Emergency Management in Neurology
Series Editor: Elio Agostoni

Elio Agostoni *Editor*

Emergencies in Neuromuscular Disease

Springer

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Series Editor
Elio Agostoni
Department of Neurosciences
ASST Grande Osp Metropolitano Niguarda
Milano
Italy

This book series provides the reader with detailed information and guidance on the practical multidisciplinary management of the neurological patient in the emergency setting. A wide range of neurological emergencies are covered, and attention is also focused on management in specific patient groups. Numerous clinical cases are referred to in order to explain more clearly different aspects of practical management, and flow charts of the diagnostic and therapeutic approach are presented for all of the neurological conditions considered. The multidisciplinary nature of patient care is highlighted, with inclusion of a specific algorithm for each professional figure involved in the management.

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Editor

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Editor
Elio Agostoni
Department of Neurosciences
ASST Grande Osp Metropolitano Niguarda
Milano
Italy

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Presentation of the Series

Emergency in Neurology: A Practical Approach is a series of books which deal with the most significant chapters in the scenario of neurological emergencies, in terms of diagnosis, differential diagnosis, and therapy. One particularity of the philosophy of all the books is the close integration between the strictly clinical-scientific aspects and the organizational elements, which are so important for the efficiency and effectiveness of the treatment.

The themes of the individual volumes are as follows:

- Ischemic stroke
- Hemorrhagic stroke
- Emergencies in neuromuscular diseases
- Acute loss of consciousness
- Neurological emergency during pregnancy
- Neurological emergency in pediatrics
- Delirium, stupor, and coma
- Neurological infections
- Spinal emergencies
- Cerebral hyper-/hypotension syndrome
- Diagnostic tools in neurological emergencies
- Emergency medical network in neurological disease

All volumes are structured in the same way, each containing the following chapters:

1. The first chapter is an overview of the most recent progress in diagnosis and therapy, including the clinical, instrumental, and therapeutic aspects of the acute pathology under discussion, focusing specifically on the best clinical practices.

2. A chapter dedicated to clinical pathways and the associated organizational elements, following principles which inspired the international guidelines.
3. A review of clinical cases that are typical of the diverse clinical situations presented daily to the doctors involved in managing neurological emergencies. After the presentation of each clinical case, the reader finds a series of questions and topics regarding the case's management and some observations by the coordinator of the series.
4. A section dedicated to the differentiated algorithms used for decision-making, based on the organizational, structural, and technological features of the hospital receiving the clinical case. This final section of each book is extremely important for the day-to-day handling of neurological emergencies. This chapter aims to supply the reader with all the elements necessary to apply the guidelines and send the patient on the best clinical pathway, taking into consideration the diagnostic and therapeutic opportunities available.

The aim of this series is to provide the specialist with a useful tool for improving the outcome for patients with acute and/or time-dependent neurological pathologies, by choosing a dedicated clinical pathway according to the best practices and scenarios of the professional and organizational opportunities offered by the clinical centers.

Elio Agostoni
Department of Neurosciences
ASST Grande Ospedale
Metropolitano Niguarda
Milano, Italy

Preface

Some neuromuscular diseases involve rapid and progressive muscle weakness and represent real clinical emergencies. Being able to hypothesize the etiopathological mechanism of hyposthenia is essential from the earliest stages of access to an emergency department. In this regard the role of a neurologist in the emergency department is indispensable. A detailed analysis of all the conditions that may occur in an acute phase goes beyond the purpose of this book that is meant to be a quick reference in the daily management of neuromuscular emergencies. The book deals with the main neuromuscular diseases on the basis of anatomo-clinical localizations. We will analyze the diseases affecting the anterior horns of the spinal cord (tetanus) and those that affect the nerve roots and the nerves (GBS, multiple mononeuritis, porphyria), the neuromuscular junction (MG and botulism), and finally the muscles (rhabdomyolysis, malignant hyperthermia, periodic paralysis).

The structure of this volume is different from previous volumes of the series; the book contains three main sections: the first one (Part I) is an overview of the most recent progress in diagnosis and therapy, including the clinical, instrumental, and therapeutic aspects of the acute pathology under discussion, focusing specifically on the best clinical practices. In Part II real clinical cases are collected, and this part includes also the clinical pathways and the associate organizational elements, following principles which inspired the international guidelines. The third section (Part III) includes the algorithms for decision-making in case of myasthenia gravis, inspired not only by the clinical aspects but also by the

organizational, technological, and professional characteristics of the hospital caring for the acute patients and the various settings (A, B) in which clinicians manage patients. These algorithms are to be considered as reference material for helping physicians in selecting the most adequate pathway according to the hospital facilities available. The decisional algorithms are organized and diversified into two main situations that suggest the same number of different practical behaviors aiming at guaranteeing the best care, albeit in different organizational situations. This really brings to the fore the concept of network and of organization through the HUB and spoke model.

This book applies a dynamic methodology to deal with current diagnostic aspects and the latest directions in the guidelines. Real clinical cases are introduced which record the various stages of the problems, the diagnostic-therapeutic decisions, and the patients' clinical pathways: the decision to include these cases derived from observing the daily reality, which is then presented to the reader in a critical way through the reflections and comments of clinical experts. The importance of this book lies in its determination to put the best clinical practices into real-life contexts, without losing sight of the organizational characteristics of the hospitals receiving the patient with acute neuromuscular disease.

Milan, Italy Elio Agostoni

Contents

Abbreviations

AAEM	American Association of Electrodiagnostic Medicine
Ab	Antibodies
ACC	American College of Cardiology
AchRs	Acetylcholine receptor antibodies
ADP	Adenosine diphosphate
AHA	American Heart Association
AIDP	Acute inflammatory demyelinating polyneuropathy
δ-ALA synthetase	δ-aminolevulinic acid synthetase
AMAN	Acute motor axonal neuropathy
AMSAN	Acute motor and sensory axonal neuropathy
ANCA	Antineutrophil cytoplasm antibodies
AntiAChE	Acetylcholinesterase inhibitor
ASMAN	Axonal sensorimotor neuropathy
ATP	Adenosine triphosphate
BGA	Blood gas analysis
BS	Babinski sign
CACNA1S	Calcium voltage-gated channel subunit alpha1 S
CB	Conduction block
CBC	Cell blood count
CDC	Centers for Disease Control and Prevention
CIDP	Chronic inflammatory demyelinating polyneuropathy
CJ	*Campylobacter jejuni*
CK	Creatine kinase

cMAP	Compound Motor Action Potential
CPK	Creatine phosphokinase
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CSS	Churg-Strauss syndrome
CT	Computed Tomography
CV	Conduction Velocity
CVC	Central venous catheter
DIC	Disseminated intravascular coagulation
DL	Distal latency
DNA	Deoxyribonucleic acid
DT	Dispersion time
ECG	Electrocardiogram
EFNS/ENS	European Federation of Neurological Societies/European Neurological Society
EMG	Electromyography
EMHG	European Malignant Hyperthermia Group
ENG	Electroneurography
ER	Emergency room
ESR	Erythrocyte sedimentation rate
IV	intravenous
FVC	Forced vital capacity
GBP	Gabapentin
GBS	Guillan-Barrè syndrome
GOT	Glutamic-oxaloacetic transaminase
GVHR	Graft-versus-host reaction
HCV	Hepatitis C virus
ICU	Intensive care unit
IgG	Immunoglobulin G
MH	Malignant Hyperthermia
INF	Interferon
I-SID-GBS	International second IVIg (intravenous immunoglobulin) dose in GBS (Guillan-Barrè syndrome)
IVCT	In vivo contracture test
IVIg	Intravenous immunoglobulin

LDH	Lactate dehydrogenase
LEMS	Lambert Eaton myasthenic syndrome
LLN	Lower limit of normal
LMWH	Low molecular weight heparins
LRP4	Low-density lipoprotein receptor
LS	Lumbar sacral
MCV	Motor conduction velocity
MD	Muscular dystrophy
mEGOS	Modified Erasmus GBS (Guillan-Barrè syndrome) Outcome Scale
MFS	Miller Fisher syndrome
MG	Myasthenia gravis
MGFA	Myasthenia Gravis Foundation of America
MH	Malignant hyperthermia
MHN	Not susceptible malignant hyperthermia
MHSc	Malignant hyperthermia susceptible to caffeine
MHSh	Malignant hyperthermia susceptible to halothane
MHShc	Malignant hyperthermia susceptible to halothane and caffeine
MIP	Maximum inspiratory pressure
MIR	Masseter inhibitory reflex
MND	Motor neuron disease
MRC	Medical Research Council
MRI	Magnetic resonance
MUAP	Motor unit action potential
MuSK	Muscle-specific kinase
NAMHG	North American Malignant Hyperthermia Group
NCS	Nerve conduction studies
NGS	Next-generation sequencing
NH	Non-Hodgkin
NHLBI	National Heart, Lung, and Blood Institute
NMR	Nuclear magnetic resonance

NSAIDs	Nonsteroidal anti-inflammatory drugs
OT	Osteo-tendon
OXC	Oxcarbazepine
PCR	Polymerase chain reaction
PE	Plasma exchange
PMC	Potential motor compounds
PT	Prothrombin time
PTT	Partial thromboplastin time
QMGS	Quantitative myasthenia gravis score
RCF	Reversible conduction failure
RCT	Randomized controlled trial
RNA	Ribonucleic acid
RX	Radiation X
RYR1	Ryanodine receptor 1
SAP	Sensitive action potential
SCP	Stimolazione cutaneo plantare (Cutaneous plantar response)
SF-EMG	Single-fiber electromyography
SLE	Systemic lupus erythematosus
SR	Repetitive stimulation
TNF	Tumor necrosis factor
TR	Tendon reflexes
TRF	Treatment-related fluctuations
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
VAS	Visual Analogue Scale
VATET	Video-assisted thoracoscopic extended thymectomy
VC	Vital capacity

Contributors

Elio Agostoni Head of the Department of Neurosciences, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

Ilaria Costi Department of Neurology and Stroke Unit, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

Dante Facchetti Department of Neurology and Stroke Unit, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

Stefano Jann Department of Neurology and Stroke Unit, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

Andrea Rigamonti Department of Neurology, ASST Lecco, Lecco, Italy

Elena Pinuccia Verrengia Department of Neurology, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

Part I
Neuromuscular Disease: Recent Progress in Diagnosis and Therapy

Chapter 1
Neuromuscular Disease: An Overview

S. Jann

Although most patients with neuromuscular diseases can be treated as outpatients, some of them complain rapid and progressive muscle weakness and represent real clinical emergencies. Being able to hypothesize the etiopathological mechanism of hyposthenia is essential from the earliest stages of access to an emergency department. In this regard the role of a neurologist in the emergency department is indispensable. A detailed analysis of all the conditions that may occur in an acute phase goes beyond the purpose of this book that is meant to be a quick reference in the daily management of neuromuscular emergencies. The book deals with the main neuromuscular diseases on the basis of anatomo-clinical localizations. We will analyze the diseases affecting the anterior horns of the spinal cord (tetanus) and those that affect the nerve roots and the nerves (GBS, multiple mononeuritis, porphyria), the neuromuscular junction (MG and botulism), and finally the muscles (rhabdomyolysis, malignant hyperthermia, periodic paralysis).

S. Jann
Department of Neurology and Stroke Unit, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
e-mail: stefano.jann@ospedaleniguarda.it

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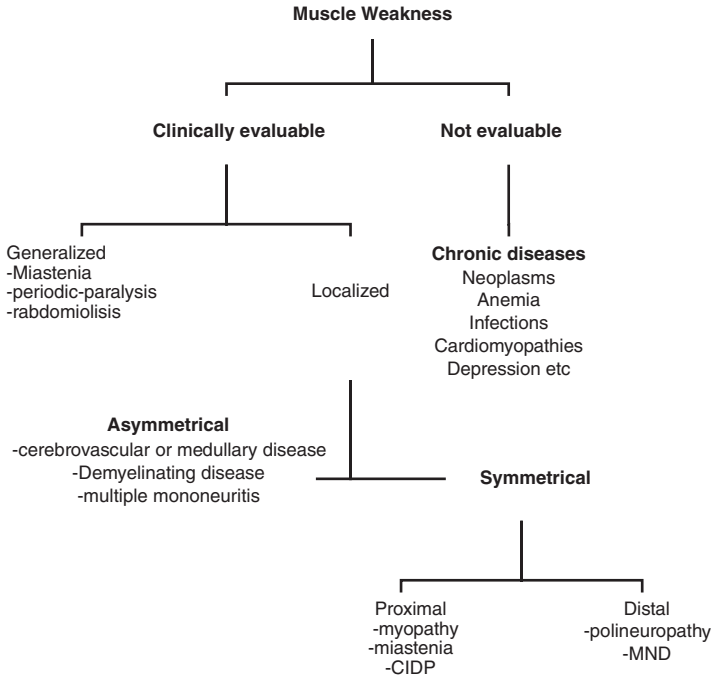

Algorithm 1 Diagnostic algorithm for patients with muscle weakness

In all cases there must be an initial approach aimed at confirming the diagnosis of muscle weakness, which will be followed by an attempt to determine the causes of muscle weakness (Algorithm 1):

- Clinical history analysis
- Clinical exams
- Laboratory exams

The elements of a clinical history that are useful for diagnosis are obviously the preexistence of a neuromuscular disease that may be exacerbated as a result of drugs or bacterial infections; the pre-existence of systemic diseases, medications, or food (botulinum toxin infection, e.g., fish infected with ciguatera, etc.); and the presence of sensory or dysautonomic symptoms.

Collecting a proper drug history is very important to exclude iatrogenic causes:

- Diuretics (hypokalemia)
- Corticosteroids, statins, colchicine, cocaine, cyclosporine, penicillamine (myotoxic effects)
- Amiodarone (demyelinating neuropathy)
- Magnesium-based preparations (hypermagnesemia)

Clinical examination should include evaluation of vital signs and presence of clinical signs of dysautonomia.

The weakness distribution/localization is very important:

- Proximal (basically myopathic) or distal and length dependent (basically neuropathic)
- Symmetrical or asymmetrical
- Involvement or lack of involvement of cranial nerves

Presence or absence of reflexes further helps to clarify the etiology of the symptoms, as well as the presence of dysautonomic sensory disorders. In extremely rapid and acute forms, the need for hospitalization in an ICU must be assessed.

The laboratory tests required in this phase include:

- Blood count (to assess the presence of significant anemia)
- Leukocyte formula (e.g., to highlight a possible eosinophilia)
- ESR and CRP
- CPK (if high it is index of myopathy)
- Indices of hepatic necrosis (transaminases)
- Renal functionality and electrolytes

An EKG should be performed to highlight possible abnormalities related to electrolyte imbalances or dysautonomia.

Our clinical reasoning must answer the following questions:

- Is there a high and imminent risk of respiratory failure?
- Is it necessary to involve the intensive care unit (Table 1.1)?
- Are motor, sensitive, and dysautonomic deficits consistent with our clinical suspicion?
- Is the patient's medical history consistent with our clinical suspicion?

Table 1.1 Factors to be considered when deciding to intubate

General
– Increasing generalized muscle weakness
– Dysphagia
– Dysphonia
– Dyspnea on exertion and at rest
Subjective
– Rapid shallow breathing
– Tachycardia
– Weak cough
– Interrupted speech (gasping for air)
– Use of accessory muscles
– Abdominal paradoxical breathing
– Orthopnea
– Weakness of trapezius and neck muscles: inability to lift head from bed
– Inability to perform single-breath count: count from 1 to 10 in single expiration (roughly equal to FVC <1.0 L)

Table 1.1 (continued)

–	Cough after swallowing
Objective	
–	Decreased level of consciousness (have a lower threshold to control the airway if patient requires transfer or movement to unmonitored areas)
–	Hypoxemia
–	Vital capacity <1 L or 20 mL/kg or 50% decrease in VC in 1 day
–	Maximum inspiratory pressure >−30 cm H_2O
–	Maximum expiratory pressure <40 cm H_2O
–	Hypercarbia (a late finding)

Chapter 2
Tetanus

S. Jann, D. Facchetti, and I. Costi

Tetanus is a disease caused by the action of a neurotoxin produced by *Clostridium tetani* and mainly present in the soil. This neurotoxin enters the body through wounds, ulcers, and burns and its incubation period is about 1 week. The mortality rate is approximately 13% in elderly individuals.

The toxin is transported in a retrograde intra-axonal way to the anterior horn of the spinal cord or brainstem and in a transsynaptic way to inhibitory interneurons where it prevents the release of inhibitory neurotransmitters. This results in a state of motor neuron hyperexcitability with extremely painful muscle spasms and functional impotence.

Initially the patient shows contraction of the masseter (lockjaw) and the mimic muscles of the face. In severe cases it leads to an axial hypertonia that determines grotesque postures (opisthotonus) and extremely painful muscle spasms triggered by involuntary movements and emotional stimuli.

The main and potentially fatal complications are respiratory failure linked to muscle spasms, bronchopulmonary infections,

S. Jann (✉) • D. Facchetti • I. Costi
Department of Neurology and Stroke Unit, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
e-mail: stefano.jann@ospedaleniguarda.it

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rhabdomyolysis, acute renal failure, and also hyperadrenergic autonomic symptoms such as high blood pressure and tachyarrhythmias [1].

Electromyography: The rare cases of infection caused by *Clostridium tetani* in today's society accounts for the scarcity of descriptions of the neurophysiological findings. It is reported [2] a detectable alteration of inhibitory circuits such as alteration or suppression of silent time, in particular masseteric silent time (masseter inhibitory reflex, MIR).

The reflex is elicited by electrical stimulation of the II or III trigeminal branch and it is derived from the jaw muscle bilaterally. A single electrical stimulation causes two bilateral distinct inhibitory responses identified as SP1 and SP2, of which the presence and symmetry of latency are generally assessed. Both responses can be abolished or altered by tetanus [2]. An alteration of R1 responses to the blink reflex and an increased activity of EMG insertion with difficulty to decontract have also been reported [3].

The therapy is based on airway control and treatment of muscle spasms with high doses of benzodiazepines, baclofen, and dantrolene, and if necessary the patient is curarized.

Intravenous administration of penicillin and metronidazole and anti-tetanus human immunoglobulin complete the medical treatment of these patients [4]. Recovery is slow and can take many months.

References

1. Bunch TJ, Thalji MK, Pellikka PA, Aksamit TR (2002) Respiratory failure in tetanus: case report and review of a 25-year experience. Chest 122(4):1488–1492
2. Poncelet AN (2000) Blink reflexes and the silent period in tetanus. Muscle Nerve 23(9):1435–1438
3. Jain S, Ashok PP, Maheshwari MC (1982) Local tetanus: a case report with neurophysiological studies. J Neurol 228:289–293
4. Ganesh Kumar AV, Kothari VM, Krishnan A, Karnad DR (2004) Benzathine penicillin, metronidazole and benzyl penicillin in the treatment of tetanus: a randomized, controlled trial. Ann Trop Med Parasitol 98(1):59–63

Chapter 3
Guillain-Barré Syndrome

S. Jann, D. Facchetti, and I. Costi

The Guillain-Barrè Syndrome (GBS) or acute inflammatory demyelinating polyneuropathy (AIDP) is one of the most frequent emergencies in the neuromuscular field. With the almost complete disappearance of poliomyelitis, the GBS is now the most common cause of acute flaccid paralysis in healthy individuals.

It has a variable annual incidence between 1.2 and 1.9 cases per 100,000 inhabitants per year. It can occur at any age even if the incidence tends to increase with age. Both sexes are involved by the disease even if there is a slight predominance in male patients [1].

The most likely etiopathogenetic hypothesis is that of an autoimmune disease. This hypothesis is supported by an increased frequency of cases after vaccination, during immune system diseases such as Hodgkin's lymphoma, SLE, and sarcoidosis; and the preexistence of infections due to *Campylobacter jejuni* (30%), *Mycoplasma* (5%), and hepatitis E (5%) [2].

S. Jann (✉) • D. Facchetti • I. Costi
Department of Neurology and Stroke Unit, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
e-mail: stefano.jann@ospedaleniguarda.it

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Recently, in French Polynesia, 42 cases of axonal form of GBS secondary to Zika Virus have been described [3]. A CJ previous infection is present in about one third of GBS cases, but only one out of about 5000 patients with gastroenteritis will develop GBS [4]. This means that a preexistent infection is not enough to develop the disease, but there must be a special host susceptibility.

Some lipo-oligosaccharidic antigens of the CJ outer membrane are in common with the gangliosides of human nerves, and this molecular mimicry can determine a cross-reactivity with Ab against CJ that cross-react with the gangliosides of human nerve [2].

The typical clinical picture is a progressive symmetrical muscle weakness of the four limbs with potential involvement of the respiratory muscles and cranial nerves. The clinical picture can be asymmetric at onset but quickly becomes symmetrical. The disease Nadir is achieved in 10–15 days in 98% of the cases. The pain is a key symptom often present at onset, and it is usually localized in the lower back and lower limbs.

One third of patients have pain before the onset of hyposthenia (up to 1–3 weeks) and typically a pain with both nociceptive and neuropathic characteristics. In certain cases there are some dysautonomic symptoms, characterized by hypotension or the presence of dangerous cardiac arrhythmias.

This involvement of small nerve fibers is prognostically unfavorable and may contribute to the patient's death [5]. Even a paralytic ileus may complicate the course of GBS and should be carefully considered.

The term GBS applies to a group of acute polyradiculoneuritis that differ from each other either because of the clinical picture or of the different pathogenesis (demyelinating or axonal):

- AIDP (acute inflammatory demyelinating polyneuropathy)
- AMAN (acute motor axonal neuropathy)
- AMSAN (acute motor and sensory axonal neuropathy)
- MFS (Miller Fisher syndrome)

In Europe almost 90% of GBS is due to AIDP [6].

3.1 GBS variants

Fisher syndrome

- Ophthalmoplegia, ataxia, areflexia
- ±Bilateral facial nerve paresis
- Associated with anti-GQ1b Ab

Acute motor sensory axonal neuropathy (5% of GBS cases)

- Severe and diffuse axonal damage
- Abrupt and explosive onset
- Severe paralysis, minor sensory features
- Slow and poor recovery

Pandysautonomia

- Severe orthostatic hypotension, anhidrosis, dry eyes and mouth, fixed pupils, arrhythmia, bowel/bladder dysfunction
- Areflexia without somatic motor/sensory involvement

Other variants

- Initial cervico-brachial-pharyngeal muscle involvement
- Generalized ataxia without dysarthria or nystagmus
- Facial and abducens weakness, distal paresthesias, proximal leg weakness

The GBS diagnosis is mainly clinical and is based on the rapid evolution of weakness and the preexistence of an infectious disease. The early loss of deep tendon reflexes is a typical and necessary feature for the diagnosis. Over the years several diagnostic criteria have been suggested. The best known are those of Asbury and Cornblath from 1990 [7], but recently the Brighton Collaboration [8] has developed other diagnostic criteria ranging from level 1 (the highest level of diagnostic certainty) to level 4; diagnosis is possible only because there are no alternatives (Table 3.1).

Other symptoms instead make the diagnosis dubious. They are summarized in Table 3.2.

Table 3.1 Key diagnostic criteria and Brighton case definitions for Guillain-Barré syndrome

	Level of diagnostic certainty			
Diagnostic criteria	**1**	**2**	**3**	**4**
Bilateral and flaccid weakness of limbs	+	+	+	+/–
Decreased or absent deep tendon reflexes in weak limbs	+	+	+	+/–
Monophasic course and time between onset-nadir 12 h to 28 days	+	+	+	+/–
CSF cell count <50/μL	+	+ [a]	–	+/–
CSF protein concentration > normal value	+	+/–[a]	–	+/–
NCS findings consistent with one of the subtypes of GBS	+	+/–	–	+ /–
Absence of alternative diagnosis for weakness	+	+	+	+

+ present; – absent; +/– present or absent
NCS nerve conduction studies, *GBS* Guillain-Barré syndrome
[a]If CSF is not collected or results are not available, nerve electrophysiology results must be consistent with the diagnosis Guillain-Barré syndrome

Table 3.2 Features suggesting another diagnosis

Sensory level, severe bladder, or bowel dysfunction
Marked asymmetry
CSF pleocytosis
Very slow nerve conduction velocities, multiple relapses or chronic course
Persistent abdominal pain and psychiatric signs

Table 3.3 GBS-TRF patients vs. A-CIDP patients [9]

GBS-TRF patients:
More frequent cranial nerve dysfunction
More rapid onset of weakness
More severe weakness
Only one or two TRF's
First TRF sooner compared to the deterioration in A-CIDP
TRF(s) occurs <2 months from onset
A-CIDP patients:
No ventilatory support
More demyelinating features on EMG
When three or more exacerbations
When deterioration occurs >2 months from onset

Some forms of GBS show a fluctuating trend linked to the administration of therapies (treatment-related fluctuations) and are not easily distinguished from CIDP with acute onset. Table 3.3 summarizes the criteria to be applied to distinguish the two forms.

In addition to the clinical picture, there are some tests that can be of support in the diagnosis:

- CSF exam: this is especially useful to exclude infectious diseases that may initially arise diagnostic doubts. In that case there is definitely an increase in the number of CSF cells. GBS can be found in the well-known albumincytological dissociation with increased CSF protein against absent cells or less than 10/mmc. Eighty percent of the patients have less than 5 cells/mmc, and 15% have less than 50 cells/mmc.

It is important to remember that in most cases the CSF is normal in the first week. In the first 3 days, only 50% of the patients show high protein levels; this percentage reaches 88% at 10 days.

- Antiganglioside antibodies search at the time is only useful to diagnose the MFS, since nearly 90% of the patients show Ab anti GQ1b [10]. Antibodies to GM1 and GD1a have been described in axonal variants (AMAN and AMSAN) that are infrequent in Europe.
- ENG/EMG: it helps to discriminate between demyelinating and axonal forms and to assess the involvement of not yet clinically compromised limbs.

The results may be markedly different in relation to earliness or not of the examination regarding the onset of symptoms and the different variants. Early diagnosis is complicated by the fact that:

- As far as we know, there are no internationally accepted criteria for GBS electrodiagnosis [11, 12].
- Unfortunately, the various criteria proposed over the years in the literature are different in terms of sensitivity and specificity [11–13]
- Some criteria include only the presence of demyelination without distinguishing between acute and chronic forms and excluding axonal variants

– Even the most sensitive neurophysiological tests do not reach 100% and are not specific enough in the early stages.

In recent decades many different diagnostic criteria have been proposed for the different forms (acute inflammatory demyelinating neuropathy or AIDP, or acute motor axonal neuropathy AMAN, acute motor and sensory axonal neuropathy or AMSAN) (Tables 3.4, 3.5 and 3.6).

In typical AIDP forms, the early detection is the increase of the minimum F wave latency and/or a reduced persistence due to demyelination of the roots; the increase entity considered significant for demyelination varies in different case series; the same reason leads to the early disappearance of H response of the tibial nerve.

The following signs are generally detected later: increase of motor distal latencies (the significance of increase of distal latency varies in different series), temporal dispersion defined as an increase in the duration of proximal CMAP> 30% compared to distal CMAP, and nerve conduction blocks defined as an amplitude ratio of the proximal/distal CMAP less than 0.7 (or 0.5 in other series) which is considered significant if found outside the common compression sites (ulnar nerve at the elbow, peroneal nerve at the fibula capitellum).

The slowing of motor conduction velocity is not generally evident before 2–3 weeks from onset and may be of little significance in the differential diagnosis of patients with concomitant diseases (diabetes, kidney failure), which may account for a preexistent neuropathy.

In such cases, comparing the sural nerve's sensory action potential (SAP) with that of the median and ulnar nerves seems to be particularly useful.

A normal SAP of the sural nerve with altered SAP of the median and/or ulnar nerve (sural sparing) [14], suggests an inflammatory form (especially a demyelinating form, although the sural sparing finding has been described even in cases of ASMAN), rather than a chronic length-related neuropathy.

Table 3.4 Recent criteria for AIDP [12]

	Ho et al. (1995)	Hadden et al. (1998)	Dutch GBS study group (1995)	Rajabally et al. (2015)
	At least one of the following problems involving two nerves	**At least one of the following problems involving two nerves**	**At least one of the two following nerves**	**At least one of the following in two nerves**
MCV	<90% LLN (<85% if amplitude cMAP<50% LLN)	<90% LLN (<85% se cMAP amplitude<50% LLN)	<70% LLN	<70% LLN
DL	>110% ULN (>120% if cMAP amplitude <LLN)	>110% ULN (>120% if cMAP amplitude<LLN)	>150% ULN	>150% ULN
TD	"Unequivocal"*	Not taken into consideration	cMAP distal/proximal duration ratio>150% ULN or distal duration>300% ULN	Not taken into consideration

CB	Not taken into consideration	Proximal to distal ratio<0.5 with cMAP width>20% LLN	Amplitude reduction compared to ULN different in the various trunks >16% ulnar >11% median >41% peroneal	Proximal to distal ratio <0.7 in at least two nerves
F wave	>120% ULN	>120% ULN	>150% ULN	>120% ULN (>150% ULN if distal cMAP amplitude<50% LLNo Lack of response with cMAP distal amplitude >20% LLN

MCV motor conduction velocity, *DL* distal motor latency, *TD* dispersion time, *CB* conduction block, *LLN* lower limit of normal, *ULN* upper limit of normal

Table 3.5 Criteria for AMAN [13]

Ho et al. (1995) (both necessary)	Hadden et al. (1998) (both necessary)
No signs of demyelination according to criteria in table	No signs of demyelination according to criteria in Table 3.1, but for one in a nerve with cMAP amplitude<10% LLN
cMAP amplitude<80% LLN in at least two nerves	cMAP amplitude<80% LLN in two nerves

Table 3.6 Criteria for AMSAN [15]

No evidence of demyelination
Distal cMAP amplitude <80% LLN as AMAN
Sensory action potential amplitude (SAP) <50% in at least two nerves

In AMAN, in addition to the detection of CMAP of an already distally reduced amplitude, the so-called reversible conduction failure (RCF) can be detected in cases with positive antiganglioside antibodies (anti-GM1 and anti GD1 a). This RCF consists of a temporary nerve conduction block, which is not due to segmental demyelination but to a blocked conduction in the node of Ranvier. This in turn is caused by the presence of antiganglioside antibodies that resolve without evidence of temporal dispersion, which is typical of demyelination processes.

RCF can occur at a distal level with a cMAP which initially has a reduced amplitude and normal or only slightly increased latency, which recovers amplitude within a few days, unlike what occurs in axonal degeneration and subsequent regeneration. This poses a further problem in the early formulation of prognosis regarding recovery.

The absence or reduced persistence of the F waves (but not the presence with increased latency) is described and is frequent in the acute phase of AMAN, as in AIDP forms.

The study of sensory nerve conductions is not included in the criteria for AIDP and AMAN, although in AIDP (and forms of chronic immune-mediated demyelinating neuropathy, CIDP) the sural sparing finding has an important role in differential diagnosis with other types of neuropathy.

In the Miller Fisher variant, conduction velocity in the limbs may be normal or only slightly altered with possible detection of a slight reduction in cMAP amplitude; conduction blocks and temporal dispersion are rarely detected. In SAPs, reduced amplitude generally ranges from moderate to marked, with frequent sural sparing.

At the beginning, EMG with coaxial needle may show only a reduced recruitment which is proportional to the degree of muscle weakness in involved muscles; this element appears suggestive of peripheral nerve dysfunction when a reduced number of recruited motor units are observed, in association with an increase in the firing rate (high firing rate).

Albers et al. [16] have reported the frequent presence of myokymic discharges, or discharges of 3–10 potentials of high-frequency motor unit (30–60 Hz), at regular intervals of 0.5–3 s, in the acute phase of the GBS.

The onset of denervation activity in the form of fibrillation potentials and positive slow waves occurs later: it takes 2–3 weeks from the occurrence of an axonal degeneration; it is detected earlier in the muscles next to the lesion location and subsequently in more distal muscles.

In summary, strong elements of suspicion which have an impact on diagnosis in emergency, regardless of subtype which often cannot be determined in the acute phase, are:

- Increased latency, absent F waves or waves of reduced persistence where conduction velocity and motor amplitudes are preserved
- Increased distal motor latencies with preserved velocity conduction (and not a hypothermic limb)
- Conduction blocks
- Sural sparing
- Where detectable using needle examination, a reduced recruitment of motor unit action potentials, with increase of the discharge frequency, distinguishes peripheral paralysis from central paralysis (and also from antalgic or “functional”).

In spite of the improvements in the management of GBS patients, mortality and disability rates remain high. Up to 25% of severe cases may experience respiratory insufficiency which requires invasive ventilation.

Knowing the outcome of GBS cases is important in deciding the most appropriate treatment and directing more resources toward cases which have a poor long-term prognosis. In order to clarify this aspect, Dutch neurologists have validated a scale (mEGOS—modified Erasmus GBS outcome scale; Table 3.7), which can be used to predict little or no recovery at 6 months from the first week of hospitalization. The parameters taken into consideration are advanced age, previous gastroenteritis, and the presence of a low score on the MRC scale both on admission and at 1 week [17].

Table 3.7 Modified Erasmus GBS outcome scores [17]

Prognostic factors	**Score**	**Prognostic factors**	**Score**
Age at onset, years		Age at onset, years	
≤40	0	≤40	0
41–60	1	41–60	1
>60	2	>60	2
Preceding diarrhea[a]		Preceding diarrhea[a]	
Absent	0	Absent	0
Present	1	Present	1
MRC sum score (at hospital admission)		MRC sum score (at day 7 of admission)	
51–60	0	51–60	0
41–50	2	41–50	3
31–40	4	31–40	6
0–30	6	0–30	9
mEGOS	0–9	mEGOS	0–12

mEGOS modified Erasmus GBS outcome score, *MRC* Medical Research Council

[a]Diarrhea in the 4 weeks preceding the onset of weakness

The management of GBS patients requires a totally multidisciplinary approach. The presence of neurologists, physiatrists, resuscitators, nurses, and physiotherapists is required. The objective of these specialists is to reduce the disabling symptoms of the patient, improve their quality of life, and decrease the risk of complications. A nasogastric tube must be inserted to prevent inhalation in cases of dysphagia; wearing elastic stockings and administering LMWH can be helpful in preventing deep venous thrombosis; respiratory functions must be monitored closely to prevent respiratory failure.

3.2 Therapy

Several meta-analyses and the Cochrane review confirmed that plasmapheresis and IVIg are equally effective in reducing the degree of disability at 4 weeks and the need for and duration of assisted ventilation, mortality, and residual disability [18].

Plasmapheresis must be initiated between 2 and 4 weeks after the onset of symptoms, with sessions every 2/3 days for plasma exchange with a total of about five volumes of plasma.

IVIg are administered according to the usual pattern of 0.4 g/kg/day for 5 consecutive days. The convenience, availability, and minor invasiveness of IVIg have transformed it into the preferred treatment in neurology.

Clinicians must often answer the following questions:

- IVIG after plasmapheresis? There is no evidence of efficacy.
- Steroids alone or in combination with plasma exchange or IVIg? There is no evidence of efficacy.
- To treat or not to treat patients with mild symptoms and mild disability or the Miller Fisher benign variant? There are no studies on this issue and normally the decision is made case by case.
- What is the best thing to do for patients who do not respond or worsen after an initial improvement? It is not yet clear what should be done. Some data, however, are known: PE after IVIg and IVIg after PE are not more

effective than single treatments. A second IVIg cycle seems to have a positive effect, but an international study is currently in progress (I-SID-GBS).

References

1. Govoni V, Granieri E (2001) Epidemiology of the Guillain-Barre syndrome. Curr Opin Neurol 14:605–613
2. Yuki N, Hartung HP (2012) Guillain-Barré syndrome. N Engl J Med 366:2294–2304
3. Cao-Lormeau V-M, Blake A, Mons S et al (2016) Guillain-Barré syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. Lancet 387:1531–1539
4. Tam CC, Rodrigues LC, Petersen I, Islam A, Hayward A, O'Brien SJ (2006) Incidence of Guillain-Barré syndrome among patients with Campylobacter infection: a general practice research database study. J Infect Dis 194(1):95–97
5. Ruts L, van Doorn PA, Lombardi R, Haasdijk ED, Penza P, Tulen JH et al (2012) Unmyelinated and myelinated skin nerve damage in Guillain-Barré syndrome: correlation with pain and recovery. Pain 153:399–409
6. Hadden RD, Cornblath DR, Hughes RA, Zielasek J, Hartung HP, Toyka KV et al (1998) Electrophysiological classification of Guillain-Barre´ syndrome: clinical associations and outcome. Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group. Ann Neurol 44:780–788
7. Asbury AK, Cornblath DR (1990) Assessment of current diagnostic criteria for Guillain-Barré syndrome. Ann Neurol 27(suppl):S21–S24
8. Sejvar JJ, Kohl KS, Gidudu J, Amato A, Bakshi N, Baxter R et al (2011) Guillain-Barré syndrome and fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 29:599–612
9. Ruts L, Drenthen J, Jacobs BC, van Doorn PA (2010) Distinguishing acute-onset CIDP from fluctuating Guillain-Barré syndrome: a prospective study. Neurology 74:1680–1686
10. Yuki N (2009) Fisher syndrome and Bickerstaff brainstem encephalitis (Fisher-Bickerstaff syndrome). J Neuroimmunol 215:1–9
11. Fokke C, van den Berg B, Drenthen J et al (2014) Diagnosis of Guillain-Barre´ syndrome and validation of Brighton criteria. Brain 137:33–43

12. Scarpino M, Lolli F, Carrai R, Lanzo G, Spalletti M, Barilaro A, Fattapposta F, Amantini A, Grippo A (2016) Diagnostic accuracy of neurophysiological criteria for early diagnosis of AIDP: a prospective study. Clin Neurophysiol 46:35–42
13. Uncini A, Kuwabara S (2012) Electrodiagnostic criteria for Guillain-Barrè syndrome: a critical revision and the need for an update. Clin Neurophysiol 123(8):1487–1149
14. Derksen A, Ritter C, Athar P, Kieseier BC, Mancias P, Hartung HP, Sheikh KA, Lehmann HC (2014) Sural sparing pattern discriminates Guillain-Barre syndrome from its mimics. Muscle Nerve 50:780–784
15. Capasso M, Notturno F, Manzoli C, Uncini A (2011) Involvement of sensory fibers in axonal subtypes of Guillain-Barre syndrome. J Neurol Neurosurg Psychiatry 82:664–670
16. Albers JW, Donofrio PD, McGonagle TK (1985) Sequential electrodiagnostic abnormalities in acute demyelinating polyradiculoneuropathy. Muscle Nerve 8(6):528–539
17. Walgaard C, Lingsma HF, Ruts L, van Doorn PA, Steyerberg EW, Jacobs BC (2011) Early recognition of poor prognosis in Guillain-Barre syndrome. Neurology 76:968–975
18. Hughes RA, Swan AV, van Doorn PA (2012) Intravenous immunoglobulin for Guillain-Barré syndrome. Cochrane Database Syst Rev (7):CD002063

Chapter 4
Porphyria

S. Jann, D. Facchetti, and I. Costi

The porphyrias are a group of metabolic diseases caused by an enzyme defect involved in heme biosynthesis which is the main product of porphyrin metabolism.

In addition to hemoglobin and myoglobin, heme is a metalloprotein integrated in microsomal cytochrome P450 in the liver and is involved in the transport chain of mitochondria electrons. It participates in the metabolism of many substances and drugs, some of which can trigger porphyria attacks [1].

The reduction of heme concentration leads to activation of δ-aminolevulinic acid (ALA) synthetase enzyme, which increases the metabolic pathway of porphyrins. The induction of cytochrome P450 by some substances, such as barbiturates, alcohol, or the reduced supply of carbohydrates, determines a stimulation of ALA synthetase.

The accumulation of precursors of the heme metabolism, ALA and porphyrins, and the reduction of the heme synthesis itself are responsible for the porphyrias, some of which are

S. Jann (✉) • D. Facchetti • I. Costi
Department of Neurology and Stroke Unit, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
e-mail: stefano.jann@ospedaleniguarda.it

E. Agostoni (ed.), *Emergencies in Neuromuscular Disease*, Emergency Management in Neurology,
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characterized by neuropathies.Acute neuropathy during a porphyria attack is usually secondary to delays in diagnosis and therefore in the treatment of acute attacks. Neuropathy usually occurs after several attacks which are characterized by unexplained abdominal pain, nausea and vomiting, emission of dark urine, possible episodes of psychomotor agitation, possible seizures, and frequent bullous skin lesions.

This neuropathy is predominantly motor and mostly axonal, with rapid onset. It predominantly affects the proximal limb muscles and can worsens up to a complete tetraplegia with dysphagia and respiratory failure.

It is associated with autonomic neuropathy, which is responsible for abdominal pain, constipation, and pseudo-obstruction as well as tachycardia and orthostatic hypotension. There are seldom sphincter disorders. The mechanism of the neuropathy is not known but appears to be associated with a neurotoxicity of accumulated precursors or with a disorder of the fast axonal transport which is heavily energy dependent [2].

There are three forms of porphyria of neurological interest: they can be differentiated by the different enzyme deficiency involved and are transmitted through an autosomal dominant disorder. They are acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria. These are called acute porphyrias and are characterized by acute attacks with the characteristics mentioned above, alternated by periods of quiescence.

The attacks are usually triggered by drugs (mainly cytochrome P450 inductors), alcohol, and fasting. Attack prevention is therefore linked to the removal of these risk factors, but acute attack management involves the administration of glucose and intravenous hematine.

The diagnosis involves dosage of urinary porphobilinogen.

The characteristics of the electrodiagnostic study are those of an axonopathy, reduced amplitude of motor potential compounds (AMPC), motor conduction velocity preserved or slightly reduced (CV), and normal distal latency of CMAP [1].

Conduction blocks or time dispersion is usually absent. If present, F waves and H reflex have normal latencies [2]. The sensory action potentials (SAP) and sensitive CV can be preserved even in nerves with marked motor involvement.

Electromyographic examination with needle concentric electrode (EMG) in the initial stages shows only a reduction in the recruitment of motor units, which are activated at high frequency. This reduction is proportional to loss of strength.

The signs of active denervation characterized by abundant fibrillation activities appear after approximately 3 weeks. They start from the proximal muscles and often display a patchy distribution of affected and spared muscles. In the recovery phase short, polyphasic, low-amplitude rising potentials may be recorded.

In the acute phase, potentials in the proximal muscles are reported as having reduced amplitude and duration and as being quickly recruited. These features, together with the presence of fibrillation and positive slow waves, may be confused with a myopathic picture (1). Electromyographic studies after clinical recovery may show findings of a residual chronic subclinical neuropathy.

Acute neuropathy during a porphyria attack needs the same attention and multidisciplinary management that is used for other acute neuropathies, such as GBS. It is not rare to find that some patients who have been diagnosed with Guillain-Barre syndrome actually suffer from porphyria neuropathy. Where necessary, admission to an ICU is required.

The neuropathy should be treated with i.v. heme arginate as soon as possible because although this does not improve the previous nerve damage, it prevents further damage. A daily infusion of 3 mg/kg is initially required and must therefore be reduced in both dose and frequency in accordance with clinical improvement.

References

1. Albers JW, Fink JK (2004) Porphyric neuropathy. Muscle Nerve 30:410–422
2. Lin CSY, Krishnan AV, Lee MJ, Zagami AS, You HL, Yang CC et al (2008) Nerve function and dysfunction in acute intermittent porphyria. Brain 131:2510–2519

Chapter 5
Vasculitis

S. Jann, D. Facchetti, and I. Costi

The neuropathies associated with vasculitis occur more often as multiple asymmetric mononeuropathies of the four limbs, less frequently as asymmetric axonal polyneuropathies and even more rarely take on the characteristics of axonal, symmetrical, distal, length-dependent polyneuropathy [1].

The symptoms usually evolve gradually, but sometimes the onset is very rapid and the patient quickly deteriorates to tetraplegia, sometimes associated with respiratory failure.

The prevalence of neuropathy in positive ANCA vasculitis is 8% at onset, substantially identical both in microscopic polyangiitis and granulamatosis with polyangiitis (Wegener's syndrome). The cumulative prevalence at a 5-year follow-up is 15% [4].

In polyangitis granulomatosis with eosinophilia, or Churg-Strauss syndrome, the incidence of neuropathy is higher and reaches 55–75% of cases [5]. Peripheral neuropathy is one of the most frequent and most severely disabling complications of Churg-Strauss syndrome (CSS).

S. Jann (✉) • D. Facchetti • I. Costi
Department of Neurology and Stroke Unit, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
e-mail: stefano.jann@ospedaleniguarda.it

E. Agostoni (ed.), *Emergencies in Neuromuscular Disease*, Emergency Management in Neurology,
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The pathological mechanism is a granulomatous vasculitis resulting in a focal ischemic necrosis which is multiple and asymmetric in the nerves involved, and results in axonal damage. In addition to ischemic damage, the effect of neurotoxic substances released by eosinophils has been observed. Fragmented areas of demyelination may be associated. On the whole, the incidence of neuropathy in these three forms of systemic vasculitis is 47% [6].

Polyarteritis nodosa and mixed cryoglobulinemia may also involve the peripheral nervous system with an inflammatory-ischemic mechanism in 25–75% of cases, consisting mainly of multiple mononeuropathy and less frequently symmetric axonal polyneuropathy [7].

Vasculitic neuropathies which complicate diseases of the connective tissues, such as rheumatoid arthritis, lupus erythematosus and Sjogren's syndrome, are rare and mostly represented by symmetric axonal polyneuropathy [7]. The multineuropathy of the cranial nerve in Sjogren's syndrome must be remembered, as well as the sarcoidosis and sensory neuronopathy (ganglionopathy) in Sjogren's syndrome [7].

Finally, there may be non-systemic vasculitic neuropathies (that is to say vasculitis which are limited to the peripheral nervous system) [7], with the same clinical and electrophysiological characteristics which can reach 30% of cases, depending on the different series.

Unlike distal symmetric neuropathies and chronic acute inflammatory demyelinating neuropathies, there are no established diagnostic criteria for multiple mononeuropathies, even if an extensive examination of the nerves of the four limbs is usually required and the involvement of at least two nerves in both sensory and motor components must be demonstrated.

The purpose of the electrodiagnostic examination is to demonstrate the involvement of the peripheral nervous system, describe the distribution, confirm the nature of axonal injury and show a possible subclinical involvement in some apparently spared regions. The neurophysiological examination is moreover useful as a guide for a possible biopsy.

The neurophysiolgical follow-up then allows the initial diagnosis to be confirmed, the first hypothesis can be redirected and the evolution and response to treatment followed. The electrodiagnostic study must follow strict guidelines such as those defined in the American Academy of Electrodiagnostic Medicine [2], and meet the diagnostic criteria for diagnosis of polyneuropathy, as regards also the electromyographic assessment [3].

Neuropathies during vasculitis usually lead to the involvement of both motor and sensitive axons, which initially cause a focal axonal damage that is then followed by Wallerian degeneration. This damage results in sensory and motor disorders distributed in the territory of one or more nerves, which are clinically displayed as paresthesia, anesthesia, muscle weakness, areflexia in different regions, and followed by muscle atrophy of denervated muscles.

The neurophysiological study in multineuropathies involves an extensive evaluation of sensory and motor conduction in various nerves of the upper and lower limbs and should cover at least the peroneal, tibial, sural nerves bilaterally as well as the median and ulnar nerves on both sides, including stimulation to axilla and to Erb's point in the search for proximal lesions. Radial, axillary and musculocutaneous nerves might be studied later for clinical interest.

More frequently (59%) the findings show a multiple mononeuropathy with cMAP and SAP reduction or disappearance, which is associated with preserved or slightly reduced motor and sensory CV and absence of significant temporal dispersion. F waves are absent or reduced in amplitude and, if present, with normal latency. cMap and SAP distal latencies are normal.

The distribution of these findings is typically asymmetrical; it affects some regions of the upper or lower limbs, even proximal, and spares others completely.

Less frequent (41%) are the ubiquitous findings of reduced cMAP and SAP, asymmetrical or symmetrical, with a predominance of the lower limbs and a distal-proximal gradient as observed in length-dependent distal axonal neuropathy [6].

In Churg-Strauss syndrome there is a more marked prevalence of multineuropathy, which is found in 68% of cases compared to the symmetric polyneuropathy that accounts for 24%, and a minority of other neuropathies such as mononeuropathy or neuropathy of the cranial nerves [8].

A distinctive feature of neuropathies during vasculitis are the pseudo conduction blocks, due to ischemic lesions caused by vasa nervorum, which may constitute a confounding factor with inflammatory demyelinating polyneuropathy.

A pseudo conduction block is a reduction in the amplitude of the cMAP resulting from an electroneurographical study of motor conductions following a proximal stimulus, with amplitude of CMAP preserved upon distal stimulus. The difference in amplitude disappears in the following days or weeks when the distal cMAP is also reduced.

Although pseudo conduction blocks initially correspond to the more restrictive criteria of the electrophysiological definition of conduction blocks, they are not [9] caused by focal demyelination but by axonal damage. Pseudo conduction blocks may be confused with conduction blocks, but an examination performed in the next days (5–7 days) shows that the reduction of the cMAP amplitude extends along the whole nerve distally to the lesion [10].

This phenomenon is due to Wallerian degeneration resulting from focal axonal damage. It is neither usually associated with the slowing of motor CV caused by injuries, nor with cMAP temporal dispersion.

It is therefore necessary to carry out serial electroneurographic examinations that can demonstrate Wallerian degeneration, which is the expression of ischemic axonal damage, in the days following the onset of neuropathy, in order to evaluate the differential diagnosis with conduction blocks that characterize acquired demyelinating neuropathies.

There have however been reports of electrophysiological findings of true conduction blocks, and pathological findings of focal demyelination during nerve ischemia, both in animal models and in human beings, and they have been attributed

to *segmental demyelination* or a block of rapidly reversible metabolic conduction [1, 10].

Early electromyographic examination of the involved muscles does not show any fibrillation or positive slow waves, which appear after 15–20 days, initially in the proximal muscles and then in the distal ones, as a characteristic of axonal injury.

The EMG findings in the acute phase are limited to a reduction of the recruitment of motor units with a high-frequency pattern, as can be observed in lesions of the peripheral nervous system.

Signs of chronic neurogenic damage with increased MUAP amplitude and duration, polyphasic morphology and reduced recruitment, appear only later. In the initial phase of reinnervation, which proceeds in the proximal-distal direction as it is linked to an axonal regeneration, MUAP are characterized by reduced amplitude and duration and marked polyphasia. They can be confused with potentials caused by myopathic damage, if not for the reduced recruitment.

Among the complications of diabetes, usually type II, there is acute onset of lumbar radiculo-plexopathy which is sometimes bilateral and which may extend distally and be extremely painful. The marked proximal weakness may be severely disabling.

The cause is a vasculitis of roots and nerve trunks of the lumbar plexus, resulting in axonal damage and Wallerian degeneration that lead to muscle atrophy, which is sometimes permanent and disabling [7].

The electromyographic findings in the acute phase are pseudo conduction blocks and the disappearance of the F responses in the nerves of the leg, followed by an axonopathy of the major nerves of the lumbosacral plexus. The motor nerve conduction of the femoral nerve need to be studied for groin stimulation and derivation from the quadriceps.

The study of sensory antidromic conduction of the saphenous nerve to the medial surface of the leg allows the differential diagnosis with an L3 radiculopathy. Electromyographic examination at 15–21 days will confirm and quantify the extent of axonal damage.

In all cases of vasculitis of the peripheral nervous system, both primitive and associated with other diseases, a nerve biopsy can be useful. In this case it may be useful to take either the sural nerve at the lateral malleolus or the superficial peroneal nerve in the middle of the tibial region.

There are neither guidelines nor RCT, but only treatment recommendations with regard to the therapy.

The most useful drug is steroid, either administered orally (prednisone 1 mg/kg) or intravenously (methylprednisolone 1 g/day for 5 days). The steroid treatment should be continued for several months and should usually be associated with immunosuppressive drugs from the very beginning.

Cyclophosphamide (1000 mg/m^2 i.v. monthly for at least 6 months), azathioprine (1.5–2 mg/kg orally daily), methotrexate (10 mg sc per week) are the most widespread. Worth mentioning are the excellent results achieved with rituximab (anti-CD20) in cryoglobulinemia, either alone or combined with antiviral treatment for HCV.

References

1. Sandbrink F, Klion AD, Floeter MK (2001) "Pseudo-conduction block" in a a patient with vasculitic neuropathy. Electromyogr Clin Neurophysiol 41:195–202
2. England JD, Gronseth GS, Franklin G, Miller RD et al (2005) Distal symmetric polyneuropathy: a definition for clinical research. Report of the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Muscle Nerve 31:113–123
3. American Association of Electrodiagnostic Medicine (1999) Guidelines in electrodiagnostic medicine. Muscle Nerve 22(suppl 8):S3–S300
4. Suppiah R, Hadden RDM, Batra R, Arden NK, Collins MP, Guillevin L et al (2011) Rheumatology 50:2214–2222
5. Wolf J, Berger R, Mutallib S, Buggle F, Grau AJ (2010) Neurologic complications of Churg-Strauss syndrome: a prospective multicentric study. Eur J Neurol 17:582–588

6. Cattaneo L, Chierici E, Pavone L, Grasselli C, Manganelli P, Buzio C, Pavesi G (2007) Peripheral neuropathy in Wegener's granulomatosis, Churgh-Strauss syndrome and microscopic polyangiitis. J Neurol Neurosurg Psychiatry 78:1119–1123
7. Gorson KC (2007) Vasculitic neuropathies. An Update. Neurologist 13:12–19
8. Nagashima T, Cao B, Tacheuchi N, Chuma T, Mano Y, Fujimoto M et al (2002) Clinicopathological studies of peripheral neuropathy in Churg-Strauss syndrome. Neuropathology 22:299–307
9. Olney RK (1999) Guidelines in electrodiagnostic medicine: consensus criteria for the diagnosis of partial conduction block. Muscle Nerve 22(suppl):S225–S229
10. McCluskey L, Feinberg D, Cantor C, Bird S (1999) "Pseudo-Conduction block" in vasculitic neuropathy. Muscle Nerve 22:1361–1366

Chapter 6
Myasthenia Gravis

A. Rigamonti

Myasthenia gravis (MG) is an acquired autoimmune disease of the neuromuscular junction characterized by fluctuating weakness and fatigability of the striated skeletal muscle [1, 2].

Myasthenia is part of the group of autoimmune channelopathies, diseases characterized by the presence of antibodies directed against the receptor structures of the neuromuscular junction. In addition to myasthenia gravis, they include Lambert-Eaton myasthenic syndrome and neuromyotonia.

Most patients present IgG1 antibodies directed against the acetylcholine receptor (AChRs) located on the postsynaptic membrane [3]. A variable portion of patients, defined as seronegative, do not have antiAchRr antibodies but have antibodies against a muscle-specific tyrosine kinase (MuSK) [4, 5]. Other antibodies directed against different antigens targets, such as LRP4 (low-density lipoprotein receptor 4) [6] and agrin [7], have been recently identified in patients who tested negative for Ab antiAchR and Ab anti-MuSK.

A. Rigamonti
Department of Neuroscience, ASST Lecco, Lecco, Italy
e-mail: andrea.rigamonti@ospedale.lecco.it

E. Agostoni (ed.), *Emergencies in Neuromuscular Disease*,
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6.1 Epidemiology

Myasthenia gravis is a rare disease. According to a review of 55 studies [8] conducted between 1950 and 2007 it has an estimated incidence of 5.3 cases per million person-years and a prevalence of 77.7 cases per million. The prevalence of the disease has increased since the middle of last century: this is due to an improvement in diagnostic accuracy, an aging population and increased longevity of the patients affected.

The incidence of the disease in boys and girls before puberty is similar, whereas after puberty the male:female ratio is 4:6. The disease can start at any age: the incidence in female patients peaks in the third decade and in the sixth to seventh decades in male patients [9].

6.2 Pathophysiology

Myasthenia gravis is a disease that meets the criteria of autoimmune diseases mediated by autoantibodies [1, 2], more specifically:

1. Most patients have pathogenic antibodies which react against a specific antigen;
2. There are animal models of the disease created by passive transfer of antibodies;
3. The disease responds to immunomodulatory/immunosuppressive therapies.

Eighty to 90% of patients with generalized MG have antibodies against the acetylcholine receptor (Ab antiAchR). The receptor is a protein, consisting of five different subunits, which assemble to form a ion channel [10]. The antibodies interact with different antigenic epitopes of the receptor and belong to the class of immunoglobulins IgG1. These antibodies have the ability to functionally inhibit the AchR, accelerate degradation and promote lysis by complement activation [11]. The factor which causes the immune system to loose tolerance against AchR is still unknown; however it is believed that the thymus plays an important role, given the

presence in its context of myoid cells, which expresses the receptor and can act as antigen presenting cells [12].

Ten percent of patients with generalized myasthenia gravis don't have Ab-antiAchR and are defined as seronegative. In 40–70% of seronegative Caucasian patients, antibodies against a muscle-specific tyrosine kinase receptor (MuSK) have been identified. [4, 5, 13] Similar values have been reported in the Japanese case series [14]. This tyrosine kinase is located at the neuromuscular junction and is involved in the stabilization processes of AchR at the level of post-synaptic membrane [15]. MUSK antibodies positive myasthenia gravis might recognize pathophysiological mechanisms different from Ab antiAchR positive myasthenia. The anti-MuSK antibodies belong mainly to the IgG4 subclass which does not activate complement, however IgG1 subclasses are present in low concentrations and are able to activate complement when they bind to MuSK [16].

In patients who test negative for Ab antiAchR and anti-MusK, the presence of antibodies directed against protein 4 related to lipoprotein (LRP4) has been recently reported. In larger series [17–19] antibodies against LRP4 have been reported in 2.09% of double seronegative cases.

These antibodies are IgG1, which are able to activate the complement and thus they are potentially pathogenic. However, more research is needed to confirm this hypothesis.

6.3 Clinical Features

The basic clinical features of the disease are fluctuating weakness and fatigability of the striated voluntary muscles. Two main forms can be distinguished with reference to the districts involved: ocular MG, which affects only the extra-ocular muscles, and generalized MG involving the striated skeletal muscles with possible involvement of the bulbar district [9].

Typically, muscle weakness fluctuates during the day: it tends to be worse in the afternoon or evening, increases

during physical work and is relieved by rest. In the early stages of the disease, symptoms may be absent upon awakening, whereas they tend to be constantly present with the progression of the disease, even if moderate to severe fluctuations are possible [20]. Despite the fact that myasthenia gravis can produce weakness in any muscle group, there are some manifestations that are quite characteristic [20]:

- More than 50% of patients show ocular symptoms (ptosis and diplopia): about half of these will develop generalized symptoms within 2 years;
- Approximately 15% of patients present bulbar symptoms (dysarthria, dysphagia, fatigability when chewing);
- Less than 5% of patients present isolated proximal muscle weakness.

Less commonly presenting patterns include: isolated neck weakness (dropped head); isolated weakness of the respiratory muscles; distal muscle weakness.

Ocular muscles. Weakness of the eyelid muscles can cause ptosis. Ptosis can occur bilaterally and then improve in one of the eyes causing unilateral ptosis, or it may be unilateral at the beginning and then become bilateral. Involvement of the extraocular muscles causes binocular diplopia which can be horizontal or vertical, in more severe cases it can lead to ophthalmoparesis/ophthalmoplegia. Pupils are always spared.

Bulbar muscles. The mandibular musculature is often involved causing weakness during chewing. The patient often reports that this occurs halfway through the meal. When mandibular weakness is present at rest, patients hold their fingers under the jaw to keep the mouth closed. Weakness of the oropharyngeal muscles causes dysarthria and dysphagia. The patient is affected by rhinolalia because of the weakness of palatal muscles. The symptoms worsen with prolonged speech. Dysphagia may be relevant, and there is often nasal regurgitation.

Facial muscles. Facial muscles are often involved, causing reduced expression, weak eye closure, difficulty in whistling, puffing out cheeks and a typical smile called a “snarl smile”:

the central part of the lips is lifted while the corners of the mouth can not be lifted

- Axial musculature. The flexors and extensors of the neck are commonly affected and this can lead to the head falling forwards.
- Limb muscles. Weakness predominantly affects the proximal muscles (deltoids, quadriceps and psoas) of the upper and lower limbs. In addition to the proximal muscles, the extensor muscles of the fingers and wrist are also commonly involved.

Respiratory musculature. Involvement of respiratory muscles (diaphragm, intercostal) can cause respiratory failure.

The natural history of the disease is characterized by exacerbations and remissions. The most active phase of the disease usually coincides with the first 5–7 years. Symptoms usually peak in the first 2–3 years of the disease. In a U.S. case study carried out on 1976 patients, the symptoms reached maximum severity within 2 years in 82% of the cases [21].

In an Italian retrospective study carried out on 1152 patients, the symptoms of 77% of the patients reached their nadir in the first 3 years [22]. Spontaneous remissions occur in 10–15% of cases in the first 10 years of illness. About 50% of patients presenting with ocular symptoms developed generalized symptoms within 2–3 years. There are no predictive factors; in particular the presence of Ab antiAchR, a positive response to the decremental repetitive stimulation or a positive single fiber elctromyography are not predictive of generalization.

The life expectancy of a myasthenic patient is currently comparable to the life expectancy of the general population. The mortality rate is 20–30% at 10 years in untreated cases. Most clinicians believe that the disease involves three phases, although these are modified and influenced by the current immunotherapies:

- An active phase characterized by large fluctuations and severity of symptoms, which occurs in the first 5–7 years of onset; most myasthenic crises occur in this period;

– A period of stability in which symptoms persist but are stable enough and can be worsened by intervening factors such as infections, reduction of drug dose, surgical stress;
– A third phase in which remission of the disease is possible in the course of immunotherapy or after its suspension.

In literature there are different MG classifications, more precisely Osserman and Jenkins' classification [23] and the classification of the Myasthenia Gravis Foundation of America (MGFA) [24]. The Osserman and Jenkins' classification [23] distinguishes the following forms:

- Group I: pure ocular MG
- Group IIA: mild generalized MG
- Group IIB: generalized MG with bulbar disorders
- Group III: "fulminant" MG (rapidly evolving MG reaching maximum severity within 6 months and involving respiratory muscles)
- Group IV: chronic MG (severe evolution of patients with modest disease for 2 or more years).

The Myasthenia Gravis Foundation of America (MGFA) stressed the importance of a grading system and standardized clinical evaluation, which is why in 2000 it proposed some standard recommendations in clinical research on myasthenia, recommendations drawn up by an ad hoc Task Force (Task Force of the MGFA, 2000) [24]. Here, in summary, is the classification of MG currently proposed by MGFA:

- Class I: ocular MG;
- Class II: mild generalized Myasthenia:

  IIA: with predominant involvement of the limb muscles
  IIB: with predominant involvement of the limb and prevalent involvement of bulbar-respiratory muscles

- Class III: mild generalized Myasthenia:

  IIIA: with prevalent involvement of limb muscles
  IIIB: with involvement of the limb and predominant impairment of bulbar-respiratory muscles

- Class IV: severe generalized Myasthenia:

  IVA: with predominant involvement of the limb muscles;
  IVB: with involvement of the limbs and prevalent impaired bulbar muscles.

- Class V: Defined by the need for intubation, with or without mechanical ventilation, with the exception of intubation used during the routine postoperative period; the nasogastric tube falls into the IVB category.

6.4 Diagnostic Tests

The diagnostic tests are intended to confirm the clinical diagnosis formulated on the basis of clinical history and physical examination. We distinguish:

1. Tests at the patient's bedside (ice test and tensilon test);
2. Serological tests;
3. Neurophysiological tests;
4. Radiological examinations;

1. The ice test and the Tensilon test (edrophonium chloride) can be considered as clinical examination extensions, rather than as true laboratory tests.

   (a) The ice test is used in patients with ptosis. It is based on the physiological principle that neuromuscular transmission improves by cooling the muscle. In practice, a bag containing ice is placed on the eyelids, which are kept closed for 2 min. The bag is then removed and it is immediately assessed whether there has been an improvement in the ptosis. The sensitivity of the test is about 80% in patients with severe ptosis [25, 26].
   (b) Edrophonium chloride (Tensilon), available in 10 mg vials, is an acetilcolinesterasis inhibitor that has a rapid and short duration of action (5–10 min). The test should be given to patients with evidence of ptosis or

ophthalmoparesis, in whom it is easy to observe improvement after administration of the drug. Ten milligrams of the drug are intravenously administered while the heart rhythm is checked for the possible onset of a slowdown in atrio-ventricular conduction. The drug is administered as follows: a first dose of 2 mg followed by another dose of 2 mg every 60 s up to a total dose of 10 mg. The clinical response is then assessed. This test has 80–90% sensitivity, but its specificity is rather low [3].

2. Serological test:
   (a) Antireceptor acetylcholine antibody dosage: the dosage of anti-AChR antibodies is performed in serum according to the radioimmunoassay (RIA) method using human acetylcholine receptor as antigen [27]. These antibodies are present in about 85% of patients with generalized disease [3]; furthermore almost all patients with myasthenia gravis and thymoma are seropositive for these antibodies [28]. However, they are present only in 40–55% of patients with ocular myasthenia [3]. These antibodies are highly specific for myasthenia gravis, rare cases of false positives low titer have been reported in the Lambert Eaton syndrome (5%), in motor neuron disease (3–5%) and in polymyositis (<1%)
   (b) Anti-MuSK antibodies dosage. Antibodies against specific muscle receptor tyrosine kinase (MuSK) have been reported in 38–50% of patients with generalized MG who tested negative for Ab antiAchR [4, 5, 14, 17, 29]. These antibodies are not usually present in patients who only have ocular myasthenia, although rare cases have been described [30].

Typically, patients with generalized forms positive for Ab antiAchR do not have anti-MuSK antibodies, even if one case study reported that 11% of the patients showed double positivity [14]. The analysis of available clinical case studies regarding MuSK positive patients

showed that these antibodies define a category of patients with some special features. They are usually female patients with prevalent involvement of the ocular and bulbar areas (oculo-bulbar form) and a high incidence of respiratory failure. Furthermore, there is a low incidence of thymic pathology.

It is also reported that these patients display a poor response to inhibitors of acetylcholinesterase but a good response to plasmapheresis and immunosuppressive therapies [4, 5, 14, 17, 29].

(c) Anti-titin antibodies and ryanodine antibodies: in addition to the anti-AchR antibodies, patients with MG may have antibodies directed against the striated muscle components, in particular against the titin protein and against the ryanodine receptor (component of the sarcoplasmic reticulum involved in calcium release).

The pathogenic role of these antibodies has not yet been defined. A correlation has been observed between positivity of these antibodies and the presence of thymoma. Their presence can be considered as a tumour marker. Therefore, they are useful in patients with uncertain evidence of thymic enlargement or when recurrence of a thymic tumor is suspected [31, 32].

(d) Lastly, in cases of seronegative myasthenia, specialized laboratories can search for the presence of low affinity antiAchR IgG or anti LPR4 antibodies.

3. Neurophysiological tests.

The neurophysiological tests (repetitive nerve stimulation and single fiber EMG) can show a deficit of neuromuscular transmission and thus significantly contribute to the diagnosis. In generalized myasthenia gravis, the sensitivity of repetitive nerve stimulation (RNS) and single-fiber electromyography (SF-EMG) is respectively 75% and 95% (34–35). In the ocular forms RS can be negative

in up to 50% of cases while the SF-EMG has a sensitivity of 85–95%. (34–35)

(a) Repetitive stimulation (RNS). This is the neurophysiological test which is most commonly used when myasthenia gravis is suspected. The examination is performed placing a recording electrode on the muscle and stimulating the corresponding motor nerve.

The nerve is repeatedly stimulated at low frequency (2–5 Hz) and then the corresponding compound muscle action potential (CMAP) is recorded. Myasthenia patients typically show a reduction of the CMAP amplitude between the I and IV/V response (decremental response). The test is considered positive if there is a decrease of at least 10%.

The study can be carried out on different muscles; it is generally useful to test symptomatic districts. In addition, sensitivity appears to be greater in the proximal muscles than in the distal muscles (e.g. trapezoid more sensitive than abductor V), even if stimulation is better tolerated on distal muscles.

(b) Single fiber electromyography (SF-EMG). The SF-EMG is technically more challenging than the RNS. The method allows the simultaneous recording of the action potential of two muscle fibers innervated by the same motor axon.

The time interval between the two potentials is defined as 'jitter'. In myasthenia gravis, the loss of the safety factor of neuromuscular transmission determines an increase in jitter. The increase in jitter is not specific to myasthenia gravis, because it can also be found in other conditions such as motor neuron disease, polymyositis, peripheral neuropathies, Eaton-Lambert. However, these diseases have other associated electroneurographic and electromyographic findings, such as to allow an adequate neurophysiological differential diagnosis.

To maximize SFEMG sensitivity, a facial district muscle and a limb are typically tested.

We report the recommendations regarding neurophysiological tests proposed by the AAM (American Association of Electrodiagnostic Medicine) [34] based on a review of the literature:

- The RNS must be carried out on a nerve corresponding to a symptomatic district and the resut is considered positive when a reproducible decrease of at least 10% of the amplitude of the potential between the I and IV/V response is detected in at least one district.
  Please respect the following conditions:
  - Discontinue anticholinesterase therapy at least 12 h before the test;
  - Immobilize the limb if possible;
  - Adjust stimulating rate between 2 and 5 Hz;
  - Adjust basal stimulation, post-tetanic stimulation or post-exercise at 2–5 Hz followed by stimulation at regular intervals from 30 s to 1 min, for 5 min;
  - Maintain skin temperature as close as possible to 35 °C.
- If RNS is normal, but there is a strong suspicion of MG, an examination by SF-EMG must be carried out, at least in one symptomatic region; if this is negative but there is a strong clinical suspicion, the investigation must be performed on a second region. The results are considered pathological if more than 10% of the pairs of potential have a higher jitter than normal, the average jitter exceed the standard limits or impulse blocking is present.

4. Radiological investigations. Radiological investigations refer to the radiological assessment of the mediastinum. More than 75% of generalized MG patients who test positive for Ab antiAchR show abnormalities of the thymus. In about 85% of cases thymic hyperplasia and in 15% of cases thymic tumors, mainly thymoma [35].

A chest CT scan with contrast or magnetic resonance imaging for mediastinal evaluation is part of the diagnostic workout in patients with myasthenia gravis. There are no controlled litterature study comparing the two methods, in order to determine which is the most suitable for the diagnosis of thymoma and thymic hyperplasia.

In case of doubts in radiological results antitina/ryanodine antibody testing may be usefull, as they are associated with the presence of thymoma.

5. Collateral investigations: autoimmune pathologies of the thyroid are quite frequently associated with MG (3–8% of cases), dosing TSH and antithyroid antibodies is therefore useful, regardless of the presence of symptoms attributable to thyroid dysfunction. Furthermore, it can be associated with many other autoimmune diseases, but the need for further investigation in the field of autoimmunity will be dictated by the clinical features of each patient.
Recommendations on the use of diagnostic tests:

   – Clinical data is of great importance, particularly the association between weakness, fatigability, and fluctuation of symptoms (in the absence of muscle atrophy and preserved tendon reflexes) are a crucial aspect in guiding diagnostic suspicion;
   – The dosage of specific autoantibodies has the highest sensitivity and specificity in generalized MG; their positivity can make the neurophysiological assessment unnecessary;
   – In patients showing generalized symptoms and negativity for Ab antiAchR dosage, repetitive stimulation should be performed, and antiMuSK antibodies should be dosed; in patients with seronegative ocular MG and a proceed with a SFEMG test, which has the highest sensitivity;
   – Dosage of acetylcholine antireceptor antibodies has a purely diagnostic use, and variations in antibody titer is not usefull for therapeutic approach.

6.5 Differential Diagnosis

The main differential diagnoses in Myasthenia Gravis, keeping in consideration both the purely ocular form and the generalized form, include:

Thyroid ophtalmopathy
Eaton-lambert myasthenic syndrome
Myopathies with involvement of the ocular area (oculopharyngeal dystrophy, myotonic dystrophy, mitochondrial myopathies with or without progressive ophthalmoplegia);
Acute poliradicolonevritis;
Motor neuron diseases;
Alteration of one or more cranial nerves;
Encephalic trunk diseaes;
Organophosfate poisoning, botulism;
Congenital myasthenic syndrome;
Myasthenia induced by penicillamine.

6.6 Therapy

There are several treatment stategies in the management of patients with Myasthenia Gravis. The therapeutic approach follows some basic principles, but it is largely individualized according to the clinical characteristics of the patient. Therapy is generally decided on the basis of age, severity of illness, and possible involvement of the bulbar and/or respiratory system.

Neither the autoantibody titers, nor the entity of decremental response of RNS influence the therapeutic approach, that is clinically determined.

The available therapeutic strategies are:

1. Anti-acetylcholinesterase drugs (AntiAChE);
2. Immunosuppressive therapy;

3. Immunomodulatory therapies;
4. Surgical treatment (thymectomy).

1. AntiAChE drugs play a purely symptomatic role; they inhibit the metabolism of acetylcholine thus increasing its availability at the neuromuscular junction, facilitating the link with the specific receptor, and favoring muscle contraction [36].

   There are no randomized controlled trials on the use of antiAChEs, but individual case studies and clinical experience have demonstrated a proven effectiveness. The duration of action is maximal within 2–3 h, for this reason they must be administered repeatedly during the day. AntiAChEs usually represent the first line of treatment, also because of their relative safety and ease of use.

   Pyridostigmine (Mestinon) is the usual choice; neostigmine is commercially available but it is not generally used.

   It is important to note that:

   – Most of the patients who suffer from generalized MG, at least in the initial phase, show good/excellent clinical response to AntiAChEs;
   – In purely ocular MG forms, the patients' response is often unsatisfactory or completely absent;
   – The response to AntiAChEs can vary in different muscle groups; the dosage must therefore be adjusted according to the relative importance of the most compromised and functionally relevant regions;
   – The failure to find a significant clinical effect does not justify a progressive increase of dosage, but suggest that an immunosuppressive treatment must be started.

   The dosages used range from 60 to 120 mg in four administrations per day (every 3.5–4 h). There is also a 180 mg modified-release form which can be administered before going to bed when it is necessary to reduce fatigue on awakening.

   Side effects: muscarinic (diarrhoea, upset stomach, increased bronchial secretions and saliva) occur

most frequently. Particular attention must be paid to the increase in bronchial secretions and drooling in patients who already have difficulty swallowing and wheezing. Increasing the dose in an attempt to reduce muscle deficiency is not recommended for these patients. Nicotinic-type side effects can include muscle cramps and twitching and more rarely an accentuation of muscle weakness (cholinergic crisis, difficult to observe at commonly used doses).

2. Immunosuppressive therapy.

Immunosuppressive drugs are necessary for patients who are symptomatic despite treatment with pyridostigmine, or whose symptoms return after a temporary response to pyridostigmine. The choice of immunosuppressive drug type is based on considerations that take into account the clinical picture, the speed of the drug's action, its side effects, the patient's comorbidities. Here below we report the levels of evidence and recommendation regarding each form of treatment, followed by some general considerations.

(a) Corticosteroids:

Remission or improvement of the clinical picture is reported in 70–80% of myasthenic patients treated with corticosteroids. Observational studies and clinical experience support the efficacy of glucocorticoids in the treatment of myasthenia gravis. Limited evidence from randomized, controlled trials likewise suggests that glucocorticoid treatment offers significant short-term benefit in MG compared with placebo. [36–39].

Indications:

- Patients with generalized or bulbar myasthenia;
- Patients with purely ocular disabling forms;
- Myasthenic crisis.

Prednisone (0.75–1 mg/kg daily) is administered in a single dose in the morning; this dosage is maintained

up to the maximum clinical improvement achievable (average within 2 months) [38]. In purely ocular forms, a starting dose of 25–50 mg/day is quickly effective in most cases.

Glucocorticoid tapering can be done with the final goal of achieving either a daily or alternate-day regimen. We usually reduce the dose of 10% every 6–8 weeks. The same diagram also applies to purely ocular forms. It is important to note that the start of steroid treatment in patients with generalized MG—especially in those with bulbar impairment—requires hospitalization, given the possible clinical deterioration that could significantly impair chewing and swallowing and could worsen respiratory failure; in these patients it is useful to associate treatment with plasmapheresis or immunoglobulin (see below).

Ocular MG does not require hospitalization. The most frequent side effects related to steroid therapy are cushingoid appearance, cataracts, weight gain, metasteroid diabetes, hypertension and osteoporosis. The patients rarely develop mental disorders. If the glucocorticoids cannot be tapered below a reasonably acceptable level without recurrence of symptoms, or if the patient does not respond satisfactorily, then other immunotherapeutic agents are usually needed, either to supplant the glucocorticoids or as a "glucocorticoid-sparing" agent.

Some recommendations are important for patients treated with steroids, in particular:

- Follow a diet poor in sodium and carbohydrates;
- Check bood pressure periodically;
- Check glycemic balance periodically;
- Perodically check ocular tension and transparency of the lens;
- Undergo an annual Computed Bone Mineralometry (in the spine) in order to assess bone mineralization
- Establish a preventive therapy for osteoporosis with calcium, bisphosphonates and Vitamin D.

(b) Immunosuppressive drugs:
Indications:

- Poor effectiveness of steroids, frequent clinical relapses;
- Need for a drastic reduction of the steroid dosage because of major side effects or in patients who have contraindications to high-dose steroids;

Azathioprine:

Azathioprine is the most frequently immunosuppressant used in the treatment of MG; the drug is metabolized at 6-mercaptopurine, which inhibits the synthesis of DNA and RNA and interferes with the function of T-lymphocytes. A randomized controlled trial has demonstrated the efficacy of azathioprine as a steroid-sparing agent [40] and clinical studies support its efficacy [41, 42]. It is important to highlight the slowness of the drug's action, which should be administered for at least 1 year before establishing effectivness. Therefore this drug cannot be considered useful for quickly reducing neurological deficits. Azathioprine is administered at a dosage of 2.5–3 mg/kg per day, in 2–3 doses. The treatment must be started gradually with 50 mg daily for the first week and increased to 50 mg every week until the required dose is achieved, according to the patient's weight. The drug should be administered on a full stomach to prevent gastric intolerance. It is important to check haematology and liver function every week at the beginning of treatment, then once a month when the required dose has been reached; blood tests should be performed periodically throughout the duration of the treatment in order to promptly detect the onset of toxicity.

The most frequent side effects are: gastric intolerance, myelosuppression and hepatotoxicity. There are no studies that provide clear information on duration of treatment with azathioprine after obtaining clinical remission or a satisfactory clinical improvement; discontinuation of the drug is therefore a decision to be assessed case by case, bearing

in mind that it is possible to observe reactivation of the disease after discontinuation [43].

Cyclophosphamide

Cyclophosphamide is an alkylating agent, with a strong immunosuppressive action on T and B lymphocytes. Evidence of its effectiveness derives from a controlled study of 23 myasthenic patients [44]. Cyclophosphamide is an alternative to azathioprine in the following cases: when azathioprine is ineffective after an adequate evaluation period (at least 1 year); when there is azathioprine intolerance; when it is necessary to establish an immunosuppressive treatment because of serious contraindications to the use of high-dose prednisone or the appearance of serious side effects from steroid such as to require a rapid reduction; when there is prolonged refractoriness to combined treatment (steroid+another immunosuppressive therapy).

An important limitation of the drug derives from its major side effects, especially from its effect on the reproductive system in terms of infertility.

This drug can be administered orally at a dose of 2.5–3 mg/kg/day (split into two to three doses), or alternatively it can be administered in bolus i.v. monthly, at a dose of 0.750–1 g/m^2.

Similarly to what happens with azathioprine, treatments with this drug should be delivered gradually, blood and urine tests should be carried out regularly in order to check possible occurrence of hemorrhagic cystitis: in this respect it is necessary to force diuresis by increasing the daily fluid intake and associating the administration of acetylcysteine two to three times a day in order to protect the bladder mucosa.

Side effects include alopecia, nausea and vomiting; hemorrhagic cystitis, infertility, amenorrhea. As far as haematology is concerned, the same considerations made for azathioprine are valid.

Cyclosporine

Cyclosporine is an immunosuppressant that reduces the production of IL-2, inhibits the function of T-helper lympho-

cytes and dampens T lymphocyte-dependent immune responses. A randomized controlled study on 20 MG patients showed that cyclosporine was effective in improving clinical score compared to placebo [45–46]. These conclusions were also reached by open and retrospective studies [47].

However, the incidence of significant side effects should be emphasized, in particular nephrotoxicity and blood hypertension. Cyclosporine is considered a third line drug and its administration is limited to patients who have not responded to treatment with azathioprine, mycophenolate, and cannot be treated with cyclophosphamide. The dosage is 3 mg/kg/day (minimum dose, taking into account that with higher doses of 5–6 mg/kg/day there is an increased risk of renal toxicity). There should be periodic monitoring of blood urea nitrogen, creatinine, creatinine clearance and blood pressure.

Mycophenolate Mofetil

Mycophenolate mofetil with its active metabolite (mycophenolic acid) is an inhibitor of purine nucleotide synthesis and has a selective effect on proliferating lymphocytes.

Some open label clinical studies [48, 49] and two retrospective studies [50, 51] suggest the potential efficacy and steroid-sparing effect of mycophenolate. However, these results were not confirmed by three randomized clinical trials [52–54]. Mycophenolate is indicated in patients who have not responded to treatment with azathioprine.

The recommended dosage is 2 g/day, divided into two doses. The drug is generally well tolerated and the most common adverse side effects are gastrointestinal, mostly nausea or diarrhea. It is necessary to wait at least 5 months before a clinical benefit can be observed.

Methotrexate

Methotrexate is an immunosuppressive agent that reduces the synthesis of purines and pyrimidines and interferes with DNA synthesis. A recent single-blind trial [55] proposed methotrexate as an alternative to azathioprine; further prospective studies are needed to confirm this finding.

Tacrolimus (FK506)

Tacrolimus is is an immunosuppressive macrolide molecule similar in action to cyclosporine; indeed it acts on T lymphocyte proliferation by inhibiting the activated pathway mediated by calcineurin. Tacrolimus is less neprotoxic than cyclosporine. In a number of uncontrolled studies, tacrolimus has been used successfully to treat MG at low doses (generally 3 to 8 mg/day) [56, 57]. It should be considered when there is no response to azathioprine, or as an alternative to mycophenolate or cyclophosphamide. The most common side effects include hyperglycemia, hypomagnesemia, tremors and numbness.

Rituximab

Rituximab is a monoclonal antibody against CD20 positive B cells. There is no randomized trial evidence regarding the effectiveness of rituximab in MG. However, a large and growing number of case series support its use in patients with refractory myasthenia gravis [58, 59]. Some of these studies suggest its efficacy in MuSK positive patients [60, 61].

Etanercept

Etanercept is a recombinant protein consisting of the receptor for tumour necrosis factor (TNF) joined to the Fc portion of human IgG1. This drug binds TNF and blocks its interaction with the receptor on the cell surface. Experimental models of autoimmune myasthenia have shown that blocking TNF-alpha, a proinflammatory cytokine, suppresses the disease. A pilot study lasting various months used the drug in 8 MG patients. Seven of them improved and one of them deteriorated [62]. Further studies are needed to better define the safety and potential effectiveness of the drug in MG.

3. *Immunomodulatory therapy.* The aim of immunomodulatory treatments used in MG is to obtain rapid clinical improvement, especially in patients with bulbar involvement.

These treatments include: (a) plasmapheresis, and (b) high-dose intravenous immunoglobulin.

Indications:

- Serious bulbar or generalized forms, especially in rapid clinical deterioration;
- Treatment of myasthenic crises;
- Insufficient response to ongoing immunosuppressive therapy;
- Clinical deterioration at the start of steroid therapy;
- Period of non-effectiveness of immunosuppressive therapy;
- Preparation for thymectomy (in patients with severe or generalized bulbar forms).

Therapeutic Apheresis

Plasmapheresis: The rationale of plasmapheresis lies in the rapid removal of circulating antibodies (by centrifugation or membrane filtration), with the aim of obtaining rapid clinical improvement. The clinical response occurs over a period of days and continues for 4–6 weeks. There are no adequate RCT studies on the effectiveness of plasmapheresis, but many case series have documented the short-term efficacy in MG, particularly in patients with myasthenic crisis [63, 64].

Experts believe that the proposal of controlled trials is unethical in MG and thus plasmapheresis is recommended as a short-term treatment. As shown in the Cochrane review [64], there is no uniformity in the apheretic protocols adopted in the available studies, particularly regarding the number of sessions, the characteristics of patients included in the studies, and evaluation methods. It is important to note that:

- There are no clinical parameters predictive of clinical efficacy of plasmapheresis in the individual patient;
- There is no correlation between autoantibody titer and effectiveness of plasmapheresis;

- Positivity of the acetylcholine antireceptor antibody titer is not a necessary requirement to indicate the procedure;
- Plasmapheresis should be considered, in most cases, as an "acute" treatment which is useful for temporarily resolving the neurological deficit;
- The minority of patients who do not respond to immunosuppressive therapy (assessed for an appropriate period) may benefit from apheretic treatments repeated at regular intervals. In this regard the Cochrane review points out that there are no RCT trials regarding long-term outcome of MG patients treated with plasmapheresis [64].

Assessment and preparation of patient for apheresis treatment:

1. Verification of clinical indication according to strictly neurological criteria (medium to severe myasthenic patients, especially with a deficit of bulbar muscles, respiratory failure patients, intensive care patients);
2. Internist's evaluation in order to rule out any contraindications, in particular cardiovascular diseases, coagulation deficit, ongoing anticoagulation therapy, concomitant infectious processes;
3. Evaluation of vascular access in order to predict the need for central access
4. Informing the patient about the procedure and obtaining an informed consens.

Side effects: Hypotension and/or bradycardia, bleeding complications, possible onset of general perioral numbness or cramping due to temporary hypocalcemia induced by citrate. Multiple plasmapheresis cycles can lead to inadequate peripheral venous access leading to the need for central access; chronic catheter-related complications such as infection and thrombosis may occur.

IgG selective immunoadsorption is a plasma treatment technique which can selectively remove IgG immunoglobulins (and thus autoantibodies which are relevant from a

pathogenic viewpoint). This method involves the use of a) filters containing protein A derived from staphylococcal wall or b) filters containing sheep polyclonal anti-human IgG.

High-dose intravenous immunoglobulin. Several open studies have supported the short-term effectiveness of immunoglobulin administered intravenously at high doses; the main ongoing studies are also re-evaluated in the Cochrane review on the topic [65]. Two randomized studies comparing immunoglobulin and plasmapheresis did not show a significant difference in the effectiveness of the procedures within 15 days of their administration [63, 66]. Immunoglobulins have the same rationale and indications mentioned above for therapeutic plasmapheresis. They represent a useful alternative where there are inadequate vascular accesses and where there are cardiovascular-related contraindications to plasmapheresis.

Administration schedule: 2 g/kg total dose, administered in 2–5 days. It is worth pointing out that, especially in patients with severe bulbar disorders, plasmapheresis seems to provide faster clinical improvement compared to immunoglobulins.

Side effects: immunoglobulins are generally well tolerated. Patients frequently report headaches, which tend to reduce by slowing the rate of administration. The most serious effects, though rare, include the possible occurrence of aseptic meningitis, thrombotic phenomena, anaphylaxis, blood hyperviscosity. Particular attention should be paid to the administration of high doses of immunoglobulins in patients with pre-existing cardiovascular diseases, kidney failure, paraproteinemia. As already noted for plasmapheresis, in selected patients refractory to conventional therapy, an approach with periodic administration of immunoglobulins should be offered; however, this practice has not been validated by controlled studies.

4. Surgical therapy: thymectomy

   Thymectomy aims at removing the potential source of origin and/or maintenance of the autoimmune process underlying the disease. Pending the results of the MGMTX

trial [67], there are no RCT studies that unequivocally demonstrate the effectiveness of thymectomy. This is a randomized, multicenter comparative study between thymectomy versus no surgery in severe generalized Ab antiAchR positive patients treated with steroid therapy.

The role of thymectomy and its impact on the natural history of the disease was reviewed by an ad hoc Task Force sponsored by the Myasthenia Gravis Foundation of America (MGFA) [68]. The literature taken into consideration was not homogeneous in regard to clinical evaluation methods, associated therapies and especially the definition clinical remission. This systematic analysis led to the following conclusions:

- Detection of a higher relative median remission rate for operated patients compared to non-operated patients;
- Presence of bias in all studies, with different prognostic variables regarding the basic characteristics of the patients in the study populations;
- Positive association between thymectomy and improved outcome after univariate analysis (taking into account individual variables such as gender, age and severity of disease;
- Absence of clearcut evidence of improvement after thymectomy in multivariate analysis.

Hence, the authors "are not able to determine from available studies whether the association found between thymectomy and clinical improvement is due to thymectomy or if it is simply the result of differences in the basic characteristics between operated and non-operated patients". On this basis, the authors conclude that for patients with autoimmune myasthenia without thymoma, thymectomy can be recommended as an option to increase the likelihood of improvement or remission.

Thymectomy currently has the following indications:

(a) Patients with radiologic evidence of thymic enlargement (especially in case of thymomas), regardless of age at onset of the disease;

(b) Patients suffering from generalized and/or bulbar forms, even without radiological signs of thymic enlargement with onset in middle age (<60 years) or at a young age;
(c) There is yet insufficient evidence to justify thymectomy in myasthenia patients with late onset and no signs of thymic enlargement;
(d) Data concerning thymectomy in seronegative patients with antiMuSK antibodies are still limited; usually these patients did not present thymic pathology, however some cases associated with thymic hyperplasia have been reported in literature [69].

It is important to remember that thymectomy is not an urgent therapeutic procedure and the patient should therefore undergo surgery in the best clinical conditions to avoid any possible post-surgical deterioration.

The objective of thymectomy is to ensure the greatest possible removal of thymic tissue: in addition to the thymus, the adipose mediastinal and cervical tissue must be removed as it may contain thymic tissue islands.

There are four different surgical procedures: transcervical thymectomy, transternal thymectomy, combined thymectomy (transternal + transcervical) and minimally invasive thymectomy (video-assisted or robotic-assisted).

All methods ensure the removal of the thymus; the difference lies in the amount of adipose perithymic tissue removed.

The video-thoracoscopic enlarged thymectomy (VATET) was introduced some years ago. This technique enables wide visualization and exploration of the mediastinal space and the removal, in addition to the thymus, of the adipose tissue from the pericardium to the thyroid, without sternotomy. This method is much less invasive and better tolerated by the patient than the traditional technique [70].

A minimally invasive thymectomy can be proposed as the method of choice in all patients with a radiologically normal thymus, or with an enlarged thymus due to hyperplasia; in cases of thymoma the methodology should be discussed case by case considering the size of the lesion and its radiological features [70].

6.7 Myasthenic Crisis

6.7.1 Definition

Myasthenic crisis is a life-threatening condition that involves a rapid deterioration of neuromuscular function with respiratory failure and severe impairment of bulbar innervated muscles. It is a critical condition that requires hospitalization in an intensive care unit (ICU) and may lead to intubation and mechanical ventilation.

6.7.2 Epidemiology

Approximately 10–20% of myasthenic patients experience at least one myasthenic crisis during the course of the disease [71], the annual risk of developing a crisis being approximately 2–3% [72]. In 15–20% of patients a myasthenic crisis may be the first manifestation of the disease [72]. Most myasthenic crises occur in the first years after diagnosis, when the disease is in its most active phase.

6.7.2.1 Clinical Picture

Patients who develop a myasthenic crisis generally experience an exacerbation of weakness and fatigability of bulbar and limb muscles before the crisis. In some cases however, patients may show respiratory failure which is disproportionate in comparison with bulbar/generalized symptoms and more rarely, respiratory failure may be the only clinical manifestation [73].

A myasthenic crisis can be determined by several precipitating factors including inflammatory/infectious processes, surgery, pregnancy, breastfeeding, reduction of immunosuppressive therapy. Several drugs may also interfere with neuromuscular transmission and are considered precipitating factors. Finally, in some casesa myasthenic crisis occurs spontaneously as part of the natural history of the disease.

6.7.3 *Management of Myasthenic Crisis*

The approach to myasthenic crisis involves:

- Admission to ICU;
- Evaluation of swallowing and placement of nasogastric tube;
- Evaluation of respiratory function and elective intubation if the clinical evaluation or pulmonary function tests indicate respiratory insufficiency;
- Immunomodulatory treatment (plasmapheresis or immunoglobulin) which will be associated (or
- modified if already in progress) with an immunosuppressive treatment. The severity of the clinical picture generally imposes the start of steroid treatment or its increase up to full dose as described above.
- Identification and treatment of any precipitating factors (e.g. intercurrent infectious processes, contraindicated drugs …)
- Start weaning off mechanical ventilation when lung function has improved and only after starting treatment with plasmapheresis or immunoglobulin.

Evaluation of respiratory function is based both on clinical signs/symptoms and on respiratory muscle function tests [74–76]. Clinical signs or symptoms of respiratory failure are breathlessness, hypophonia, increased respiratory rate, involvement of accessory respiratory muscles, abdominal flail chest.

Vital capacity (VC) and maximum inspiratory pressure (MIP) are the main parameters used to monitor the strength of respiratory muscles. VC reflects the mechanical function of both the inspiratory and expiratory muscles; it is assessed by asking the patient to take a big breath and then exhale forcefully into a spirometer.

On the other hand MIP provides information on the inspiratory force; it is assessed by asking the patient to inhale against a closed valve and measuring the pressure that is generated at mouth level.

Typically, intubation is recommended when VC drops below 15–20 mL/kg and MIP is less than −30 cm H_2O; in the presence of clinical signs of respiratory distress; in the case of metabolic acidosis or ineffective removal of secretions. [74–76].

In intubated patients it is preferable to suspend anticholinesterases medications in order to avoid excessive secretions. Plasmapheresis and intravenous immunoglobulins are used in the treatment of myasthenic crisis in order to achieve rapid improvement of the clinical picture: the effectiveness of these treatments is however limited in time (3–4 weeks); it is therefore necessary to add appropriate steroid treatment.

The rationale for plasmapheresis lies in the rapid removal (by centrifugation or membrane filtration) of circulating antibodies. As shown in the Cochrane review on the subject [64] there is no uniformity in apheretic protocols. One classic scheme provides five exchanges (3–5L of plasma each) in 7 or 14 days. Although done daily in some circumstances, exchanges done every other day are probably more effective in reducing the antibody levels due to the time it takes for the extravascular immunoglobulin to re-equilibrate after each plasma exchange. Intravenous immunoglobulins, like plasmapheresis, allow rapid clinical improvement. The total administered dose is 2 g/kg in 2–5 days.

There are no randomized studies that have compared plasmapheresis or intravenous immunoglobulins with placebo in the treatment of myasthenic crisis. On the contrary a randomized controlled trial [66, 77] showed a comparable efficacy for plasmapheresis and intravenous immunoglobulins in case of myastenic crisis. After 2 weeks a similar number of patients improved in both groups. Although at 2 weeks a larger number of patients in the immunoglobulin group (17.5%) had a QMGS score (quantitative myasthenia gravis score) which was worse than patients treated with plasmapheresis (2%), this difference was not significant. This data is also confirmed by a systematic review on the subject [65].

Many experts, however, prefer plasmapheresis as first line treatment, since it is more rapid in determining clinical improvement. Others, by contrast, prefer intravenous immuno-

globulins because they are easier to administer and with lower incidence of severe side effects. The decision to start weaning off mechanical ventilation should be individualized for each patient. Generally, in the myasthenic patient, some spontaneous breathing trials should be attempted:

- After the patient begins treatment with plasmapheresis/;
- When there is evidence of improvement in respiratory muscle strength (CV > 15–20 mL/kg, MIP more negative than −30 cm H_2O);
- When the secretions are manageable;
- With adequate cough.

The complications most commonly associated with myasthenic crisis are fever, infections (pneumonia, bronchitis, urinary tract infection, sepsis), deep venous thrombosis, heart failure, cardiac arrhythmias and cardiac arrest.

Improved therapies and intensive treatments have dramatically improved the prognosis of myasthenic crisis, whose mortality rate has decreased from 75% in the 1950s to 5% in the 1990s [78].

6.8 General Scheme for Treating the Myasthenic Patient

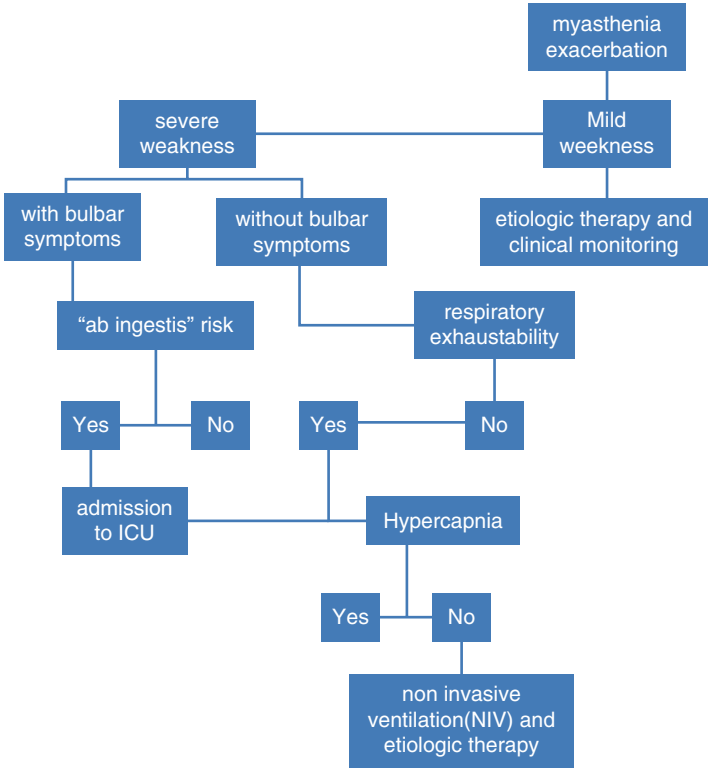
1. The initial treatment involves the use of antiAChE; in case of poor response, especially in cases with bulbar signs, it is worth starting a steroid treatment; antiAChE is very quickly effective, so if it does not have an effect, steroid/immunosuppressive therapy must be prescribed prematurely;
2. If there is a clinical relapse, if the steroid is ineffective, or if major side effects appear, consider the combined therapy of steroid + immunosuppressant (first choice: azathioprine);
3. The presence of thymoma represents an absolute indication to thymectomy; stabilize the patient with proper treatment using antiAChE and/or immunosuppressive drugs before surgery; do not perform urgent surgery.

4. Except for patients with thymoma, thymectomy is recommended for patients with disease onset in middle age or at a young age; there are no data to support the efficacy of thymectomy in patients with exclusively bulbar myasthenia; if possible, consider a minimally invasive technique;
5. Plasmapheresis and immunoglobulins represent an emergency therapeutic options for patients with serious generalized and/or bulbar forms (including patients already on assisted ventilation, for whom the time spent in intensive care can be reduced); in rare cases refractory to drug therapy, a chronic treatment with plasmapheresis, intravenous immunoglobulin or selective immunoadsorption should be used.
6. In patients with partial or total respiratory failure consider, apart from mechanical ventilation, the early use of immunomodulatory therapy (plasmapheresis and high-dose immunoglobulins) in conjunction with immunosuppressive therapy at full doses;
7. Instruct the patient to come to regular follow-up outpatient visits, especially patients receiving chronic steroid treatment, so as not to prolong every single current dose;

6.8.1 Drugs Contraindicated in Myasthenic Patients

Aminoglycoside antibiotics, antiarrhythmic drugs belonging to quinidines and beta-blockers, curare drugs and others releasing non-depolarizing substances, can directly interfere with neuromuscular transmission and thus cause deterioration of the disease.

Because of their muscle relaxant action, benzodiazepines can accentuate an existing ventilatory defect. Clinical deterioration was also reported during treatment with chloroquine and penicillamine, which can induce the synthesis of specific antibodies as well as the disease in susceptible individuals (symptomatology ceases several weeks after discontinuation of the drug). There is no contraindication to local anesthesia.



Algorithm for the early management of myasthenia gravis exacerbation.

References

1. Drachman DB (1994) Myasthenia gravis. N Engl J Med 330:1797–1810
2. Vincent A (2002) Unraveling the pathogenesis of myasthenia gravis. Nat Rev Immunol 2:797–804
3. Meriggioli MN, Sanders DB (2009) Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. Lancet Neurol 8(5):475–490

4. Hoch W, McConville J, Helms S, Newsom-Davis J, Melms A, Vincent A (2001) Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. Nat Med 7:365–368
5. McConville J, Farrugia ME, Beeson D et al (2004) Detection and characterization of musk antibodies in seronegative myasthenia gravis. Ann Neurol 55(4):580–584
6. Zhang B, Tzartos JS, Belimezi M et al (2012) Autoantibodies to lipoprotein-related protein 4 in patients with double-seronegative myasthenia gravis. Arch Neurol 69:445–451
7. Cossins J, Belaya K, Zolowska K et al (2012) The search for new antigenic targets in myasthenia gravis. Ann N Y Acad Sci 1275:123–128
8. Carr AS, Cr C, McCarron PO et al (2010) A systematic review of population based epidemiological studies in myasthenia gravis. BMC Neurol 18(10):46
9. Engel AG (1994) Acquired autoimmune myasthenia gravis. In: Engel AG, Franzini-Armstrong C (eds) Myology. McGraw-Hill, New York, pp 1769–1797
10. Karlin A, Akabas MH (1995) Toward a structural basis for the function of nicotinic acetylcholine receptors and their cousins. Neuron 15(6):1231
11. Drachman DB, Adams RN, Josifek LF, Self SG (1982) Functional activities of autoantibodies to acetylcholine receptors and the clinical severity of myasthenia gravis. N Engl J Med 307:769
12. Hohlfeld R, Wekerle H (2008) Reflections on the "intrathymic pathogenesis" of myasthenia gravis. Neuroimmunology 201–202:21–27
13. Liyanage Y, Hoch W, Beeson D, Vincent A (2002) The agrin/muscle-specific kinase pathway: new targets for autoimmune and genetic disorders at the neuromuscular junction. Muscle Nerve 25(1):4
14. Ohta K, Shigemoto K, Kubo S et al (2004) MuSK antibodies in AChR Ab-seropositive MG vs AChR Ab-seronegative MG. Neurology 62:2132
15. Ghazanfari N, Fernandez KJ, Murata Y, Morsch M, Ngo ST, Reddel SW, Noakes PG, Phillips WD (2011) Muscle specific kinase: organiser of synaptic membrane domains. Int J Biochem Cell Biol 43(3):295–298
16. Leite MI, Jacob S, Viegas S, Cossins J, Clover L, Morgan BP, Beeson D, Willcox N, Vincent A (2008) IgG1 antibodies to acetylcholine receptors in 'seronegative' myasthenia gravis. Brain 131:1940

17. Deymeer F, Gungor-Tuncer O, Yilmaz V, Parman Y, Serdaroglu P, Ozdemir C, Vincent A, Saruhan-Direskeneli G (2007) Clinical comparison of anti-MuSK- vs anti-AChR-positive and seronegative myasthenia gravis. Neurology 68(8):609
18. Higuchi O, Hamuro J, Motomura M, Yamanashi Y (2011) Autoantibodies to low-density lipoprotein receptor-related protein 4 in myasthenia gravis. Ann Neurol 69(2):418–422
19. Pevzner A, Schoser B, Peters K, Cosma NC, Karakatsani A, Schalke B, Melms A, Kröger S (2012) Anti-LRP4 autoantibodies in AChR- and MuSK-antibody-negative myasthenia gravis. J Neurol 259(3):427
20. Hoosterhuis HJGH (1997) Clinical aspects and epidemiology. In: Myasthenia gravis. Groningen Neurological Press, Groningen, pp 17–48
21. Grob D, Brunner N, Namba T, Pagala M (2008) Lifetime course of myasthenia gravis. Muscle Nerve 37(2):141
22. Mantegazza R, Beghi E, Pareyson D, Antozzi C, Peluchetti D, Sghirlanzoni A et al (1990) A multicenter follow-up study of 1152 patients with myasthenia gravis in Italy. J Neurol 237:339–344
23. Osserman KE, Jenkins G (1971) Studies in myasthenia gravis: review of a twenty-year experience in over 1200 patients. Mt Sinai J Med 38:497–537
24. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America, Jaretzki A III, Barohn RJ, Ernstoff RM, Kaminski HJ, Keesey JC, Penn AS, Sanders DB (2000) Myasthenia gravis. Recommendations for clinical research standards. Neurology 55:16–23
25. Sethi KD, Rivner MH (1987) Swift TR Ice pack test for myasthenia gravis. Neurology 37(8):1383
26. Golnik KC, Pena R, Lee AG, Eggenberger ER (1999) An ice test for the diagnosis of myasthenia gravis. Ophthalmology 106(7):1282
27. Vincent A, Newsom-Davis J (1985) Acetylcholine receptor antibody as a diagnostic test for myasthenia gravis: results in 153 validated cases and 2967 diagnostic assays. J Neurol Neurosurg Psychiatry 48:1246–1252
28. Choi Decroos E, Hobson-Webb LD, Juel VC, Massey JM, Sanders DB (2014) Do acetylcholine receptor and striated muscle antibodies predict the presence of thymoma in patients with myasthenia gravis? Muscle Nerve 49(1):30–34

29. Vincent A, McConville J, Farrugia ME, Newsom-Davis J (2004) Seronegative myasthenia gravis. Semin Neurol 24(1):125
30. Caress JB, Hunt CH, Batish SD (2005) Anti-MuSK myasthenia gravis presenting with purely ocular findings. Arch Neurol 62(6):1002
31. Baggi F, Andreetta F, Antozzi C, Simoncini O, Confalonieri P, Labeit S, Cornelio F, Mantegazza R (1998) Anti-titin and antiryanodine receptor antibodies in myasthenia gravis patients with thymoma. Ann N Y Acad Sci 841:538–541
32. Yamamoto AM, Gajdos P, Eymard B, Tranchant C, Warter JM, Gomez L et al (2001) Anti-Titin antibodies in myasthenia gravis. Right association with thymoma and heterogeneity of nonthymomatous patients. Arch Neurol 58:885–890
33. Oh SJ, Kim DE, Kuruoglu R, Bradley RJ, Dwyer D (1992) Diagnostic sensitivity of the laboratory tests in myasthenia gravis. Muscle Nerve 15(6):720
34. AAEM Quality Assurance Committee, American Association of Electrodiagnostic Medicine (2001) Literature review of the usefulness of repetitive nerve stimulation and single fiber EMG in the electrodiagnostic evaluation of patients with suspected myasthenia gravis or Lambert-Eaton myasthenic syndrome. Muscle Nerve 24(9):1239
35. Castleman B (1966) The pathology of the thymus gland in myasthenia gravis. Ann N Y Acad Sci 135(1):496
36. Rowland LP (1980) Controversies about the treatment of myasthenia gravis. J Neurol Neurosurg Psychiatry 43:644–659
37. Pascuzzi RM, Coslett HB, Johns TR (1984) Long-term corticosteroid treatment of myasthenia gravis: report of 116 patients. Ann Neurol 15:291–298
38. Sghirlanzoni A, Peluchetti D, Mantegazza R, Fiacchino F, Cornelio F (1984) Myasthenia gravis: prolonged treatment with steroids. Neurology 34:170–174
39. Schneider-Gold C, Gajdos P, Toyka KV, Hohlfeld RR (2005) Coticosteroids for myasthenia gravis. Cochrane Database Syst Rev (2):CD002828
40. Palace J, Newsom-Davis J, Lecky B, The Myasthenia Gravis Study Group (1998) A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. Neurology 50:1778–1783
41. Witte AS, Cornblath DR, Parry GJ, Lisak RP, Schatz NJ (1984) Azathioprine in the treatment of myasthenia gravis. Ann Neurol 15:602–605

42. Mantegazza R, Antozzi C, Peluchetti D, Sghirlanzoni A, Cornelio F (1988) Azathioprine as a single drug or in combination with steroids in the treatment of myasthenia gravis. J Neurol 235:449–453
43. Hohlfeld R, Toyka K, Besinger UA, Gerhold B, Heininger K (1985) Myasthenia gravis: reactivation of clinical disease and of autoimmune factors after discontinuation of long term azathioprine. Ann Neurol 17:238–242
44. De Feo LG, Schottlender J, Martelli NA, Molfino NA (2002) Use of intravenous pulsed cyclophosphamide in severe, generalized myasthenia gravis. Muscle Nerve (1):31–36
45. Tindall RS, Rollins JA, Phillips JT, Greenlee RG, Wells L, Belendiuk G (1987) Preliminary results of a double-blind, randomized, placebo-controlled trial of cyclosporine in myasthenia gravis. N Engl J Med 316:719–724
46. Tindall RSA, Phillips JT, Rollins JA, Wells L, Hall K (1993) A clinical therapeutic trial of cyclosporine in myasthenia gravis. Ann N Y Acad Sci 681:539–551
47. Ciafaloni E, Nikhar NK, Massey JM, Sanders DB (2000) Retrospective analysis of the use of cyclosporine in myasthenia gravis. Neurology 55:448–450
48. Ciafaloni E, Massey JM, Tucker-Lipscomb B, Sanders DB (2001) Mycophenale mofetil for myasthenia gravis. Neurology 56:97–99
49. Chaudhry V, Cornblath DR, Griffin JW, O'Brien R, Drachman DB (2001) Mycophonelate mofetil: a safe and promising immunosuppressant in neuromuscular diseases. Neurology 56:94–96
50. Meriggioli MN, Ciafaloni E, Al-Hayk KA, Rowin J, Tucker-Lipscomb B, Massey JM, Sanders DB (2003) Mycophenolate mofetil for myasthenia gravis: an analysis of efficacy, safety, and tolerability. Neurology 61:1438–1440
51. Hehir MK, Burns TM, Alpers J et al (2010) Mycophenolate mofetil in AChR-antibody-positive myasthenia gravis: outcomes in 102 patients. Muscle Nerve 41:593
52. Sanders DB, Hart IK, Mantegazza R et al (2008) An international, phase III, randomized trial of mycophenolate mofetil in myasthenia gravis. Neurology 71:400
53. Muscle Study Group (2008) A trial of mycophenolate mofetil with prednisone as initial immunotherapy in myasthenia gravis. Neurology 71:394
54. Meriggioli MN, Rowin J, Richman JG, Leurgans S (2003) Mycophenolate mofetil for myasthenia gravis: a double-blind, placebo-controlled pilot study. Ann N Y Acad Sci 998:494

55. Heckmann JM, Rawoot A, Bateman K et al (2011) A single-blinded trial of methotrexate versus azathioprine as steroid-sparing agents in generalized myasthenia gravis. BMC Neurol 11:97
56. Konishi T, Yoshiyama Y, Takamori M, Yagi K, Mukai E, Saida T, Japanese FK506 MG Study Group (2003) Clinical study of FK506 in patients with myasthenia gravis. Muscle Nerve 28:570–574
57. Yoshikawa H, Mabuchi K, Yasukawa Y, Takamori M, Yamada M (2002) Low-dose tacrolimus for intractable myasthenia gravis. J Clin Neurosci 9(6):627–628
58. Lebrun C, Bourg V, Tieulie N, Thomas P (2009) Successful treatment of refractory generalized myasthenia gravis with rituximab. Eur J Neurol 16:246
59. Zebardast N, Patwa HS, Novella SP, Goldstein JM (2010) Rituximab in the management of refractory myasthenia gravis. Muscle Nerve 41:375
60. Stein B, Bird SJ (2011) Rituximab in the treatment of MuSK antibody-positive myasthenia gravis. J Clin Neuromuscul Dis 12:163
61. Díaz-Manera J, Martínez-Hernández E, Querol L et al (2012) Long-lasting treatment effect of rituximab in MuSK myasthenia. Neurology 78:189
62. Rowin J, Meriggioli MN, Tüzün E et al (2004) Etanercept treatment in corticosteroid-dependent myasthenia gravis. Neurology 63:2390
63. Gajdos P, Chevret S, Clair B, Tranchant C, Chastang C, for the Myasthenia Gravis Clinical Study Group (1997) Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. Ann Neurol 41:789–796
64. Gajdos P, Chevret S, Toyka K (2002) Plasma exchange for myasthenia gravis. Cochrane Database Syst Rev (4):CD002275
65. Gajdos P, Chevret S, Toyka K (2012) Intravenous immunoglobulins for myasthenia gravis. Cochrane Database Syst Rev (12):CD002277
66. Barth D, Nouri MN, Ng E et al (2011) Comparison of IVIg and PLEX in patients with myasthenia gravis. Neurology 76(23):2017–2023
67. Wolfe GI, Kaminski HJ, Jaretzki A et al (1998) Development of a thymectomy trial in nonthymomatous myasthenia gravis patients receiving immunosuppressive therapy. Ann N Y Acad Sci 998:473–480

68. Gronseth GS, Barohn RJ (2000) Practice parameter: thymectomy for autoimmune myasthenia gravis (an evidence based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 55:7–15
69. Lauriola L, Ranelletti F, Maggiano N, Guerriero M, Punzi C, Marsili F, Bartoccioni E, Evoli A (2005) Thymus changes in anti-MuSK-positive and -negative myasthenia gravis. Neurology 64:536–538
70. Mantegazza R, Baggi F, Bernasconi P, Antozzi C, Confalonieri P, Novellino L, Spinelli L, Ferrò MT, Beghi E, Cornelio F (2003) Video-assisted thoracoscopic extended thymectomy and extended transternal thymectomy (T-3b) in non-thymomatous myasthenia gravis patients: remission after 6 years of follow-up. J Neurol Sci 212:31–36
71. Wendell LC, Levine JM (2011) Myasthenic crisis. Neurohospitalist 1(1):16–22
72. Berrouschot J, Baumann I, Kalischewski P, Sterker M, Schneider D (1997) Therapy of myasthenic crisis. Crit Care Med 25(7):1228–1235
73. Mier A, Laroche C, Green M (1990) Unsuspected myasthenia gravis presenting as respiratory failure. Thorax 45(5):422
74. Juel VC (2004) Myasthenia gravis: management of myasthenic crisis and perioperative care. Semin Neurol 24(1):75
75. Jani-Acsadi A, Lisak RP (2007) Myasthenic crisis: guidelines for prevention and treatment. J Neurol Sci 261(1-2):127–133
76. Chaudhuri A, Behan PO (2009) Myasthenic crisis. QJM 102(2):97–107
77. Bril V, Barnett-Tapia C, Barth D et al (2012) IVIg and PLEX in the treatment of myasthenia gravis. Ann N Y Acad Sci 1275:1–6
78. Alshekhlee A, Miles JD, Katirji B, Preston DC, Kaminski HJ (2009) Incidence and mortality rates of myasthenia gravis and myasthenic crisis in US hospitals. Neurology 72(18):1548

Chapter 7
Botulism

A. Rigamonti

7.1 Definition

Botulism is a potentially fatal neuroparalytic syndrome caused by the action of a neurotoxin produced by the bacterium *Clostridium botulinum*. *Clostridium botulinum* is a diverse group of anaerobic gram-positive bacteria that produces spores. The spores are resistant to approximately 100°C for 5 h. These bacteria are ubiquitous and can be easily isolated from the surface of fruit, vegetables, and fish and are present in soil and in marine sediment around the world [1].

Botulism can occur in different forms, which can be distinguished on the basis of the acquisition mode [2]:

- Food botulism: caused by the ingestion of food contaminated with botulinum toxin
- Infant botulism: caused by the ingestion of spores which then colonize the host gastrointestinal tract and release toxin produced in vivo (this can occur, though more rarely, in adults)

A. Rigamonti
Department of Neuroscience, ASST Lecco, Lecco, Italy
e-mail: andrea.rigamonti@ospedale.lecco.it

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- Wound botulism: infection of a wound by the *Clostridium botulinum* with subsequent in vivo production of the neurotoxin
- Inhalation botulism: linked to inhalation of the toxin in aerosol form, as can happen in cases of bioterrorism
- Iatrogenic botulism: linked to the use of the botulinum toxin for cosmetic purposes

7.2 Pathogenesis

There are eight different types of toxins produced by *C. botulinum*, indicated by the letters A to H. Of these eight types A, B, E, and rarely F, G, and H cause disease in humans. The toxin is composed of a light chain and a heavy chain. Regardless of the route of entry into the body, the toxins spread through the bloodstream and reach the peripheral cholinergic synapses both at the neuromuscular junction and the ganglia level of the autonomic nervous system, where they bind to a specific receptor (synaptotagmin II) localized at the level of presynaptic membrane [3, 4].

The heavy chain binds to the receptor, allowing the light chain to be translocated within the nerve cell by means of an endocytosis mechanism [5]. Once entered into the cell cytoplasm, the toxin inhibits the normal acetylcholine release mechanism at the presynaptic terminal. Restoration of the normal transmission mechanism requires the appearance of new axon terminals and the formation of a new synapse, a process that occurs over approximately 6 months.

Botulinum toxin is the most powerful bacterial toxin and one of the most powerful existing poisons. It is estimated that 1 g of botulinum toxin in aerosol form can kill 1.5 million people.

7.3 Epidemiology

In the United States, an average of 110 cases of botulism is reported per year by the Centers for Disease Control and Prevention (CDC). Infant botulism accounts for about 72%

of the cases, food-related botulism accounts for 25%, and the remaining 3% is due to wound botulism. In cases where botulism is suspected, it is essential to collect a detailed history of the patient in order to search for possible sources of exposure, referring in particular to the preparation of food stored in the home, exposure to other possible food sources, the use of drug injecting, and the use of botulinum toxin for cosmetic purposes.

7.4 Clinical

Botulism generally has an acute onset involving bilateral impairment of the cranial nerves associated with a descending flaccid quadriplegia [6]. In food contamination the symptoms usually occur between 12 and 36 h after ingestion of the toxin. Prodromal gastrointestinal symptoms such as nausea, vomiting, abdominal pain, diarrhea, and dry mouth can be present. Cranial nerve involvement occurs early and compromises both intrinsic (mydriasis fixed) and extrinsic (paralysis of the III, IV, and VI cranial nerves) ocular mobility which results in blurred vision, ptosis, diplopia, dysphagia, and dysarthria. Facial weakness may also appear. The descending muscle weakness usually progresses to affect the trunk, the upper limbs, and finally the lower limbs up to tetraparesis/flaccid plegia. The involvement of the diaphragmatic muscles can cause respiratory failure requiring intubation. Infant botulism rarely appears with such a dramatic picture as in the adult forms and is typically characterized by hypotonia, weakness, weak cry, and constipation.

Some American CDCs suggest that the following should be considered as core elements of botulism:

- Absence of fever
- Preserved state of consciousness
- Absence of sensory deficits except for blurred vision
- Symmetrical motor deficit
- Normal heart rate or bradycardia and normal blood pressure.

Wound botulism can have different characteristics from food contamination, as there are no gastrointestinal prodromal symptoms, and it may be associated with high fever, the latter probably determined by coinfection of the wound by non-clostridial bacteria species.

7.5 Diagnostic Tests

Clinical suspicion is of fundamental importance in diagnosing botulism.

There are serological tests for detecting the toxin and analysis of vomit and feces, and the suspected food source can reveal the presence of the toxin. Often in cases of infant botulism, the search for the toxin in the serum is negative. It is therefore necessary the isolation of spores of *C. botulinum* from stool cultures or to identify toxins on stools. Nevertheless, anaerobic cultures can take up to 6 days to allow growth and identification of the microorganism, and identification of the toxin on stools may take from 1 to 4 days.

Dosage of the toxin in the serum can also be negative in the case of wound botulism: it is therefore necessary the isolation of the microorganism from wound swabs.

The neurophysiological tests are important to support the clinical suspicion and, from a pathophysiological point of view, they are the expression of a presynaptic blockade of acetylcholine release.

The sensory conduction studies are normal. The motor conduction studies show a reduced amplitude of the compound muscle action potential (CMAP) with normal distal latency and motor conduction velocity. The needle examination (EMG) in botulism is peculiar. Signs of denervation in the form of fibrillation and sharp waves are quite common; in fact, the toxin is a powerful blocker of the neuromuscular junction so that the muscle fibers are chemo-denervated. The motor unit potentials (MUAP) may be normal or small, of short duration and polyphasic such as myopathic MUAP.

Low-frequency repetitive stimulation (EMG-SR) determines a decremental response, while after brief exercise (10 s) or after high-frequency stimulation (30–50 Hz), an incremental response is observed. This relief is present in moderate forms or in the early stage of botulism; it must still be emphasized that even in these cases, the increase is never equal to that observed in the Lambert-Eaton syndrome and a less than 100%.

In cases of severe botulism, when acetylcholine release falls below the threshold, neither brief exercise nor high-frequency stimulation determines an incremental response. Therefore, the absence of an incremental response does not completely rule out the diagnosis of botulism. The single-fiber electromyography (SF-EMG) shows an increased jitter and blocking phenomena, indicative of a dysfunction of the neuromuscular junction [7].

7.6 Differential Diagnosis

The main differential diagnosis of botulism includes:

- Myasthenia gravis
- Lambert-Eaton myasthenic syndrome
- Acute inflammatory polyradiculoneuritis
- Poliomyelitis
- Brainstem stroke
- Poisoning from heavy metals
- Poisoning from tetrodotoxin or shellfish

7.7 Therapy

Patients with signs and symptoms suspicious for botulism should be hospitalized immediately and subjected to monitoring of their respiratory function in order to identify early signs of respiratory failure, which is the major cause of death in affected individuals.

Monitoring of respiratory function includes evaluation of pulse oximetry, arterial blood gas analysis, spirometry and clinical evaluation of ventilation and protection of the upper airways.

Intubation should be performed in patients with an inadequate defense of the upper airway or vital capacity of less than 30% of the appraised value. In dysphagia patients, the placement of a nasogastric tube is necessary in order to avoid the risk of aspiration; in cases of paralytic ileus, it is also necessary to start with parenteral nutrition.

From the point of view of pharmacological treatment, two botulinum antitoxin therapies are available: heptavalent antitoxin from equine serum and immunoglobulins derived from human serum [8, 9].

The first is used to treat children over 1 year of age and for adults, and the other for children under 1 year of age.

In cases of suspected botulism poisoning, the Poison Control Center must be contacted for assistance, in order to receive indications on how to treat the patient with antitoxin and how to find it.

If clinical suspicion is high, and the clinical picture is rapidly deteriorating, treatment should be started as early as possible, without waiting for the results of the diagnostic tests.

The heptavalent antitoxin contains antibodies with 7 of the 8 toxins produced by *Clostridium botulinum* (A to G) and is administered intravenously. The most common side effects include headache, fever, shivers, rash, itching, and nausea. Since the antitoxin is derived from horse serum, anaphylaxis and serum sickness can occur. Some studies have reported an incidence of 20% for serum sickness and 3% for anaphylaxis [10]. Immunoglobulins derived from human serum are administered intravenously in cases of infant botulism in children younger than 1 year.

Treatment with antibiotics is not supported by clinical trials: however, antibiotics are recommended in the case of wound botulism after administering antitoxin [11]. Penicillin G is generally used (three million units IV every 4 h for adults), which

provides adequate coverage against other clostridial species. In patients who are allergic to penicillin, an alternative is metronidazole (500 mg IV every 8 h). However, antibiotics are not recommended in cases of infant botulism or gastroenteric contamination in the adult, as the lysis of intraluminal *C. botulinum* could increase the amount of absorbed toxin.

7.8 Prevention

Since most botulism cases come from food contamination, the most critical aspect of prevention is the proper handling and preparation of food. Respecting appropriate standards for cooking times, pressure, and temperature when preparing canned and preserved foods at home will help to destroy the spores. Food contained in damaged cans (cans with cracks, holes, dents, or bulges) should not be consumed. Finally, botulinum toxin is highly heat sensitive; home-canned food must therefore be boiled for at least 10 min before eating it, in order to make it safe.

Children who are less than 1 year old should not eat honey to prevent infant botulism. The most important measure for preventing wound botulism is to properly assess and treat infected wounds.

7.9 Prognosis

Patients with botulism generally require prolonged periods of hospitalization—from 1 to 3 months. Thanks to the supportive care and early treatment of respiratory failure, mortality has been reduced and accounts for 5–8% [12]. The death rate for infant botulism, the most common form in the United States, is less than 1% [13]. In minor cases we generally see a complete recovery, while in severe cases, long-term ventilation may be needed, and dysautonomic disorders and fatigue may persist for years.

7.10 Guidelines and Management Aspects in Neuromuscular Junction Diseases

In recent years, guidelines have been drafted about ocular and generalized myasthenia gravis (myasthenia gravis during pregnancy) [14–16]. There appear to be no guidelines regarding botulism. In the following table, we have summarized the most important points of these guidelines.

Myasthenia gravis in pregnancy: guidelines of a multidisciplinary working group of the United Kingdom (UK)
Norwood et al. [14]
Key points
Importance of preconception planning
Pyridostigmine, cortisone (at lower doses), and azathioprine can be used
Mycophenolate and methotrexate are teratogenic and contraindicated in pregnancy
Monitoring of gestational diabetes in patients on steroid therapy
Aim for vaginal delivery supported by an experienced multidisciplinary team
Monitoring of the newborn baby after giving birth because of the risk of transient neonatal myasthenia
Giving birth at home is not recommended
EFNS/ENS guidelines for treating ocular myasthenia
Kerty et al. [15]
Key points
Start pyridostigmine
Add steroid if the symptoms are not controlled (necessary in most cases)

Next step azathioprine
Some reports suggest that thymectomy can reduce the risk of secondary generalization
Generalized myasthenia: Guidelines from the Association of British Neurologists
Sussman et al. [16]
Key points
First-line tests: anti-AChR antibodies, thyroid function tests, radiological study of the thymus
Second-line tests: anti-MuSK antibodies, neurophysiology, brain NMR
The guidelines provide protocols of "dosage to increase" for pyridostigmine and steroids both for ocular and generalized myasthenia, including the option of alternate-day administration
Attention is given to the prevention of osteoporosis
Azathioprine as a first-line treatment in patients who do not achieve remission with prednisolone or who require long-term therapy with doses above 15–20 mg every other day
Use of IVIg and plasmapheresis in myasthenic crisis
Thymectomy should be performed in a specialized center by an experienced surgeon
Thymectomy in MG not associated with thymoma is a "reasonable" option for patients <45 years who test positive for anti-AChR Ab

7.10.1 Criteria for Patient Management

The management needs of myasthenic patients vary according to their clinical conditions:

(a) With exclusive involvement of the ocular district, the patient can start both a diagnostic and therapeutic path.
(b) Patients suffering from mild/severe generalized weakness, especially if associated with symptoms concerning

bulbar and respiratory innervated musculature, must be hospitalized in order to quickly define the diagnosis and to start the appropriate treatment protocol.

(c) Patients without severe bulbar impairment and requiring periodic immunomodulatory treatment with immunoglobulin (e.g., IV immunoglobulin) can be managed in an outpatient setting. A brief period of hospitalization may be taken into consideration in the case of chronic apheretic treatment through plasmapheresis/immunosorbent.

Emergency treatment is suitable for patients who have deficits in bulbar muscle innervation which pose a danger to the patient's safety; patients suffering from swallowing and breathing deficits are included in this category. Under these conditions, hospitalization is necessary for an adequate clinical assessment, to define the degree of ventilatory autonomy and to position nasogastric tube for feeding and therapy administration. However, treatment with steroids must be given when the patient is hospitalized because of possible further deterioration of the clinical picture due to therapy initiation.

Patient follow-up provides a periodic reassessment by means of outpatient visits; the reassessment deadlines depend on the clinical picture and the type of treatment undertaken. In particular, patients on steroid treatment are reassessed every 2–3 months for the appropriate changes in current dosage of the steroid in progress. Patients exclusively treated with immunosuppressant medication may be reassessed at less frequent intervals; periodic monitoring of blood counts is necessary, in order to highlight the specific side effects of the drug being administered.

The myasthenic patient is managed through an interdisciplinary approach which involves many professionals and several departments and services. In particular:

- The department of neurology and neuromuscular diseases outpatients service, as points of reference for the diagnosis and therapy of the myasthenic patient
- Neurophysiological services, for the neurophysiological diagnosis

- Radiology/neuroradiology facilities, to study the mediastinum by chest CT or MRI scan or to perform brain NMR when a differential diagnosis is needed for patients with complex disorders of the brain stem, or in any case with relevance to the central nervous system
- Dialysis services or transfusion centers, when plasmapheresis treatments are necessary
- The intensive care unit, for assessing patients with respiratory failure and managing patients who require mechanical ventilation
- Analysis laboratories for detecting antibodies
- Day-hospital service for immunomodulatory treatment with immunoglobulin.

References

1. Dowell VR Jr (1984) Botulism and tetanus: selected epidemiologic and microbiologic aspects. Rev Infect Dis 6(suppl 1):S202
2. Abrutyn E (1998) Botulism. In: Fauci AS, Isselbacher KJ, Braunwald E (eds) Principles of internal medicine, 14th edn. McGraw-Hill, New York, p 904
3. Jin R, Rummel A, Binz T, Brunger AT (2006) Botulinum neurotoxin B recognizes its protein receptor with high affinity and specificity. Nature 444:1092
4. Chai Q, Arndt JW, Dong M et al (2006) Structural basis of cell surface receptor recognition by botulinum neurotoxin B. Nature 444:1096
5. Black JD, Dolly JO (1986) Interaction of 125I-labeled botulinum neurotoxins with nerve terminals II. Autoradiographic evidence for its uptake into motor nerves by acceptor-mediated endocytosis. J Cell Biol 103:535
6. Bleck TP (2005) Clostridium botulinum (botulism). In: Mandel GL, Bennett JE, Dolin R (eds) Principles and practice of infectious diseases, 6th edn. Churchill Livingstone, Philadelphia, p 2822
7. Padua L, Aprile I, Monaco ML et al (1999) Neurophysiological assessment in the diagnosis of botulism: usefulness of single-fiber EMG. Muscle Nerve 22:1388
8. Centers for Disease Control and Prevention (CDC) (2010) Investigational heptavalent botulinum antitoxin (HBAT) to

replace licensed botulinum antitoxin AB and investigational botulinum antitoxin E. MMWR Morb Mortal Wkly Rep 59:299
9. FDA news release. FDA approves first botulism antitoxin for use in neutralizing all seven known botulinum nerve toxin serotypes. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm345128.htm. Accessed 25 March 2013
10. Sellin LC (1984) Botulism- an update. Mil Med 149:12
11. American Academy of Pediatrics (2015) Botulism and infant botulism (Clostridium botulinum). In: Kimberlin DW, Brady MT, Jackson MA, Long SS (eds) Red Book: 2015 Report of the Committee on Infectious Diseases, 30th edn. American Academy of Pediatrics, Elk Grove Village, p 294
12. Varma JK, Katsitadze G, Moiscrafishvili M et al (2004) Signs and symptoms predictive of death in patients with foodborne botulism--Republic of Georgia, 1980-2002. Clin Infect Dis 39(3):357
13. Arnon SS, Schechter R, Maslanka SE et al (2006) Human botulism immune globulin for the treatment of infant botulism. N Engl J Med 354:462
14. Norwood F, Dhanjal M, Hill M et al (2014) Myasthenia in pregnancy: best practice guidelines from a UK multispecialty working group. J Neurol Neurosurg Psychiatry 85(5):538–543
15. Sussman J, Farrugia ME, Maddison P et al (2015) Myasthenia gravis: association of British Neurologists' management guidelines. Pract Neurol 15(3):199–206
16. Kerty E, Elsais A, Argov Z et al (2014) EFNS/ENS Guidelines for the treatment of ocular myasthenia. Eur J Neurol 21(5):687–693

Chapter 8
Malignant Hyperthermia

E.P. Verrengia

8.1 Definition

Malignant Hyperthermia (MH) is a pharmacogenetic disorder of skeletal muscle, a "pharmacogenetics" myopathy [1, 2]. Patients are predisposed to develop a serious state of muscle hypermetabolism during general anaesthesia, such as halogen-containing volatile anaesthetics and/or succinylcholine.

The discovery of a gene-related pathogenesis, particularly if related to mutations in the gene encoding the ryanodine receptor, and possible treatment with a specific antagonist of the ryanodine receptor (Dantrolene), has meant that MH is now a condition which is potentially treatable in Emergency.

E.P. Verrengia
Department of Neurology, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
e-mail: ElenaPinuccia.Verrengia@OspedaleNiguarda.it

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8.2 Epidemiology

MH is prevalent in young male adults. The incidence of episodes of malignant hyperthermia ranges from 1:5000 to 1:50,000/100,000 anaesthesias [2]. The average age ranges from 39 years according to [1] to 23 years according to the Canadian study [3], with a prevalence in the male population [3, 4].

8.3 Pathogenesis

The physiological and biochemical mechanisms that determine malignant hyperthermia are to be found in the regulation of calcium in skeletal muscle. According to recent epidemiological studies, the agents that trigger the disorder of calcium homeostasis are succinylcholine alone or in association with volatile anaesthetics. The latter are hypnotic inhalers used in general anaesthesia, including sevoflurane, desflurane, isoflurane, enflurane and halothane.

MH episodes depend on a functional alteration of the ryanodine receptors which affect uncontrolled release of calcium through the sarcoplasmic reticulum, with an increased concentration of cytoplasmic calcium. This mechanism determines muscle activation with an abnormal increase of cell metabolism and consequent high consumption of oxygen, carbon dioxide production and heat generation.

In the skeletal muscle, calcium channels are regulated by a protein: the ryanodine receptor (RYR1). Cav 1.1 is a voltage-dependent channel that activates RYR1 [5]. Mutations (variations) of genes that encode these two proteins are responsible for the increased susceptibility of some patients to the development of MH. In 70–75% of cases it involves one of the RYR1 gene variant [5, 6]; less frequently a CACNA1S variant is detected which encodes an alpha Cav 1.1. subunit.

Finally, there are cases in which no variant has been identified furthermore, some RYR1 mutations are associated with rare myopathies and some have been described in association with both MH and “central core” myopathies. Given the co-existence

or association of MH with rhabdomyolysis other genes have been identified, which may possibly be involved in the pathogenesis of the disease, such as CPT2, PYGM, ACADM, AMPD1, VLCAD. Next Generation Sequencing (NGS), a technology which allows rapid sequencing of human DNA, will identify new mutations and their correlation with MH [5–7].

Relatives of patients who have an increased susceptibility to MH should not, if possible, be treated with anaesthetics. When the diagnosis is genetic and transmission of the disease is autosomal dominant, children of the affected patients have a 50% chance of developing MH.

An association is frequently found between exercise hyperthermia (exertional heat illness) and MH. The alteration of calcium homeostasis is common to both diseases. Exertional heat illness is a subclinical myopathy that appears after extreme physical exertion.

Some myopathies have an increased susceptibility to malignant hyperthermia: myotonia associated with sodium channels, hypokalemic periodic paralysis, myopathy multiminicore.

8.4 Diagnosis

European Guidelines [8] have been developed in Europe, and there is a US registry [9] with guidance on the diagnosis and management of malignant hyperthermia.

The history is important not only for investigating any previous episodes, but also because there are some associated diseases such as “Central Core” myopathy.

Diagnosis of MH is primarily based on clinical suspicion and on bio-humoral exams.

The main clinical characteristics of the MH patient are muscle rigidity, tachycardia, acidosis, hyperthermia, hyperkalemia and an increased concentration of carbon dioxide (CO_2) at the end of expiration. These parameters, and their importance according to the normal values, are summarized in the Clinical Grading Scale developed in 1994 by Larach et al. [10] (Table 8.1), which allows a certain or possible diagnosis to be reached.

Table 8.1 MH diagnostic tool

Item	Score
Rigidity	
Generalized muscular rigidity (in absence of shivering due to hypothermia, or during or immediately following emergence from general inhalational anaesthesia)	15
Masseter spasm shortly following succinylcholine administration	15
Muscle breakdown	
Elevated creatine kinase >20,000 IU after anaesthetic that included succinylcholine	15
Elevated creatine kinase >10,000 IU after anaesthetic without succinylcholine	15
Cola colored urine in perioperative period	10
Myoglobin in urine >60 μg/L	5
Myoglobin in serum >170 μg/L	5
Blood/plasma/serum K+ >6 mEq/L (in absence of renal failure)	3
Respiratory acidosis	
$PETCO_2$ > 55 mmHg with appropriately controlled ventilation	15
Arterial $PaCO_2$ > 60 mmHg with appropriately controlled ventilation	15
$PETCO_2$ > 60 mmHg with spontaneous ventilation	15
Arterial $PaCO_2$ > 65 mmHg with spontaneous ventilation	15
Inappropriate hypercarbia (in anaesthesiologist's judgment)	15
Inappropriate tachypnea	10
Increase in temperature	
Inappropriately rapid increase in temperature (in anaesthesiologist's judgment)	15

Table 8.1 (continued)

Item	Score
Inappropriately increased temperature >38.8 °C (101.8?F) in the perioperative period (in anaesthesiologist's judgment)	10
Cardiac involvement	
Inappropriate sinus tachycardia	3
Ventricular tachycardia or ventricular fibrillation	3
Other indicators that are not part of a single process. (These should be added without regard to double-counting)	
Arterial base excess more negative than ?8 mEq/L	10
Arterial pH <7.25	10
Rapid reversal of MH signs of metabolic and/or respiratory acidosis with I.V. dantrolene	5

The Canadian study reports that the most frequent symptoms are: hyperthermia (>38.8) (66.7%), sinus tachycardia (>120 bpm) (62%), hypercapnia (51.9%), rigidity of the masseter muscle (34.9%) and generalized muscle stiffness in 25.6% of the patients.

The symptoms may occur during anaesthesia or in the postoperative period. The rise in temperature can be transient (lasting 20 min) or late, in which case body temperature must be carefully monitored in the ICU. The hyperpyrexia can reach 44°. The temperature may increase by 1–2° every 5 min in patients with a poor prognosis. This condition causes increased oxygen consumption, high CO_2 production due to dysfunction of vital organs, and an increased risk of DIC (disseminated intravascular coagulation). These parameters (metabolic/respiratory acidosis, oxygen and carbon dioxide) can be evaluated on an arterial level by hemogasanalysis (HGA).

Clinical Grading Scale for IM: raw score

Interpreting the raw score: MH rank and qualitative likelihood

Raw score range	MH rank	Description of likelihood
0	1	Almost never
3–9	2	Unlikely
10–19	3	Somewhat less than likely
20–34	4	Somewhat greater than likely
35–49	5	Very likely
50+	6	Almost certain

Hypermetabolism and hypoxia lead to widespread muscle damage. Among the bio-humoral diagnostic tests, the Guidelines suggest that the creatinine-kinase (CK) value test is one of the bio-humoral diagnostic tests to be carried out. The persistence of increased values of CK, even higher than 10,000–20,000 IU/L, is shown in association with a greater susceptibility to MH. There are numerous pathological conditions that can determine an increase in CK; the test therefore has low sensitivity and specificity.

If muscle damage is extensive it is also possible to detect myoglobinuria, which causes renal failure.The in vivo contracture test (IVCT) is a validated and useful method for diagnosis. Two modes of execution and interpretation of results have been developed by the European Group for the Study of Malignant Hyperthermia (EMHG) [8] and the North American group for Malignant Hyperthermia (NAMHG). Both protocols are based on muscle response to halothane and caffeine, both with induction of muscle contraction properties.

The EMHG protocol distinguishes four diagnostic laboratory groups: MHShc (malignant hyperthermia susceptible to halothane and caffeine), MHSh (malignant hyperthermia susceptible to halothane), MHSC (malignant hyperthermia susceptible to caffeine) and MHN unchanged (normal: no susceptibility to caffeine or halothane). NAMHG considers as positive those patients with an abnormal response to both (halothane and caffeine) and negative those patients whose tests are both negative.

RYR1 and CACNAIS molecular genetic diagnosis should be indicated as diagnostic tests confirming the predisposition to MH. The European Guidelines [8] indicate a possible parallel diagnostic path which includes both DNA screening and muscle biopsy, with the contracture test in vivo. The decision as to which procedure to follow depends on the characteristics of the patient's condition, the characteristics of the hospital where he or she is under treatment, and the urgency with which test results are awaited (e.g. the patient is awaiting surgery).In urgent cases, the mainstay of diagnosis is clinical suspicion based on the signs and symptoms reported by the patient.

Patients with a persistent increase in CK, or patients symptomatic for possible muscle pain, should undergo a neurological evaluation which includes an electromyographic examination as part of the diagnostic tests to rule out myopathy, before the administration of anaesthesia agents that may cause malignant hyperthermia.

Results which suggest the patient is suffering from myopathy, to be looked for in the proximal muscles of the four limbs, are: CMAP amplitude and reduced duration associated with a recruiting interference at submaximal contraction, and sometimes in the presence of spontaneous fibrillation activity and positive slow waves. In myopathic forms there may be some bizarre high-frequency discharges.

8.5 Differential Diagnosis

There are several conditions that can mimic MH during anaesthesia: sepsis, anaphylaxis, thyroid dysfunction, serotonin syndrome, pheochromocytoma, increased iatrogenic temperature, cocaine overdose, neuroleptic malignant syndrome.

8.6 Management and Treatment

Prognosis of an MH crisis depends on how early treatment is started.

Crisis management of malignant hyperthermia should be rapid: it consists of interrupting exposure to a trigger (succinylcholine and/or volatile anaesthetics), administration of a specific therapy (Dantrolene) and adoption of supportive and prevention measures against possible complications [11].

When exposure to trigger agents is interrupted, anaesthesia must be ensured through I.V. administration of sedatives or opioids.

Hyperventilation with 100% O_2 must be carried out until end-tidal CO_2 values decrease and become normal.

Dantrolene, a derivative of hydantoin, acts as a specific antagonist of the ryanodine receptor by inhibiting the release of calcium from the sarcoplasmic reticulum. Side effects are rare, but there have been reports of prolonged breathing problems, tissue necrosis after accidental extravascular injection, nausea, vomiting, headache and dizziness.

Dantrolene dosage varies, depending on the patient's clinical response or the amount needed to alleviate symptoms. The dosage must return the monitored parameters to a standard range. A dosage of 5 mg/kg of Dantrolene over 24 h is recommended if the initial loading dose was of 2.5–5 mg/kg. A higher dose is recommended over the 24 h (10 mg/kg) if the initial dose is 7.5–10 mg/kg. The maximum cumulative dose is 20 mg/kg [11].

If there is hyperthermia, ice packs can be placed on the groin, under the armpits and on the neck, or nasogastric lavage can be performed with iced solutions. If there is arrhythmia, calcium channel blockers must not be administered.

It is important to perform blood tests with blood count, blood gas analysis, serum CPK, myoglobinaemia, myoglobinuria with clotting profile every 6–12 h. If hyperkalemia is detected, continue hyperventilation and correct blood glucose with insulin (if necessary).

Use diuretics and mannitol to achieve the following diuresis value: 2 mL/kg/h.

DIC occurs when body temperature exceeds 41°.

Despite treatment with Dantrolene, the syndrome may recur; therefore the patient must be monitored in an intensive care unit for at least 36 h.

8.7 Outcome and Mortality

The main complications that can lead to death are: renal failure, heart failure, DIC, pulmonary edema and compartment syndrome. Renal failure is reported in some studies [3] as the most frequent complication; on the contrary, in the American registry Larach et al. report altered state of consciousness and cardiac dysfunction as the main consequences of malignant hyperthermia [4].

An unfavourable outcome is associated with either a delay in the administration of Dantrolene [3] or inadequate monitoring of hyperthermia [9].

Mortality, which in the past could reach 42.3% [12], currently ranges from 6.5 to 15% according to the most recent studies [1–12].

References

1. Rosero EB, Adesanya AO, Timaran CH, Joshi GP (2009) Trends and outcomes of malignant hyperthermia in the United States, 2000 to 2005. Anesthesiology 110:89–94
2. Rosenberg H, Davis M, James D, Pollock N, Stowell K (2007) Malignant hyperthermia. Orphanet J Rare Dis 2:21. doi:10.1186/1750-1172-2-21
3. Riazi S, Larach MG, Hu C, Wijeysundera D, Massey C, Kraeva N (2014) Malignant hyperthermia in Canada: characteristics of index anaesthetics in 129 malignant hyperthermia susceptible probands. Anesth Analg 118(2). www.anaesthesia-analgesia.org
4. Larach MG, Gronert GA, Allen GC, Brandom BW, Lehman EB (2010) Clinical presentation, treatment, and complications of malignant hyperthermia in North America from 1987 to 2006. Anesth Analg 110:498–507
5. de Carvalho Correia AC, Silva PCB, da Silva BA (2012) Malignant hyperthermia: clinical and molecular aspects. Rev Bras Anestesiol 62(6):820–837
6. Bandschapp O, Girard T (2012) Malignant hyperthermia. Swiss Med Wkly 142:w13652

7. Fiszer D, Shaw M-A, Fisher NA, Carr IM, Gupta PK, Watkins EJ, de Sa DR, Kim JH, Hopkins PM (2015) Next-generation sequencing of RYR1 and CACNA1S in malignant hyperthermia and exertional heat illness. Anesthesiology 122:1033–1046
8. Hopkins PM, Rüffert H, Snoeck MM, Girard T, Glahn KPE, Ellis FR, Müller CR, Urwyler A on behalf of the European Malignant Hyperthermia Group (2015) European Malignant Hyperthermia Group guidelines for investigation of malignant hyperthermia susceptibility. Br J Anaesthesia 115(4):531–9
9. Marilyn Green Larach, Barbara W. Brandom, Gregory C. Allen, Gerald A. Gronert, Erik B. Lehman (2014) Malignant hyperthermia deaths related to inadequate temperature monitoring, 2007–2012: a report from The North American Malignant Hyperthermia Registry of the Malignant Hyperthermia Association of the United States. 119(6). www.anaesthesia-analgesia.org
10. Larach MG et al (1994) A clinical grading scale to predicate malignant hyperthermia susceptibility. Anesthesiology 80:771–779
11. Schneiderbanger D, Johannsen S, Roewer N, Schuster F (2014) Management of malignant hyperthermia: diagnosis and treatment. Ther Clin Risk Manag 10:355–362
12. Migita T, Mukaida K, Kawamoto M, Kobayashi M, Yuge O (2007) Fulminant-type malignant hyperthermia in Japan: cumulative analysis of 383 cases. J Anesth 21:285–288

Chapter 9
Rhabdomyolysis

E.P. Verrengia

9.1 Definition

In 2002, the American College of Cardiology (ACC), the American Heart Association (AHA) and the National Heart, Lung and Blood Institute (NHLBI) issued a joint definition of rhabdomyolysis in connection with the use of statins and their toxicity. Rhabdomyolysis appeared to be characterized by muscular symptoms with a substantial elevation of creatine kinase, typically greater than 11 times the normal limit, together with kidney disease and, usually, with brown urine and myoglobinuria [1]. Rhabdomyolysis is, more simply, a condition characterized by an injury or an insult to the skeletal muscle which determines the release of the myocellular components [2], leading to an increase in the blood levels of the intracellular components of the major muscles such as CK, aldolase, LDH, GOT, myoglobin, potassium, and moreover hyperuricaemia and hyperphosphatemia. As rhabdomyolysis is a potentially fatal condition, it requires rapid recognition and early treatment.

E.P. Verrengia
Department of Neurology, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
e-mail: ElenaPinuccia.Verrengia@OspedaleNiguarda.it

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9.2 Diagnosis

Diagnosis is made collecting the patient's medical history, the clinical picture, the presence of dark urine (myoglobinuria) and an increase in the levels of creatine phosphokinase (CPK).

Through a detailed medical history, emergency doctors may be able to identify what triggered the symptoms, as, for example, in the case of drug toxicity or intercurrent infections.

The clinical pictures with which rhabdomyolysis occurs vary from subclinical or mild disease, in which there are no muscular symptoms but only an increase in intracellular muscle components in the blood, to severe syndromes [3] in which the muscle damage is expressed by pain, weakness and swelling of the affected muscles. In a study which included 77 hospitalized patients, 50% of them reported muscle pain and 15% had muscle swelling [4]. Symptoms may develop over a few hours or a few days. The commonly reported classical triad includes myalgia, muscle weakness and myoglobinuria (tea-coloured urine). These characteristics are, however, present in fewer than 10% of cases [5].

Diagnosis

Triad features: myalgia, muscle weakness, myoglobinuria (tea-coloured urine)

Medical history (triggers)

Clinical features
Common symptoms: myalgia, muscle weakness, fever
Other symptoms: muscle swelling, nausea, vomiting, confusion, arrhythmias, coma

Blood tests
Increased CPK, aldolase, LDH, GOT, myoglobin, potassium, uric acid, phosphate
Increase in renal function tests (urea, creatinine)

Urinalysis
Myoglobinuria

Diagnostic elements at an early stage.

Blood tests may be abnormal in the early stage.

CPK is active in skeletal muscle and catalyses the transportation of a phosphate group from creatinine to adenosine diphosphate (ADP), determining adenosine triphosphate (ATP) and creatinine (C). There are three CPK isoenzymes.

CPK-MM is mainly present in skeletal muscle but little in the myocardium, and it is the value that mostly rises in the case of rhabdomyolysis. CPK-MB is present in the myocardium; CPK-BB is present in the brain and kidney [2]. After muscle insult, the plasma level of serum CPK-MM increases after 2–12 h and reaches a peak after 3–5 days.

CPK-MM values are the most reliable and are considered gold-standard values in the identification of rhabdomyolysis. Typically, CPK values greater than at least five times the upper normal value are considered significant [6].

Myoglobin, an iron-containing protein capable of binding oxygen and contained in the muscle cells, rises rapidly in the blood after the muscle damage. The serum myoglobin values increase within the first 1–3 h, peak at 8–12 h and fall within the normal range within 24 h. The sensitivity of myoglobin decreases after 24 h from muscle insult. Myoglobinuria is the result of the inability of the kidney to retain excess myoglobin. Urine may be dark, "tea-coloured", when the myoglobin values are above 100 mg/dL. Diuresis can be contracted with the risk of acute renal failure. In a case series, 80% of hospitalized adult patients had dark urine [7].

CBC can be useful for counting leukocytes, which increase in the presence of inflammation/infection, and platelets, which are reduced in the case of disseminated intravascular coagulation (DIC). Hypoalbuminaemia and anaemia may indicate damage to the muscle exerted on the capillaries, with passage of fluid into the interstitial space and possible hypovolemic shock.

The levels of aldolase, lactic dehydrogenase and hydrobutyric aminotransferase are high in cases of rhabdomyolysis.

There are several guidelines, studies and case studies on the usefulness of electromyography in rhabdomyolysis. Performing an electromyographic examination in the acute

phase of the disease is still good practice and provides important information about the severity of muscle damage. Furthermore, the EMG examination should be repeated, especially in patients who remain symptomatic or with a persistent hyperCKaemia after removing the triggering cause.

The neurophysiological study of rhabdomyolysis patients shall primarily rely on electromyographic examination with a concentric needle electrode.

In forms caused by a systemic agent, and in generalized forms, the proximal muscles are symmetrically analysed and in particular: biceps, deltoids and quadriceps and some distal muscle including in particular the gastrocnemius.

In forms with focality such as trauma, crush syndromes and forms of prolonged immobilization, the electromyographic study will be directed mainly at affected areas such as a limb or a whole half-body.

Regardless of the cause—traumatic, toxic, infectious or secondary to metabolic diseases—the electromyographic study findings are characterized by an activity similar to that found in myopathies and in inflammatory myopathies in particular. The very early presence of spontaneous activity (fibrillation type) will be observed, as well as the recording of a polyphasic motor unit potential of low amplitude and short duration.

In patients who suffer repeated episodes of rhabdomyolysis and recurrent myoglobinuria or exertional myoglobinuria, especially if they are associated with fatigue, myalgia and persistent hyperCKaemia, an electromyographic examination should be performed, even outside the episode, in order to find possible predisposing myopathies such as inherited metabolic myopathies.

In traumatic forms caused by prolonged immobilization, and in forms associated with compartment syndrome, mononeuropathies may overlap mononeuropathies or compression-related sensor-motor multineuropaties. In these cases an electroneurographic examination is recommended, targeted at the affected nerves, for the evaluation of neuropathies by direct injury.

Additional tests may be muscle investigation, such as a muscle MRI or biopsy, possibly brain CT scan in the case of impaired sensitivity and X-rays if bone fractures are suspected.

9.3 Etiopathogenesis

Regardless of the cause, what happens within the muscles is the direct damage to myocells, with an alteration of energy production which supports muscle cells function. In resting muscle, ion channels (sodium/potassium pump and sodium/calcium exchangers) maintain a low concentration of intracellular calcium and sodium and high potassium levels within the myocell.

Depolarization of the muscle cell is linked to the influence of calcium from the sarcoplasmic reticulum to the cytoplasm, providing muscle contraction by binding actin-myosin. All these processes are mediated via energy in the form of adenosine triphosphate (ATP). Any insult that affects the myocell causes an alteration in the balance between intracellular and extracellular electrolytes.

This situation causes an intracellular influx of sodium and calcium ions, resulting in a recall of intracellular water. Intracellular calcium causes a myofibrillar contraction with additional depletion of ATP. Calcium also determines the activation of a series of processes with further damage to the ion channels. These processes result in a necrosis of muscle fibres and the release into the blood stream of the elements normally contained in the muscle [5].

Cases of rhabdomyolysis have been described in Second World War soldiers who were subjected to severe physical trauma.

There are various causes for rhabdomyolysis: from acquired forms to drugs, concomitant disease or forms that can be associated with rhabdomyolysis. The main etiologies are summarized in Table 9.1.

Table 9.1 Main causes of rhabdomyolysis

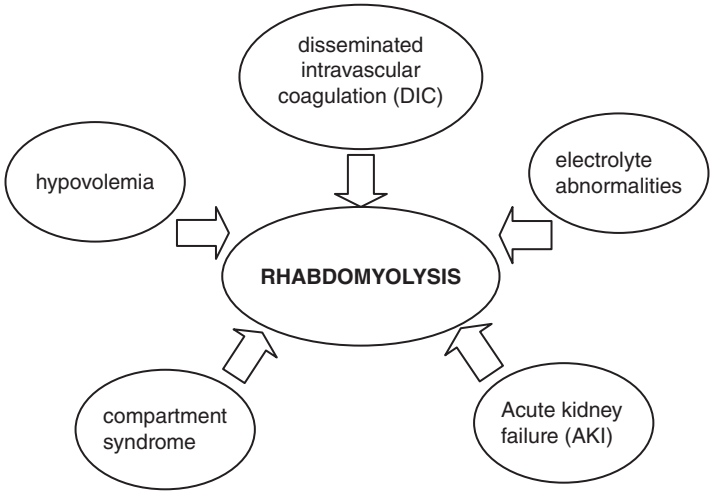
Aetiology	
Alcohol	
Drugs	Heroin, cocaine, methamphetamine Antidepressants (tricyclic antidepressants, venlafaxine, sertraline, escitalopram), antihistamines, antipsychotics (haloperidol, clozapine, olanzapine, risperidone, quetiapine), statins, antiretroviral, colchicine, lithium, INF-alpha, levofloxacin
Electrolyte imbalance	Hypokalemia, hypophosphatemia, hyponatremia
Endocrine disorders	Diabetes, thyroid dysfunction, primary aldosteronism, adrenal insufficiency, central diabetes insipidus, pituitary dysfunction
Renal tubular dysfunction	
Toxins, pesticides, fish, venom of some snakes	
Autoimmune myopathies	Polymyositis, dermatomyositis, inclusion body myositis
Metabolic myopathies	Disorders of glycogen metabolism, fatty acid oxidation disorders, mitochondrial disorders
Muscular dystrophies	Duchenne Muscular Dystrophy
Channelopathies	
Intolerance to physical exercise	
Sickle cell anaemia	
Traumas and compressions	Crushes, immobilization

Table 9.1 (continued)

Aetiology	
Strain	Prolonged exercise, seizure, delirium tremens
Muscle hypoxia	Occlusion of major artery, clamping of vessels during surgery
Changes in body temperature	Malignant hyperthermia, neuroleptic malignant syndrome, hypothermia

9.4 Complications and Outcome

The main complications of rhabdomyolysis are represented in the graph below.



Major complications of rhabdomyolysis

The release of components which are normally present within the muscle can also create significant *electrolyte disorders* such as hyperkalaemia and changes in the levels of calcium and inorganic phosphate.

Hyperkalaemia is an important key for the diagnosis of rhabdomyolysis and correlates to cardiac toxicity with prolonged QT interval, high T-waves, nodal arrhythmias, up to ventricular fibrillation and asystole. Neurological symptoms may go from numbness up to flaccid paralysis.

In an early stage of rhabdomyolysis, hypocalcemia may be present, related to the deposit of calcium in necrotic muscle tissue. Typically, such hypocalcemia is not symptomatic and does not need treatment. In the later stages, on the contrary, calcium is released from damaged muscle into the bloodstream, also in response to elevated levels of parathyroid hormone related to the initial hypocalcemia.

The inorganic phosphate which is normally present in the muscle is released and causes hyperphosphatemia. Uric acid is derived from conversion of purines in the liver. Therefore the levels of uric acid will be increased by the release of purines from the damaged muscle.

Hypovolemia may occur in relation to what happens in the muscles. In the intracellular compartment, water is recalled from the blood vessels because of the low potassium level. There may be swelling of the cells, causing a reduction in the circulating blood volume. This situation can evolve and lead to hypovolemic shock.

In rhabdomyolysis, *compartment syndrome* is caused by the fact that the damage occurs to the muscles that belong to a non-distensible strip. What follows is an increase in pressure with a congestion of fluids: the subsequent edema compromises lymphatic drainage and arterial perfusion. When the arterioles collapse, perfusion of muscles and nerves fails.

Prolonged ischaemia and the resulting muscle infarction can lead to the replacement of the latter with non-elastic and fibrous tissue, which is involved in severe contractures (Volkmann's contracture).

Acute renal failure is the result of nephrotoxic myoglobin. The damage that occurs in the kidney is related to the inability of glomerular cells to retain the myoglobin which is present in excessive amount in the blood. For this reason,

myoglobin may be present in the urine (myoglobinuria). Severe forms can be related to acute renal failure, a condition that must be treated promptly. It is estimated that between 10 and 46% of adults with rhabdomyolysis will experience acute renal failure [3] and that 15–33% of ARF can be caused by rhabdomyolysis [8].

Disseminated intravascular coagulation (*DIC*) is related to the dissolution of clots and subsequent uncontrolled bleeding.

9.5 Management and Treatment

Rhabdomyolysis should be treated promptly, especially considering the complications and, above all, in order to prevent kidney failure.

First of all it is necessary to assess the vital signs by applying the ABC method (airway-breathing-circulation).

If possible, use the patient's history to identify the aetiology of the muscle disorder in order to eliminate the cause.

During the diagnostic and therapeutic pathway, vital signs and EKG must be monitored. To check the fluid and electrolyte balance, placement of a Foley catheter is recommended.

The patient should be given the most important biochemical tests to confirm the diagnosis, particularly potassium levels, CPK and myoglobin tests.

Depending on the patient's condition, the following specialized physicians may be contacted: nephrologists, anaesthetist-resuscitators and orthopaedics.

Early intravenous hydration and the consequent forced diuresis are a mainstay in preventing or at least reducing the severity of kidney damage and in removing the nephrotoxic elements.

Hydration, which may be ensured via a normal saline solution, can already be initiated in the pre-hospital phase or immediately upon arrival at the hospital. The earlier the infusion of fluids, the better the outcome. The amount of intravenous fluids must be calculated on the base of the vital

parameters, urine output and objective physical examination. An output of urine of at least 200/300 mL/h [5, 6] is recommended.

Treatment with sodium bicarbonate is under discussion at the moment as some clinicians believe that alkalinization of urine reduces the percentage of serum calcium. Alkalinization of urine through sodium bicarbonate is useful for avoiding the damage caused by myoglobin on metabolites in the kidney and for preventing the crystallization of uric acid. The urinary pH must be maintained above 6.5.

Hyperkalaemia occurs early (within 12–36 h of onset) and must be corrected promptly to avoid cardiac consequences. The first-line treatment is with calcium; other measures may be either infusion of insulin with glucose, intravenous administration of sodium bicarbonate and inhalation of beta2-agonists. Kayexalate removes potassium from the cycle, but it takes some hours to act. If hyperkalaemia persists after these treatments, dialysis is useful.

The use of diuretics such as furosemide or mannitol is recommended when there is blood loss or dehydration, even if it increases the hypovolemia. Diuretics dilute nephrotoxic substances and ensure a higher urine output. Furosemide can be used, but it may acidify the urine. Mannitol, an osmotic diuretic, ensures increase of urine flow and dilution of nephrotoxic metabolites and creates a hyperosmolar gradient which facilitates the passage of fluid from the interstices into the bloodstream. The dosage is 1 g/kg intravenously in 30 min or 25 g intravenously followed by 5 g/h up to a maximum total dose of 120 g/day. Mannitol increases the flow and glomerular filtration rate. Therefore it is not recommended in a very early phase because it can increase kidney damage.

DIC treatment through coagulation factors, fresh frozen plasma or platelet transfusions should be carefully evaluated.

Compartment syndrome requires an orthopaedic consultation for a possible fasciotomy.

Hemodialysis is indicated in hyperkalaemia and metabolic acidosis patients. It is just as useful in acute congestive heart failure conditions or in pulmonary edema.

9.6 Outcome

The outcome depends on the type of population, causes and comorbidities.

The prognosis is closely related to how early measures were taken to prevent renal failure (in particular, hydration within 24 h). Acute renal failure is associated with a higher risk of mortality [9]. In the different studies, mortality ranges from 1.7 to 46% [3–9].

References

1. Pasternak RC, Smith SC Jr, Bairey-Merz CN et al (2002) ACC/AHA/NHLBI clinical advisory on the use and safety of statins. Stroke. 33(9):2337–2341
2. Nance JR et al (2015) Diagnostic evaluation of rhabdomyolysis. Muscle Nerve 51(6):793–810
3. Melli G et al (2005) Rhabdomyolysis an evaluation of 475 hospitalized patients. Medicine (Baltimore) 84:377–385
4. Gabow PA et al (1982) The spectrum of rhabdomyolysis. Medicine (Baltimore) 61:141–152
5. Torres PA et al (2015) Rhabdomyolysis: pathogenesis, diagnosis, and treatment. Ochsner J 15:58–69
6. Cervellin G, Comelli I, Lippi G (2010) Rhabdomyolysis: historical background, clinical, diagnostic and therapeutic features. Clin Chem Lab Med 48(6):749–756
7. Grossman RA et al (1974) Nontraumatic rhabdomyolysis and acute renal failure. N Engl J Med 291:807–811
8. Kasaoka S, Todani M, Kaneko T et al (2010) Peak value of blood myoglobin predicts acute renal failure induced by rhabdomyolysis. J Crit Care. 25(4):601–604
9. Delaney KA, Givens ML, Vohra RB (2012) Use of Rifle criteria to predict the severity and prognosis of acute kidney injury in emergency department patients with rhabdomyolysis. J Emerg Med 42(5):521–528

Chapter 10
Periodic Paralysis

E.P. Verrengia

10.1 Definition

Periodic paralysis related to potassium levels is included in the context of channelopathies or disorders related to the dysfunction of ion channels. In their severe form, these diseases require prompt treatment in an emergency/urgency regime.

An epidemiological study conducted in England recruited all patients suspected of having non-dystrophic myotonia and periodic paralysis in the period between 1997 and 2011. Five hundred and ninety-three patients were analyzed with the following prevalence data: hyperkalemic periodic paralysis 0.13/100,000 (95% CI 0:13 to 0:20), hypokalemic periodic paralysis 0.17/100,000 (95% CI 0:10 to 0:17), and Andersen-Tawil Syndrome 0.08/100,000 (95% CI 0:05 to 0:10) [1].

Hypokalemic periodic paralysis is described as a sporadic form (20% of cases), while the remaining patients show an autosomal-dominant inheritance with a mutation of the CACNA1S (70% of cases), and less frequently the SCN4A gene [2].

E.P. Verrengia
Department of Neurology, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
e-mail: ElenaPinuccia.Verrengia@OspedaleNiguarda.it

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Triggers, or the factors that cause this disease, are fasting and resting after exercise. The disease is most frequently diagnosed in young adults [2].

SCN4A is the most frequently detected gene in periodic hyperkalemic paralysis. SCN4A is involved in coding the Sodium channel. This gene is also involved in congenital paramyotonia, although in different loci. The mode of transmission of the disease is, as for the hypokalemic form, autosomal-dominant.

Onset of symptoms is typically in childhood, most commonly in the first decade of life, or in the second decade at the latest.

Factors facilitating the onset of this disease are physical effort, ethanol, foods rich in carbohydrate, emotions, and stress [2]. Andersen-Tawil syndrome is a combination of a periodic paralysis which is sensitive to potassium levels, ventricular arrhythmias, and characteristic physical aspects (short stature, hypertelorism, scoliosis, syndactyly, micrognathia) with KCNJ2 (ATS1) gene mutation, which encodes potassium channel Kir2.1 in 66% of cases.

There are secondary forms of periodic paralysis related to increased or decreased potassium levels. Hyperkalemia may occur in connection with Addison's disease, hypoaldosteronism, potassium-sparing diuretics or excessive support with potassium, chronic renal failure, or rhabdomyolysis. Similarly we also consider reductions in potassium levels during thyrotoxicosis, renal tubular acidosis, hyperaldosteronism, overuse of diuretics, corticosteroids, or alcoholism.

10.2 Clinical Features

In both diseases, the patient complains muscle weakness that is worse in the morning upon waking but can appear at any time of day or night. The phenotype expression ranges from mild to severe, from focal forms to a more widespread muscle involvement [2].

In periodic hyperkalemic paralysis, the symptomatology has a variable duration from some minutes to a few hours (typically <2 h); attacks rarely persist for days. Complete paralysis is rare, the legs are the limbs most frequently involved, and bulbar impairment is rarely present.

Flaccid and generalized paralysis is more common in hypokalemia. The duration of symptoms varies, but the symptoms can persist for several days.

In both forms the neurological examination shows, in addition to a muscle weakness, a reduction, or abolition of tendon reflexes (ROT) during attacks, with restoration of normal reflexes outside the attacks. Some patients may experience weakness involving the proximal muscles of the limbs and the shoulder and/or pelvic girdle as neurological sequelae, especially in hyperkalemic forms of paralysis.

Cardiac arrhythmias associated with generalized weakness are usually attributed to less frequent entities of periodic paralysis, such as *Andersen-Tawil syndrome*.

10.3 Diagnosis

Diagnosis is made in the acute phase on the basis of the patient's history (search for triggers), symptomatology, general and neurological examination, biohumoral exams, and electrocardiogram (EKG). The need for electromyography (EMG), muscle biopsy, and stress testing can be evaluated in order to confirm the diagnosis in asymptomatic patients or in the acute phase in differential diagnosis [3].

In addition to the clinical picture, the biochemical tests carried out during attacks can detect an increase or decrease in serum potassium levels. Less frequently, an increase in potassium occurs at the end of the attack and the diagnosis can be retrospective.

In the asymptomatic phase, patients present electrolytes within normal range.

EKG alterations in relation to reduced levels or increased potassium are very useful: in hypokalemia there may be prolongation of QT or PR, bradycardia, or T-wave flattening, whereas in hyperkalemia there may be an increase in wave amplitude.

Electrophysiological study during an acute episode of hypokalemic paralysis is characterized by a reduction or non-excitability of compound muscle action potential (CMAP) in the affected muscles. In the most severe forms, EMG signs of rhabdomyolysis may be associated.

Outside the acute episode, the neurophysiological study results are usually normal or the EMG may show nonspecific signs of myopathy.

The specific neurophysiological examinations of periodic paralysis are the McManis test or compound muscle action potential test. Therapy should be discontinued before the test (for at least 72 h).

The examination consists in assessing the decrease of CMAP of a hand muscle, usually the muscle abductor V finger, after a fatigue test. It determines the amplitude of CMAP at rest, with a supramaximal stimulation of the ulnar nerve at the wrist. The patient then performs maximal isometric contraction for 5 min, interspersed every 15 sec by 3 sec of relaxation to prevent ischemia of the muscle. CMAP amplitude is measured every minute during the contraction and then every 1–2 min for 30 min.

The test is positive if it shows a 40% decrease of CMAP from baseline.

The test sensitivity is 63% in the whole group of muscle disorders of ion channels, with maximum sensitivity in primary periodic paralysis (83%). It is not however specific for hypokalemic paralysis as a positivity is observed even in hyperkalemic forms and in channelopathies of the chloride channel, as well as in the proximal form of myotonic dystrophy (PROMM) [3, 4].

Muscle biopsy may show vacuoles or tubular aggregates. These aspects are not characteristic, however, and their usefulness relates to the formulation of the diagnosis in emergency.

Stress tests can be conducted by increasing or reducing the values of potassium in the blood while ensuring a careful monitoring of cardiac function.

10.4 Management and Treatment

10.4.1 Periodic Hyperkalemic Paralysis

Potassium levels can be lowered via administration of a thiazide diuretic [3, 4]: hydrochlorothiazide 25–50 mg/day or chlorothiazide 250–1000 mg/day.

Acetazolamide has a known efficacy: the mechanism is however unknown. The starting standard dosage is 125 mg/day, which may be increased up to a maximum of 1500 mg/day divided into three doses, alternatively, diclofenamide 50 mg twice daily, or 100 mg divided into two doses.

Different measures can be taken, depending on the clinical picture. For mild clinical pictures, oral administration of carbohydrates can be useful, as well as intravenous administration of glucose; for moderate to severe forms, administration of a beta-adrenergic receptor agonist, intravenous insulin (with glucose), and calcium carbonate can be useful.

10.4.2 Hypokalemic Periodic Paralysis

It is necessary to ensure the support of potassium (40 mEq of potassium chloride slow release) or potassium-sparing diuretics (triamterene or spironolactone 25–100 mg/day) [3–5].

In emergency they can be used in an alternative way:

- Potassium chloride intravenously (0.05–0.1 mEq/kg or 20–40 mEq/L in 5% of mannitol)
- Potassium salts orally (0.25 mEq/kg) every 30 min until the strength disorder resolves

In both cases, cardiac monitoring via ECG is essential.

References

1. Horga A et al (2013) Prevalence study of genetically defined skeletal muscle channelopathies in England. Neurology 80:1472–1475
2. Griggs RC (1995) Periodic paralysis and myotonia. In: Griggs RC, Mendell JR, Miller RG (eds) Evaluation and treatment of myopathies. FA Davis, Philadelphia, pp 318–354
3. David S (2008) Saperstein. Muscle channelopathies. Semin Neurol 28(2):260–269
4. Quinn C et al (2015) Myotonic disorders and channelopathies. Semin Neurol 35:360–368
5. Statland JM, Barohn RJ (2013) Muscle channelopathies: the nondystrophic myotonias and periodic paralyses. Continuum 19(6):1598–1614

Part II
Case Studies

Chapter 11
Case Study: Atypical GBS

Elena Pinuccia Verrengia, Stefano Jann, and Andrea Rigamonti

RDL, 60-year-old male. Negative family history. Entrepreneur. Normal living habits.

Type 2 diabetes mellitus since 1998 in sufficient compensation compensation (glycosilated Haemoglobin 7.8%). Patient was treated with metformin and diet. In 2002 heterologous bone marrow transplantation for NH large cell lymphoma. Earlier treatment with chemotherapy. Patient was later treated with cyclosporine and steroids because of GVHR. In October 2002 lymphoma was considered in remission. In December 2002 acute onset of burning, stabbing, distal pain in the lower limbs, with inability to maintain upright position. The blood tests carried out in the ER were normal except for fasting glucose: 148 mg%, glycosilated haemoglobin 7.4%. RX LS spine was normal. Neurological examination was normal except for bilat-

E.P. Verrengia
Department of Neurology, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

S. Jann (✉)
Department of Neurology and Stroke Unit, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
e-mail: stefano.jann@ospedaleniguarda.it

A. Rigamonti
Department of Neurology, ASST Lecco, Lecco, Italy

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eral lower limb areflexia. No pain relief with NSAIDs, even intravenously. He was Hospitalized in the department of hematology. Blood test results were normal except for fasting glucose. Plasma assay of cyclosporine was normal. Neurophysiological tests(motor and sensory CV and needle examination) were normal. CSF examination was normal (absence of atypical cells). Spine MRI was normal. No evident signs of recurrence of lymphoma. Neurological examination: negative Lasègue test, normal strength at the four limbs, normal evaluation of the large-caliber sensory fibers, hyperalgesia and allodynia involving the feet, bilateral areflexia at the lower limbs. Pain made deambulation impossible. Presence of dysautonomic symptoms.

Quality and intensity of pain: VAS 10/10. Burning, stabbing, and lancinating pain that was worsened by contact with the sheets. It was associated with vasomotor phenomena and dyshidrosis. No results from i.v. morphine infusion (except major sedation). Three days after onset of symptoms, there was the onset of bilateral facial paralysis. Seven days later the neurophysiological control showed proximal conduction blocks, prolonged F-waves, and early denervation in the distal muscles. CSF control detected albumin-cytological dissociation. The diagnosis of Guillain-Barrè-Syndrome with atypical onset was made. Treatment with IVIg 2g/kg in five days and pain treatment with oral Gabapentin 2400 mg daily and oral Oxcarbazepine 1800 mg daily was started. Rapid and progressive pain relief was achieved. At 6 months the patient was again asymptomatic.

Neuropathic pain is a frequent initial symptom in GBS, mainly in children (approximately 40% of cases). In one series of 223 adult patients with GBS, pain was present in 55% of cases, but only 18% of these had neuropathic pain. In the remaining cases, the pain was nociceptive and related to muscular or osteoarticular problems. Burning dysesthesia may last many months. Methylprednisolone does not seem to show any effect on the presence and intensity of pain.

11.1 Case Study 2 (Atypical)

MR, 17-year-old female. Born with normal childbirth. Birth weight 4.200 kg, preeclampsia. No parental consanguinity. One cousin with Down syndrome (possibly mosaic).

No other information of genetic interest. Retroperitoneal hemangioma operated at birth. A general examination showed four light coffee-colored patches of varying diameter (one on the neck made of other small spots) as well as foot dysmorphism characterized by flat feet with asymmetrical toes (II and IV toes longer bilaterally), prominent instep, and tendency to internal rotation. The patient arrived in the emergency department because of the sudden onset of flaccid paralysis of the right arm. Physical examination showed:

- Mild dysphonia.
- Right arm falling alongside the right shoulder lower than the left.
- Abduction and elevation plegia of the right upper limb, valid adduction.
- Severe weakness of forearm flex and plegia of the extension of the same limb. No other neurological deficits to the remaining limbs.
- Areflexia of the right arm. Reflexes were weak in the left arm and absent in the lower limbs. An MRI of the spine was performed in the emergency room with negative results, as well as an ENG/EMG showing the absence of SAP in the right arm, which also had severe alteration of the proximal and distal cMAP . No spontaneous activity was detected at the needle examination. Neurophisiological examination was normal in the left arm or in the legs. A CSF test was performed. Results were normal regarding cell count (absent) and proteins. Blood tests showed the presence of Epstein-Barr virus genome 1720 copies/mL and cytomegalovirus genome 380 copies/mL. Two days after admission, the clinical picture was changing dramatically: the patient was dysphagic, especially for liquids, and dysphonic, requiring NIV. No deficit of intrinsic or extrinsic ocular motility. No deficit of the facial nerve. Muscle weakness of the upper limbs still appeared asymmetrical. The right arm appeared almost completely plegic. The left arm had a slight predominantly distal weakness, notably on the dorsal flexion of the hand.

Deep tendon reflexes disappeared everywhere. She complained complete weakness of the right leg with areflexia. The left leg showed severe weakness mainly proximal with areflexia (the patient was unable to raise it up off the bed). Plantar response was normal bilaterally. Sensory examination was normal. The patient could discriminate touch and puncture adequately throughout the body.

The patient received an IVIg cycle (2 g/kg for 5 days), which lead to a slight improvement in dysphagia and dysphonia. After a week she underwent a new CSF analysis and a new ENG/EMG, the results of which confirmed the diagnosis of AIDP (GBS). We believed the nadir of the disease had been reached and that a slow and gradual improvement may then follow.

After a further 4 days, the patient again had dyspnea and dysphagia and was therefore intubated and the nasogastric tube reinserted. Fourteen days after the end of the first IVIg cycle, the patient was deteriorating clinically, and so a second IVIg cycle was delivered at the same dose (2 g/kg 5 days). After the end of the second cycle, the patient appeared to be improving. She was extubated and could breathe adequately.

The patient's voice was stronger, she could take fluids orally without difficulty and move her left arm easily lifting it off the bed. The strength was normal in the left leg.

The strength of the right limbs was substantially unchanged and there was an almost complete hemiplegia of the limbs themselves. Two months after the onset of symptoms, the patient shows a marked weakness of the right limbs, which she could lift up 15–20 cm off the bed. Only mild or no weakness of the left limbs. No sensory deficits, no sphincter problems. The patient was eupneic and not dysphagic.

11.2 Clinical Case

11.2.1 Clinical History

Fifty-five-year-old man with a medical history of arterial hypertension and dyslipidemia.He was admitted to the emergency department complaining of a dry mouth, blurred

vision, and difficulty swallowing solid and liquid food, which started after dinner. Within a few hours, there was rapid progression of symptoms with developement of ptosis, diplopia, dysarthria, weakness of facial muscles and respiratory difficulties. The neurological examination showed slightly reactive mydriatic pupils, limitation of eye movements in the horizontal plane, bilateral ptosis, dysarthria, dysphagia, and weakness of the proximal muscles of four limbs. Deep tendon reflexes were widely hypovalid; all sensory modalities and coordination were normal. There was no history of recent infection, vaccinations, tick bites, journeys, or exposure to toxins.

11.2.2 Synthesis

This is the clinical history of a man who presented with acute onset of rapidly progressive weakness involving extraocular, bulbofacial, respiratory, and axial muscles. Weakness was associated with pupillary involvement and hypovalid deep tendon reflexes.

The main diagnostic hypotheses included Guillain-Barré syndrome, myasthenia gravis, Eaton-Lambert myasthenic syndrome, botulism, porphyria, Lyme disease, and organophosphorus intoxication. Blood tests and cerebrospinal fluid (CSF) examination were normal. The patient underwent a series of neurophysiological investigations:

Nerve conduction studies

Motor NCS

Nerve/position	Latency (ms)	Amplitude (mV)	Velocity (m/s)	F-wave (m/s)
S facial—ORB oculi				
Anterior tragus	NR	NR		
S ulnar—ADM				
Wrist	2.75	2.5		NR
B elbow	6.35	2.3	58.3	

(continued)

(continued)

Nerve/position	Latency (ms)	Amplitude (mV)	Velocity (m/s)	F-wave (m/s)
R median—APB				
Wrist	3.2	3.5		NR
Antecubital fossa	6.8	3.2	54.1	
S COMM peroneal—EDB				
Ankle	4.10	2.1		NR
Fib head	9.60	1.9	43.1	
D COMM peroneal—EDB				
Ankle	3.90	1.3		
Fib head	9.75	1.1	41.5	
D tibial (knee)—AH				
Ankle	5.20	2.2		NR
Knee	14.30	1.8	42.3	

SENSORY NCS

Nerve/position	Latency (ms)	Amplitude (μV)	Velocity (m/s)
S ulnar—digit V			
Wrist	2.7	30.1	49.1
R median—digit II			
Wrist	3.2	25	47.3
R sural—lat malleolus			
Calf	3.4	7.5	43.1
L sural—lat malleolus			
Calf	3.3	8.1	44.1

NEEDLE EMG

EMG summary table

	Spontaneous					MUAP			Recruitment
	IA	**Fib**	**PSW**	**Fasc**	**H.F.**	**Amp**	**Dur.**	**PPP**	**Pattern**
R first interosseous	1+	None	None	None	None	1–	1–	1+	Early
R biceps brachii	1+	2+	None	None	None	1–	1–	1+	Early
L deltoid	1+	1+	None	None	None	1–	N	1+	Interference
R vast medialis	1+	None	None	None	None	1–	N	1+	Interference
L tib Anterior	1+	1+	1+	None	None	1–	1–	1+	Early
R gastrocn (med)	1+	None	None	None	None	1–	1–	N	Interference
R tib anterior	1+	1+	1+	None	None	1–	1–	1+	Early
L iliopsoas	1+	1+	1+	None	None	1–	1–	1+	Early

Repetitive nerve stimulation

Nerve	Recording	Stimulation frequency/ exercise	Decrement/increment
Left ulnar	ADM	3 Hz	12% decrement
		20 Hz	150% increment
		10 s exercise	200% increment
Right facial	Nasalis	3 Hz	15% decrement
		20 Hz	200% increment
		10 s exercise	250% increment

11.2.3 What Kind of information Did We Obtain from Neurophysiological Data?

The combination of widely reduced CMAP amplitude with normal distal latency and conduction velocity, associated with normal sensitivity conduction, suggested among the possible diagnostic hypotheses: myopathies, motor axonal neuropathy, motor neuronopathies, polyradiculopathies, or neuromuscular junction disorders.

To assess the hypothesis of a neuromuscular junction disease, an EMG with repetitive nerve stimulation was performed. Low-frequency stimulation showed a decremental response; howeverfacilitation and high-frequency stimulation showed an incremental response, suggesting a presynaptic disorder of the neuromuscular junction.

The electromyographic examination documented increased insertional activity and the presence of spontaneous activity in the form of fibrillation and jasper in various muscles, suggesting acute denervation. Furthermore, myopathic features were detected in some muscles.In summary, the neurophysiological findings were consistent with a presynaptic disorder of the neuromuscular junction with denervating features.

The clinical picture of a rapidly progressive descending paralysis, together with electrophysiologic findings were compatible with a diagnosis of botulism. Subsequently, the patient revealed that he had consumed homemade fruit jam. The triva-

lent antitoxin was administered within 24 h, with a slow and gradual improvement of the clinical picture over the following weeks. Botulinum toxin type B was isolated in the patient's serum and stools.

11.2.4 Why Were Myasthenia Gravis and Lambert-Eaton Myasthenic Syndrome Excluded?

MG may present with an acute onset of extraocular, bulbar, axial, and respiratory weakness. However, autonomic dysfunction does not characterize MG. Furthermore, even if a decremental response to low frequency repetitive nerve stimulation is typical for MG, an incremental response to high frequency stimulation or after brief exercise and the presence of reduced CMAP amplitude are not consistent with the diagnosis of MG. Furthermore, although MUAPs may be small and short with early recruitment, the presence of spontaneous activity is unusual in MG.

The combination of reduced CMAP amplitude and incremental response to high frequency repetitive nerve stimulation or after brief exercise is typical of Lambert-Eaton myasthenic syndrome (LEMS). However, needle examination is usually normal in LEMS. There are also important clinical differences between LEMS and botulism. LEMS typically presents with proximal weakness and areflexia with progressive deterioration over months,on the contrary botulism is characterized by acute onset and rapid progression of symptoms.

11.2.5 What Other Diagnoses Might Be Taken into Consideration?

Neurophysiological tests help distinguish botulism from other causes of acute paralysis—Guillain-Barré syndrome, porphyria, tick paralysis, poliomyelitis—which may present reduced CMAP amplitude but do not present incremental response to repetitive nerve stimulation.

Furthermore, Guillain-Barré syndrome reveals typical signs of demyelination on nerve conduction studies (increase in distal latencies, F-wave elongation, reduced conduction velocity, conduction blocks) and a reduced recruitment of MUAPs on needle EMG. Other important clinical aspects to bear in mind in differential are that tick paralysis presents with rapidly ascending weakness and porphyria is accompanied by abdominal pain and psychiatric disorders, while organophosphorus intoxication is accompanied by miosis and fasciculations.

As far as intoxication by organophosphorus is concerned, conduction studies can document repetitive CMAPs after a single stimulus, but there is no incremental response after high-frequency repetitive stimulation or after brief exercise.

11.2.6 How Do You Explain the Electrodiagnostic Signs Associated with Botulism?

Botulinum toxin binds to the presynaptic terminals and reduces the release of acetylcholine from autonomic and motor nerve terminals. This causes the detection of low-amplitude CMAP, with normal values of distal latencies and motor conduction velocity. Sensory nerve action potentials are not altered. High-frequency repetitive stimulation, or brief exercise, determines an increased release of acetylcholine quanta and higher endplate potentials: consequently, a greater number of muscle fibers reach the threshold value and this leads to an increase in CMAP amplitude. In the most severe cases of botulism however, the neuromuscular junction may be so blocked that even facilitation from brief exercise or high frequency repetitive stimulation may not be able to raise the endplate potentials above threshold. In such cases muscle fiber are chemo-denervated from the botulinum toxin and fibrillation potentials are noted on needle EMG examination.

Part III
Differentiated Decisional Algorithms

Chapter 12
Differentiated Decisional Algorithms Based on the Technical and Organizational Characteristics of the Hospital Receiving the Clinical Case

Elena Pinuccia Verrengia, Stefano Jann, and Andrea Rigamonti

This chapter presents the algorithms for decision-making in case of myasthenia gravis, inspired not only by the clinical aspects but also by the organizational, technological, and professional characteristics of the hospital caring for the acute patients. A summarizing table (decisional algorithm) classifies the various settings (A, B) in which clinicians manage patients. These algorithms are to be considered as reference material

E.P. Verrengia
Department of Neurology, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

S. Jann (✉)
Department of Neurology and Stroke Unit, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
e-mail: stefano.jann@ospedaleniguarda.it

A. Rigamonti
Department of Neurology, ASST, Lecco, Italy

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for helping physicians in selecting the most adequate pathway according to the hospital facilities available.

The decisional algorithms are organized and diversified into two main situations that suggest the same number of different practical behaviors aiming at guaranteeing the best care, albeit in different organizational situations. This really brings to the fore: the concept of network and of organization through the hub and spoke model.

Legend for the Algorithms

Ab AchR: autoantibodies against acetylcholine receptor
Ab MuSK: autoantibodies against muscle-specific kinase
RNS: repetitive nerve stimulation
SFEMG: single-fiber EMG
ICU: intensive care unit
PE: plasma exchange
IVIg: intravenous immunoglobulin
MG: myasthenia gravis

12.1 Differentiated Decisional Algorithms

12.1.1 Decisional Algorithms

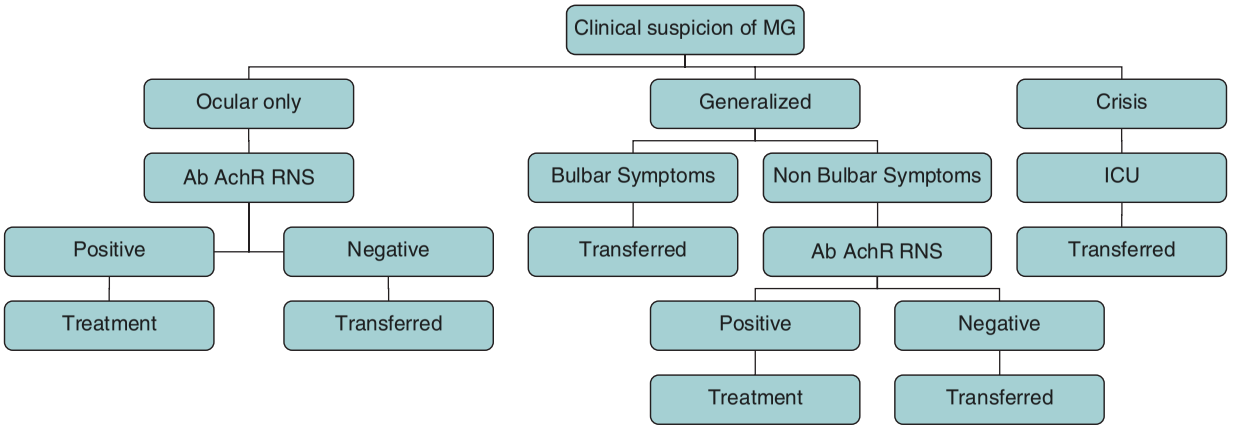
Setting A:

Emergency department 24/7
Radiology services 24/7
Laboratory services 24/7
Department of medicine
Consultant neurologist

Setting B:

Emergency department 24/7
Radiology services 24/7
Laboratory services 24/7
Department of neurology with specialist in neuromuscular disorders
Neurologist 24/7

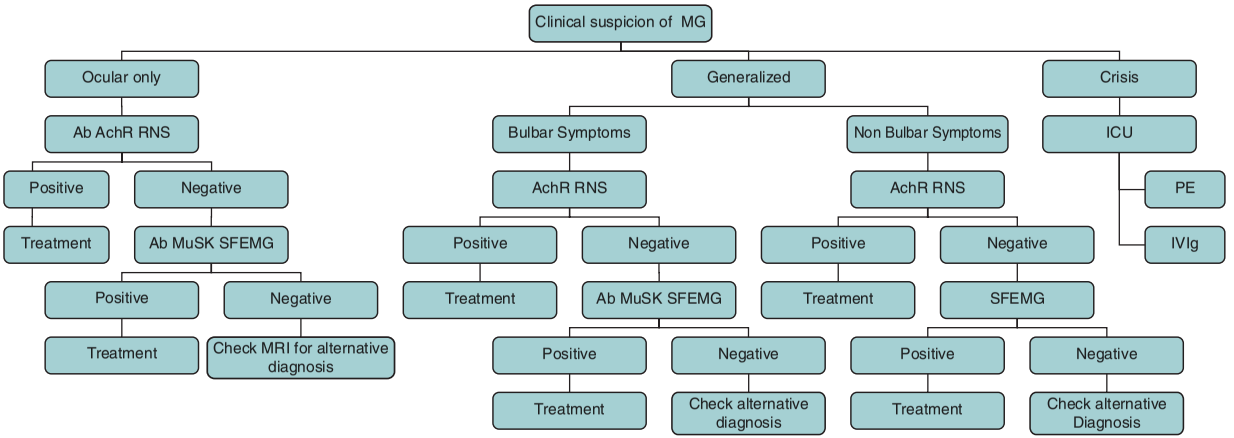
First algorithm: “setting A”



Legend:

Ab AchR: autoantibodies against AcetylCholine Receptor
RNS: Repetitive Nerve Stimulation
ICU: Intensive Care Unit
MG Miastenya gravis

Second algorithm: “setting B”



Legend:

Ab AchR: autoantibodies against AcetylCholine Receptor
Ab MuSK: autoantibodies against Muscle Specific Kinase
RNS: Repetitive Nerve Stimulation
SFEMG: Single Fiber EMG
ICU: Intensive Care Unit
PE: Plasma Exchange
IVIg: Intravenous Immunoglobulin