muscle biopsy, which shows dystrophic changes, with no specific histologic abnormalities. Laminin 2 chain (formerly named merosin) is among a family of large extracellular trimeric glycoproteins that surrounds muscle fibers. Patients with merosin-negative immunofluorescent stain of muscle biopsy (merosin deficiency) present with profound hypotonia, severe weakness, often remain unable to ambulate independently, and have associated neuropathy [28]. A detailed large clinical and pathologic study showed that patients with merosin-positive congenital muscular dystrophy characteristically have milder weakness and hypotonia, less severe joint contractures, and a relatively benign course [29]. Fukuyama form of congenital muscular dystrophy is primarily seen in Japan and presents with severe muscular dystrophy, arthrogryposis, mental retardation, and associated CNS abnormalities [30]. The disease is secondary to Fukutin deficiency, an essential extracellular protein, expressed in various tissues. Serum CK is increased in the early stages only. Needle EMG examination shows myopathic features, and the muscle biopsy reveals a dystrophic pattern. The family history is consistent with autosomal-recessive inheritance, although many cases are isolated [31].

Benign Congenital Hypotonia

The term *benign or essential congenital hypotonia* is applied to a group of infants with mild hypotonia and good muscle strength, well-preserved or hypoactive tendon reflexes, and no other clinical manifestations. The prevalence of benign congenital hypotonia is around 3–4 % of hypotonia causes in hypotonic series, and the diagnosis is reached by exclusion of other specific disorders. EMG studies and serum CK are invariably normal. Muscle biopsy may not be warranted in all cases and is usually normal or may show only nonspecific minor abnormalities, such as small fibers of both histochemical types. Muscle tone eventually improves to within the broad limits of normal, usually around the age of 8–10 years [32].

Other Causes of Hypotonia

Hypotonic infants due to systemic diseases represent a large number of FIS causes; thus, assessment of the floppy infant general health as the first step is essential. Several systemic disorders that influence the CNS, such as sepsis, heart failure due to significant congenital heart disease, and some metabolic and endocrine disorders, can be associated with significant hypotonia in infancy (Table 77.4). Hypothyroidism, malnutrition, malabsorption, and renal tubular acidosis are among the more common conditions. These infants usually have severe hypotonia, with only marginal weakness, but they usually have other features of their systemic illness. Infants who have suffered significant hypoxic-ischemic insult often have hypotonia for weeks or months before they develop increased muscle tone. Connective tissue disorders, such as Marfan syndrome or Ehlers-Danlos syndrome, often are associated with hypotonia at birth or during early childhood. These infants manifest significant hypotonia, normal strength and reflexes, and hypermobility of the joints. Infants with inborn errors of metabolism may be hypotonic and can be diagnosed by metabolic screens.

Table 77.4 Systemic causes of hypotonia

Sepsis
Congenital heart disease
Endocrine (hypothyroidism)
Nutritional (malabsorption, malnutrition)
Metabolic (renal tubular acidosis, hypercalcemia)
Hypoxic-ischemic insult
Connective tissue disorders (Marfan and Ehlers-Danlos syndromes)
Maternal medications (psychotropics, benzodiazepines)

Certain drugs administered during pregnancy may cause hypotonia in neonates. Psychotropic drugs taken during late pregnancy may cause neonatal symptoms, including withdrawal symptoms and a floppy infant [33]. Because of rapid placental transfer and slow fetal elimination, benzodiazepines taken in high doses during late pregnancy and labor may cause FIS [34].

Arthrogryposis Multiplex Congenita

Arthrogryposis multiplex congenital (AMC) is a descriptive syndrome characterized by multiple congenital joint contractures, alone or in association with other conditions. In 1841, Otto first described this entity, and in 1923, Stern coined the term arthrogryposis multiplex congenital [35, 36].

AMC is a rare condition with an incidence of 1 in 5,000–10,000 live births. It appears to result from a number of disorders, with a common factor of decreased fetal movements during embryonic formation of joints. Several major causes of AMC are identified, including CNS developmental defects, motor unit disorders, connective tissue abnormalities, space limitations within the uterus, intrauterine vascular insults, and maternal diseases (Table 77.5). AMC may also be a manifestation of specific syndromes, including chromosome trisomy 18 and 21, Möbius, prune belly, and Zellweger syndromes [37]. In addition, there is a group of inherited

Table 77.5 Causes of arthrogryposis multiplex

Fetal causes
Central nervous system developmental defects
Motor unit disorders
Connective tissue abnormalities
Distal arthrogryposis
Armyoplasia
Congenital syndromes
Chromosomal trisomy, Möbius and Zellweger syndromes
Maternal causes
Uterine abnormalities
Tumors, deformities, vascular insult
Maternal diseases
Diabetes, viral infections, drugs

disorders, with phenotypic variation and overlap, known as distal arthrogryposes. They are characterized by multiple congenital contractures of the distal limbs alone or associated with other discrete anomalies but without primary neurologic or neuromuscular disease that affects limb function [38].

CNS developmental defects known to be associated with arthrogryposis include migrational brain disorders, severe hypoplasia of the cerebellum, pyramidal tract degeneration, ischemic brain damage, cortical frontal atrophy, and cerebral abnormalities associated with congenital myopathies. Seizures and severe learning disorders are commonly associated with arthrogryposis secondary to a brain disorder [39–41].

When AMC is associated with *motor unit disorders*, they are usually of the neurogenic rather than myopathic type, among which SMA I is a common cause. Other SMA variants, such as the autosomal-recessive form and dysgenesis of the anterior horn cells, may be associated with neurogenic arthrogryposis [42]. Arthrogryposis has been described in a few patients suffering with hereditary peripheral neuropathy [43]. Congenital muscular dystrophy, nemaline myopathy, central core disease, and various other congenital myopathies are sometimes associated with AMC [44]. Arthrogryposis is also reported in isolated cases of mitochondrial myopathies and congenital myasthenic syndromes. Muscle biopsy and EDX studies are very useful in establishing the diagnosis [45, 46].

Connective tissue abnormalities, including developmental abnormalities of the tendons and joints, pterygium syndrome, and congenital contractural arachnodactyly, may result in limited fetal movements and AMC [47]. Oligohydramnios, intrauterine tumors (especially fibroids), and uterine deformities may limit the space and cause decreased intrauterine fetal movements with subsequent higher incidence of arthrogryposis. Arthrogryposis also is reported in association with impaired vascular supply, maternal diabetes mellitus, hyperthermia, various viral infections, and certain drugs during pregnancy. Armyoplasia is a sporadic syndrome characterized by an absence of limb muscles, which are replaced by fibrous and fatty tissue. The newborn has multiple limb abnormalities and joint contractures.

Joint contractures may be diagnosed prenatally by ultrasound. Careful prenatal and perinatal history, clinical examination, and relevant investigations are needed to determine the etiology of arthrogryposis, as the prognosis and genetic implications vary. The mainstay of treatment for affected infants is physiotherapy, splinting, and orthopedic surgery, along with optimizing medical care.

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Rhabdomyolysis and Myoglobinuria

78

Devanshi Jadhav and Henry J. Kaminski

Introduction

Rhabdomyolysis (lysis of skeletal muscle cells) is a potentially lethal syndrome with a broad spectrum of clinical and biochemical findings. Myalgia, pigmenturia, and elevated activity of serum creatine kinase (CK) are the common features. Fulminant rhabdomyolysis may be associated with severe metabolic disturbances and involvement of other organ systems. Cardiac arrest, compartment syndrome, and acute renal failure are the major complications. The first cases of death secondary to rhabdomyolysis appear in the Book of Numbers; Israelites died after eating quail, which had been fed on hemlock (a reported cause of rhabdomyolysis) [1, 2]. The prevention of life-threatening complications of rhabdomyolysis strongly depends on early diagnosis and adequate therapy. Since the repair mechanism of striated muscle functions very well, the prognosis of appropriately treated rhabdomyolysis is excellent.

Rhabdomyolysis denotes an acute or subacute event, which leads to necrosis of striated muscles. The clinical features vary widely from moderate muscular symptoms to life-threatening complications. Rhabdomyolysis occurs in a wide array of settings: alcohol abuse, drug addiction, excessive exercises, severe physical trauma, and attempted suicide. Neurologists deal with the clinical complications of rhabdomyolysis in several clinical scenarios. Patients with severe rhabdomyolysis may be comatose and subsequently develop significant metabolic disturbances involving the central and peripheral nervous systems. Other patients with mild or recurrent rhabdomyolysis may present with exercise-related neuromuscular manifestations requiring a search for an underlying metabolic defect, while rhabdomyolysis may also develop as a sequelae of seizures or withdrawal of antiparkinsonian medications [3, 4]. The chapter reviews the present state of knowledge of the clinical and biochemical diagnosis of rhabdomyolysis; its pathophysiology, classification, provocative factors, and associated diseases; and the management of patients including diagnostic and therapeutic guidelines. The authors acknowledge the work of the original authors, Aad Verrips, Petra Poels, and JM Gabreëls, upon which much of the present contribution is based [5].

Definition

Rhabdomyolysis is defined as a clinical and biochemical syndrome resulting from skeletal muscle injury that alters the integrity of the muscle cell membrane sufficiently to allow the release of muscle cell contents, including myoglobin, creatine phosphokinase, potassium, aldolase, lactate dehydrogenase, and glutamic oxaloacetic transaminase into the blood. Rhabdomyolysis may cause visible pigmenturia as a result of myoglobin in the urine, which leads to myoglobinuria often used as a synonym for rhabdomyolysis. Bowden et al. suggested the term rhabdomyolysis to highlight that the fundamental problem in myoglobinuria concerns the muscle and is not primarily related to either myoglobin or renal failure [6]. In fact, myoglobinuria does not exist without rhabdomyolysis, but rhabdomyolysis does not necessarily result in visible myoglobinuria, and many other constituents of muscle are released into the blood.

No strict criteria exist for the diagnosis of rhabdomyolysis, probably due to the diversity of its clinical presentation, but we offer the following as criteria based on existing literature:

1. An event of muscle destruction with manifestations confined to the muscles or with involvement of other systems, resulting in general weakness or specific organ

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diseases such as cardiomyopathy, neuropathy, encephalopathy, or nephropathy.
2. An increase in serum levels of skeletal muscle enzymes, particularly CK. The degree of elevation of serum CK level is arbitrary but should be at least fivefold normal (>975 IU/l) [7].
3. An increase in the level of serum and urinary myoglobin.

Pathogenesis

Rhabdomyolysis is the result of a direct muscle injury or an altered relationship between energy production and energy consumption in muscle. The development of muscle cell necrosis is thought to start at the plasma membrane, including the sarcolemma and T-tubule, where several adenosine triphosphate dinucleotide-consuming ion transport systems are located (Fig. 78.1).

The balance between the intra- and extracellular calcium concentration is of crucial importance for muscle cell integrity [8]. In the intact muscle fiber, there is a steep calcium gradient across the plasma membrane, the extracellular calcium concentration being manyfold higher than the intracellular concentration. The binding of calcium with high affinity to a large number of cellular components is one efficient mechanism to keep the intracellular free calcium concentration at low levels [9]. The sodium/potassium pump is critical for calcium homeostasis and muscle cell integrity. The sodium/potassium pump at the plasma membrane regulates the active transport of sodium out of the cell and potassium into the cell. The activity of this pump appears to be regulated by sodium potassium-activated adenosine triphosphatase (sodium/potassium -ATPase) and is dependent on sufficient ATP supply. When the Na^+/K^+ pump malfunctions because of energy depletion or direct injury to the plasma membrane, an influx of sodium chloride and water into the cell occurs [10]. Osmotic swelling then leads to muscle cell injury. Subsequently, an exchange of sodium for calcium ions, via a protein carrier exchange mechanism, promotes increased influx of calcium ions across the membrane and subsequent activation of calcium-dependent proteases, contributing to muscle injury.

Calcium ions are sequestered by the sarcoplasmic reticulum (SR) that contains different calcium-transporting systems for the uptake of calcium and the release of calcium back to the cytosol (Fig. 78.2). Once the integrity of the muscle membrane and SR membrane is lost, an increased influx of calcium ions overloads the mitochondria. The mitochondria have an impressive capacity for calcium uptake and will store excess calcium for a relatively long time. However, when the level of mitochondrial calcium loading becomes intolerable to the organelle, the excess calcium is released from the mitochondria into the cytosol. The functional and structural damage of the mitochondria and the ensuing lack of energy create a vicious cycle as less energy becomes available for pumping calcium out of the cell (Fig. 78.2).

The elevated level of intracellular calcium activates phospholipase-A_2 resulting in the accumulation of lysophospholipids in the muscle cell and raises the activity of neutral proteases to a level that becomes destructive to the muscle cell. The elevated cytoplasmic calcium level will enhance the interaction of actin and myosin filaments leading to

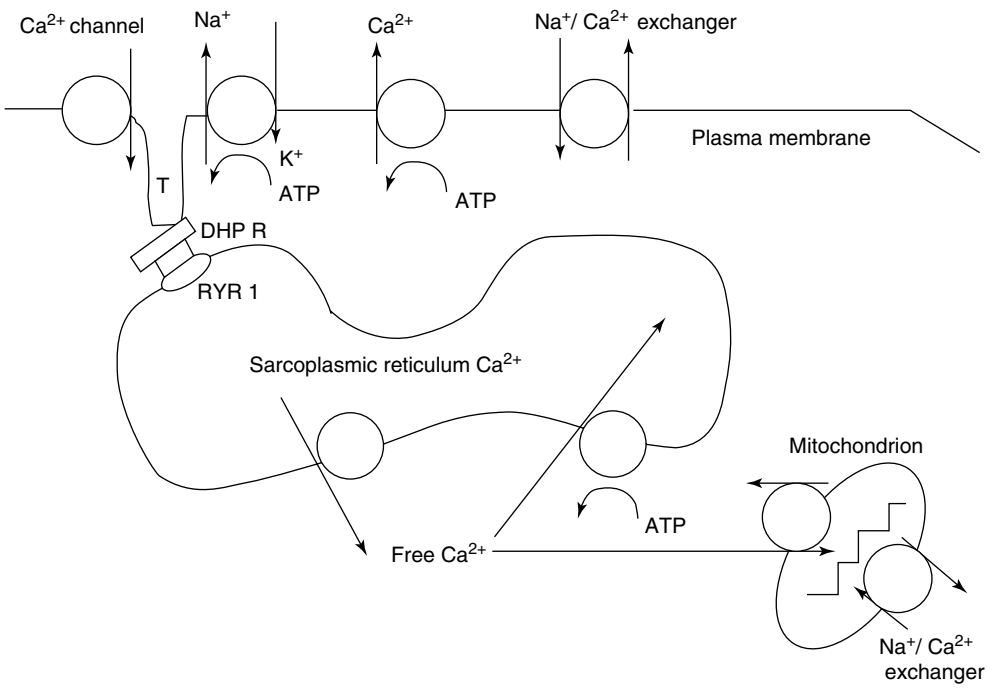

Fig. 78.1 Schematic representation of calcium release and uptake by the muscle cell and its organelles (Reproduced from Poels and Gabreëls [160])

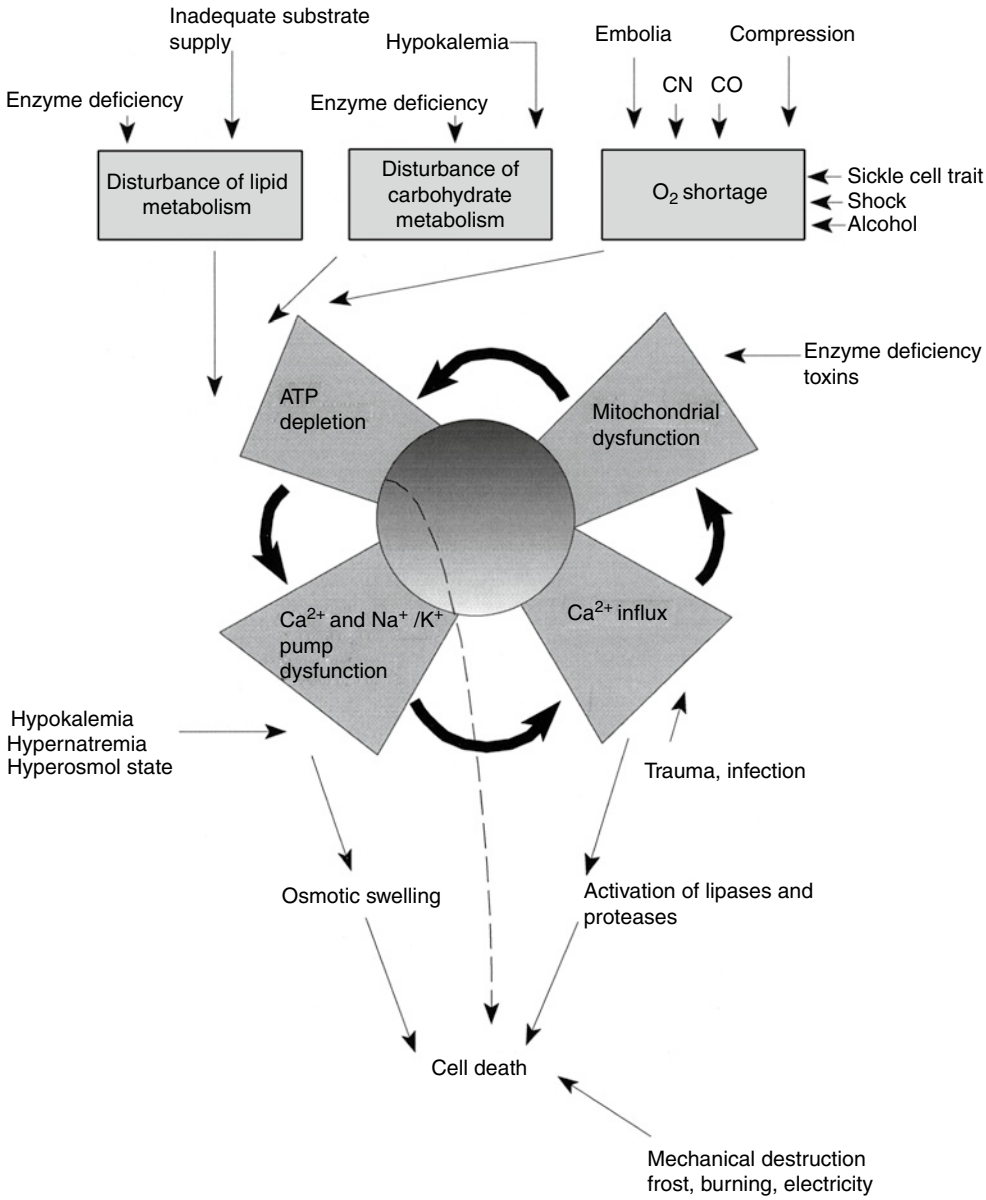

Fig. 78.2 Schematic representation of the process of muscle cell necrosis and its causative factors (Reproduced from Poels and Gabreëls [160, p. 178])

myofibrillar hypercontractures and, if the calcium level is critically high, to damage of the muscle cell [11].

Biochemical Features

Myoglobin

Myoglobin functions as an oxygen store and carrier, important in maintaining the ability of skeletal muscles to consume oxygen and generate contraction. This small protein (17,800 kDa) is rapidly filtered through the renal glomeruli. Myoglobinuria (leading to tea colored urine) is estimated to cause 5–25 % [12] of cases of renal failure with serum levels above 300 μg/l and develops in most patients excreting more than 1,000 μg/l [13]. A rise in serum myoglobin level precedes an increase in serum CK. The concentration of myoglobin in serum returns to normal 1–6 h after cessation of muscle injury due to the rapid clearance of myoglobin by both renal excretion and metabolism to bilirubin [13]. Therefore, determination of myoglobin in serum and urine is helpful only for the early diagnosis of rhabdomyolysis, and the absence of elevated levels of serum myoglobin does not eliminate the diagnosis of rhabdomyolysis.

Pigmenturia may also occur in patients with hemoglobinuria or porphyria, but the clinical presentations differ. The combination of a positive o-toluidine test, gold–brown pigmented casts in urine, the absence of erythrocyturia, colorless serum, and a normal haptoglobin level confirms the diagnosis myoglobinuria. Assay methods using specific antibodies against myoglobin are the most sensitive tests since antibodies to myoglobin do not cross-react with hemoglobin. Radioimmunoassay and enzyme-linked immunoassay have

a sensitivity high enough to measure normal contents of myoglobin in serum and urine [14].

Serum Creatine Kinase

CK plays an important role in metabolism by catalyzing the reversible transfer of the terminal phosphate group of ATP to creatine to form phosphocreatine. The laboratory abnormality most suggestive of rhabdomyolysis is an elevation of serum CK to at least fivefold normal. Destruction of about 200 g of muscle causes an elevation of serum CK.

Human tissues contain three isoenzymes of CK: MM, MB, and BB. The predominant sources of CK-MM isoenzyme are skeletal and cardiac muscle. The CK-BB isoenzyme is found in brain tissue and CK-MB isoenzyme mainly in cardiac but also in skeletal muscle. In rhabdomyolysis, an elevation of total CK, especially of CK-MM isoenzyme, is found, accompanied by an increase of myoglobin in serum and urine. Involvement of myocardium is likely if the isoenzyme CK-MB exceeds 5 % of the total CK activity [15].

Serum CK concentration begins to rise 2–12 h after onset of muscle injury, peaks in 1–3 days, and declines within 3–5 days after muscle injury ceases. Serum CK levels remain elevated longer than myoglobin levels because of its relatively slow clearance with a serum half-life of about 1.5 days. The elevation of serum CK level in acute attacks of rhabdomyolysis is transient and may reach a level of 100,000 IU/l, being many times higher than in most other conditions. Persistently and moderately elevated serum CK levels are also present in many common myopathies and other disorders, including hypothyroidism, but are not accompanied by massive muscle necrosis with pigmenturia.

Carbonic Anhydrase III

For diagnostic purposes, serum CK and myoglobin are generally used to demonstrate skeletal muscle damage in rhabdomyolysis. Carbonic anhydrase III is an even more specific marker of skeletal muscle injury than are myoglobin and serum CK, as it is not present in myocardium [16, 17].

Potassium, Calcium, and Phosphate

When the integrity of muscle cell membrane is disrupted, other protein and nonprotein cellular components are also released into the circulation. Clinically critical biochemical findings in rhabdomyolysis are hyperkalemia, hypocalcemia, and hyperphosphatemia. Muscle necrosis of about 150 g will release in excess of 15 mmol potassium, sufficient to acutely elevate serum and extracellular fluid potassium concentrations [7]. The resulting hyperkalemia may lead to cardiac arrhythmias. Hypocalcemia in the initial phase of rhabdomyolysis is attributed to deposition of calcium salts in necrotic muscle [18]. This appears to result from the release of large amounts of organic and inorganic phosphate into the circulation, elevating the calcium phosphate product with subsequent deposition of calcium salts into muscle and other tissues [18]. Another cause of the initial hypocalcemia may be a fall in plasma levels of 1,25-dihydroxycholecalciferol due to hyperphosphatemia [19]. During the later stage, an excessive rise in calcium may occur, when calcium is mobilized from damaged muscle again. Another cause of hypercalcemia is attributed to secondary hyperparathyroidism, triggered by hyperphosphatemia [11, 20]. Other laboratory findings include elevated serum levels of aminotransferases, aldolase, lactate dehydrogenase, creatinine, urea, hydroxybutyrate, and uric acid. Hyperuricemia is the result of enhanced cellular release of purine precursors, which are converted to uric acids by the liver. The uric acid concentration, in general, is correlated with the serum CK level [11].

Clinical Presentation

There is great heterogeneity in the clinical presentation of rhabdomyolysis, which is probably due to the diversity of its etiological factors [21]. The clinical features are divided into (a) muscular manifestations accompanied by pigmenturia, (b) systemic disturbances, and (c) complications resulting from involvement of other organ systems.

Muscular manifestations consist of muscle pain, swelling, tenderness, stiffness, contractures, and weakness. However, in one study, only 50 % of the patients with rhabdomyolysis presented with muscular signs and symptoms [7]. Rhabdomyolysis may involve all striated muscles diffusely or focally. Usually the postural muscles of the thighs, calves, and the lower back and the muscles of the arms are painful and weak. When edema develops, the muscles become stiff and tender to palpation. Muscle swelling of the calves may result in contractures and loss of ankle jerks. Rhabdomyolysis may also extend to the muscles of the chest, abdomen, palate, and throat and to the masticatory muscles. In general, the muscle repair mechanisms seem to function extremely well, as the permanent damage to muscle that results from traumatic and non-traumatic events is surprisingly minimal. Usually, the muscle disorder is self-limited and leads to complete recovery within days or weeks.

Systemic disturbances may be prominent in fulminant rhabdomyolysis, leading to general malaise, fever, tachycardia, abdominal pain, nausea, and vomiting. High levels of urea may result in encephalopathy with impaired consciousness, agitation, and confusion. Depression of cerebral metabolism is followed by hypoventilation, leading to hypoxia and respiratory acidosis. The major complications of rhabdomyolysis are cardiac arrest, compartment syndrome, and acute renal failure.

Fulminant rhabdomyolysis associated with severe hyperkalemia and hypocalcemia may induce a life-threatening complication of cardiac arrest. Hyperkalemia is cardiotoxic,

which may be potentiated by hypocalcemia. The development of the compartment syndrome is another complication of severe rhabdomyolysis in which the muscle swelling may produce compression of adjacent vessels and nerves within tight fascial compartments. When the compartmental pressure exceeds the arterial pressure, secondary ischemic necrosis and muscle destruction result. Compartment syndrome in non-traumatic rhabdomyolysis is usually subsequent to prolonged coma or immobilization following overdose of various drugs, where the patient's own body weight may raise the external pressure on muscles. The direct toxicity of alcohol and heroin on muscles is very likely to be of additional importance.

Acute renal failure may be life threatening and the most frequently reported complication of rhabdomyolysis. The frequency of acute renal failure in rhabdomyolysis is not known, but it is described in a third to nearly half of patients in large case series [10, 22]. Why this complication develops in only some patients is not known. Renal insufficiency may develop in patients who are compromised in some manner that influences renal function [23] or may be related to the quantity of myoglobin released into the circulation. The major theories that have been advanced to explain its development include factors related to renal circulation and direct tubular injury:

- Back leak of filtrate through the damaged tubular epithelium to the peritubular circulation [24].
- Renal ischemia as a result of vasoconstriction of renal arterioles due to intravascular hypovolemia.
- Associated shock with impaired renal flow and decreased glomerular filtration rate.
- Tubular obstruction by precipitation of pigmented casts in the ultra filtrate. The formation of intraluminar casts in combination with the renal tubular secretory Tamm–Horsfall protein is facilitated by the acid pH of the tubular fluid.
- Tubular injury by direct toxicity of myoglobin in itself or indirect toxicity by the heme pigments released from myoglobin in the presence of hypovolemia and aciduria. The overwhelming quantities of free iron cannot be stored into ferritin and facilitate the generation of free radicals [25, 26].
- Release of neutral proteases or vasoactive kinins from injured skeletal muscle cells that may directly damage the kidney [27].

Classification and Etiology

Rhabdomyolysis may be categorized in several ways: traumatic and non-traumatic forms or endogenous and exogenous types and hereditary and acquired forms. Any classification, however, has its limitations, as there is often more than one trigger for an attack of rhabdomyolysis. In some patients, genetic causes overlap with nongenetic causes. Recurrent attacks of rhabdomyolysis in patients with hereditary metabolic myopathies are usually induced by exercise, but exercise may also induce rhabdomyolysis in patients without known genetic disorders. Rhabdomyolysis associated with drug-induced coma may be caused by trauma, immobilization, hypoventilation, shock, or metabolic acidosis. A study of 77 patients with recurrent attacks of rhabdomyolysis found known muscle enzyme defects in half. This would suggest that the remaining patients harbored as yet unidentified genetic disorders [28].

Table 78.1 Causes of hereditary rhabdomyolysis

Deficiencies of glycogenolytic enzymes
Myophosphorylase (McArdle's disease)
Phosphorylase kinase
Phosphofructokinase (Tarui's disease)
Phosphoglycerate kinase
Phosphoglycerate mutase
Lactate dehydrogenase
Abnormal lipid metabolism
Carnitine palmitoyltransferase deficiency I and II
Carnitine deficiency
Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
Short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
Late-onset medium-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
Very long-chain acyl-coenzyme A dehydrogenase deficiency
Various genetic disorders
Idiopathic rhabdomyolysis
Autosomal dominant myoglobinuria
Myoadenylate deaminase deficiency
Malignant hyperthermia
Monocarboxylate transporter
Neuroleptic malignant syndrome
Dystrophin-associated muscular dystrophies
Mitochondrial mutations

Hereditary Causes of Rhabdomyolysis

Hereditary causes of rhabdomyolysis include disorders of glycogen and lipid metabolism, other genetic diseases such as malignant hyperthermia [29], and endogenous disorders without identified causes (Table 78.1) [1, 30]. In hereditary disorders associated with rhabdomyolysis, the number of recognized metabolic defects has increased during the last two decades and will increase as genetic diagnosis improves.

Recurrent rhabdomyolysis is characteristic of a number of inherited glycogen storage diseases of muscle. Defects in enzymes of glycogenolysis associated with rhabdomyolysis are myophosphorylase, phosphorylase kinase,

phosphofructokinase (PFK), phosphoglycerate kinase (PGK), phosphoglycerate mutase (PGAM), and lactate dehydrogenase (LDH). Exercise is the most important triggering factor in patients with glycogenolytic enzyme defects. The metabolic block in glycogenosis causes a disturbance in energy production early during intense exercise.

Intense exercise of normal skeletal muscle produces intracellular acidosis and increases intracellular inorganic phosphate levels, both of which reduce the calcium sensitivity and tension-generating capacity of the contractile proteins [31]. In skeletal muscles with impaired myoglycolysis or impaired myoglycogenolysis, intense exercise, particularly if performed under ischemic conditions, produces electrically silent muscle contractions called contractures. Experiments in an animal model of impaired myoglycolysis and impaired myoglycogenolysis demonstrated that the initial metabolic abnormalities causing contractures are elevated ADP levels, depletion of creatine phosphate, and elevated intracellular Ca^{+2} levels combined with no change in intracellular pH and only a small increase in intracellular inorganic phosphate. At the onset of contracture, the level of ATP was not reduced. The tension present in contracture resulted from a combination of elevated intracellular Ca^{+2} and increased sensitivity of the contractile proteins to Ca^{+2}. Depletion of creatine phosphate prevents conversion of ADP to ATP and ATP levels drop [32]. When ATP levels fall below a critical level, cellular metabolism is disrupted. This results in loss of integrity of membranes and muscle necrosis, especially of the type 2 fibers, which depend primarily on glycolysis [33]. Exercise intolerance, muscle cramps, and pigmenturia are the primary manifestations of glycogenolytic disorders.

In most patients, the first symptoms begin before the age of 20 years, and the attacks of rhabdomyolysis are intermittent and exercise induced. In glycogenolytic disorders, the inheritance is usually autosomal recessive, except for PGK deficiency, which is X-linked. Serum CK is persistently increased 5- to l0-fold. In certain of the disorders during the ischemic forearm test, the normal rise of lactate in venous blood is small or completely absent [34]. Histological examination shows an accumulation of glycogen beneath the sarcolemma and histochemical staining for the abnormal glycogenolytic enzyme is negative. The activity of the individual glycogenolytic enzyme and its content may also be biochemically measured in muscle tissue.

Myophosphorylase deficiency (*McArdle's disease*) was identified in 1959 [35]. Exercise intolerance is most prominent during the first 10 min of intensive exertion. After brief rest, the patient may resume exercise; this so-called second wind phenomenon is characteristic of myophosphorylase deficiency [36]. In a review of patients with McArdle's disease, slightly over 50 % had overt myoglobinuria and elevated serum CK levels, indicative of rhabdomyolysis [36]. In half of patients, the rhabdomyolytic attacks occurred once or twice, while the others more frequently. Exercise was the main precipitating factor. Acute renal failure developed in 6–8 % of patients, who eventually all recovered. Tonin et al. [28] screened muscle biopsies of 30 patients with exercise intolerance without myoglobinuria and found myophosphorylase deficiency in 17. Therefore, as myoglobinuria is not an obligatory consequence of McArdle's disease, many patients with only exercise intolerance may not be identified with the disorder. McArdle's disease is the second common disorder of muscle metabolism, after carnitine palmitoyltransferase (CPT) deficiency, causing exercise-induced rhabdomyolysis.

Phosphorylase kinase deficiency, a cause of benign hepatomegaly in infancy, is rarely reported to cause rhabdomyolysis [37]. However, in 77 muscle biopsies of patients with rhabdomyolysis, Tonin et al. found phosphorylase kinase deficiency in four [28] and concluded that the importance of this enzyme defect as a cause of rhabdomyolysis is underestimated.

Phosphofructokinase (*PFK*) *deficiency* (Tarui's disease), which was described in 1967 [38], has only rarely been associated with rhabdomyolysis [39]. The clinical picture is identical to that of myophosphorylase deficiency: a lifelong intolerance to strenuous exercise with pain and stiffness of exercising muscles. However, a few patients with PFK deficiency are reported with onset in older age with progressive limb weakness and therefore should be considered in the differential diagnosis of late-onset myopathy [28].

Three defects of terminal glycolysis are PGK deficiency, PGAM deficiency, and LDH deficiency [40, 41]. PGAM deficiency and lactate dehydrogenase (LDH) deficiency are clinically characterized by exercise intolerance, muscle cramps, and recurrent rhabdomyolysis but with no fixed weakness. They do not cause a complete block of the glycolytic pathway and do not result in severe glycogen accumulation on muscle biopsy. Phosphoglycerate kinase (PGK) deficiency was first described by DiMauro in a 14-year-old boy with rhabdomyolysis and renal failure after intense exercise [41]. The enzyme defect is also expressed in erythrocytes, in fibroblasts, and muscle cultures. PGK deficiency is an X-linked recessive trait and usually associated with hemolytic anemia, mental retardation, and seizures.

Recurrent rhabdomyolysis is also a characteristic feature of disorders of lipid metabolism including carnitine palmitoyl transferase (CPT) II deficiency, carnitine deficiency, short-/medium-/long-/very long-chain and multiple acyl-coenzyme A dehydrogenase deficiencies, electron transfer flavoprotein (ETF) deficiency, ketoacyl CoA thiolase deficiency, and trifunctional enzyme deficiency [12]. Carnitine palmitoyltransferase (CPT) I and II deficiency, a disorder of lipid metabolism. CPT I and II deficiency [38] proved to be the most common hereditary disorder causing rhabdomyolysis in the patients studied by Tonin and colleagues [28]. CPT I

and II are responsible for the transport of long-chain fatty acids across the mitochondrial membrane, before which the fatty acids must be esterified with carnitine. In patients with CPT I and II deficiency, muscle pain and rhabdomyolysis develop after strenuous exercise for a prolonged time without adequate intake of food or during prolonged stress, in contrast to rhabdomyolysis in glycogenolytic disorders, which occurs in the initial phase of exercise. In CPT I and II deficiency, attacks of rhabdomyolysis may be successfully prevented by maintenance of adequate intake of carbohydrates during long periods of exercise.

The high frequency of rhabdomyolysis in CPT deficiency is in contrast with its rarity in mitochondrial myopathies [42], acid maltase deficiency [39], and in systemic carnitine deficiency [43]. Deficiency of CPT results in recurrent rhabdomyolysis, while deficiency of the substrate carnitine predominantly causes lipid storage myopathy [44]. The reason for the difference in clinical presentations is not clear. Recurrent attacks of rhabdomyolysis have been described in only three patients with myopathic carnitine deficiency [45–47] and in one patient with a secondary carnitine deficiency syndrome due to long-chain acyl-CoA dehydrogenase deficiency [48].

Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD) is a defect of mitochondrial fatty acid beta-oxidation that may induce rhabdomyolysis. These deficiencies may become manifest during infancy with hypoglycemic coma, hepatic steatosis, and hypocarnitinemia. Another manifestation is cardiomyopathy. In addition, LCHAD deficiency has specific features, including peripheral neuropathy and chorioretinopathy. Female carriers of LCHAD deficiency are prone to preeclampsia-related pregnancy complications. Diagnosis is suggested by 3-hydroxylated acylcarnitine species in blood [49].

Tein et al. described a 16-year-old girl with short-chain L-3-hydroxyacyl-coenzyme A dehydrogenase deficiency resulting in juvenile-onset recurrent myoglobinuria, hypoketotic hypoglycemic encephalopathy, and hypertrophic/dilated cardiomyopathy [50].

Very long-chain acyl-coenzyme A dehydrogenase deficiency (VCHAD) is an adult-onset myopathy very similar to CPT II deficiency, caused due to a mutation in the acyl-coenzyme A dehydrogenase, very long-chain (ACADVL) gene. It is characterized by rhabdomyolysis and myoglobinuria after exercise or fasting and detected by immunohistochemistry. Voermans et al. reported two patients who were otherwise healthy with episodic exercise-induced rhabdomyolysis [51].

A family with "autosomal dominant myoglobinuria" has been reported, in which ten individuals of both sexes in four successive generations suffered from myoglobinuria, precipitated by a febrile illness. Four individuals suffered acute renal failure, which in two was reversed only after dialysis. In one, a mitochondrial disorder was suspected, but no mutation in the mitochondrial DNA was identified. The authors suggested that the myoglobinuria in this family was caused by a nuclear-encoded mutation affecting the respiratory chain [52].

Myoadenylate deaminase (*MAD*) *deficiency* was first described in 1978 in five patients with exertional myalgia [53]. MAD is involved in purine nucleotide breakdown by catalyzing the irreversible deamination of adenosine monophosphate to inosine monophosphate while ammonia is formed. This reaction is active during muscle contraction, especially during ischemic exercise. The clinical features are rapid fatigue and weakness or cramping following vigorous exercise. In some patients, exertional rhabdomyolysis was described [53–55]. The normal rise in ammonia in venous blood is small or absent during the ischemic forearm test. In the study of Tonin et al. [28], three patients with rhabdomyolysis had an isolated MAD deficiency. As MAD deficiency is often associated with other well-defined disorders, for example, amyotrophic lateral sclerosis [55], hypokalemic periodic paralysis [56], dermatomyositis [57], and progressive systemic sclerosis [58], a coincidental association of MAD deficiency with other causes of rhabdomyolysis cannot be excluded. Although its pathogenic significance in muscle disorders has not been clearly defined [34], MAD deficiency does impair energy production [59]. Verzijl et al. demonstrated the same underlying molecular defect, a C34T transition, in inherited and acquired MAD deficiency in a Dutch population and found the same frequency of the mutant MAD allele in the general population as in patients with neuromuscular complaints. Their conclusion was that secondary MAD deficiency is merely a "coincidental" finding and that MAD deficiency is a harmless genetic variant [60].

In addition to metabolic causes, recurrent rhabdomyolysis is attributed to a number of incompletely characterized genetic defects. Mitochondrial mutations in genes encoding succinate dehydrogenase/complex II deficiency, complex III deficiency, coenzyme Q10 deficiency, cytochrome Q10 deficiency, and cytochrome c oxidase deficiency have been identified in association with clinical features suggestive of mitochondrial disease, such as progressive external ophthalmoplegia [12].

In two brothers with recurrent rhabdomyolysis, a defect of the mitochondrial energy-transducing system due to multiple deletions of mitochondrial DNA was reported [61]. Monocarboxylate transporter 1 (MCT1) mutations (the gene for the red cell lactate transporter also expressed in skeletal muscle) were described in patients with subnormal erythrocyte lactate transport plus manifestations of muscle injury on exercise and heat exposure [62].

Malignant hyperthermia (MH) is a life-threatening form of rhabdomyolysis [63], which is characterized by a

hypermetabolic state of skeletal muscle, associated with extreme muscle rigidity and rhabdomyolysis, rapidly rising body temperature to 41°C or and above, metabolic acidosis, cardiac arrhythmia, and disseminated coagulopathy. A genetic defect in the ryanodine receptor gene, *RYR1* (MHS1 locus) on chromosome 19q13.2, has been identified as a cause of 70–80 % of patients. Mutations in the *CACNA1S* (MHS5 locus) that encode the α_1-subunit of the skeletal muscle dihydropyridine receptor L-type calcium channel account for 1 % of all cases. Three additional loci have been mapped, but the genes have not been identified: MHS2, linked to chromosomal locus 17q11.2-q24; MHS4, linked to chromosomal locus 3q13; and MHS6, linked to chromosome 5p. In a single family, MHS3, linked to chromosomal 7q21-q22, has been associated with a mutation in the calcium channel alpha-2 gene but it has not been found to have an association with MHS in other studies [64]. MH is almost always observed after administration of volatile anesthetics, for example, halothane, and depolarizing muscle relaxants such as succinylcholine. Isolated episodes of rhabdomyolysis are described and induced by physical or emotional stress [29, 65].

The clinical manifestations of MH are similar to the neuroleptic malignant syndrome (NMS). Patients receiving neuroleptics may also develop a potentially lethal disorder, characterized by moderate hyperthermia, instability of the autonomic nervous system, muscle rigidity, and myoglobinuria accompanied by an increase in serum CK [66]. All neuroleptic medications, synthetic narcotics, and tricyclic antidepressants may induce NMS [67, 68]. Different from MH, however, is the gradual development of signs and symptoms in NMS. Another difference is the central disorder in NMS and the presumed sarcolemmal defect in MH. There has been no genetic defect associated with NMS.

Acquired Causes of Rhabdomyolysis

The majority of patients who develop rhabdomyolysis have no underlying neuromuscular disease but are exposed to a range of inciting factors or events (Table 78.2). Genetic susceptibility is not considered to be responsible for the development of rhabdomyolysis: any human who is stressed sufficiently, exposed to drugs or toxins, or suffers from metabolic disorders or infectious diseases may develop rhabdomyolysis.

In large series of patients with rhabdomyolysis [7, 69], alcoholism and drug abuse are responsible for the majority of cases. Ethanol itself may have a direct toxic effect on muscles [70] and interfere with muscle metabolism [71]. In contrast to alcohol-induced rhabdomyolysis, which is marked by muscle pain, acute hypokalemia myopathy observed in alcoholics is characterized by rapidly developing painless muscle weakness [72]. A subclinical chronic myopathy may proceed to acute muscle necrosis after a sustained period of alcohol abuse and starvation [72]. Involvement of the heart muscle, resulting in cardiomyopathy, has been described [73]. Chronic alcoholism leads to muscle atrophy, primarily of type 2 fibers [74]. Histological analysis reveals necrosis and invasion of degenerated fibers by leucocytes and macrophages [75]. At an ultrastructural level, there is dilatation of sarcoplasmic reticulum, increased fat and glycogen, and distorted mitochondria [70].

Table 78.2 Causes of acquired rhabdomyolysis

Toxic
Alcohol, drugs, and toxins (see Table 78.3)
Excessive muscle exercise
Sports and military training
Status epilepticus, convulsions, prolonged myoclonus, status asthmaticus, acute dystonia
Direct muscle injury
Crush, burning, freezing, electric shock, lightning stroke, prolonged immobility, compartment syndrome
Ischemic injury
Compression, vascular occlusion, sickle cell trait
Metabolic disorders
Diabetic ketoacidosis, nonketotic hyperosmolar coma, hypothyroidism, hypophosphatemia, hyponatremia, hypokalemia, hypocalcemia
Infections
Bacterial, viral
Heat-related syndromes
Toxic shock syndrome, heat stroke, hypothermia
Inflammatory myopathies
Polymyositis, dermatomyositis
Other
Anticholinergic syndrome, withdrawal of L-Dopa

Four patients have been described with end-stage renal failure on hemodialysis who developed rhabdomyolysis after major surgery [76]. This possibly underappreciated complication was manifest by extreme hyperphosphatemia, hypocalcemia, and elevated CK. The possible precipitating factors included opiates used for anesthesia and postoperative pain control, anesthetic agents, and surgical position. As treatment options, the authors suggested increasing dialysis to control hyperphosphatemia and hypocalcemia [76]. Surgery itself, particularly in a prolonged position, may be a causative factor for rhabdomyolysis [77–79].

Rhabdomyolysis has developed in patients exposed to a great variety of *drugs and toxins* with a direct effect on muscle, including heroin [80], cocaine [81], amphetamine [82], phencyclidine [83], theophylline [84], antihistamines [85], antihyperlipidemics [86], barbiturates, antibiotics, beta-blockers, and several other myotoxic drugs (Table 78.3) [1, 87–91]. Some drugs and toxins exert a direct toxic effect

Table 78.3 Drugs and toxins associated with rhabdomyolysis

Drugs
Acetaminophen, amphetamines, amphotericin B, antibiotics (several), antihistamines, azathioprine, bactrim, barbiturates, bezafibrate, caffeine, clofibrate, cocaine, epsilon aminocaproic acid, ethanol, glycyrrhetinate (licorice, carbenoxolone), β-HMG-CoA reductase inhibitors, imatinib mesylate, iron dextran, isoniazid, lamotrigine, lithium, LSD, marijuana, meprobamate opiates, mineralocorticoids, phencyclidine, phenytoin neuroleptics, rohypnol, serotonin reuptake inhibitors, strychnine, succinylcholine suxamethonium, theophylline, vasopressin, zidovudine
Toxins
Carbon monoxide, *C. Diff* toxin, gasoline, Haffs fish, plasmocid, staphylococcal toxin, streptococcal toxin, tetanus toxin, toluene, typhoid toxin

on muscles, but in many others, the underlying mechanisms are not clear. Neuroleptics may primarily affect the central nervous system. The abrupt withdrawal of L-dopa medication in parkinsonian patients [92] may lead to clinical features similar to NMS and the central anticholinergic syndrome, consisting of dry mouth, dilated pupils, urinary retention, increased body temperature, and rhabdomyolysis. Overdose of certain drugs such as heroin and barbiturates is associated with rhabdomyolysis, which may be due to secondary factors like muscle compression in coma, delirium, and hyperthermia. Rhabdomyolysis has frequently been observed after chronic ingestion of compounds and drugs associated with hypokalemia, including licorice, carbenoxolone, laxatives, and diuretics [93, 94].

Several case reports of rhabdomyolysis describe envenomation by snakes, hornets, spiders, and scorpions containing myotoxins, probably phospholipases, that proved to cause rhabdomyolysis [95]. Two large epidemics of acute attacks of rhabdomyolysis occurred after ingestion of contaminated fish [96]. Eating quails, fed with hellebore or hemlock, has also been associated with fatal outbreaks of rhabdomyolysis [2, 97].

Rhabdomyolysis may occur due to *strenuous exercise*, especially in untrained individuals [98]. A lack of heat acclimatization, profuse sweating, insufficient intake of salts and high ambient temperature, resulting in hemodilution and hyponatremia, contribute to the development of rhabdomyolysis [99]. Extreme muscle activity with pathological conditions, such as generalized convulsions [100], status epilepticus [101], and status asthmaticus [102]; prolonged myoclonus [103]; severe dystonia [104]; or acute psychosis [105] may result in rhabdomyolysis.

Heat stroke is a disorder manifested by rhabdomyolysis and metabolic encephalopathy, anhydrosis, and hyperthermia. Heat-related syndromes are reported in users of phenothiazines, which may impair temperature regulation [106]. Heatstroke may develop in older individuals secondary to exhaustion [107], amphetamine abuse [82], and in patients with sickle cell trait [108]. Heat-related syndromes may be complicated by disseminated coagulopathy.

Direct muscle injury occurs in crush [109], ischemic injuries [110], burns, frostbite [111], electric shock, or lightning stroke [112]. Prolonged immobility during surgery [113] and pressure palsies in comatose patients seem also to interfere with the energy metabolism of muscles, resulting in rhabdomyolysis.

Metabolic depression may directly affect muscles or indirectly disturb energy metabolism. Diabetic ketoacidosis [114], nonketotic hyperglycemia [115], and hypothyroidism [116] are the primary disorders affecting muscle cell integrity or distorting cellular energy processes. Rhabdomyolysis induced by hypokalemia is associated with the intake of several medications and compounds but is also observed in miscellaneous disorders like anorexia nervosa [117]. Bartter's syndrome [118], renal tubular acidosis [119], total parenteral nutrition [120], and electrolyte disturbance following small-bowel resection [121]. Hyponatremia, due to water intoxication, as a cause of rhabdomyolysis was described in a patient with psychogenic polydipsia [122].

Inflammatory muscle diseases, such as polymyositis and dermatomyositis, are frequently associated with rhabdomyolysis [123]. Patients with chronic inflammatory myopathy also appear more susceptible to attacks of rhabdomyolysis [124].

Rhabdomyolysis occurs in a variety of systemic infections [125] and may be related to fever [126], the effect of toxins, or a direct injury of skeletal muscle by infectious agents. Rhabdomyolysis is described secondary to bacterial infections including typhoid fever [127], *Staphylococcus* [128], Streptococcus pneumonia [129, 130], and infection by *Shigella*, *Salmonella*, *Herbicola lathery*, and *Escherichia coli* [131]. Legionnaires' disease [132], leptospirosis [133], and *Clostridium perfringens* infection [134] are also reported in association with rhabdomyolysis. Rhabdomyolysis may play a role in the toxic shock syndrome [135] due to toxin production or from dehydration, rigors, and fever. It is associated with staphylococcus aureus and Group B streptococcus, and cases have been reported with Group C streptococcus [136] and characterized by hypotension, fever, encephalopathy, erythematous rash, liver disease, and renal failure.

Influenza is the most common trigger for developing virus-induced rhabdomyolysis [137]. Many viruses may cause rhabdomyolysis, including Epstein–Barr [138], coxsackie [139], herpes [140], adenovirus [141], enterovirus, and echoviruses [142] as well as in association with human immunodeficiency viral infection [143].

The primary etiologies of *acute rhabdomyolysis in children* are associated with anoxic–ischemic encephalopathy (including sudden infant death, near drowning [144, 145], and other life-threatening events), electrolyte disorders, severe hyperthermia, poisonings, and hereditary myopathies.

Non-traumatic rhabdomyolysis must be suspected in these circumstances, requiring blood CK measurements. In children, clinical signs are variable and nonspecific [146].

Diagnosis

The diagnostic procedures recommended depend on the clinical presentation, the severity of the muscular manifestations, the presence of complications, and the presumed etiological factors. In general, the diagnostic pathway may be divided into three main steps:

1. Confirmation of the diagnosis of rhabdomyolysis and its common pathogenic causes
2. Estimation of the risk for developing acute renal failure and prevention of other complications in the acute phase
3. Search for an underlying metabolic disorder or genetic defect

The diagnosis of rhabdomyolysis is suspected from the patient's presentation and may be confirmed by an increased serum CK and myoglobin. In the initial phase, myoglobin in the urine may be established by radioimmunoassay.

Careful evaluation of the patient's history and laboratory data will promote prompt treatment and minimize the complications associated with rhabdomyolysis. Analyses of arterial blood for pH, P_{CO2}, and P_{O2} should be performed and measurement in serum should be made of sodium, potassium, chloride, CO_2 content, calcium, phosphate, albumin, uric acid, lactate dehydrogenase, aspartate aminotransferase, bilirubin, alkaline phosphatase, urea, and creatinine. The urinary output and pH of the urine should be quantitated. Attention must be paid to exogenous toxins, such as illicit drugs, alcohol, and prescribed drugs, the most common cause of rhabdomyolysis [22].

When the underlying pathogenesis is not clear, and especially with recurrent rhabdomyolysis, the patient should be assessed for a genetic disorder of muscle metabolism [22]. Evaluation of the medical history must be directed to the familial occurrence of muscular symptoms, exercise intolerance, anesthesia-induced muscle problems, and the presence of the second wind phenomenon (see Chap. 63).

Physical examination usually reveals no abnormalities and only rarely slight muscle atrophy or weakness. Computed tomography and particularly gadolinium enhanced magnetic resonance imaging may be helpful in determining the extent of muscle damage [147]; however, their clinical value has not been assessed.

Biochemical assessment consists of measuring the activities of glycogenolytic enzymes in erythrocytes and of CPT I and II in leucocytes and serum carnitine and organic acids in urine. Electromyography is only of value in the acute phase of rhabdomyolysis when myopathic findings may be present. On muscle biopsy, light-microscopic findings of necrosis of muscle fibers are rather nonspecific and of little value in differential diagnosis. Histochemical examination, however, may reveal glycogen accumulation or increased lipid deposits indicating a glycogenolytic enzyme deficiency or disorder of lipid metabolism. Enzyme histochemical examination may reveal deficiency of glycogenolytic enzymes or MAD. Biochemical investigation of muscle biopsy may yield important information about carnitine content and CPT I and II activity, oxidation of fatty acids, pyruvate oxidation, and mitochondrial metabolism. The activity of glycogenolytic enzymes may be measured in muscle tissue biochemically or determined by chromatographic or electrophoretic examination, or their contents may be determined by immunological methods.

Treatment

Management of rhabdomyolysis includes two aspects: supportive medical care in the acute stage and treatment or elimination of the underlying cause.

Acute Management

Renal Failure

The treatment in the acute phase of rhabdomyolysis consists of maintenance of adequate circulating blood volume and sufficient diuresis to prevent acute tubular necrosis. Intravenous administration of 4–11 l of normal saline solution may be necessary to maintain blood pressure and urine output. Volume expansion is essential to increase urinary output and to dilute the concentration of myoglobin. While there is evidence that supports prompt intravenous volume expansion, there is no adequate evidence to support one particular crystalloid. There is no significant benefit to forced diuresis with either loop diuretics or osmotically active agents; however, the one study did not stratify by disease and included all etiologies for acute renal failure in addition to rhabdomyolysis [148]. Because an acidic urine favors myoglobin-induced nephrotoxicity, alkalinization of the urine by adding sodium bicarbonate to the intravenous fluids has been advocated [149]. But two independent investigations failed to demonstrate a difference between resuscitation with saline versus a bicarbonate solution in the prevention of rhabdomyolysis-induced renal failure [1]. The use of sodium bicarbonate is controversial as very large quantities of bicarbonate may aggravate hypocalcemia [10]. Alkalinization of the proximal tubular fluid pH by the administration of the carbonic anhydrase inhibitor acetazolamide is not beneficial [150].

Treatment with an iron-chelating agent such as dysferoxamine awaits clinical validation. The radical scavenging

agent glutathione may further deplete intracellular ATP stores and thus contribute to the proximal tubular injury. The hyperuricemia may respond to saline diuresis. Xanthine oxidase inhibitors may not prevent hyperuricemia acutely, if there is ongoing muscle necrosis [150].

If oliguria persists and medical treatment is not sufficient to overcome renal failure, dialysis may be necessary to manage hyperkalemia, acidosis, or volume overload. Uremic encephalopathy may be an indication for dialysis as well. Intravenous glucose and insulin help drive the extracellular potassium into the intracellular compartment. Hemodialysis and continuous (arteriovenous or venous–venous) hemofiltration restore fluid and electrolyte balance more quickly than peritoneal dialysis. Peltonem et al. suggests patients treated with hemodiafiltration and forced alkaline diuresis had a much higher clearance of the plasma myoglobin than that of patients receiving forced alkaline diuresis alone [151]. There are advantages and dangers of commonly suggested drugs used in acute renal failure (see Reference [149]).

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) should be treated with fresh frozen plasma, clotting factors only if there is a bleeding. Epsilon aminocaproic acid, an antifibrinolytic drug, should be avoided as treatment because of rhabdomyolysis as a potential adverse effect [152].

Compartment Syndrome

Prevention of compartment syndrome may be achieved by careful clinical or intracompartmental pressure monitoring followed by urgent decompressive fasciotomy when necessary. Nerves are damaged by external pressure, ischemia, and increased intracompartmental pressure. Tissue pressure measurements possibly aid in the decision of whether or not surgical intervention is indicated. If the interstitial muscular pressure during 8 h exceeds 35 mmHg, fasciotomy is recommended.

Hypocalcemia

Infusion of calcium salts to counteract the effects of hyperkalemia is not recommended in the presence of hyperphosphatemia, as it may cause calcium phosphate deposition in soft tissue. Unless there is a threat of hyperkalemic cardiac rhythm disturbance, calcium infusion is not indicated [153].

Treatment or Elimination of the Underlying Cause

In acquired recurrent rhabdomyolysis, withdrawal of the toxic drug or compound is the treatment of choice. Eventually, oral ingestion of the causative agent may be treated with gastric lavage or activated charcoal or elimination may be forced by diuresis, hemofiltration, or hemodialysis [152].

In the case of a glycogenolytic enzyme deficiency or a disorder in lipid metabolism, advice should be given about adequate intake of food in relation to exercise. In MH and NMS dantrolene, sodium is the medication of choice to prevent muscle necrosis. Since MH is almost always observed after administration of volatile anesthetics, for example, halothane, and depolarizing muscle relaxants such as succinylcholine, these anesthetic agents must be avoided in these patients. A combination of cooling, hydration, and intravenous administration of dantrolene sodium are the therapy of choice and may be life saving.

Several therapies have been tried to improve exercise tolerance in glyco(geno)lytic disorders and to prevent attacks of rhabdomyolysis. Oral supply of glucagon or glucose has no long-lasting effect. In PFK deficiency, glucose has a negative effect on exercise tolerance as it cannot be used as energy supply and even impedes lipolysis. Wagenmakers et al. [154] suggested that especially physical training would stimulate the mitochondrial oxidative processes and improve exercise tolerance in myophosphorylase deficiency.

Patients with disorders of lipid metabolism (CPT I, II, LCHAD, SCHAD deficiency) should receive frequent, low-fat, high-carbohydrate meals and should never skip meals. Prolonged exercise should be avoided and intravenous glucose should be provided early in any illness associated with a diminished oral intake [155].

Conclusion

Rhabdomyolysis is common. The clinical manifestations vary widely from mild myalgia to severe muscle weakness with involvement of other organ systems. Measuring serum CK and myoglobin should confirm the diagnosis. The subsequent metabolic disturbances may be life-threatening factors. Cardiac arrest, acute renal failure, and the compartment syndrome are the major complications of severe rhabdomyolysis. The etiologic factors of rhabdomyolysis are numerous and of diverse origin. Alcoholism, drugs and toxins, strenuous exercise, infections, and metabolic disorders are the most common etiologies in acquired rhabdomyolysis.

For some patients, rhabdomyolysis may be prevented. An accurate history may reveal patients with MH or other neuromuscular disorders in whom specific anesthetic management is mandatory. In other high-risk patients groups, that is, patients with end-stage renal failure or alcoholics, an unsuspected factor, like surgery, may trigger the onset of rhabdomyolysis. Physicians must be made aware of the occurrence of drug interactions, for example, β-hydroxy methylglutaryl coenzyme A reductase inhibitors (statins) with erythromycin [156], cyclosporine [156–158], or ketoconazole [159], which increase the risk

of rhabdomyolysis. Clinicians should also be vigilant in taking a careful history for hereditary disorders, especially in those with a suggestion of skeletal muscle involvement, that may place a patient at risk for rhabdomyolyis.

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Eosinophilia-Myalgia Syndrome, Eosinophilic Fasciitis, and Related Fasciitis Disorders

79

Jeffrey A. Allen and John Varga

The fasciitis disorders represent a diverse group of chronic, frequently progressive diseases characterized by inflammation and excessive accumulation of collagen in the subcutaneous tissue. The pathogenesis of the fasciitis disorders is still mysterious. To a smaller or larger degree, these disorders share clinical and histopathological features with systemic sclerosis (SSc), the prototype systemic fibrosing disorder. The fibrosing disorders have in common marked fascial fibrosis that often occurs as part of a systemic disorder affecting multiple organ systems. This heterogeneous category of conditions include eosinophilia-myalgia syndrome (EMS), the toxic oil syndrome (TOS), and eosinophilic fasciitis (diffuse fasciitis with eosinophilia, DFE), as well as a broad group of localized or systemic disorders. Some of these are listed in Table 79.1. Patients with these disorders may seek medical care from a variety of specialists, including rheumatologists, neurologists, and dermatologists.

Eosinophilia-Myalgia Syndrome (EMS)

Introduction

In 1989, an outbreak of the eosinophilia-myalgia syndrome (EMS) [1, 2], a previously unknown illness with the abrupt onset of constitutional symptoms, myalgia, and marked peripheral eosinophilia, was recognized. While more than 1,500 patients were reported to the Centers for Disease Control and Prevention (CDC), there are estimates that many more cases occurred [3, 4]. Among its multisystem manifestations, EMS was associated with prominent neuromuscular involvement.

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Etiology and Pathogenesis

Epidemiological studies revealed a strong association between the use of L-tryptophan (LT)-containing products and EMS [5]. In almost all cases, the source LT was traced to a single manufacturer [6–8]. In late 1989, the US Food and Drug Administration (FDA) issued a nationwide recall of LT-containing products. With the removal of tryptophan from consumer markets, the number of new EMS cases diminished rapidly [9]. Detailed analysis of implicated LT revealed more than 60 trace impurities, 6 of which were associated with EMS [10, 11]. The best characterized of these is 1,1′ethylidenebis (L-tryptophan) (EBT) [12, 13]. EBT studies have duplicated some, but not all, EMS-like features, including stimulation of fibroblast proliferation and eosino-

Table 79.1 Selected fibrosing disorders

Primary cutaneous fibrosis	Organ-related fibrosis	Systemic fibrosis
Localized forms of scleroderma	Idiopathic pulmonary fibrosis	Systemic sclerosis
Scleroderma	Cryptogenic cirrhosis	Retroperitoneal fibrosis
Scleromyxedema	Sclerosing cholangitis	Metastatic carcinoid
Eosinophilia-myalgia syndrome	Primary biliary cirrhosis	Chronic graft versus host disease
Toxic oil syndrome	Retroorbital fibrosis	Radiation fibrosis
Eosinophilic fasciitis (diffuse fasciitis with eosinophilia)	Riedel struma	Nephrogenic systemic fibrosis
Dupuytren contracture	Mesangial fibrosis	
Keloids	Cystic fibrosis-associated fibrosing	
Peyronie disease		

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phil modulation [14–16]. Nonetheless, the role of EBT in EMS remains uncertain [17]. Later studies identified other EMS-associated impurities, including 3-(Phenylamino)alanine or PAA [18–20]. PAA shares chemical properties with 3-(N-phenylamino)-1,2-propanediol (PAP) linked to the 1981 toxic oil syndrome (TOS) epidemic in Spain and thus generated particular interest. PAP can undergo biotransformation to PAA and both can be converted into quinone imine intermediate metabolites by similar bioactivation pathways. These compounds are reactive toward nucleophiles present on many biological molecules [21]. In addition to EBT and PAA, other recognized EMS-associated LT impurities include 2-(3-indolylmethyl)-L-tryptophan, 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-(2-3b)-indole-2-carboxylic acid, and 2-(2-hydroxy indoline)-Trp [22, 23].

Despite the strong association between EMS and LT ingestion, 2 % of individuals with EMS reported no history of LT use and other cases antedated the 1989 epidemic when LT products were not available [3]. In 2005, the FDA lifted the LT import alert and LT was once again available in US markets. In 2011, a new patient with EMS was identified [24]. This patient developed the classic clinical and histopathological features of EMS following LT exposure.

The incidence of EMS even among epidemic LT users was very low [6–8, 25, 26]. Risk factors included larger doses of LT and increasing age [26]. Polymorphisms in immune response genes also seem to be important. HLA-DRB1 and DQA1 allele typing performed on patients with documented LT ingestion showed that HLA-DRB1*04 and DQA1*0601 were EMS risk factors, whereas DRB1*07, DQA1*0501, and DQA1*0201 were protective [27, 28]. These observations indicate a role for genetic factors in regulating susceptibility for EMS in exposed individuals.

The major pathological processes in EMS are inflammation and fibrosis. The primary findings are (1) mononuclear inflammatory cells with occasional eosinophils in the subcutaneous fat, septa, fascia, around blood vessels and nerves, and in the muscle perimysium and epimysium (Fig. 79.1); (2) endothelial cell swelling; and (3) collagen accumulation in subcutaneous areas with fibrosis [29–32]. Although intact eosinophils may be absent in affected tissues, the eosinophil degranulation products major basic protein and eosinophil derived neurotoxin are often prominent. The histopathological findings in EMS are distinctive but not unique [33–44].

The pathogenesis of EMS is thought to involve exposure to certain preparations of LT in a genetically susceptible host that trigger acute inflammation and eosinophil activation with resulting chronic tissue fibrosis [45–56]. Dysregulated cellular immunity appears to play an important role in the acute phase. This is supported by recognition of inflammatory cell infiltration in patients with active EMS [57], altered ratios of T-cell phenotypes of peripheral blood monocytes, lack of local complement activation, a paucity of B cells, and absence of immunoglobulin reactivity [58]. The etiologic agent(s) may act directly on mononuclear cells, possibly mediated via the toll-like receptor innate immune receptors leading to production of inflammatory cytokines and chemokines, which could then activate tissue eosinophils and convert them to a hypodense phenotype. Once activated, eosinophils can release additional cytotoxic molecules and cytokines such as interleukin-4 [54], granulocyte-macrophage colony-stimulating factor (GM-CSF) [55, 56], interleukin-5 [59], and transforming growth factor-beta (TGF-ß) [60]. TGF-β is considered to be paramount in inducing fibrogenesis [24, 60, 61]. Gene expression profiling of lesional EMS tissues has demonstrated activation of TGF-ß pathways, with consequent upregulation of collagen genes associated with extracellular matrix production and remodeling [24, 60, 62, 63]. These findings suggest that eosinophil-derived TGF-ß may drive the chronic fibrotic response in EMS.

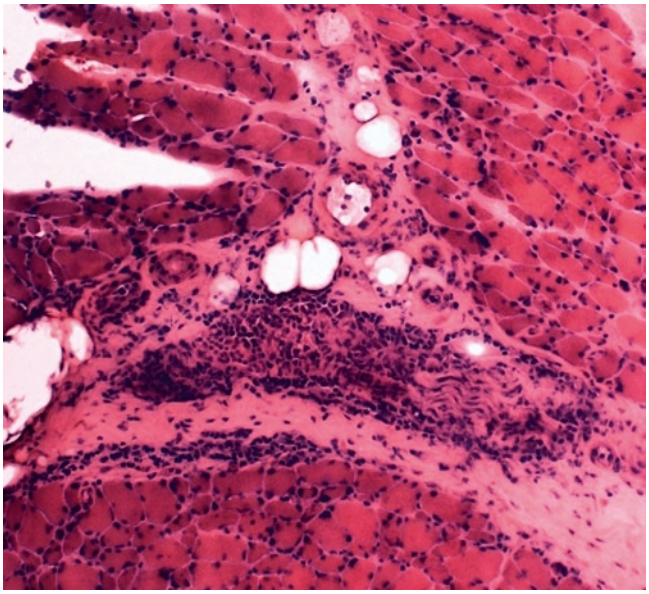

Fig. 79.1 Histopathological changes in skeletal muscle in a patient with EMS. Note the presence of perimysial inflammation (Hematoxylin and eosin stain, magnification ×250)

The exact etiologic agent responsible for EMS has yet to be identified. Impurities recognized within implicated LT have generated interest, although other uncharacterized impurities may likewise be responsible. Notably, EMS has been reported in individuals who have never consumed LT and in individuals consuming LT free of the previously implicated impurities [24, 64, 65]. These cases suggest that xenobiotics other than LT or perhaps LT itself may trigger a similar pathologic process. The potential role of eosinophils in fibroblast activation and connective tissue accumulation is further supported by the association of various forms of pathological fibroses with tissue eosinophilia shown in Table 79.2.

Table 79.2 Association of eosinophils or eosinophil degranulation with pathological states of fibrosis

Diffuse fasciitis with eosinophilia
Eosinophilia-myalgia syndrome
Riedel struma
Asthma (bronchial subepithelial fibrosis)
Systemic sclerosis
Retroperitoneal fibrosis
Sclerosing mediastinitis
Pulmonary fibrosis

Clinical Presentation

EMS is a multisystem disorder with variable degrees of severity. Muscle, nerve, fascia, skin, and lung are most commonly affected. The clinical course consists of acute and chronic phases. In the acute phase, most patients develop severe myalgias, weakness, numbness, paresthesias, rash, and swelling [1, 4, 18, 66–71]. Complete blood count (CBC) classically reveals profound eosinophilia that resolves immediately when treated with glucocorticoids or otherwise spontaneously improves within 2–6 months [3, 27, 72–75]. Many patients evolve into a chronic phase, with persistent cutaneous, neuromuscular, and pulmonary involvement.

Neuromuscular

Objective evidence of myopathy and/or neuropathy is present during the first 18 months in many patients [67]. Prominent muscular manifestations of EMS include myalgia, cramps, and a predominantly proximal extremity weakness. Electrodiagnostic (EDX) studies may be indicative of a myopathy with abnormal spontaneous activity (fibrillation potentials and positive sharp waves) along with early recruitment of short-duration, low-amplitude, polyphasic motor unit action potentials [76]. Muscle biopsies often show extensive perimysial and epimysial inflammation (fasciitis) along with excessive perimysial connective tissue fibrosis surrounding the muscle [24, 32, 34, 77]. Endomysial inflammation is usually sparse and, when present, concentrated in perivascular areas. Muscle fiber atrophy and necrosis are less commonly observed.

Neuropathy has been reported in 14–40 % of individuals with EMS and in some patients may be the most prominent clinical feature [3, 35, 36, 56, 72, 78]. The neuropathy may be a painful sensory polyneuropathy, sensorimotor polyneuropathy, purely motor polyneuropathy involving distal muscles, or mononeuropathy multiplex [43, 79]. Cutaneous hypersensitivity with allodynia, burning, or extreme discomfort to light touch is common. A rapidly evolving proximal and distal sensorimotor polyneuropathy similar to Guillain-Barré syndrome occurs infrequently (<5 %) and may progress to respiratory failure and death [80]. EDX testing and nerve histopathology typically reveal evidence of axonal degeneration [36, 42]. Less commonly EDX studies show a demyelinating peripheral nerve process [35, 40]. Epineurial and perivascular inflammatory cell infiltration may be seen on biopsy of affected nerve.

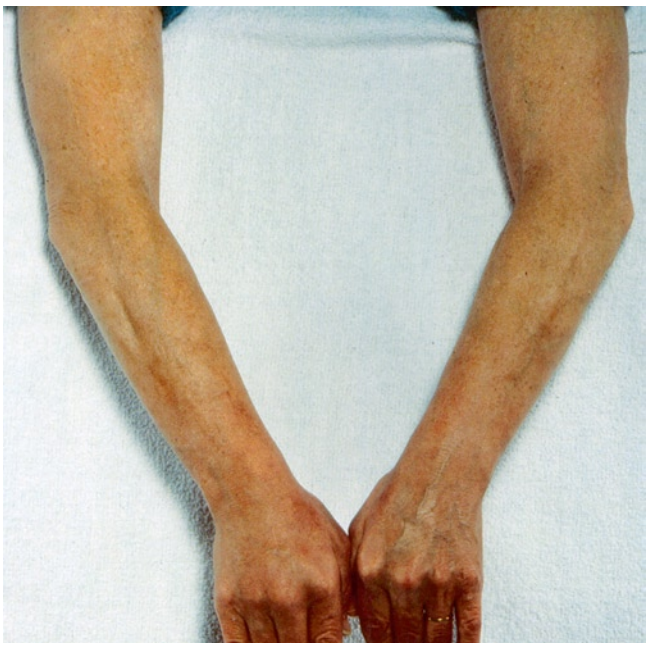

Fig. 79.2 Elbow contractures with associated "groove sign" in a patient with EMS (Photograph courtesy of Dr. Joseph Duffy, Mayo Clinic)

Skin

Fasciitis or other cutaneous manifestations develop in most EMS patients. An acute, transient erythematous, maculopapular rash may be followed by mottled hyperpigmentation. Edema and induration often precede fasciitis. Cutaneous changes most commonly affect the distal forearms and legs and at times lead to joint contractures (Fig. 79.2). Some patients also develop alopecia, localized morphea, and intense pruritus. Thickened fascia, deep dermal fibrosis, and accumulation of mononuclear cells and eosinophils are typically apparent on skin biopsy [81].

Pulmonary

Pulmonary symptoms, including cough and dyspnea, are seen in as many as 60 % of patients. Rarely pulmonary hypertension develops, which gradually resolves except in a few catastrophic cases. Lung biopsies performed in a small number of patients have shown vasculitis and perivasculitis with chronic interstitial pneumonitis [37].

Other

Stroke and encephalopathy are occasionally seen [34, 82]. Although many EMS patients describe neurocognitive symptoms, evidence of organic CNS involvement is

lacking [83]. Palpitations, tachycardia, and chest pain have been reported. The prevalence of cardiac abnormalities is unknown, although life-threatening rhythm disturbances appear to be uncommon. Cardiac autopsy specimens have demonstrated neural lesions throughout the conduction system and inflammatory lesions of the small coronary arteries, similar to the neuropathology seen in skeletal muscle [84]. Gastrointestinal abnormalities, including pancreatitis, malabsorption, and cholangitis, have been observed. Eosinophil infiltration within the bowel mucosa has been appreciated in some patients [85].

Differential Diagnosis

Although the clinical and histopathological features of EMS are unusual, they are not unique. Eosinophilia is seen in a wide spectrum of disorders including atopic diseases, parasitic infections, drug ingestion, hematological diseases, and a variety of connective tissue diseases.

In atopic illness, eosinophilia is low grade and not accompanied by myalgia. Trichinosis may cause myalgia, periorbital edema, and eosinophilia. Most patients have a history of consuming pork or meat of wild mammals. Diagnosis relies on positive serology or demonstration of larvae in muscle. Churg-Strauss syndrome occurs in patients with asthma, nasal polyposis, or sinusitis and is associated with skin rashes, pulmonary infiltrates, and neuropathy. Necrotizing vasculitis of small blood vessels and necrotizing extravascular granulomas distinguish Churg-Strauss syndrome from EMS. Systemic sclerosis (SSc) and EMS are both multiorgan disorders that may have prominent skin thickening and induration. Unlike EMS, SSc is further characterized by Raynaud phenomenon, mat-like telangiectasias, and SSc-related autoantibodies. Muscle involvement is estimated to be at least 14 % but (unlike EMS) is typically accompanied by elevated CK levels. Furthermore, peripheral eosinophilia is rare. Nephrogenic systemic fibrosis (NFS) is a multiorgan fibrosing disorder that primarily affects the skin but may also involve the lungs, heart, and liver. Muscle involvement is unusual but may occur. Renal insufficiency and exposure to gadolinium-containing contrast distinguishes NFS from EMS. The idiopathic hypereosinophilic syndrome (HES) is a heterogeneous group of disorders associated with diffuse organ involvement and extreme eosinophilia that (unlike EMS) persists for more than 6 months [86]. Fibromyalgia has only a superficial resemblance to EMS, namely, myalgias. The hallmark clinical, laboratory, and histopathological features of EMS are not present in patients with fibromyalgia [87]. Diffuse fasciitis with eosinophilia (DFE – see below) shares many features with EMS. Symptoms in DFE are usually less severe and multisystem involvement less frequent (Table 79.3) [88–90]. Finally, EMS bears a striking resemblance to the toxic oil syndrome (TOS) which is discussed later.

Table 79.3 Clinical features of syndromes associated with fasciitis

Feature	EMS	TOS	DFE
Female/male ratio	4/1	9/1	1/1
Myalgia	+++	+++	++
Dyspnea	+	++	–
Cough	+	+	–
Skin rash	+++	++	–
Pulmonary infiltrates	+	++	–
Swelling	++	++	++
Muscle weakness	+	+	+/–
Fasciitis	++	++	++
Peripheral neuropathy	+	++	–
Eosinophilia	++	+	+++
ANA	+	+	–

EMS eosinophilia-myalgia syndrome, *TOS* toxic oil syndrome, *DFE* diffuse fasciitis with eosinophilia
+++ very frequent or prominent; ++ occasional; + infrequent/rare; +/– generally absent; – absent

Evaluation and Diagnosis

There is no diagnostic test for EMS. A detailed history (with particular attention to LT ingestion) and physical examination are essential to make the correct diagnosis. Laboratory data and histopathological analysis of skin, fascia, and/or muscle provide extremely valuable supportive information. Due diligence need be applied to exclude other similar conditions.

In addition to peripheral eosinophilia, laboratory studies may show modestly elevated levels of aldolase. Creatine kinase is usually normal [71]. The discrepancy between these two muscle-associated enzymes can be helpful in differentiating EMS from other myopathies. Erythrocyte sedimentation rate, rheumatoid factor, and levels of IgE, complement, and cryoglobulin (all markers of immune dysfunction) are usually normal. EDX studies may show myopathic with abnormal spontaneous activity (fibrillation potentials and positive sharp waves) and early recruitment of short-duration, low-amplitude, and polyphasic motor unit action potentials [76]. It also may reveal neuropathic abnormalities with evidence of axonal degeneration [36, 42] and less commonly a demyelinating polyneuropathy [35, 40]. Histopathologic analysis of involved tissues usually demonstrates typical features of EMS as previously discussed.

Shortly after the discovery of EMS in 1989, the *CDC case definition* was developed for epidemiological surveillance [68]. It required (1) peripheral eosinophil count greater than 1,000 cells per mm^3, (2) generalized debilitating myalgia, and (3) no evidence of infection or neoplasm that would explain eosinophilia or myalgias. An expert EMS panel subsequently proposed revised diagnostic criteria that were shown to be 97 % specific for EMS [91–93]. Revised criteria require (1) the presence of eosinophilia, myalgia, and either rash, edema, pulmonary involvement, or neuropathy within 6 months of illness onset or (2) either (a) fasciitis, neuropathy, and myalgia or muscle cramps or (b) any three or more of the following: fasciitis,

myopathy, neuropathy, or eosinophilia occurring within 24 months of illness onset. A diagnosis of EMS cannot be made in the presence of another infectious, inflammatory, or neoplastic condition that could account for these abnormalities.

Treatment

The response to therapy has generally been disappointing. In acute EMS, glucocorticoids typically correct the eosinophilia and may be helpful in improving myalgia, clearing pulmonary infiltrates, and resolving edema [78]. However, no evidence exists that glucocorticoids improve long-term outcome [94]. Prolonged treatment with glucocorticoids or other cytotoxic medications is not recommended [95]. A variety of immunomodulating medications have been used for EMS [96]. Although favorable responses have occasionally been reported, very small treatment numbers, the possibility of spontaneous improvement, and short follow-up limit the interpretation of these case reports. Therapy of chronic disability is targeted at amelioration of continuing symptoms and is focused on physical therapy, pain control, and psychological support [97].

Natural Course and Prognosis

Early in the outbreak, EMS caused serious illness resulting in the hospitalization of 30–70 % of patients with a mortality rate of 2 %. The majority of deaths occurred within 6 months of illness onset, most of which were related to neuropathy and myopathy complications (pneumonia, respiratory failure, and sepsis) [67, 84]. Poor prognostic indicators included severe disease at onset [74], increasing age, and multiorgan involvement [98].

Chronic disability largely results from cutaneous, neuromuscular, and pulmonary involvement mediated on the basis of persistent fibrosis. The most common features of chronic EMS are proximal weakness, paresthesias, numbness, muscle cramps, myalgia, joint pain, and scleroderma-like skin changes [78, 99, 100]. Although symptoms generally improve to some degree over 24 months, up to 88 % of patients manifest more than 3 of these symptoms after 3 years [78].

The Toxic Oil Syndrome (TOS)

Introduction

The toxic oil syndrome (TOS) was an epidemic illness with prominent diffuse fasciitis and neuromuscular involvement that occurred in Spain in the spring of 1981. The new disease was first recognized after an 8-year-old boy died with acute pulmonary insufficiency. Six of eight family members also became ill. Over 20,000 individuals were ultimately affected, and more than 11,000 hospital admissions related to TOS occurred within several months of the outbreak [101, 102].

Etiology and Pathogenesis

Epidemiological studies showed a close relationship between TOS and consumption of industrial grade rapeseed oil. At the time, rapeseed oil could not be legally imported into Spain as a food substance, only as an industrial lubricant after denaturation with aniline. Once in Spain, the oil was illegally de-denatured by a refining process that removed almost all of the aniline and was subsequently mixed with other seed oils, animal fats, poor quality olive oil, or chlorophyll to produce the desired color. The resulting adulterated oil was sold as pure olive oil.

The number of TOS cases dropped sharply following removal of the oil from the market [103, 104]. Several impurities were proposed as the etiologic agent. Analyses of implicated oils demonstrated that free aniline and aniline derivatives were significantly associated with case-related samples. Another case-related contaminant, 3-phenylamino-1,2-propanediol (PAP) [18–20], generated particular interest when it was recognized that PAP shares chemical properties with the EMS tryptophan impurity PAA (see EMS; Etiology and Pathogenesis). Nonetheless, attempts to reproduce TOS-like biologic phenomena in vitro and in vivo have not been successful [105, 106], and the precise identity of the etiologic agent has not been determined [107–109].

The pathogenesis of TOS remains undefined. The most prominent pathological feature in TOS is a non-necrotizing vascular lesion principally affecting the intima of all types of blood vessels. Perivascular mononuclear inflammation was common, which typically progressed to intimal proliferation, with fibrosis and thrombosis. Inflammation was also noted in the fascia, the perineurium of peripheral nerves, the perimysium and epimysium, and occasionally muscle spindles and intramuscular nerves [110, 111].

Clinical Presentation

The latency between TOS and the ingestion of contaminated oil was between 4 and 10 days. After a prodromal period, three relatively well-defined phases [112] were recognized: the acute phase (0–2 months) with major lung involvement, the intermediate phase (2–4 months) with features of thrombotic phenomena and pulmonary hypertension, and the chronic phase (>4 months) with marked neuromuscular involvement. New symptoms cease to appear 8–10 months after onset.

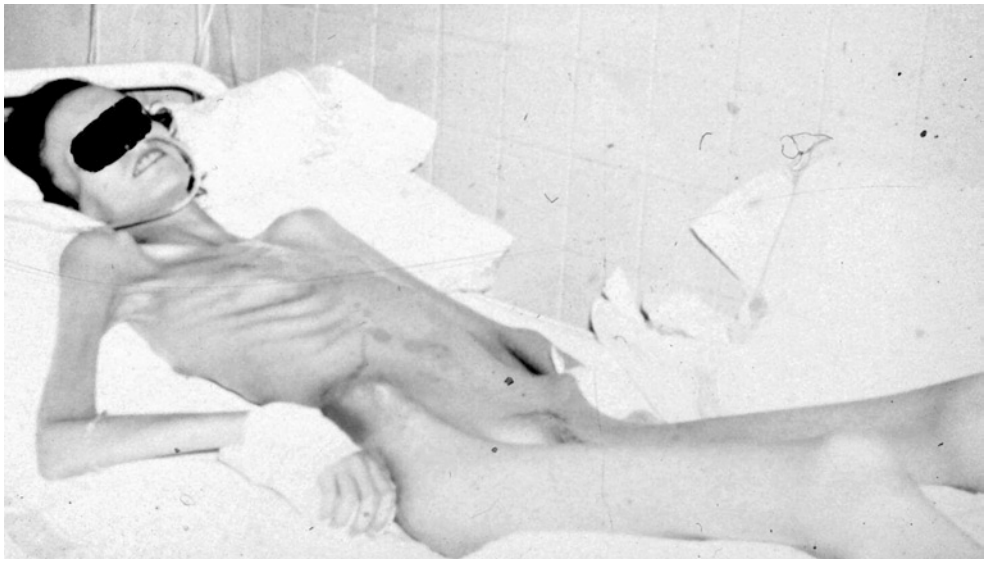

Fig. 79.3 Severe muscle atrophy in a Spanish patient with advanced TOS

Neuromuscular

Myalgias and cramps, often severe and diffuse, were common in the acute and intermediate phases of the illness. About half of patients also developed a neuropathy, usually during the intermediate phase. EDX studies typically revealed an axonal process affecting sensory and motor nerve fibers. The neuropathy may be generalized affecting both proximal and distal areas and length-dependent or multifocal affecting multiple individual nerves. EDX may also reveal a superimposed myopathic process [113]. In some individuals, the neuropathic or myopathic process led to dysphagia and respiratory failure. Histopathologic analysis revealed inflammatory cell infiltration of the perimysium and around intramuscular nerves in muscle and into the epineurium and perineurium areas in peripheral nerve [114]. Non-necrotizing vasculitis was a prominent pathological feature in all affected organ systems, including muscle and nerve [115].

The chronic phase of TOS in some patients was characterized by progressive muscle wasting (Fig. 79.3) diffuse and symmetric polyneuropathy and fasciitis. Although inflammatory muscle involvement likely accounted for the early TOS neuromuscular symptoms, the chronic phase was driven by the progressive neuropathic process. The most distinctive pathological features during the chronic phase were neurogenic muscular atrophy, degeneration of myelinated axons, perineurial fibrosis, and endomysial fibrosis [114, 115]. In some individuals, muscle atrophy and weakness led to hand deformities and wrist contractures (Fig. 79.4). The most severe cases progressed to complete quadriplegia, respiratory failure requiring mechanical ventilation, or death.

Fig. 79.4 Contractures of the interphalangeal joints of the hand associated with peripheral neuropathy in a patient with late-stage TOS

Pulmonary

The onset of illness was classically associated with striking respiratory symptoms including shortness of breath and cough. Chest radiographs usually showed a diffuse interstitial and alveolar pattern described as non-cardiogenic pulmonary edema. Histopathological studies of lung tissue in the early phase revealed interstitial edema with little or no inflammation. Most patients recovered from this transient acute illness. Some, however, developed fulminant respiratory failure, which was the most common cause of early death [106]. In the intermediate phase of the illness, pulmonary hypertension secondary to pulmonary vessel thrombosis occurred in up to 20 % of TOS patients. Although many spontaneously resolved, in a small subset of patients, it had a malignant and fatal course [116–118]. Respiratory failure, sometimes requiring mechanical ventilation, during the chronic phase of the illness was typically due to progressive polyneuropathy.

Psychological

Many patients complained of psychological difficulties. A nonspecific syndrome that included nightmares, insomnia, anxiety, aggressiveness, difficulty concentrating, or memory difficulty was common. EEGs, brain imaging, and brain autopsy studies were generally normal. Although most patients slowly improved, some did not. Persistent psychological symptoms described as "reactive disaster syndrome" have been reported in approximately 10 % of affected individuals [119].

Other

Fever, pruritic rash, nausea and vomiting, diarrhea, headache, and malaise were common, especially during the acute phase of the illness. Skin rashes varying in appearance from macules or papules to eczema-like patches were frequent and in most patients cleared within 2 weeks. During the thrombotic intermediate phase, some patients developed ischemic cerebral infarction or intracerebral hemorrhage. Acute encephalopathy and seizures were rarely reported. Systemic thrombotic phenomena also included mesenteric and hepatic vein thrombosis.

Differential Diagnosis

Individual clinical findings of TOS are seen in other illnesses. Interstitial pulmonary infiltrates may be encountered in a variety of infectious or hypersensitivity pneumonias. The skin rashes described in early TOS are not specific and resemble those seen in other fasciitis syndromes. Generalized, multifocal axonal neuropathy or mononeuropathy multiplex may occur in any condition that affects the vasa nervorum and may be one component of several multiorgan diseases in which the pathologic process is driven by systemic vasculitis. Several diseases of unknown etiology, such as DFE, eosinophilic perimyositis, and EMS, share certain characteristics with TOS (Table 79.3) [120, 121]. Although TOS in the early stages with acute non-cardiogenic pulmonary edema and later with neuropathic involvement was more severe than EMS, the "average patient" with either disease has remarkably similar clinical manifestations and outcome [122].

Evaluation and Diagnosis

In 1981, the Spanish Clinical Commission proposed a TOS case definition [123]. However, like EMS, there is no diagnostic test for TOS. History and physical are essential to make the diagnosis. EDX studies typically revealed an axonal sensorimotor length-dependent neuropathy, or multifocal mononeuropathy multiplex, sometimes associated with a superimposed myopathic process [113]. Histopathological analysis of affected tissues can provide supportive information. Laboratory studies often showed high levels of peripheral blood eosinophils during the acute and intermediate phases. Increased aldolase with normal CK, hypothyroidism, elevated transaminases, Th2 cytokines (IL-4 and IL-5), IgE, antinuclear, anti-smooth muscle, and antimitochondrial and antiparietal autoantibodies have also sometimes been observed [124]. Compared to the general population, TOS patients have been shown to have a higher prevalence of cardiovascular risk factors, including diabetes, hypertension, and hyperlipidemia [125]. Immunogenetic studies have found that, as in EMS, the HLA-DR4 allele may influence disease susceptibility [126].

Treatment

Patients were initially treated with a variety of antibiotics without success. Although glucocorticoids reduced eosinophil count and led to improvement within hours in very severe pulmonary cases, they did not consistently control other symptoms nor prevent development of the chronic phase of TOS.

Prognosis

Although many TOS cases had severe initial symptoms, some patients improved without apparent sequela [127]. In most the illness evolved into the intermediate and chronic phases with chronic myalgia, muscle cramps, weakness, respiratory symptoms, edema, sicca syndrome, and weight loss [107]. No predictors were identified for development of the chronic phase that occurred in almost 60 % of patients [128]. More than 800 deaths were reported, most occurring within the first year of the disease [129].

Since the end of the 1980s, the main clinical deficits in most individuals have stabilized or improved. However, some degree of chronic disability is common. Approximately 15 % of patients experience total or partial disability [107, 130]. In 2 separate studies performed 18 years [131] and 12 years [132] after the epidemic, weakness, sensory complaints, fatigue, arthralgia, myalgias, sleep difficulty, and memory difficulty were commonly reported in TOS patient groups.

Eosinophilic Fasciitis (Diffuse Fasciitis with Eosinophilia)

Introduction

Eosinophilic fasciitis is clinically characterized by symmetrical skin induration, often accompanied by swelling of the extremities and joint contractures leading to impaired mobility. The syndrome, perhaps better called diffuse fasciitis with eosinophilia (DFE), was first described in 1974 by Shulman

[133]. In the original description, Shulman emphasized the distinctness of the syndrome from scleroderma/systemic sclerosis, with rapid onset of induration of the extremities and striking peripheral blood eosinophilia. The pathological hallmarks of DFE are fibrosis of the fascia and subcutaneous tissue, with or without eosinophilic infiltration of affected tissue.

Etiology and Pathogenesis

The cause of DFE is unknown. Several triggers have been proposed including an antecedent history of vigorous exercise or trauma [134], *B. burgdorferi* infection [135], and toxic exposures. DFE occasionally occurs with other autoimmune conditions, and in up to 15 % of patients, an underlying hematological disorder or malignancy may be uncovered [134]. Nonetheless, the casual relationship between any trigger, autoimmune disease, or malignancy remains unproven.

Like EMS and TOS, eosinophils appear to play a prominent early role in DFE. The association of degranulating eosinophils in tissues with pathological fibrosis is a recurrent finding in the broad group of eosinophilic illnesses (Table 79.2). Once activated, eosinophils are capable of expressing multiple growth factors and cytokines that have been implicated in tissue remodeling and fibrosis [63]. Elevated serum levels of the type two cytokine interleukin-5 and other pro-fibrotic molecules including TGF-β have been reported in patients with DFE [136]. Tissue infiltrating eosinophils may be able to generate a local fibrogenic response by increased expression of TGF-β and eosinophil-derived inducers of fibrogenesis. Fibroblasts derived from the fascia of patients with DFE produce increased amounts of collagen and display elevated levels of mRNAs for type I, type III, and type VI collagens in vitro compared to fibroblasts derived from the adjacent dermis [137].

The histopathological hallmark in established DFE is fascial fibrosis and collagen accumulation. The fibrosis may extend from the fascia into the lower dermis with entrapment of the dermal appendages, the subjacent muscle perimysium, and occasionally into the adipose tissue with panniculitis. The epidermis is usually spared. An inflammatory infiltrate, characterized predominantly by macrophages and CD8+ T cells, may be striking particularly in the early stages of the disease [138]. Eosinophils are usually observed within the affected tissues but may not be present when biopsies are obtained after institution of corticosteroid therapy. Even in the absence of eosinophils, eosinophil degranulation and tissue deposition of major basic protein may be demonstrated by immunohistochemistry, indicating the "footprint" of eosinophil inflammation and degranulation. Inflammation may extend into the adjacent muscle perimysium, but muscle fiber necrosis is not typically present. Inflammation is often perivascular, but true vasculitis is not seen.

Clinical Presentation

DFE affects men and women of all ages but is more common in males (2:1 ratio) and most often affects adults from ages 30 to 60 years [134]. The onset is generally rapid. Most patients experience symmetric spreading of skin changes over days to weeks.

Neuromuscular

Myalgias may be present early in the disease but gradually resolve. Variable degrees of muscle weakness may be present depending on the extent to which the fibrotic and inflammatory process affects the perimysial connective tissue and subjacent muscle fibers. Generalized or multifocal neuropathies are rare. A very small number of DFE associated multiple mononeuropathies have been reported, one of which demonstrated perivascular inflammatory cell collections around epineurial arterioles on sural nerve biopsy [139]. Conversely, carpal tunnel syndrome almost certainly due to median nerve compression at the wrist rather than inflammation has been frequently reported [134]. Extensive fibrosis involving the trunk or neck may be complicated by respiratory difficulty or dysphasia.

Skin and Fascia

The forearms and calves are the most severely affected, followed by the trunk. The hands, feet, and face are generally spared. DFE confined to a single limb, the arms, or legs is rare but has been described. Edema is usually the first visible abnormality to appear, resulting in a dimpling orange peel ("peau d'orange") skin appearance, followed by induration of subcutaneous tissues. If the dermis becomes fixed to the fascial and muscular layers, the uplifted arm may reveal the so-called groove sign with skin puckering and indentation along the course of veins. The skin is often warm, sometimes erythematous, and typically becomes hyperpigmented. The most superficial skin epidermal layer should maintain normal elasticity. With chronic disease, joint contractures and limited mobility can develop.

Other

Typically there is no visceral organ involvement. Fatigue, weight loss, fever, and other constitutional symptoms may be reported in some patients. Raynaud's phenomenon is usually absent.

Differential Diagnosis

The clinical, serological, and histopathological features as well as the pattern and distribution of skin involvement help to distinguish DFE from other fibrosing disorders. Although DFE may be confused with scleroderma/systemic sclerosis,

the absence of characteristic scleroderma associated autoantibodies, sparing of the fingers, and lack of Raynaud phenomenon in DFE are helpful diagnostic clues to differentiate this disease from scleroderma. Additionally, telangiectasia, gastric vascular ectasia, and pulmonary vascular injury are hallmark features common to systemic sclerosis but absent in DFE.

Evaluation and Diagnosis

DFE diagnostic criteria has been proposed but not validated. The most recent proposed criteria require both the typical clinical and histopathological DFE features for diagnosis (major criteria). One major criterion can be replaced by any two of the following minor criteria: eosinophilia, hypergammaglobulinemia, muscle weakness and/or elevated aldolase, groove sign and/or peau d'orange, or hyperintense fascia on T2-weighted MRI imaging [140]. Appropriate exclusionary data must be applied.

The diagnosis of DFE should be established by a full thickness excisional skin biopsy. Especially if weakness is present, extension of the biopsy into the muscle is encouraged. The leading edge of the affected skin, usually the forearm, is the optimal biopsy site. As outlined above, the histopathological findings include fascial fibrosis with infiltration by macrophages, CD8+ T cells, and often eosinophils.

Peripheral blood eosinophilia $>0.5\times10^9$/l is universal early in the disease. Inflammatory markers (erythrocyte sedimentation rate and C-reactive protein) are frequently elevated. Protein electrophoresis usually shows polyclonal hypergammaglobulinemia. Although aldolase is often elevated, CK is usually normal or only mildly elevated. Tests for serum antinuclear and other antibodies are usually negative. Other hematological abnormalities including aplastic anemia, thrombocytopenia, and lymphoproliferative disorders are occasionally observed [141]. MRI can provide supportive data and perhaps is a useful tool to monitor the disease course. Fluid-sensitive MRI images may reveal fascial thickening and edema [142].

Treatment and Prognosis

There are no controlled trials of therapeutic interventions for the treatment of DFE. The optimal immunosuppressant drug, dose, and treatment duration are uncertain. Reports of uncontrolled trials claiming therapeutic efficacy are numerous in the literature but are difficult to interpret. In clinical practice, most consider prednisone 0.5–1 mg/kg daily (or equivalent corticosteroid) first-line DFE treatment. Most patients experience complete or partial improvement with normalization of peripheral eosinophilia over weeks to months [134, 143]. High-dose corticosteroids are generally continued until the beneficial response is maximized (often weeks to months), followed by very slow tapering over several months to a year or more.

Although DFE is generally considered a benign disease with occasional spontaneous remissions, some patients may be refractory to corticosteroid treatment and some patients may relapse when tapered from corticosteroids [134]. Younger age and involvement of the trunk have been associated with residual cutaneous fibrosis and may be considered unfavorable prognostic indicators [144]. Multiple other agents used alone or in combination with corticosteroids have been reported. Histamine receptor blockers (e.g., cimetidine), hydroxychloroquine, methotrexate, mycophenolate mofetil, azathioprine, infliximab, UVA photochemotherapy, cyclophosphamide, and cyclosporine have been used with variable degrees of success. In all patients, physical therapy is important to prevent and improve joint contractures.

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Neuropathic Pain and Other Chronic Musculoskeletal Pain Conditions

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Introduction

Neuropathic pain and certain other types of chronic pain occur as a result of maladaptive changes in the peripheral and central nervous system. The same peripheral and central nervous system pathways involved in normal, protective mechanisms of pain are involved in disease states of chronic pain. Chronic pain occurs as a result of neural plasticity, with changes in the structure and function of neurons and glia. These changes occur at the level of the receptors and gene regulatory proteins, leading to phenotype switch of certain neurons and altered function. Understanding the pathophysiology of chronic pain affords the opportunity to more optimally manage symptoms, using a scientific rational mechanistic treatment approach.

Neuropathic Pain

The International Association for the Study of Pain in 1979 defined pain as "an unpleasant sensory and emotional experience." Neuropathic pain is a form of chronic maladaptive pain, which was recently redefined as pain due to "a lesion or disease affecting the somatosensory system" [1, 2]. That definition encompasses all causes of neuropathic pain, irrespective of etiology or symptom description. Symptom descriptors commonly used to describe neuropathic pain include electric shock-like, shooting, stabbing, burning, lancinating, lightening-like, or radiating. This is in contrast to "somatic" or non-neuropathic pain, commonly described using terms such as throbbing, dull, or aching; it should be noted that the latter descriptors of pain can overlap in both neuropathic and non-neuropathic pain conditions. The presence of neuropathic pain can further be characterized as "definitive," "probable," or "possible," based on features including the presence of a localizing neuroanatomical distribution of pain, a history of some illness or injury expected to affect the somatosensory system, and demonstration of that illness or injury by objective examination findings, diagnostic testing, and/or other diagnostic criteria [2].

In addition to neuropathic pain, there are other types of chronic pain, such as pain due to inflammatory and musculoskeletal conditions as well as non-neuropathic/noninflammatory musculoskeletal pain, which can result in pathophysiological changes in the nervous system. Despite their seemingly different etiology and underlying mechanisms, distinguishing neuropathic from non-neuropathic pain can be difficult clinically, particularly as both processes may exist concurrently. Understanding its pathogenesis may however allow the clinician to better manage neuropathic pain, as well as other forms of chronic pain.

In contrast to neuropathic pain, nociceptive pain, also known as "physiologic pain," refers to acute pain generated as a result of tissue injury activating an intact nervous system; nociceptive pain usually results in "adaptive neural responses." Nociceptive pain is self-limited in nature, subsiding and resolving with subsidence of the tissue injury. While nociceptive pain is distinguished from neuropathic pain by the absence of an abnormality within the nervous system, the patient's subjective symptoms may be indistinguishable.

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Pathophysiology

Nociceptive pain processing occurs in different regions or "stations" of the nervous system, including the peripheral nervous system, spinal cord, and brain. The structures and pathways that transmit the normal pain signal to the brain are the same as those pathologically involved in transmitting the abnormal pain signal in chronic pain conditions. The normal

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response to acute pain is protective or adaptive; however, in chronic pain conditions, pain itself becomes a disease state due to plasticity changes within the nervous system.

Perception of pain is an important protective, physiologic warning signal of potential tissue damage [3]. Transduction refers to the phenomenon whereby certain signals (mechanical, chemical, or thermal) acting on specialized nociceptors become converted into an electrical signal occurring as a result of depolarization of cell membranes. Conduction occurs when that electrical signal travels along primary afferent fibers to the dorsal horn of the spinal cord. Inside the spinal cord, transmission occurs via ascending pathways, including the spinothalamic and spinoparabrachial (spinoreticular and spinomesencephalic) tracts. These signals are then relayed to the thalamus and then to the somatosensory cortex. Once these impulses reach the somatosensory cortex, pain perception occurs.

In addition to the ascending pathways, pain perception is also affected by an important descending pathway, which modulates pain transmission. Thus, pain is a dynamic bidirectional process. The descending pathway normally has an inhibitory function; inhibitory interneurons project from the brainstem to the dorsal horn of the spinal cord and thus can modulate pain signaling from the dorsal horn into the higher structures (thalamic and cortical). Whereas the spinothalamic tract projects to the thalamus and somatosensory cortex, allowing the cognitive perception of pain and localization of pain, an affective response also occurs as a result of the relay of signals from the spinoparabrachial tract into the parabrachial nuclei of the brainstem which project to the hippocampus and amygdala [3].

Pain sensation can be spontaneous or stimulus-induced. In the latter, and in normal pain (adaptive or nociceptive) situations, as the intensity of a given stimulus is increased, pain will not be perceived below a certain threshold. Above that threshold, the sensation may then be perceived as pain, with the pain perception increasing proportional to the increase in stimulation. However, in chronic pain conditions, plasticity ensues, neurons become sensitized, and, as a result, stimuli of subthreshold intensity can elicit pain; this phenomenon is referred to as allodynia, defined as pain in response to touch or mechanical stimulation. There are various types of allodynia: dynamic, static, and thermal. Static allodynia is usually elicited by applying a single light pressure stimulus and is thought to be due to sensitized C-nociceptors, whereas mechanical allodynia is tested by moving a brush or soft cloth and is due to activation of A-beta afferent fiber activation. Hyperalgesia refers to a heightened perception of pain for a given pain stimulus, due to a shift in the sensitivity curve. Hyperpathia is a complex abnormal sensation. It refers to a slightly delayed but then an abnormally painful and exaggerated pain response, especially in reaction to repeated stimuli, reflecting summation and aftersensation (Fig. 80.1).

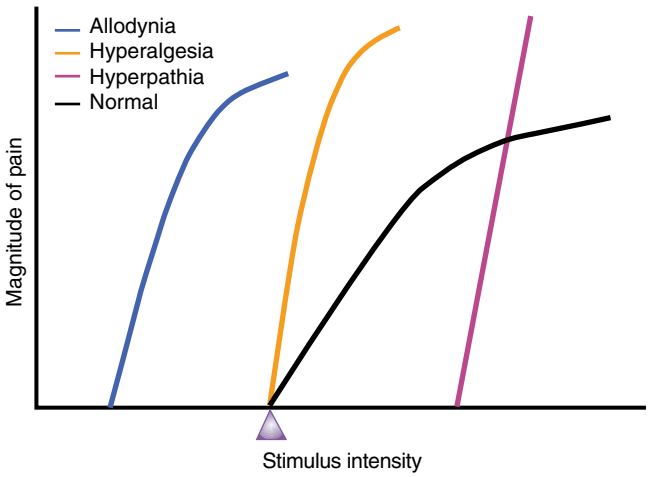

Fig. 80.1 Changes in pain sensation in stimulus-induced chronic pain conditions

As mentioned above, physiologic pain occurs as a consequence of acute nociceptor activation and is a protective and adaptive phenomenon. While the focus of this discussion is on neuropathic pain, other types of pain, including chronic inflammatory joint pain and noninflammatory, non-neuropathic pain, deserve mention. Inflammatory joint pain occurs as a consequence of tissue damage or inflammation; pain pathways and structures are normal but are functioning abnormally. Noninflammatory, non-neuropathic pain occurs as a result of an abnormal central processing of normal input. For example, patients with fibromyalgia (see "Fibromyalgia" section below) experience an augmentation of the pain signal transmission [4, 5]. Fibromyalgia is an example of maladaptive pain, where structures are normal and pathways are intact but the function of those pathways is abnormal. Diagnoses of maladaptive pain conditions such as fibromyalgia may be difficult to establish, as the structures involved are expected to be normal, limiting the utility of diagnostic testing.

Neuropathic and other chronic maladaptive pain may occur as a result of injury and/or pathological changes at various levels or "stations" of the nervous system, including the peripheral nervous system, the spinal cord, and the brain.

Station 1: Peripheral Nervous System, Peripheral Sensitization (PNS)

The peripheral nervous system consists of specialized nerve fibers that transmit distinct signals. *A-beta fibers* are large myelinated afferent fibers that conduct information about touch and pressure sensation. These fibers have a low threshold for activation and transmit signals at a fast velocity (50–60 m/s). A-beta fibers may be measured with nerve conduction studies. Although the physiologic role of A-beta fibers is to transmit touch and pressure sensation, these fibers may also

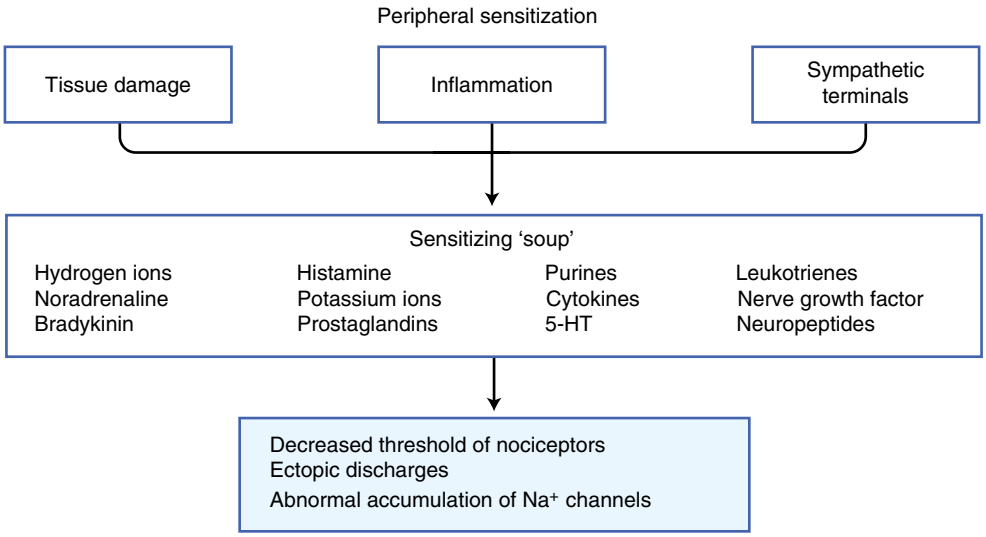

Fig. 80.2 Peripheral sensitization and the sensitizing "soup" (Adapted from Siddall and Cousins [19])

conduct pain signals as a result of plasticity in the dorsal horn of the spinal cord in certain pathologic conditions.

A-delta fibers are smaller, thinly myelinated fibers, which are activated by heat, cold, and pressure sensation. These fibers have a high threshold for activation and transmit signals at a slower velocity (5–30 m/s). *C fibers* are unmyelinated and respond to heat, mechanical, and chemical stimulation. C fibers have a high threshold and transmit signals slowly (1 m/s or less). Certain neuropathies may preferentially affect certain nerve fibers; for example, selective small fiber neuropathies involve A-delta and C fibers and result in normal nerve conduction study parameters. Conversely, large fiber neuropathies affect A-beta fibers, result in abnormal nerve conduction study parameters, and may not be associated with pain.

While nerve conduction study parameters are expected to be normal in small fiber neuropathies, the diagnosis may be established with skin biopsy and assessment of epidermal nerve fiber density using special immunostaining to quantify the number and density of the epidermal nerve fibers;[6] if normal, this can effectively rule out the presence of a small fiber neuropathy. Other diagnostic tests that may be utilized in small fiber neuropathies include quantitative sensory testing and autonomic testing (such as quantitative sudomotor axon reflex testing (QSART) and thermoregulatory sweat testing).

Ion channels play an essential role in transduction of the pain response in both physiologic and neuropathic pain. Additionally, the targeting of specific ion channels underlies the mechanism of many medications used to treat neuropathic pain. Electrogenesis refers to the change in membrane voltage that occurs at the distal aspect of the axon as a result of mechanical, thermal, or chemical stimuli [7], and sodium channels play a crucial role in membrane excitability. The "pacemaker" zone of the axon determines the neuron's excitability. The presence of a stimulus results in the opening of some sodium channels; if the stimulus reaches threshold, an action potential is generated as a result of the opening of voltage-gated sodium channels. Sustained firing of action potentials occurs in neuropathic pain and occurs as a result of the activation of voltage-gated sodium channels and changes in the peaks of intrinsic oscillations that occur in the membrane potentials of some sensory neurons [7]. Changes within the pacemaker zone as well as the development of ectopic pacemaker zones occur in neuropathic pain and contribute to the phenomenon of peripheral sensitization [7]. Membrane-stabilizing medications (see below) are of benefit in neuropathic pain in part because of the suppression of ectopic pacemakers.

The excitability of neurons is likely the consequence of three cellular processes that impact sodium (and other ion) channels: trafficking, up- and downregulation of gene expression, and altered kinetics [7]. Focal injury to the axon may affect transport of sodium channels along the axon, resulting in accumulation of sodium channels, thereby generating an ectopic pacemaker.

Interactions between the peripheral nervous system and the immune system may impact the pain response. With the occurrence of initial injury, nociceptors become activated in the periphery by "a sensitizing soup," the products of tissue inflammation including histamine, prostaglandin E, serotonin, bradykinin, adenosine triphosphate, free radicals, and ions such as potassium and hydrogen (Fig. 80.2). These activate afferent fibers, lowering their threshold to thermal and mechanical stimuli. Receptors involved include the tyrosine kinase A (TrkA) receptor, a nerve growth factor receptor, and TRPV1 (transient receptor potential vanilloid type 1) [8]. Capsaicin is an agonist of the TRPV1 receptor; when activated, substance P is released, which can activate neighboring endothelial cells and mast cells, causing more

release of histamine and bradykinin, which can further sensitize those nociceptors [9]. Additional immune system-mediated molecules such as tumor necrosis factor, interleukin 1, and interleukin 6 may also contribute to peripheral sensitization of nociceptors. Chronic inflammatory conditions resulting in activation of these receptors may then result in activation of intracellular kinases (such as protein kinase C and protein kinase A). Sensitization is mediated through activation of these intracellular kinases, which can result in phosphorylation of sensory neuron-specific (SNS) sodium channels and the TRPV1 receptor [10].

Proliferation and abnormal accumulation of sodium channels are known to occur at the sites of injured nerves and along neuromas [11]. This results in foci of hyperexcitability and ectopic discharges in the axon and cell body of the injured neuron [7]. Upregulation of SNS sodium channels and TRPV1 receptors is one component of the neuronal plasticity in neuropathic pain. The role of the sodium channels in peripheral nociception has been well established [12–14].

Intracellular kinases phosphorylate the voltage-gated sodium channels (e.g., 1.8 and 1.9, located on the periphery of the nociceptor), and once activated, these receptors may then be depolarized at low-intensity subthreshold stimulation or may fire independently, resulting in ectopic discharges [15].

Axon injury also alters gene expression of various other ion channel subunits and subtypes. For example, some sodium channels ($Na_v1.6$) tend to open a second time following activation, which may result in repetitive firing. A gain-of-function mutation in the $Na_v1.7$ channel results an increase in the firing capacity of some dorsal root ganglion (DRG neurons), resulting in familial erythromelalgia [7] manifesting as severe burning pain with bright red discoloration of the feet and hands, in association with ambient temperature changes. Alteration in the gene expression of specific ion channels (either inherited or by injury-induced changes) may therefore affect membrane excitability.

Unlike sodium channels, there are also voltage-gated potassium channels; activation of those results in inhibition of DRG neurons. Their function is to repolarize neurons, restoring their baseline membrane potential. Thus, development of potassium channel opener agents will likely have role in lessening peripheral sensitization. Other inflammatory mediators include prostaglandins which bind prostanoid receptors and activate adenylate cyclase, increasing the amount of cyclic AMP, further sensitizing nerve terminals. Nerve growth factor can stimulate tyrosine kinase A receptors, which can phosphorylate and sensitize TRPV1 receptors. Additionally, activation of the TrkA receptor can result in alteration of gene expression, whereby the TrkA-NGF complex is internalized and retrogradely transported to the DRG. There, it initiates gene transcription with resultant upregulation of receptors, ion channels, and release of neuropeptides, contributing to the maladaptive issues in neuropathic pain [8, 16].

Station 2: Spinal Cord, Central Sensitization (CNS)

Following activation of peripheral nociceptors, action potentials are generated and conducted to the central nervous system. The C fibers' nociceptors use glutamate as one of their neurotransmitters, and glutamate activates α-amino-3 hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors. Fast excitatory synaptic transmission is mediated by the former receptors [17]. With sustained and intense noxious stimuli, the prolonged activation of nociceptive unmyelinated C fibers results in hyperexcitability of the dorsal horn neurons and plasticity-related changes in the receptive field, a phenomenon referred to as "wind-up."[18] At the molecular level, peripheral nociceptors' activation also results in the release of substance P and neurokinin 1(NK1). Sustained activation of the neurokinin receptors located postsynaptically in the dorsal horn primes the NMDA receptors and triggers the release of intracellular calcium, resulting in upregulation of the NMDA receptors.

The NMDA receptor's ion channel is normally blocked by magnesium ions via a voltage-dependent mechanism (Fig. 80.3) [19]. The depolarization induced by calcium results in the removal of the magnesium ion and opens up the ion channel receptor. Binding of glutamate causes further influx of calcium and sodium ions intracellularly. Voltage-gated calcium channels do play a crucial role in neuropathic pain by regulating neuronal excitability and neurotransmitter release. As with sodium channels, various subtypes of voltage-gated calcium channels play different roles in pain transduction and are potential targets for neuromodulatory pain medications. N- and P/Q-type channels regulate neurotransmitter release; N-type channels trigger release from dorsal root ganglia neurons, and P/Q-type channels trigger release at central excitatory synapses [15]. The surface expression of N- and P/Q-type channels are reduced by binding of the alpha 2 delta subunit by gabapentin or pregabalin (see *treatment*, below).

Intracellular calcium leads to neuroplasticity changes, including the activation of protein kinase C. The latter can result in phosphorylation of proteins including NMDA receptors, lowering the threshold of activation; this phenomenon is referred to as short-term sensitization. Kinase activation may also phosphorylate gene regulatory proteins, which can alter gene expression, referred to as long-term sensitization. Activation of nitric oxide synthase, altered gene transcription, and the induction of early gene expression occur, which results in more chronic alteration of the responsiveness of neurons to additional stimuli [20]. The latter is an extreme example of a maladaptive state of chronic pain, in which pain may become severe and intractable [21, 22]. Furthermore, reorganization changes in the dorsal horn occur secondary to sprouting of A-beta fibers into one of the more superficial

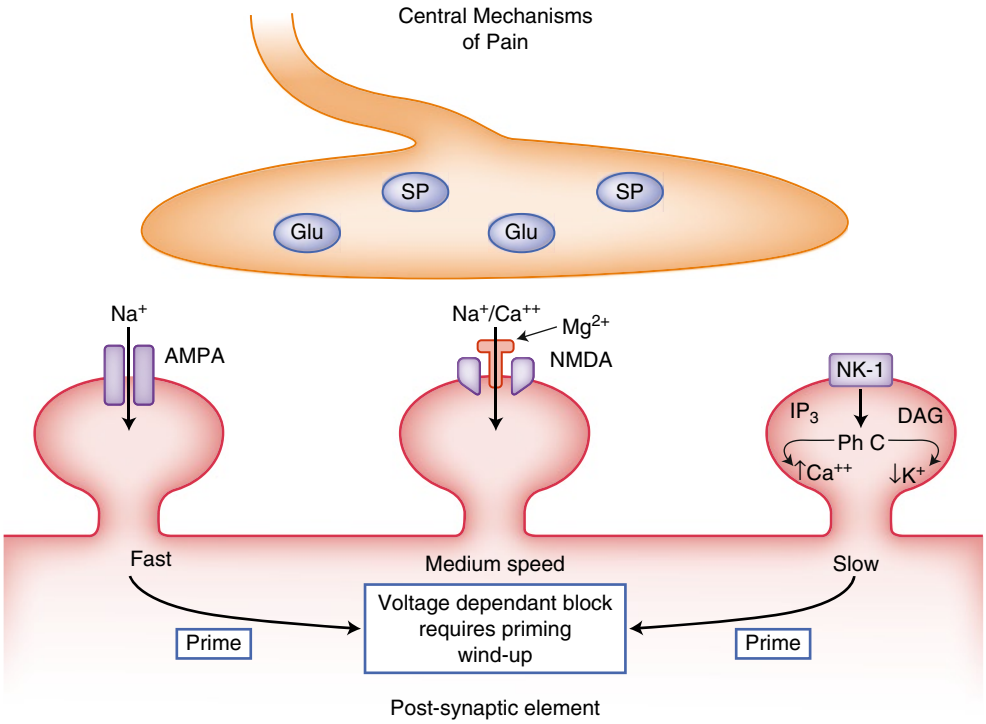

Fig. 80.3 Central mechanisms of pain at the level of dorsal horn. *SP* substance P, *Glu* glutamate, *AMPA* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, *NMDA* N-methyl-D-aspartate, *NK1* neurokinin 1, second messengers: (IP3, DAG), *IP3* inositol triphosphate, *DAG* diacylglycerol (From Siddall and Cousins [19])

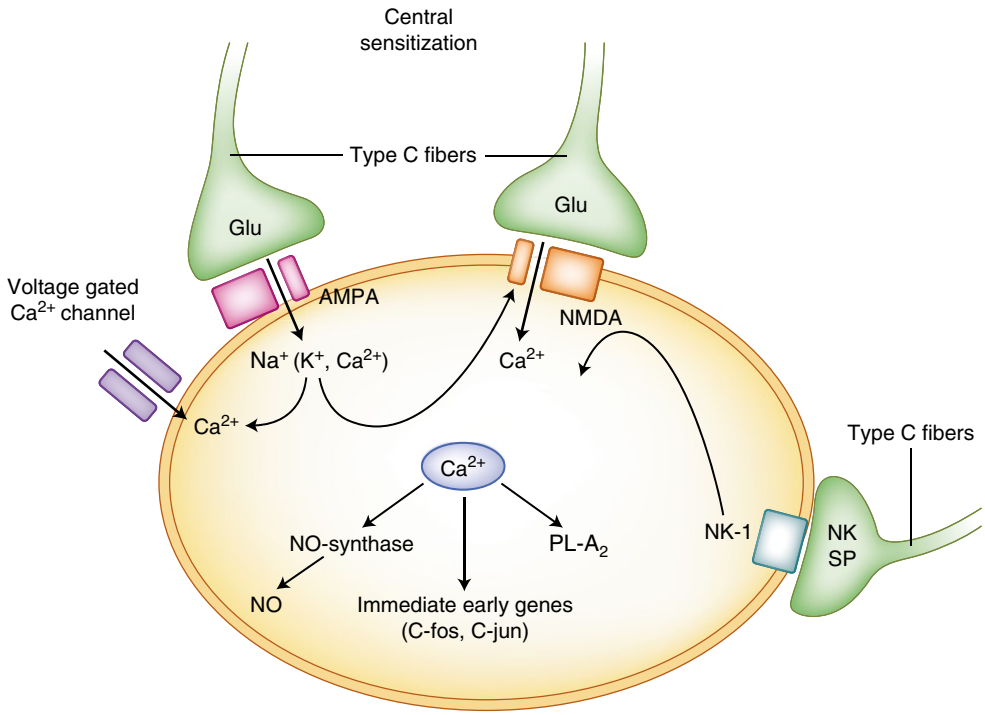

Fig. 80.4 Central sensitization in the dorsal horn. *SP* substance P, *Glu* glutamate, *AMPA* α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid, *NMDA* N-methyl-D-aspartate, *NK1* neurokinin 1, *PL-A2* phospholipase, *NO* nitric oxide (Adapted from Ollat et al. [20])

layers of the dorsal horn of the spinal cord [23–26]. All of these mechanisms do underlie the pathophysiological state of central sensitization in neuropathic pain (Fig. 80.4) [19, 20, 23, 27]. In addition to playing a role in the development of chronic pain [28], excitatory neurotransmission through the NMDA receptors has a role in the development of opioid tolerance [29, 30]. Besides the wide dynamic range neurons (WDR) in the dorsal horn which receive input from A-delta and A-beta fibers, glial cells also play an important role. An interaction between dorsal horn neurons and microglial cells is suggested by the overexpression of microglial receptors following nerve injuries. These receptors include chemokine

receptors such as CX3CR1 and adenosine triphosphate receptor (P2X4) [31]. Blocking those receptors in animals has been associated with a reduction in neuropathic pain [31]. Furthermore, the release of cytokines by microglial cells may result in further excitation and depolarization of the dorsal horn neurons, contributing to the maladaptive pain response.

Within this specialized environment of the dorsal horn of the spinal cord, inhibitory interneurons inhibit the excitatory input with GABA, glycine, endorphins, and monoamines. Perhaps more importantly, the descending spinal cord pathways originating in the rostral ventral medulla and dorsolateral pontine tegmentum terminate in the dorsal horn, synapse with the WDR neurons, and modulate the pain signal with inhibitory actions. When functioning normally, these descending pathways release both serotonin and norepinephrine, which combined can have an inhibitory effect on the dorsal horn neurons. Dysfunction of the inhibitory pathway can therefore contribute to chronic neuropathic pain. Restoring the balance or function of the descending pathways is an important aspect in the treatment of neuropathic pain.

Station 3: Brain, Central Sensitization

The "pain matrix" or network of brain pathways involved in pain perception has been identified largely by studying both normal healthy subjects subjected to painful stimuli and individuals suffering from chronic pain using functional imaging techniques, such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI), identifying activated areas in the brain [32]. The pain matrix includes the somatosensory cortex (primary and secondary), prefrontal cortex, insular cortex, anterior cingulate cortex, thalamus, hippocampus, and amygdala. These structures and their connecting circuits are particularly important in pain processing by regulating attention, emotion, anticipation, memory, and expectation states. The amygdala has an important role in attaching an emotional experience to pain. The anterior cingulate cortex is often associated with the affective component of pain, anticipation of pain, and the cognitive-attention and motor responses to pain [33]. Changes in thalamocortical rhythmic activity, possibly as a result in an imbalance between T- and P/Q-type calcium channel activation, have also been implicated in neuropathic pain [15]. Certain pharmacologic and behavioral medicine approaches may be of particular benefit in targeting the unique pathological processes occurring within the brain's pain matrix.

Treatment: A Mechanistic Approach

The appropriate treatment of neuropathic pain depends upon the establishment of a proper diagnosis, treating (when possible) the underlying cause, and targeting the various pathologic processes affecting the stations or pathways noted above, often by pharmacologic means. Neuropathic pain can result as a consequence of damage to a variety of components of the nervous system, and therefore neuropathic pain as a disease state is heterogeneous. Specific examples include diabetic peripheral neuropathy (DPN), various peripheral neuropathies, postherpetic neuralgia (PHN), trigeminal neuralgia, thalamic and spinal cord pain syndromes, and complex regional pain syndrome (CRPS). The majority of clinical trials in neuropathic pain have targeted the far more commonly occurring peripheral, rather than central, causes of pain. A detailed discussion of each of these conditions is beyond the scope of this chapter. While treatments have been studied for a variety of peripheral neuropathic pain conditions, postherpetic neuralgia and painful diabetic peripheral neuropathy (DPN) represent the prototypic neuropathic pain conditions for many clinical trials. The discussion below will focus on postherpetic neuralgia, which provides an excellent model of a neuropathic pain syndrome in which pathophysiology and treatment principles can be expanded and applied to other neuropathic pain conditions.

Postherpetic Neuralgia

The largest series to date of postmortem examination of patients who had herpes zoster infection was reported more than 110 years ago by Head and Campbell [34]. The neuropathological changes and evolution in terms of initial hemorrhagic inflammation in the sensory ganglia and nerves followed by fibrotic changes in the ganglia and degenerative changes in the sensory roots and tracts were eloquently described in their series of 20 patients. Their findings provided the basis for one of the earliest knowledge of the neurosegmental anatomy and description of the dermatomal map.

Pathology and Clinical Manifestations

Following primary varicella infection, the varicella zoster virus (VZV), a human DNA alphaherpesvirus, establishes latency in the dorsal root ganglia. It has a genome consisting of 125 kilobase pairs, encoding approximately 70 different gene products [35]. The VZV is a ubiquitous agent, and its reactivation is determined primarily by host factors perturbation.

Among various neurological disorders, herpes zoster has one of the highest incidences, occurring annually at a rate of 400/100,000 [36]. The incidence increases dramatically with age, reaching up to 12/1,000 in people older than 80 years. The lifetime risk of developing herpes zoster has been quoted to be as high as 20 % of the population [36, 37]. In the majority of patients, a prodrome of dermatomal pain (preherpetic

neuralgia) precedes the appearance of the rash by several days [38]. Rare cases of prodromal pain lasting more than 100 days have been described [39]. The rash of herpes zoster is characterized by a unilateral vesicular eruption in a dermatomal distribution, preceded by erythematous maculopapular lesions. Crusting of the lesions follows and occurs in 7–15 days in the majority of the patients. There is predilection for involvement of the thoracic dermatomes accounting for 50 % of the cases [40], followed by the ophthalmic division of the trigeminal nerve.

Herpes zoster may present as a subclinical disease, consisting of viral replication without evidence of pain, as described in some patients who undergo bone marrow transplantation [41]. This can be demonstrated by an appropriate rise in the VZV antibody titer and/or by polymerase chain reaction. Along the presentation spectrum is the entity known as zoster sine herpete, defined as a neuralgic pain condition or other neurologic syndrome but without the skin rash [42, 43]. Among some of the other neurological complications of herpes zoster include leptomeningeal spread of the infection causing inflammation of the gray matter of the ventral and dorsal horn [44]. Other described neurologic disorders include motor involvement [45], cranial polyneuritis such as the Ramsay-Hunt syndrome [46], transverse myelitis [47], meningitis [48], and cerebral angiitis [49].

There have been various definitions of postherpetic neuralgia, in terms of the temporal relationship between pain occurrence and the rash of zoster [38, 50, 51]. PHN is most commonly defined as pain arising or persisting in areas affected by herpes zoster lasting more than 3 months following healing of the skin lesions [52]. The annual incidence of PHN has been estimated to be 11/100,000, its lifetime prevalence being 70/100,000 [53]. The probability of PHN following zoster infection increases with age [54]. About 10–20 % of patients with herpes zoster will develop PHN, with an approximate incidence of 50 % in patients over the age of 60 years. The proportion of patients whose PHN persists for more than 1 year increases significantly in patients older than 60 years of age [55]. PHN risk factors include trigeminal distribution of zoster [56], severe acute pain, sensory loss, and extensive rash [51, 56]. Thermal threshold abnormalities at 3 months correlate with greater chance of PHN occurrence [57].

Immunolabeling of punch skin biopsies with PGP 9.5, an axonal marker in patients with herpes zoster [58], showed that patients with postherpetic neuralgia had lower mean number of epidermal neurites versus patients without PHN. Evidence of the reduction of the epidermal neurites was also seen on the contralateral side, unaffected by the herpes zoster rash. The latter may support the theory of spinal cord injury in this patient population.

The pain in PHN can be either spontaneous or stimulus-evoked; it can be associated with either intact sensory function or sensory loss [59] in a dermatomal distribution pattern [34]. Various pain descriptors include burning, deep pain, stabbing, sharp, throbbing, paroxysmal with lancinating component, or more commonly allodynic in nature [24, 60]. In addition to thermal sensory misperception [57, 61, 62], a spectrum of positive and negative sensory symptoms and signs occur in PHN. These range respectively from allodynia, hyperesthesia, and hyperalgesia to hypesthesia, anesthesia, and analgesia to light touch and pinprick [63, 64]. Although patients may have distinct sensory symptoms and findings, these can coexist in all combinations [65]. The area of positive sensory findings is greater than the area affected by skin scarring. In a detailed study of the clinical features of PHN, allodynia was observed in 58 % of patients [66].

Pathophysiology of PHN

Peripheral and central sensitization processes underlie the mechanism of PHN. One of the characteristic features in patients with PHN is the presence of dynamic mechanical allodynia [57]. It is thought that this phenomenon is due to activation of low-threshold A-beta mechanoreceptors into a sensitized dorsal horn [64], and reorganization changes in the dorsal horn occur secondary to sprouting of A-beta fibers into one of the more superficial layers of the dorsal horn of the spinal cord, described above [23, 25, 26, 61].

Fields and Rowbatham introduced the concept of irritable nociceptors [65]. They also described a spectrum of pathophysiological states in patients with PHN [61, 62, 65], which have implications in terms of selecting the appropriate treatment modality for a given patient. The subtypes include the following: (1) irritable nociceptors where patients manifest significant allodynia, pain intensified by capsaicin and relieved by local anesthetics; (2) deafferentation without allodynia, in which there is marked sensory loss without pain; and (3) deafferentation in conjunction with allodynia, the latter reflecting central reorganization, with the implication that the patient will respond better to antineuralgic therapy directed against central sensitization maladaptive changes rather than to agents which have peripheral mechanism of analgesia.

Pharmacologic Management

Treatment of Herpes Zoster

Oral agents approved in the United States are acyclovir, valaciclovir, and famciclovir. The latter two agents are prodrugs; valaciclovir is a prodrug of acyclovir, and famciclovir is a prodrug of penciclovir. The goals of antiviral therapy are to shorten the duration of the cutaneous lesions and reduce the incidence of acute pain, which these agents will accomplish, if initiated within 72 h of the rash onset [66–68]. Valaciclovir and famciclovir are currently considered the drugs of choice because of their pharmacokinetic profile. Antiviral therapy should be more aggressive in patients older than 60 years. In general, these patients who present with

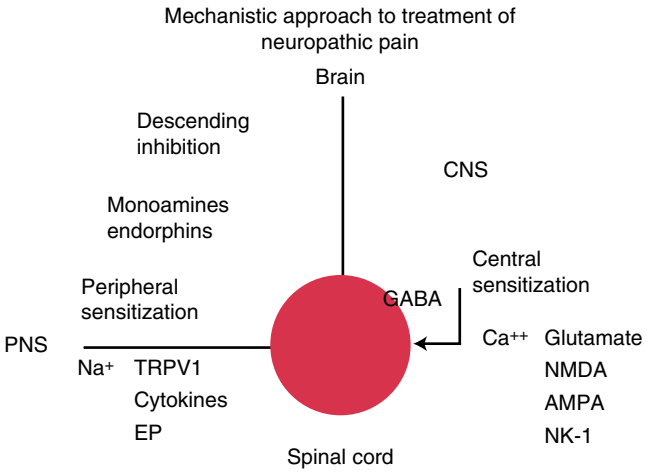

Fig. 80.5 A mechanistic approach to the treatment of neuropathic pain; *EP* prostaglandin E receptor, *TRPV1* transient receptor potential vanilloid type 1, *GABA* gamma aminobutyric acid, *AMPA* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, *NMDA* N-methyl-D-aspartate, *NK1* neurokinin 1, *PNS* peripheral sensitization, *CNS* central sensitization

significant pain at onset and who have a large number or active lesions are likely to benefit more from antiviral therapy. Unlike acyclovir, which was found not to alter the incidence of postherpetic neuralgia [69], famciclovir was found to reduce the median duration of postherpetic neuralgia in subjects over 50 years old, from 163 to 63 days, when compared to placebo [67].

Although adding corticosteroids to antiviral therapy would accelerate healing of the skin lesions and reduce the requirements of analgesic therapy, they do not affect the incidence of postherpetic neuralgia [70, 71].

Prevention of Postherpetic Neuralgia

Vaccination: A large, randomized, placebo-controlled trial assessing the benefit of a live attenuated varicella vaccine administered to individuals 60 years of age or older revealed a marked reduction in morbidity associated with herpes zoster and postherpetic neuralgia [72]. Use of the vaccine was associated with a 51.3 % reduction in the incidence of herpes zoster and a 66.5 % reduction in the incidence of postherpetic neuralgia [72].

Antidepressants: The effects of preemptive treatment using antidepressants have been studied in a randomized, double-blind, placebo-controlled study [73]. Patients older than 60 years, when treated with amitriptyline 25 mg at the time of herpes zoster diagnosis, showed a reduction in the prevalence of pain by 50 %, when compared to placebo at 6 months after the diagnosis of zoster. This finding would lend credence to the role of aggressive and/or preemptive treatment of pain to lessen the chance of neuronal sensitization and maladaptive changes in the peripheral and central nervous system.

Treatment of Postherpetic Neuralgia

Being a model of neuropathic pain, it would make sense to treat postherpetic neuralgia using a mechanistic approach (Fig. 80.5) [74]. What will be reviewed next is a discussion of some of the drugs that have demonstrated efficacy in certain clinical trials.

Descending Inhibition, Modulation of the Opiates Receptors

Opioids: Although opioids were considered in the past as being non-useful for the treatment of neuropathic pain, there has been a change in this belief, with the current consensus being that for patients refractory to various non-opioid antineuralgic agents or in need of acute pain relief, treatment with opioids should be considered. Opioids have peripheral, spinal, and supraspinal targets. The antineuralgic mechanism of their action is through direct inhibitory effects on primary nociceptive afferents and the neurons in the dorsal horn of the spinal cord. Various opioids receptor subtypes have been identified including mu, delta, and kappa [75, 76]. Opioids have a presynaptic mechanism of action by closing voltage-gated calcium channels, in the primary nociceptive afferents [77]. Activation of the presynaptic opioid receptors would result in a reduction in the release of neurotransmitters from nociceptive primary afferent fibers. Opioids also have a postsynaptic mechanism of action, resulting in hyperpolarization/inhibition of the postsynaptic dorsal horn neurons by opening of potassium channels [78]. The combined effect results in a decrease in nociceptive transmission. In the midbrain, opioids activate "off" cells and inhibit "on" cells, leading to activation of the descending inhibitory pathway on the dorsal horn neurons. Mu opioid receptor activation is also believed to interact with TRPV1 receptors, resulting in glutamate release [9]. Adverse effects including sedation, nausea, and constipation can be, however, limiting factors.

Sustained-release oxycodone has been evaluated in a randomized, double-blind, 8-week crossover trial of 50 patients [79]. In this study, oxycodone was titrated up to 30 mg twice daily. Efficacy was evaluated on a 100 mm visual analog scale (VAS). It was shown that 58 % of patients experienced moderate improvement in pain versus 18 % on placebo. The controversial issue of opioids in the treatment of neuropathic pain was addressed in a randomized, double-blind crossover trial comparing tricyclic antidepressants and opioids with placebo in PHN [80]. Each study participant was scheduled to undergo three treatment periods: one with opioid, one with tricyclic antidepressant, and one with placebo. Each treatment period lasted 2 months, with a 1-week washout period. In this study, opioids were found to have a significant effect on pain reduction with minimal cognitive effects.

Tramadol is a centrally acting opioid analgesic with weak inhibition of reuptake of norepinephrine and serotonin. A potential benefit of tramadol in PHN was exhibited in a pilot study comparing its impact on pain relief to clomipramine, a

tricyclic antidepressant (TCA) [81]. A randomized, placebo-controlled trial of tramadol also showed an improvement in the pain associated with diabetic peripheral neuropathy in patients treated with a four times per day regimen of tramadol [82]. Tapentadol is a centrally acting analgesic with both μ-opioid receptor agonist and norepinephrine reuptake inhibition activity, with minimal serotonin reuptake inhibition; trials supporting its benefit in PHN are lacking, though a benefit was seen using the extended-release formulation of tapentadol in patients with painful DPN [83]. The additional noradrenergic mechanism of action shared by tramadol and tapentadol may provide an advantage over other opioid analgesics in the management of neuropathic pain. The potential for serotonin syndrome must be considered when using these agents in combination with serotonergic medications, such as TCAs and serotonin-norepinephrine reuptake inhibitors (SNRIs).

Descending Inhibition, Modulation of the Monoaminergic Systems

Independent of their antidepressant effects, antidepressants including selective *serotonin-norepinephrine reuptake inhibitors* (*SNRIs*) have been shown to reduce the pain of PHN. These agents potentiate serotonin (5HT) and norepinephrine (NE), likely inhibitory transmitters in the descending pathway from the brainstem to the dorsal horn of the spinal cord. Multiple double-blind controlled studies have established the role of antidepressants in the treatment of postherpetic neuralgia [50, 84–88].

Agents that are mixed (NE/5HT) reuptake blockers such as nortriptyline and amitriptyline have been found to be slightly more effective than selective noradrenergic blockers such as maprotiline (a tetracyclic antidepressant) [87]. Selective serotonergic agents such as zimelidine have been found not to be effective [89]. Sedation, anticholinergic effects, hypotension, cardiac effects, and weight gain however may limit the use of the tricyclic antidepressants, which have mixed (5HT/NE) mechanism of action. This is of special importance in the elderly, the predominant population affected with intractable postherpetic neuralgia. While large randomized trials for their use in PHN are lacking, SNRIs such as duloxetine, venlafaxine, desvenlafaxine, and milnacipran have shown efficacy in other neuropathic (DPN) and/or chronic pain (fibromyalgia) trials and together with TCAs are now considered among first-line agents for the treatment of such neuropathic pain conditions.

Modulation of Peripheral Sensitization

Tricyclic Antidepressants: Unlike selective serotoninergic reuptake inhibitors (SSRIs), tricyclic antidepressants have some peripheral sodium modulation effect, which is likely a contributing mechanism in the treatment of neuropathic pain, and may also explain the greater antineuralgic effectiveness of these agents, when compared to SSRIs.

Anticonvulsants: Until the gabapentin and pregabalin trials, carbamazepine was the only agent evaluated in PHN. Carbamazepine has peripheral sodium modulation effect and was evaluated in a very small randomized clinical trial [90]. Its pain relief effect was found not too different compared to placebo, although it did help in lessening the lancinating pain component. Oxcarbazepine, a keto-analogue of carbamazepine, has modulating effect on the sodium channels and N- and P-type calcium channels [91, 92]. Activation of the latter plays a role in the development of central sensitization. Oxcarbazepine is safer and has a more favorable tolerability and pharmacokinetic profile than carbamazepine. This was found in a meta-analysis of three studies comparing it to carbamazepine in trigeminal neuralgia [93]. Oxcarbazepine has been evaluated in DPN trials; its safety was also evaluated in multicenter phase 3 studies with 12 months open-label extension [94, 95].

Lamotrigine inhibits voltage-gated sodium channels and inhibits N- and P/Q-type calcium channels and has been demonstrated to reduce pain in a variety of neuropathic pain conditions, including diabetic neuropathy [96], though data supporting its use in PHN is lacking. Additionally, the need for slow titration to reduce risk of rash with lamotrigine delays the time to therapeutic effect.

Lidocaine is a prototype sodium channel blocker. Infusion of lidocaine has been found to relieve neuropathic pain in diabetic neuropathy and in PHN [97–99]. Its systemic side effects and potential proarrhythmic effects limit its use. Topical lidocaine gel 5 % has been shown to be effective in postherpetic neuralgia [100]. Use of a lidocaine patch is a convenient means of administration, with minimal systemic absorption. Lidocaine patch 5 % has been evaluated in multiple randomized controlled trials [101–104]. In an enriched enrollment design, double-blind, crossover study of 32 patients who used lidocaine patch for at least 1 month prior to enrollment, the time to exit until the patient reported a decrease of 2 or more on categorical pain relief for 2 consecutive days was significantly longer with lidocaine patch than the vehicle patch (14 days vs. 3.8 days) [103]. In a randomized, double-blind, placebo-controlled trial of lidocaine 5 % patches for focal neuropathic pain (which included patients with PHN), treatment was clearly effective in decreasing pain and allodynia during the first 8 h following application of the patch, with a sustained benefit at 7 days [104]. A study using fMRI to assess changes in brain activity with use of lidocaine 5 % patches for PHN revealed that in addition to a reduction in spontaneous pain, short-term treatment with lidocaine (6 h) was associated with fMRI changes in affective and sensory-discriminative areas (thalamus, somatosensory cortex, insula, and anterior cingulate) and that longer-term treatment (2 weeks) was associated with changes in the reward-related regions (ventral striatum and amygdala) [105].

Capsaicin: Capsaicin, a natural product extracted from red chili peppers, stimulates unmyelinated primary afferent C fibers but depending on its concentration can also inactivate and destroy them [106, 107]. Capsaicin alters nociceptor sensitization by acting on the vanilloid receptor TRPV1, as noted above [108]. The latter is activated by noxious heat and low pH. Capsaicin seems to reduce substance P (mostly secondary to C fiber degeneration) as well as calcitonin gene-related peptide (CGRP) and vasoactive intestinal polypeptide (VIP). Substance P is an important mediator of neurogenic inflammation and primary hyperalgesia, where activation and sensitization of C mechanoheat polymodal nociceptors (CMH) occur [109–111]. Various trials using different concentration of topical capsaicin have been carried with dissimilar and nonconsistent results [112–114]. One main difficulty in using capsaicin in a double-blind, controlled study is the lack of true blinding secondary to the burning sensation induced by capsaicin [115]. This side effect as well as the need for multiple daily applications limits the use of capsaicin cream. However, multiple double-blind, placebo-controlled trials of NGX-4010, a high-concentration (8 %) capsaicin patch, have revealed a sustained improvement in pain after a single 60 min treatment [116–118]. Although a transient increase in pain was experienced by some patients, pretreatment with a topical anesthetic allows the treatment to be quite well tolerated.

Modulation of Central Sensitization

Calcium Channel Alpha 2 Delta Ligands: Gabapentin and pregabalin bind to the alpha 2 delta subunit of voltage-gated calcium channels [1, 15], decreasing the release of glutamate, norepinephrine, and substance P [119]. The alpha 2 delta site is part of the physiologic calcium channel [120], which is an important component of the phenomenon of central sensitization that occurs in neuropathic pain. The analgesic efficacy of gabapentin and pregabalin was identified in various animal models of neuropathic pain, showing a decrease in allodynia and hyperalgesia behavior.

The benefits of gabapentin in PHN were illustrated in two pivotal double-blind, placebo-controlled trials carried out in the USA [121] and UK [122]. In the US study, gabapentin was increased up to 3,600 mg, and in the UK study, the dose was titrated either 1,800 or 2,400 mg. A statistically significant difference was noted by week 1 in the UK study and by week 2 in the US study, maintained to the end of the treatment period. Given its relatively poor bioavailability, gabapentin is ideally administered three times per day and is associated with a high incidence of dizziness (28 %) and somnolence (21 %). Absorption of gabapentin occurs via a saturable transport mechanism in the proximal small intestine, resulting in decrease in the bioavailability as the dosage is increased [123]. A once-daily dosage of gabapentin was approved recently by the FDA for the treatment of PHN. This formulation utilizes an advanced polymer gastric retentive technology, allowing the gradual release of gabapentin in the small intestine. An 11-week, randomized, placebo-controlled trial in PHN revealed significant pain relief in treated patients when compared to placebo [124].

Pregabalin is a gabapentinoid with greater bioavailability than gabapentin. It is FDA-approved for the treatment of pain associated with PHN, in addition to DPN and fibromyalgia. A multicenter, double-blind, randomized, placebo-controlled trial of pregabalin for treatment of PHN at doses of either 600 mg/day (or 300 mg/day for patients with impaired renal function) showed significant reductions in pain scores and improvement in sleep in the pregabalin treatment groups [125]. Another double-blind, placebo-controlled trial of pregabalin for PHN at doses of 150 or 300 mg/day revealed significantly more responders (defined as ≥50 % decrease in mean pain score from baseline to endpoint) in both pregabalin groups (150 mg, 26 %; 300 mg, 28 %) compared to the placebo group (10 %) [126]. Sleep improved in the treatment groups as well [126]. Unlike their effect in neuropathic pain, gabapentin and pregabalin have no effect in conditions of nociceptive pain.

Additional *voltage-gated calcium channel blockers* such as topiramate, levetiracetam, and zoconotide have been investigated for management of neuropathic pain. Zoconotide, administered intrathecally, is the only of these FDA-approved for the management of severe chronic pain [96]. Levetiracetam was shown in an open-label trial to have analgesic effects and to be well tolerated in patients with PHN [96, 127], though large, randomized controlled trials are lacking. In addition to blocking of voltage-gated calcium channels, topiramate modulates voltage-gated sodium channels and potentiates GABA inhibition [96]. Despite its broad-spectrum mechanisms of action, the benefits of topiramate in neuropathic pain conditions (such as peripheral neuropathy and trigeminal neuralgia) have been variable [96]. Additionally, side effect such as cognitive slowing, sedation, and paresthesias may limit tolerability of topiramate.

NMDA Blockers: Dextromethorphan, an NMDA antagonist, was evaluated in PHN with little evidence of benefit [128, 129]. Ketamine, which is not fully selective for NMDA receptors, has been used in various neuropathic pain conditions including PHN, showing improvement of certain pain components [130–133]. Systemic effects of ketamine limit its chronic use. Memantine is a noncompetitive NMDA antagonist and unlike other NMDA receptor antagonists, it tends to be well tolerated. It has been evaluated in experimental animal models of neuropathic pain and has shown good prophylactic and antinociceptive effects [134], although clinical trials in various neuropathic pain conditions have not established efficacy.

Other Mechanisms

Nerve Blocks: Nerve blocks have been used for the treatment of herpes zoster since the 1930s. Sympathetic block in the treatment of herpes zoster was described by Rosenak in

1938 [135]. Tenicela, in a double-blind, randomized study, confirmed the efficacy of sympathetic blocks in the treatment of herpes zoster [136]. Colding noted that the earlier the block is performed after the zoster eruption, the more likely its beneficial effect. The role of nerve blocks either as a preemptive approach or as a symptomatic treatment of PHN was evaluated with controversial results [136–141]. Various trials have included the use of somatic, epidural, and sympathetic blocks. Most of these trials were however not uniform in design; they were not truly randomized or controlled studies, and some were either anecdotal reports or included a small number of patients. Thus, whereas nerve blocks can be a beneficial treatment option for acute herpes zoster pain [142], there is no conclusive scientific evidence to date or consensus establishing their role as a treatment modality in PHN.

Other Agents: Topical formulations of lidocaine with prilocaine or eutectic mixture of local anesthetics (EMLA) have been reported to be useful in uncontrolled trials [143]. EMLA cream failed to show significant benefit over placebo in a controlled trial [144].

Comparison of Different Treatment Regimens

Given the small size in individual clinical trials, it is difficult to determine outcome accuracy [145], specifically when projections of the results of clinical trials are applied to individual patients. An alternative approach would be to pool results from many neuropathic pain placebo-controlled trials using a meta-analysis approach [146, 147].

The number needed to treat (NNT) approach is considered as a benchmark analgesic efficacy index [146, 147]. NNT is defined as the number of patients needed to be treated with a given agent to obtain one patient with at least 50 % pain relief that would not have happened with a placebo. Thus, the lower the NNT number, the more efficacious is the drug. Also, the numbers needed to harm (NNH) can also be calculated for minor and major adverse effects with study withdrawal being considered a major adverse event.

In PHN, NNT with tricyclic antidepressants ranged from 1.8 to 4.1 [146], with gabapentin it was 3.2 (2.4–5) [121, 148], and with pregabalin it was 3.9 (3.3–4.7) [125, 126, 149]. NNT for oxycodone was 2.5 (1.6–5.1), although in 30 % of patients, oxycodone was an add-on therapy to tricyclic antidepressants [150]. In neuropathic pain conditions, gabapentin and pregabalin can be considered as effective as SNRIs and tricyclic antidepressants; however, unlike TCAs, gabapentin and pregabalin have fewer contraindications in terms of anticholinergic and cardiac side effects. NNT for lidocaine 5 % patch was 4.4, comparing relatively well with other treatment approaches [104]. Collins also found that there was little difference in the incidence of NNH for minor adverse effects, being around 3 for both antidepressants and gabapentin. For major adverse effects (drug-related study withdrawal), antidepressants had an NNH of 17 when compared to placebo, versus no significant difference between gabapentin and placebo [150]. These represent major considerations in terms of side effects and management issues in the elderly PHN population.

Other Approaches to the Management of Neuropathic Pain

While large randomized trials showing a benefit are lacking, acupuncture has gained broader "mainstream" acceptance as a viable approach to pain management in recent years. The precise mechanisms underlying the potential benefits of acupuncture in managing pain are not well understood, though a possible interruption in the imbalance between competing excitatory and inhibitory pain pathways has been suggested. Benefits have been reported in various neuropathic pain conditions including acute herpetic pain [151, 152]. Transcranial magnetic stimulation (TMS) is a noninvasive method that alters brain activity by causing local depolarization or hyperpolarization and may be of benefit in management of chronic pain [153, 154]. While its use has not been reported in PHN, monochromatic infrared photo energy (MIRE) treatments have been studied in patients with DPN and did not improve pain [155]. Other non-pharmacologic techniques, including relaxation training, biofeedback, hypnosis, guided imagery, and stress management, are all useful techniques that can help patients manage their pain, likely by acting at the level of the "pain matrix" and altering the affective component of pain perception.

Proposed Algorithm for Management of Neuropathic Pain

Successful treatment of neuropathic pain relies upon the establishment of a correct diagnosis, assessment of the pain, and, quite often, a multi-faceted approach to therapy. Establishment of the diagnosis is particularly important; for example, certain neuropathic pain conditions, such as trigeminal neuralgia, respond to different first-line medications, with carbamazepine or oxcarbazepine considered as first agents of choice. If treatable or preventable, the underlying condition should be treated appropriately (e.g., antiviral medications for acute herpetic neuralgia, glycemic control for diabetic polyneuropathy). Non-pharmacologic approaches, such as physical therapy, biofeedback, and stress management, are also important co-treatment approaches.

As described above, a variety of pharmacologic agents are available for the management of neuropathic pain. Many factors should be considered when selecting a medication, including mechanism of action, comorbid medical conditions (which may be either favorably or adversely impacted by the choice of medication), available evidence supporting the medication's use in neuropathic pain, potential side effects, possible drug-drug interactions, urgency of medication efficacy, medication abuse potential, and the risks of overdose (intentional or unintentional) [119, 156].

Guidelines have been developed for the treatment of various neuropathic pain conditions, particularly DPN, PHN, and other chronic neuropathic and non-neuropathic pain conditions [119, 156–160]. These guidelines are based on systematic literature reviews, randomized clinical trials, and consensus expert opinion. Consensus treatment guidelines indicate a stepwise approach in the management of neuropathic pain. Recommended *first-line treatments* include certain antidepressants, such as tricyclic antidepressants and SNRIs (such as duloxetine or venlafaxine), calcium channel alpha 2 delta ligands (gabapentin or pregabalin), and topical lidocaine.

Opioids and tramadol tend to be considered *second-line agents* for the management of neuropathic pain. However, these agents may be incorporated as first-line agents (usually in combination with medications discussed above) under special circumstances, such as the need for rapid pain relief during the titration period of a first-line medication, episodic exacerbations of severe pain, acute neuropathic pain, and neuropathic cancer pain [119]. In addition to common side effects of constipation and sedation, abuse potential must be considered when introducing opioids.

When first- and second-line medications are ineffective, poorly tolerated, or not indicated, other medications may be considered as a *third-line approach*. These include various anticonvulsants (such as carbamazepine, oxcarbazepine, lamotrigine, topiramate, valproic acid, lacosamide), other antidepressants (SSRIs, bupropion), NMDA receptor antagonists (dextromethorphan, memantine), mexiletine (a sodium channel blocker), and topical capsaicin. These medications are considered third line based on the existence of less evidence supporting efficacy, inconsistent results of randomized trials, and expert opinion.

With most medications used to treat neuropathic pain (with exceptions including opioids), pain relief tends to occur in a gradual manner, and patients should be counseled accordingly, and expectations in terms of the degree of pain relief (which typically is partial or incomplete) should be discussed with patients in detail. Counseling needs to include education about the underlying disease state and its treatment, the concept of treating chronic pain as a separate coexisting disease state, the rationale for using various medications (at times in combination), the importance of functional outcomes and improvement in quality of life, issues surrounding medication adherence, and the potential for adverse side effects. Combination pharmacotherapy using a mechanistic treatment approach is typically used in severe pain or when pain relief is partial or inadequate.

Other Chronic Musculoskeletal Pain Conditions

Fibromyalgia

As mentioned above, noninflammatory, non-neuropathic pain occurs as a consequence of dysfunction of otherwise normal structures and pathways, with fibromyalgia representing the prototypical model of this process. While considered a non-neuropathic pain syndrome, fibromyalgia may manifest with a variety of neurological symptoms including hyperalgesia, dysesthesias, weakness, or fatigue; additionally, similar pathologic neuroplasticity processes implicated in neuropathic pain may underlie the maladaptive pain response seen in fibromyalgia. Further discussion of fibromyalgia is therefore warranted.

Fibromyalgia is a chronic pain condition characterized by the presence of widespread musculoskeletal pain, without an associated "lesion" or evidence of tissue injury. Fibromyalgia is common, with a prevalence of 2.5 % in the general population; women are more commonly affected than men, and incidence peaks between 40 and 60 years of age. The pain of fibromyalgia is commonly described as aching, cramping, and dull; nonetheless, pain descriptors typically considered "neuropathic" such as burning, stinging, or electricity-like sensations may also occur. As with neuropathic pain, spontaneous pain and evoked pain are both common features of fibromyalgia. Spontaneous pain (commonly aching or soreness) occurs as a consequence of spontaneous firing of axons or dorsal horn neurons, while evoked pain (manifesting as allodynia or hyperalgesia) occurs as a result of alteration in peripheral and central neurons. While widespread musculoskeletal pain is the hallmark feature of fibromyalgia, many accompanying symptoms are common, including fatigue, sleep disturbances, forgetfulness, dysesthesias, headaches, temporomandibular disorders, weakness, fatigue, gastrointestinal symptoms (particularly irritable bowel syndrome), interstitial cystitis, and psychiatric symptoms (such as depression, anxiety, and posttraumatic stress disorder). The common coexistence of psychiatric comorbidities and absence of associated tissue injury may lead to delays in diagnosis or, worse, dismissal of symptoms as psychiatric in origin.

Functional imaging studies have revealed abnormal activation of regions within the "pain matrix" of the brain, including the somatosensory cortex, amygdala, cingulate, caudate, and thalamus [161]. As described above, these pathways are particularly important in the affective and emotional component of pain perception. Despite the abundant evidence of centrally mediated processes underlying the maladaptive pain response in fibromyalgia revealed with functional imaging, the diagnosis of fibromyalgia remains clinical. Criteria defined in 1990 by the American College of Rheumatology (ACR) include widespread pain of ≥3 months' duration in all four quadrants of the body, with pain present with palpation at ≥11 of 18 defined tender points [162]. These criteria result in a sensitivity of 88.4 % and specificity of 81.1 % [162]. "Control points" have also been proposed as regions of the body which should not be tender in fibromyalgia, though tenderness in fibromyalgia extends throughout the body, and tenderness that also involves these control points does not argue

against the diagnosis [161]. The ACR criteria do not take into account the other common associated symptoms (fatigue, sleep disturbances, etc.). More recent diagnostic criteria for fibromyalgia were developed based on a widespread pain index and symptom severity scales of various somatic symptoms, fatigue, waking unrefreshed, and cognitive symptoms [163]. These new criteria provide a method for quantifying fibromyalgia severity and an alternative method to diagnosis, without using the tender points criteria.

Sleep disturbances are common in fibromyalgia; approximately 76 % of patients with fibromyalgia awaken feeling tired or not refreshed [162]. Abnormal sleep architecture has been described in fibromyalgia patients, with a high prevalence of paradoxical alpha wave activity in deeper stages of sleep [164].

The underlying etiology of fibromyalgia remains uncertain, though a variety of factors appear to contribute. A familial component is suggested by the eight-fold increase in risk of fibromyalgia occurring in first-degree relatives of affected individuals [161]. Additionally, polymorphisms in monoamine transport or metabolism have been associated with an increase in risk of developing fibromyalgia [161]. Environmental and biological factors have also been implicated as triggers of fibromyalgia, including physical trauma (especially to the neck and trunk), infections (such as Lyme disease and Epstein-Barr virus), and psychosocial stressors. Disturbances in the autonomic system and hypothalamic-pituitary-adrenal axis (HPA) have been described in patients with fibromyalgia, though the precise nature of the disturbances and their role in pathogenesis of the condition is unclear [161]. The diffuse noxious inhibitory control (DNIC) response, which is characterized by whole-body analgesia occurring after a sustained painful stimulus, is reduced in patients with fibromyalgia. This may occur as a result of dysfunction of the descending opioidergic and serotonergic-noradrenergic pathways, from binding of opioid receptors by endogenous ligands [161]. Central sensitization and "wind-up" have also been implicated in fibromyalgia [161]. This has been validated by some functional imaging studies, supporting the concept of amplification of the normal pain response in patients with fibromyalgia [165], as well as cerebrospinal fluid measurement of certain neurotransmitters involved in nociception, such as substance P and glutamate [166, 167].

While the underlying factors resulting in fibromyalgia remain elusive, a mechanistic approach to management of pain due to fibromyalgia is useful. Treatment of non-pain fibromyalgia manifestations, including fatigue, sleep disturbances, psychiatric comorbidities, and gastrointestinal manifestations, is important. Pharmacologic options for treatment of pain include various agents, proven effective in controlled clinical trials. First-line therapeutic agents include gabapentinoids, tricyclic antidepressants (TCAs), and selective serotonin-norepinephrine reuptake inhibitors (SNRIs). The impact of TCAs and SNRIs on descending inhibitory pain pathways described in neuropathic pain likely accounts for their benefits in fibromyalgia. Several randomized controlled trials have supported the benefits of TCAs in fibromyalgia, improving pain, sleep, and fatigue [161]. Two of the only three medications approved by the US Food and Drug Administration (FDA) for the treatment of fibromyalgia, duloxetine and milnacipran, are SNRIs. Large multicenter trials have shown each to be beneficial for multiple outcome measures, independent of their impact on mood [168]. Pooled analyses of multiple randomized controlled trials of duloxetine for treatment of fibromyalgia revealed that 69 % of improvement in pain was a direct consequence of medication treatment, whereas 31 % of the pain improvement occurred as a result of improvement in mood [169]. The benefits of milnacipran in fibromyalgia were demonstrated in two randomized, double-blind, placebo-controlled trials [170]. Evidence supporting the use of selective serotonin reuptake inhibitors (SSRIs) has been less consistent [168]. Pregabalin is also FDA-approved for fibromyalgia and (as described above) shares a similar mechanism of action with gabapentin by binding the alpha 2 delta subunit of voltage-gated calcium channels. A large multicenter trial of pregabalin at a dose of 450 mg/d showed benefits in pain, fatigue, sleep, and quality of life [171].

Non-pharmacologic therapy, including patient education, graded exercise, and cognitive behavioral treatments, are extremely important and should be incorporated in the care of patients with fibromyalgia [168].

Polymyalgia Rheumatica

Many of the environmental and biological factors implicated as potential triggers of fibromyalgia listed above (infections, HPA axis dysfunction) are also common considerations in the differential diagnosis of fibromyalgia. Other conditions to consider as causes for widespread muscle pain include polymyalgia rheumatica (PMR), rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, and myopathy. Whereas fibromyalgia represents a model of noninflammatory, non-neuropathic pain, PMR, in contrast, represents a model of inflammatory pain. Like fibromyalgia, PMR results in proximal muscle pain, though features distinguishing PMR include the presence of constitutional symptoms (fever, sweats, weight loss), abnormal acute phase reactants (elevated erythrocyte sedimentation rate and C-reactive protein), a tendency to occur after age 60, and the favorable response to corticosteroids. PMR may also be associated with temporal arteritis, manifesting with headaches, temporal tenderness, jaw claudication, and the possible dreaded complication of anterior ischemic optic neuropathy with vision loss.

The underlying cause of polymyalgia rheumatica is unknown, though a combination of infectious triggers (parvovirus B19, *Mycoplasma pneumoniae* and *Chlamydia*

pneumonia) and genetic factors (including an association with the HLA DR4 allele) is suspected to play a role in the pathogenesis [172]. PMR is exceedingly rare in individuals younger than 50. Subacute onset of bilateral shoulder pain and tenderness of the upper arms are hallmark features of PMR. Additional symptoms include morning stiffness and constitutional symptoms. Weakness is not expected in PMR, though patients may report weakness as a consequence of limitations from pain. The erythrocyte sedimentation rate and/or C-reactive protein is typically elevated, though either can rarely be normal [172]. Diagnostic guidelines proposed in 2010 include an age of onset of >50, the presence of bilateral shoulder and/or pelvic girdle pain, morning stiffness, and abnormal acute phase reactants [173]. Inflammatory, infectious, endocrine, and neoplastic causes of pain and elevated acute phase reactants should be excluded as part of the evaluation of the patient with suspected PMR. Temporal arteritis occurs in up to 30 % of patients with PMR, typically manifesting with headache, jaw claudication, or visual disturbances (classically amaurosis fugax). Temporal artery biopsy may reveal characteristic inflammatory changes, though the presence of "skip lesions" may result in a falsely normal biopsy, placing additional importance upon the clinical nature of the diagnosis.

Corticosteroids are the mainstay of therapy for PMR. Management guidelines, also proposed in 2010, suggest low-dose steroid therapy (i.e., prednisolone 15 mg daily for 3 weeks) with gradual tapering in treatment-responsive patients [173]. A steroid treatment duration of 1–2 years is anticipated in most patients. Response to therapy is determined by assessment of clinical symptoms and measurement of acute phase reactants. Higher dose and/or parenteral corticosteroids may be considered in treatment-resistant patients or for relapses. Other immunomodulatory medications are also considered in refractory patients or those intolerant to corticosteroids. Long-term corticosteroid use necessitates monitoring (and when feasible, measures to avoid) side effects including osteoporosis, hypertension, diabetes mellitus, and cataracts.

Chronic Fatigue Syndrome

While not considered a pain syndrome per se, joint pains and myalgias are common accompanying features of chronic fatigue syndrome (CFS). Additionally, some of the central mechanisms implicated in neuropathic pain may be involved in the pathophysiology of chronic fatigue syndrome. Like fibromyalgia, chronic fatigue syndrome occurs in the absence of identifiable tissue injury or lesion within the nervous system and has been the topic of great debate, often mislabeled as a psychiatric illness. Diagnostic criteria were defined by the US Centers for Disease Control and Prevention in 1994 and include the development of persisting or relapsing fatigue resulting in substantial limitations present for at least 6 months, which is not relieved by rest and is not the result of a medical condition, psychiatric condition, or alcohol or substance abuse [174]. Additional symptoms including impairments in memory or concentration, sore throat, tender lymph nodes, myalgias, arthralgias, headaches, unrefreshing sleep, and malaise after exertion are also among the features included in the diagnostic criteria [174, 175]. Subsequent revisions to these diagnostic criteria have been proposed, though the 1994 criteria remain the standard [175].

The prevalence of chronic fatigue syndrome (also referred to as myalgic encephalomyelitis) ranges between 0.23 and 0.50 %, with a female to male ratio of approximately 3:1 [175]. The etiology of CFS remains uncertain, though a variety of predisposing and precipitating factors have been suggested. Inactivity in childhood and inactivity after infectious mononucleosis have been identified as risk factors, and while no genetic abnormality has yet been identified, a familial predisposition is suggested by twin studies [175]. Physical stressors, psychological stressors, and infections (including flu-like illnesses, infectious mononucleosis, Q fever, and Lyme disease) have been implicated as potential precipitants of CFS [175]. Psychological processes (such as avoidance behaviors) and social factors (such as a lack of social support) are believed to contribute to the perpetuation of CFS [175].

A study utilizing FDG PET revealed hypometabolism in the right mediofrontal cortex and brainstem [176]. A widespread reduction in 5-HT1A receptor binding potential was shown in CFS patients using a specific radioligand and PET imaging; patients with concurrent psychiatric illness or taking any medications were excluded [177]. These findings suggest a role of serotonergic pathways in CFS, either in the underlying pathophysiology or as a biological consequence of the condition. A potential role of increased oxidative stress has been proposed by recent studies revealing an increase in ventricular lactate using MR spectroscopy in patients with CFS, though similar findings were seen in patients with major depressive disorder [178].

The mainstay of CFS treatment is non-pharmacologic. Cognitive behavioral therapy (CBT) and graded exercise therapy (GET) are the only interventions consistently found to be effective [175, 179]. Adaptive pacing therapy had previously been proposed as an effective treatment but was found to add no benefit when added to routine specialist medical care in a randomized, parallel group trial [179].

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