Imitators of Epilepsy

Second Edition

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Demos

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Dedication

We would like to dedicate this book to our families.
To Nora Frenkiel, Emma, Alexander, Lenna and Martin Kaplan,
and Donna Fisher

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Preface

In writing the second edition of *Imitators of Epilepsy*, we note that the intervening years of teaching residents and medical students and the frequent consultations with patients in the clinic, only have served to highlight the special need for such a text. Even with the increasing availability of numbers of subspecialized neurology books and access to online texts, the clinician often still faces the diagnostic dilemma "was it an epileptic seizure"? Clinicians frequently hunt for the appropriate panel of questions, usually with a relatively restricted choice of helpful physical findings and investigations. As practitioners, we are most interested in the relative sensitivity and specificity of particular clinical symptoms, and those constellations of symptoms that would point (hopefully relatively accurately) to one of several similar diagnostic possibilities. Unfortunately, such a helpful paradigm is not available to guide management of the many conditions that can look like seizures. We hope that the gathering of clinical wisdom is the next best thing.

In the out-patient setting inhabited by internists, general practitioners, neurologists, emergency room physicians, and other subspecialists, patients frequently are referred for spells and to determine whether they have had seizures. Out-patient evaluation is directed at determining whether a patient has one of the many conditions that may imitate epilepsy. As in the first volume, these conditions are the focus of this book.

The most important imitators of epileptic seizures are dizziness, vertigo, syncope, and complicated migraine. Somewhat less frequently sleep disorders, transient cerebral ischemia, paroxysmal movement disorders, endocrine or metabolic dysfunction, delirium, psychiatric conditions, or transient global amnesia act as imitators. Clearly under-recognized are hyperventilation episodes, panic attacks, and other psychogenic and psychiatric paroxysmal disorders that may simulate epileptic seizures. Only a multi-volume textbook of medicine could possibly do justice to the entire range of conditions. The goal of this edition is an exposition of the differential diagnosis of seizures: how do the imitators of epilepsy present clinically, what are their particular distinguishing historical features, and what tests are helpful with diagnosis?

Expanding beyond the first edition on this subject, this edition is divided into four sections. After a chapter on an approach to diagnosing spells, the first section deals with electroencephalography of epilepsy and its imitators, as well as specialized tests of diagnosis such as measurement of serum prolactin. There are chapters on epileptic seizures that do not "look like typical" epileptic seizures, and conversely, apparent epileptic seizures that are not. A second section approaches imitators of epileptic seizures along age-based lines; i.e., what sorts of spells are likely to beset infants, children, or the elderly? A third section addresses individual imitators of epilepsy, ranging from the common to the rare, from dizziness and faintness to startle disease, arranged according to whether they might simulate partial, generalized, or both types of epileptic seizures. The volume finishes off with

hyperventilation syndrome, psychogenic seizures (with or without epilepsy), and panic disorders.

Most chapters contain a review of the basic definitions and physiology of the respective imitator, followed by the clinical characteristics, emphasizing those that may differentiate it from an epileptic event, but also mark it for what it is and give possible criteria for an alternate diagnosis. Case vignettes are used to illustrate particular aspects, along with tables that compare and contrast phenotypically similar conditions. From their experience, the authors will provide a personal perspective regarding diagnosis and treatment.

This volume is based on the diagnosis of epilepsy. A primary difficulty in diagnosing epilepsy is the variability of epileptic seizure types. Although stereotyped in a given patient, even epileptic seizures identified as arising from the same brain area may have different semiologies in different patients. Epileptic seizures may present with such disparate features as formed visual hallucinations or tingling in the left hand. Nonetheless, epileptic phenomena typically fall into recognizable clinical patterns. As many have noted, the "border lands" of epilepsy cover a vast, poorly charted territory. *Imitators of Epilepsy* will have been successful if it serves to increase the awareness of physicians for factors that distinguish epileptic seizures from their imitators, and to provide guidance to support clinical judgment in approaching patients with possible seizure disorders.

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Introduction
Approach to the Diagnosis of Possible Seizures

Robert T. Wechsler, MD, PhD
and Robert S. Fisher, MD, PhD

The patient with a "spell" of altered sensorimotor function, consciousness, or behavior presents a major diagnostic challenge, because the differential diagnosis is broad, the history is frequently sketchy, and the physical examination often is noncontributory (1,2). Under these conditions, the clinician must be able to recognize certain patterns from fragmentary clues. These patterns will point to a likely etiology for the episode and give a sensible structure to further evaluation.

Terminology in this area of medicine is confusing (3). In the following text, the word *seizure* is used to describe a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. The abnormal electrical activity may not be explicitly demonstrated, because electroencephalograms (EEGs) concurrent with the behaviors are usually lacking. If the etiology of a clinical episode is not epilepsy, then the word "seizure" should be avoided, and less specific terms should be employed. Imprecise terms also should be avoided during the evaluation of nonepileptic events. Patients sometimes refer to any event of catastrophic magnitude as a seizure or fit, such as "having a heart seizure" or "throwing a fit." Physicians may tell patients that they have nonepileptic seizures as a face-saving device; unfortunately, use of the word seizure may perpetuate the patient's foggy understanding of the underlying condition. This term also has become synonymous for psychogenic nonepileptic events and, thus, should not be applied if an alternative physiologic etiology is suspected. The term "psychogenic seizure" literally connotes an epileptic seizure generated by psychologic factors—a rare entity indeed. The term "pseudoseizure" has, rightly, fallen out of favor because the modifier "pseudo" implies faking to some patients. The term "functional" is an entrenched synonym for psychologic and psychosomatic, even though patients with functional illness tend to be dysfunctional. Whenever possible, the suspected underlying physiologic etiology should be employed in the description of transient neurological events. Some episodes of altered consciousness result from seizures, but many do not.

Table I-1 lists the most important imitators of epilepsy. Perhaps the most common cause of transient alteration of consciousness is syncope, which broadly can be divided into cardiac and noncardiac etiologies. Causes of cardiac syncope can include arrhythmias, aortic stenosis, coronary syndromes, cardiomyopathy, pulmonary embolism, pulmonary hypertension, cardiac tamponade, aortic dissection, the long QT syndrome (LQTS), and the Brugada syndrome (4–6).

As a group, noncardiac causes of syncope are more common. This category includes neurally mediated

TABLE I-1
Imitators of Epilepsy

- Syncope
  - Cardiovascular
    - Arrhythmias
    - Other cardiac and coronary syndromes
    - Circulatory obstruction
  - Noncardiogenic
    - Vasovagal syncope
    - Reflex syncope syndromes
    - Hypovolemic or hypotensive syncope
- Transient ischemic attacks
- Transient global amnesia
- Atypical migraine
- Vertigo
- Toxic and metabolic
  - Hypoglycemia
  - Waxing and waning delirium
  - Alcohol or drug-related syndromes
- Sleep disorders
- Intermittent movement disorders
- Breath-holding spells
- Gastric reflux or esophageal spasm
- Psychiatric causes
  - Nonepileptic events
  - Other conversion reactions
  - Panic attacks, anxiety, hyperventilation episodes
  - Depression
  - Malingering

reactive syncope syndromes, in which hypotension or bradycardia occur secondary to a precipitating stimulus. Examples include vasovagal syncope, carotid sinus hypersensitivity, and a variety of situational syncope syndromes including coughing, micturition, defecation, and swallowing (4–8).

Orthostatic hypotension is another important cause of syncope. It can be associated with autonomic dysfunction or be independent from it (8). Transient ischemic attacks (TIAs) in the anterior or posterior circulation can be confused with a seizure (9), as can transient global amnesia (10), drop attacks (11–13), and atypical migraine syndromes (14). A waxing-and-waning delirium can result from any of the many causes of metabolic encephalopathy, including hypoglycemia (15), as well as from a variety of toxic exposures, including alcohol (16) and the various drugs of abuse (17). Parasomnias, narcolepsy, and daytime hypersomnolence can all be associated with altered neurobehavioral function (18–20). Movement disorders associated with tics (21) or tremors and the paroxysmal kinesigenic dyskinesias (22) can all be confused with seizures.

TABLE I-2
Factors to Consider in Spell Diagnosis

- Setting for precipitating factors
- Prodrome
- Time course
- Stereotypy
- Behavior during episode
- Ameliorating factors
- Nature of recovery

Dizziness and vertigo (23–25), if recurrent and transient, can raise the concern for the presence of a seizure disorder. In infants, relatively benign episodes such as breathholding spells (26) and gastroesophageal reflux (27) can precipitate an evaluation for seizures. Psychologic causes of altered neurobehavioral function include psychogenic nonepileptic events (28) and other conversion reactions, panic attacks, anxiety, and hyperventilation episodes (29–31), malingering, and depression. Each of these is considered in detail elsewhere in this volume.

EVALUATION OF THE PATIENT WITH SPELLS: HISTORY

The key features of a spell history include setting, prodrome, time course, stereotypy, precipitating and ameliorating factors, behavior during the episode, and the nature of recovery (Table I-2).

The history should be taken from the patient and from an observer, since an alteration of consciousness by definition impeaches a patient's capacity to fully describe the episode. With complex partial or absence seizures, and in some transient ischemic attacks, it is common for a patient to maintain that there was no loss of consciousness, whereas an observer will report a clear interval of partial or complete unresponsiveness. In spell diagnosis, a phone call to an observer is always a worthwhile effort.

Setting and Precipitants

The most useful diagnostic maneuver for the evaluation of patients with spells is an elicitation of a detailed description of the onset of symptoms. Information should be obtained regarding setting. Reactive syncope is characterized by hypotension or bradycardia occurring in the setting of a precipitating stimulus such as emotional upset, phlebotomy, coughing, urination, or defecation (7,8,32). Conversion reactions also can

be associated with altered neurobehavioral function. A few convulsive jerks in a setting suggestive of syncope simply may reflect convulsive syncope, secondary to transient hypoxia, rather than epilepsy (33–36). Even a new-onset generalized tonic-clonic convulsion can represent a cardiac etiology with prolonged ischemia (34). Confusion while fasting is likely to be from hypoglycemia. Loss of consciousness upon arising after prolonged bed rest probably is hypovolemic and hypotensive in origin. Breath-holding spells in children occur in a characteristic setting: the child works up to a temper tantrum, stops breathing, turns blue, and only then has a seizure (26). Individuals may, when asked, report anxieties or phobias leading up to the episodes, thereby suggesting functional etiologies, such as hyperventilation spells, panic attacks, or conversion syndromes. Vertigo may be precipitated by sudden changes of head position, for example, upon tilting the head back to change a light bulb in the ceiling. Rarely, loss of consciousness with head position change may be a consequence of sudden alteration of intracranial pressure, as with hydrocephalus (37), colloid cyst of the third ventricle (38), or Chiari malformation (39,40). Seizures sometimes imitate the catastrophic condition, brainstem herniation (41), and vice versa. Hypoglycemia occurs in a setting of fasting or reaction to a large carbohydrate load and should be considered when neurobehavioral disturbance occurs in this setting (15). Patients with diabetes or eating disorders are prone to hypoglycemia. Alcohol consumption may be difficult to ascertain by history, but heavy ethanol intake can predispose to alcoholic blackouts and spells from simple intoxication (16).

Seizures are notable for their spontaneous occurrence at unpredictable times, with the exception of a relation to the sleep–wake cycle or the menstrual cycle. Episodes that awake an individual from sleep are not likely to be functional. To apply this principle, the historian must be clear that the attack occurred during sleep, and not soon after arousal.

Patients and observers should be asked directly what was happening just before the attack occurred and whether they have an indication of what brought about the attack. As an illustration, consider a developmentally delayed young man who is seen for episodes of nondirected violence with lack of recall for the events. The question arises whether he is having seizures. Discussion with his counselors reveals that all his episodes occur at a time of frustration with his daily tasks or interactions with others; none occur spontaneously during peaceful times. This history would weigh against epilepsy as an etiology and argue strongly for a psychiatric-behavioral cause of the spells.

Hyperventilation spells are common (29–31,42). A history of heavy breathing in a setting of anxiety may point to hyperventilation as an etiology. Unfortunately, hyperventilation often goes unobserved, because the increase in respiratory rate can be subtle. Prodromes of lightheadedness and perioral or digital numbness should raise suspicion for underlying hyperventilation spells.

Experienced physicians maintain skepticism about reported precipitants of spells. Every seizure clinic is replete with patients whose attacks only occur when the moon is full, on a particular day of the week, when they are constipated, when the weather is hot (or cold), when their spouse is present, or when they are not in a physician's office. Functional episodes have variable onsets and precipitants, often highly idiosyncratic. Conversion symptoms and anxiety attacks, although related to levels of anxiety, often occur at quiet times. When informed that spells are "stress related," patients often argue that they take place at times when they are relaxed, cheerful, and engaged in mundane activities; watching TV appears to be a favorite. On the other hand, episodes that are consistently precipitated by stressful situations are likely to be nonepileptic, and they may be functional or migrainous. The relationship of stressful settings and immediate precipitation of physiologic seizures is weak.

Peculiar precipitants argue for functional etiologies. Syndromes of "reflex epilepsies" are exceptions to this rule (43). Approximately 3% of patients with epilepsy are likely to seize when exposed to flashing lights at photic frequencies of 5 to 20 per second (44). Unusual precipitants for reflex epilepsies have been documented: sounds (45), music (46,47), singing (48), reading passages of text (49,50), drawing (51), writing (52), eating (53–55), exposure to water (56) or a hot bath (57,58), blinking (59), eye convergence (60), talking on the telephone (61), or even certain stereotyped patterns of thought (62). In our experience, the majority of cases of unusual reflex precipitants are functional. Video-EEG documentation is required to characterize usual (nonphotic) reflex precipitants.

Factitious spells (malingering) usually occur in a setting of litigation, disability evaluations, avoidance of unpleasant duties, drug-seeking, or insurance disputes. The examiner should not be shy about eliciting a history of these factors. Nevertheless, physiologic illnesses, such as posttraumatic epilepsy (63) or posttraumatic migraines (64), may be present and call for an open-minded evaluation.

The ability to precipitate a spell by suggestion is a reliable indicator of a conversion syndrome. However, several subtleties are involved in the interpretation of

spell induction, and these are considered in a section below.

Prodrome

The nature of the start of an episode is most informative. Patients should be asked to describe the prodrome of their spells in detail. Certain auras are not only characteristic of complex partial seizures, but also can aid in localization. Such auras include gastrointestinal upset, body heat or tingling, perceptual distortions, déjà vu, and inappropriate emotionality (65–68). Vasovagal syncope usually is heralded by lightheadedness, anxiety, cold clammy skin, pallor, and slowing of the heartbeat (8). Cardiac arrhythmias may be associated with palpitations, but so can several other nonspecific conditions. Such symptoms can overlap with those seen at the start of a hypoglycemic episode (15), but hypoglycemia usually also carries a recognizable gnawing hunger. A narcoleptic attack is initiated by a sense of uncontrollable sleepiness. Vestibular disease presents a sense of spinning or tilting in space. The term "dizzy" requires elaboration in order to ascertain whether the patient means vertigo, connoting vestibular disorders, or lightheadedness, connoting presyncope, migraine, or functional episodes. Vertigo itself may derive from several conditions: most commonly, medication toxicity, alcohol, benign positional vertigo, vestibular neuronitis, Meniere's syndrome, tumors or lesions of the vestibular nerve, brainstem or cerebellar disease, or vestibular migraine (24).

Complicated migraines present a wide variety of prodromes, but visual symptoms, such as shimmering lights, scotoma, or blurring of vision are common. Migrainous spells also can include more typical common migraine symptoms of headache, nausea, lightheadedness, or photophobia. The classic order of visual symptomatology followed by headache may not apply in practice; headache may precede, follow, or occur concurrently with other symptoms. Acephalgic migraine—migraine without headache—is a diagnostically difficult entity and probably more common than is generally recognized. The clinician should be aware of the ability of certain forms of complicated migraine to induce loss of consciousness (69,70).

Time Course

Epileptic seizures have a clear start and finish, usually lasting for a period of a few seconds to a few minutes. Episodes that fluctuate for hours either are exceptional cases of status epilepticus or, more likely, nonepileptic events. True status epilepticus, whether tonic-clonic or nonconvulsive, is a serious and disabling event. Patients are slow to return to normal consciousness and function after status epilepticus. When in doubt, an EEG can be helpful in diagnosis. The EEG is always abnormal during status epilepticus, although tracings may reveal only nonspecific findings, such as slowing. The "reprise phenomenon," by which a patient halts a spell, returns to relative normalcy, and then slips back into the episode, suggests a functional etiology. The famous artist Vincent van Gogh corresponded to his brother, Theo, about episodes of confusion, vertigo, distorted perceptions, and mood alterations lasting for days (71). Although van Gogh may well have had epilepsy, these particular episodes were much more likely generated by other causes, such as manic-depressive illness (72) or, less likely, vestibular disease (73). The time course was not consistent with seizures.

Unfortunately, many of the imitators of epilepsy exhibit time courses similar to seizures. Syncope, TIAs, confusional migraine, and sleep disorders can progress over an interval of seconds to minutes. In these instances, differential diagnosis must be based on other criteria.

Stereotypy

Stereotypy connotes similarity. Epileptic seizures in a given patient are fairly similar to each other. If there is an aura of heat and flushing prior to a seizure in some seizures, then this is likely to be the aura in all of those seizures exhibiting auras. Stated conversely, episodes with widely varying auras or behaviors are likely to be nonepileptic. An aura defines the site of seizure origin. Patients with true multifocal seizure origins are usually rather severely impaired, and diagnosis of epilepsy is not difficult. Exceptions do occur. The stereotypy of a true complex partial seizure will be altered by several factors: medication, environment, attentional state of the patient, and biologic variability.

Ameliorating Factors

Ameliorating factors consist of circumstances or activities employed by the patient to abort spells after they have begun. The clearest use of amelioration is paper-bag rebreathing to terminate a hyperventilation attack. Napping may terminate bouts of daytime hypersomnolence episodes or migraines, and food may shorten the duration of hypoglycemic episodes. The head-down position reverses symptoms of hypovolemic or vasovagal syncope. Lying still, perhaps in a specific posture (good ear down for benign positional vertigo), may reduce symptoms of vertigo. Anxiety attacks sometimes can be ended by relaxation exercises. Abstinence from alcohol consumption or from use of illicit drugs serve

for both diagnosis and treatment of spells related to substance abuse. Rare patients with epileptic seizures can inhibit their seizures with sensory stimulation (74). The experience of being in the hospital may in itself decrease seizure frequency (75).

Behavior during Episode

The appearance of an episode is one of the least reliable methods for diagnosing epilepsy. The entertainment industry has shown that actors convincingly can imitate seizures. Some patients are excellent actors. Additionally, the wide variety of behaviors seen during complex partial seizures grants great latitude to the appearance of a possible seizure. Chapter 3 lists a variety of behaviors observed in an epilepsy monitoring unit during seizures with documented concurrent EEG changes.

Although a variety of diagnostic strategies may be employed, beyond the history itself, video-EEG monitoring remains the most useful method for differentiating epileptic from nonepileptic events (76). Certain behaviors recognized since the days of Sir William Gowers (77) are unlikely to occur during an epileptic seizure. Video-EEG monitoring has been used extensively to catalog correlates of seizures with no EEG changes. Abrupt onset of unresponsiveness, thrashing and uncoordinated movements, rocking movements, and pelvic thrusting are particularly common in psychogenic seizures (28, 78–81).

Preservation of consciousness is impossible during a generalized tonic-clonic seizure. Patients who recall events or conversations transpiring during their generalized seizure are experiencing psychogenic or other nonepileptic episodes. This rule only applies to the period of diffusely generalized seizurelike activity, and it must be applied with caution. Many people with secondarily generalized epilepsy recall their auras or focal motor onsets. Rare cases exist in which preservation of awareness exists during bilateral tonic or clonic motor activity, presumably because of linked bilateral motor cortex seizure foci. Vague recollections of the postictal state also are physiologic. The definition of complex partial seizures requires only an alteration of consciousness, not its absence. Preservation of some awareness and (usually distorted) recall for events during a partial seizure does not rule out a diagnosis of epilepsy. Similarly, awareness and ability to recall is partially present at the start of absence seizures. Penry and associates (82) showed that stimuli presented within a few seconds after onset of EEG spike-wave discharges often were recalled; stimuli presented after more than 10 to 20 seconds of spike-waves were not.

Attention to Tasks during an Epileptic Seizure

Volitional behavior should not occur during a generalized seizure. A conversion syndrome is likely if a patient resists forcible eye opening during a generalized tonic-clonic epileptic seizure, avoids dropping limbs on the face, follows objects visually, turns repeatedly away from the examiner, preserves modesty, startles to a loud noise, or resists tickling. Conversely, failure to perform any of these actions does not rule out a conversion syndrome. Volition may be preserved in partial seizures, but it is usually of a rudimentary type.

Health care personnel inadvertently train patients in seizure behavior with leading questions. With little active intent on the part of the patient or physicians, conversion syndromes may be honed to a fine imitator of epilepsy. In such cases, even experienced clinicians may be incorrect about whether an observed episode was a seizure or conversion episode, with diagnostic errors in both directions.

Directed violence is not an expected component of epileptic seizures. Numerous defendants have employed the so-called "epilepsy defense" to explain a criminal act (83). The majority of such attempts have been unsuccessful, because most criminal acts involve complex behavior with considerable planning and cognition. A person cannot purchase a gun, drive to the victim's house, aim, and shoot during an epileptic seizure. However, aggressive acts that require little thought, such as pushing, hitting, grabbing, or shouting, are possible during seizures or the stage of postictal delirium.

Automatic behaviors can be performed during complex partial seizures. A task such as dishwashing could be completed during a seizure, although the task might be carelessly performed. Patients with complex partial seizures have been known to drive or walk home during a seizure, or find themselves in an unfamiliar location after a seizure. Such instances probably occur because complex partial seizures can disrupt memory acquisition. Responsiveness and behaviors may be relatively normal; they are simply not recalled. Similar phenomena are observed in cases of transient global amnesia.

Seizures originating in the frontal lobes present special problems in diagnosis (67, 84, 85). Perhaps the best example of this difficulty is the case of autosomal dominant nocturnal frontal lobe epilepsy (86). Previously known as paroxysmal nocturnal dystonia, this familial epilepsy syndrome was also often mistaken for night terrors or psychogenic events, but ultimately was determined to be due to a mutation in the alpha-4 subunit of the neuronal nicotinic acetylcholine receptor (87). Frontal lobe seizures characteristically are brief, associated with minimal loss of consciousness and quick return to consciousness, and may show atypical

behaviors, such as unusual facial expressions, twisting or posturing (supplementary motor cortex seizures) (88), or odd vocalizations. Their frequency can exceed dozens per day. Ictal EEG recordings may be negative during brief seizures from deep frontal foci, and serum prolactin levels from such seizures do not necessarily rise (89,90). As such, frontal lobe seizures are particularly likely to be incorrectly labeled as conversion reactions. The most difficult diagnostic cases require video-EEG monitoring, with careful direct observation.

Nature of Recovery

Immediate recovery after an apparent generalized tonic-clonic seizure favors a functional etiology. But this rule does not hold for all conditions producing loss of consciousness. Rapid recovery is common after syncope or positional vertigo. Postictal dysfunction following epileptic seizures can be divided broadly into early, intermediate, and prolonged effects. Early postictal disturbance is common in the first hour, particularly after complex partial seizures, and may include somnolence, disorientation, memory impairment, headache, and focal deficits such as paresis (91,92). Intermediate duration postictal deficits may last hours or even a few days. Postictal paresis is referred to as a Todd's paresis (92,93). Prolonged postictal dysfunction can be seen after seizure clusters or status epilepticus, in patients with underlying encephalopathy, and in the elderly. Manifestations include postictal encephalopathy (94), prolonged postictal paresis (95), and postictal psychosis (96). Conversely, an extremely prolonged recovery of a focal deficit might suggest that an episode was ischemic rather than convulsive. The coexistence of cerebral ischemia and epilepsy is possible, because cerebrovascular disease may be the most common identifiable etiology of new-onset epilepsy in the elderly. Unfortunately, clinicians have no easy method to determine whether prolonged limb weakness is a consequence of ischemia or a Todd's paresis. Further complicating the issue are rare seizures presenting primarily as hemiparesis (97,98).

EVALUATION OF THE SPELLS PATIENT: EXAMINATION

The key to spell diagnosis usually is in the history. The physical examination is of relatively limited value in the diagnosis of epilepsy, unless the examiner is able to examine a patient during a spell. Astute examiners rarely may observe clues to a syndrome associated with epilepsy, such as multiple café au lait spots or adenoma sebaceum, suggestive of tuberous sclerosis (99), or papilledema, indicative of increased intracranial pressure. Physical findings are more useful in diagnosing certain imitators of epilepsy. Table I-3 lists several potentially useful maneuvers and associated conditions. Predisposition to various forms of syncope can be detected by physical examination (4,8). Orthostatic blood pressures, allowing for at least 1 minute of standing, should be measured in patients thought to have hypovolemia or autonomic insufficiency. Cardiac auscultation may point to arrhythmias or valvular disease. Circulatory obstruction from such rare (in this setting) causes as tension pneumothorax, pericardial tamponade, or pulmonary embolus, can be detected by the cardiorespiratory examination. Transient ischemic attacks of the cerebral circulation are common. The presence of vascular bruits and abnormal peripheral pulses may provide indirect evidence for cerebrovascular disease. Abnormal sleepiness sometimes can be detected in clinic, once the clinician has calibrated the usual soporific potency of his or her clinic routine. Patients in a waxing-waning delirium show fluctuating alertness and cognition. Nystagmus and past-pointing with the eyes closed can be indicative of vestibular disease, mistaken for epilepsy.

TABLE I-3
Useful Physical Exam Maneuvers in Diagnosis of Spells

MANEUVER	CONDITION
Orthostatic blood pressures	Syncope
Listen for bruits	Cerebrovascular disease
Heart sounds	Arrhythmias, embolic sources
Check for nystagmus	Vestibular disease
Dix-Hallpike maneuver	Benign positional vertigo
Hyperventilation	Hyperventilation spells
Observe for sleepiness	Hypersomnia
Tics, tremors, chorea	Movement disorder
Mental status exam	Delirium
Nonphysiological findings	Functional disorder
Psychiatric screen	Affective or thought disorder

Anticonvulsants produce nystagmus, even in therapeutic doses; however, anticonvulsant-induced nystagmus is usually direction-changing with gaze and relatively symmetric upon looking left or right. Nystagmus from vestibular disease is most often asymmetric with directions of gaze and often comprises a rotatory component (24,100). The Dix-Hallpike maneuver, with rapid head tilt posteriorly and laterally, may bring out subtle nystagmus in positional vertigo (100). Examination for nystagmus with the ophthalmoscope may also be useful (101). Caution is indicated, because vestibular

symptoms are a recognized aura for certain complex partial seizures. With complex partial seizures, however, consciousness is altered.

A neurologic examination is useful for detection of movement disorders that might be confused with seizures. The examiner may observe tics, tremors, abnormal postures, dystonia, chorea, athetosis, myoclonus, or ballismus, suggestive of basal ganglia or motor system disease. Movement disorders often are intermittent. The distinction between certain abnormal movements and simple partial motor seizures can be difficult.

Certain patients with conversion symptoms or malingering exhibit nonphysiologic physical findings. Such findings include exact splitting of the midline with a sensory exam; regional anesthesia with preserved coordination of the impaired body part; dense numbness not corresponding to dermatomes, nerve plexi, or peripheral nerves; cylindrical tunnel vision; blindness with preserved visual fixation; distractible paralysis; and a variety of other findings.

INDUCTION OF EPISODES

It is useful to attempt the induction of an episode. This process begins by asking the patient or observers what conditions were present at the onset of the attack. These conditions should then be replicated if possible. If an attack occurred upon assuming the upright position or tilting the head back and to the left, the patient should be asked to do so in clinic. A diagnosis of orthostasis or vertigo, respectively, may emerge. Anxiety attacks related to phobias occasionally can be precipitated by putting the patient in a stressful situation.

Hyperventilation is an essential diagnostic maneuver for presumed hyperventilation spells. The procedure should be explained in advance, in clear and honest terms. In our practice, patients are told that subtle increases in rate or depth of breathing can lower the carbon dioxide in the blood, and that this in turn can alter the brain's circulation and chemistry. Hyperventilation can precipitate seizures or episodes that imitate seizures, without awareness by the patient of alterations in breathing patterns. The patient is then asked to breathe rapidly and deeply through the mouth, for a continuous time of at least 4 minutes, or until they become too symptomatic to persist. Most people become lightheaded and develop perioral or digital paresthesias during vigorous hyperventilation. A positive hyperventilation study is one that replicates the sensations and symptoms of a spontaneous spell. If a hyperventilation test is positive, the test should be repeated with attempted spell abortion by paper-bag rebreathing. The paper (never plastic!) bag over the mouth and nose recirculates exhaled carbon dioxide and rectifies hyperventilation-induced hypocarbia. Prolonged bag rebreathing does carry a potential risk for hypoxia (102) and, therefore, should be performed cautiously. Elimination of symptoms with bag rebreathing further supports a diagnosis of hyperventilation attacks and leads immediately to a therapeutic option for the spells. True absence seizures can be precipitated by hyperventilation. Precipitation of other seizure types is possible, but less common. To clarify ambiguous responses, hyperventilation can be performed with concurrent EEG monitoring.

Induction is a useful technique for the diagnosis of functional episodes (103,104). Patients with conversion symptoms may be very suggestible, allowing the induction of "psychogenic seizures" in clinic. The ability to precipitate and terminate a seizurelike episode by suggestion is strong evidence for a functional etiology. Several different methods for spells induction have been suggested. The precise method is not critical, but adherence to a few principles is very important. First, trickery and dishonesty should be avoided. We do not favor placebo injections. They may document conversion symptoms, but at the same time they can destroy the patient's trust of medical personnel. Such a loss of trust complicates subsequent medical care. Second, the patient should agree to allow a spell to be precipitated. Spell induction is a form of hypnosis (104), and like hypnosis, the patient must be guided rather than forced to an outcome. It is helpful to explain to the patient that observation of an attack is useful for diagnosis and therapy. Treatment must be directed to the right cause. On this occasion, perhaps the patient would be willing to allow an attack to occur in order to be able to choose the best treatment. A simplified list of possible etiologies can be presented in advance, including seizures, circulation problems, and subconscious psychologic (stress-related) causes. If the patient refuses to allow spell induction, we do not press the point, because failure is likely. On the other hand, induction often is successful in patients with psychogenic episodes who cooperate with induction.

In our clinic, induction is performed with a combination of hyperventilation and suggestion. The hyperventilation is used for dual purposes: testing for hyperventilation spells and as a general dissociative stimulus for the precipitation of any conversion symptom. The "dreamy-dizzy" state produced by hyperventilation provides a receptive condition for suggestion. Reassuring and positive statements are made during the hyperventilation: "You will soon be feeling dizzy"; "It will be difficult to feel your fingers"; "Soon you will start to feel strange." Such statements simply reflect the usual concomitants of hyperventilation, but they demonstrate to the patient that something is happening.

The patient is then told to nod his head as soon as he feels that his spell is coming on, so a notation can be made. The positive emphasis is on when he feels symptoms, not if he feels symptoms. Improvisation directed toward specific symptoms of the patient's reported attacks is useful. If attacks begin with left hand trembling, the examiner may comment that the left hand appears to be tremulous, or perhaps the examiner may even start it shaking to bring on the attack. Once an attack is sufficiently developed to allow characterization, suggestion is used to bring the patient back to baseline. An instruction is given to relax, breathe slowly, and let the spell pass. Encouragement is given that things are settling down. An alternative methodology uses guided imagery to produce an episode.

The next important principle of spell induction is that diagnosis occurs primarily in the "debriefing" session after an induction. It is not appropriate to induce peculiar behavior and conclude that a patient does not have seizures. The seizure may differ from the induced spell. When conversant, the patient should be asked how the episode that just took place was similar to and how it was unlike a typical spontaneous episode. A ranking of 0–10 on a scale of 0 (not at all like the spontaneous attack) to 10 (identical to the spontaneous attack) may be useful. Sometimes patients volunteer that the symptoms are stronger or weaker than a typical spell, but otherwise similar. Friends and relatives also may be asked to give opinions on similarity of an induced and spontaneous episode.

After an induction, immediate feedback should be given to the patient. If nothing resembling a typical spell occurred, we remark that hyperventilation does not seem to be a precipitating factor for the episodes. If the induction produced a psychogenic episode, then we inform the patient that the episode observed did not have the appearance of an epileptic seizure and that further evaluation is warranted. The possibility of psychologic etiologies is raised as an issue for further exploration. It is never possible to be certain that a patient does not have epilepsy, only that observed episodes are not seizures. This issue is discussed further in Chapter 4.

ROUTINE LABORATORY AND NEUROIMAGING TESTS

Most routine laboratory and neuroimaging studies contribute to the diagnosis of spells primarily by helping to rule out other etiologies. EKG, cardiac Holter monitoring, CXR, or ventilation-perfusion lung scans may be diagnostic of cardiac-induced episodes. Serum glucose can point to fasting hypoglycemia, or an abnormal glucose tolerance test may reveal reactive hypoglycemia. Glucose tolerance testing would be done only for a high index of suspicion based on the clinical history. Spells thought to be related to alcohol or drug abuse can be investigated by toxic screens of blood or urine. An impression of vestibular disease can be investigated with quantitative calorics and nystagmography. No blood tests or special diagnostic studies are presently widely accepted for the diagnosis of complicated migraine, although provocative tests, such as the histamine challenge, have been advocated by some. In general, routine laboratory studies and neuroimaging should be performed selectively in diagnosis of spells, based on a suspicion for particular etiologies.

Serum Prolactin

The measurement of serum prolactin is a useful blood test in diagnosing seizure disorders. Prolactin is a polypeptide hormone produced by the anterior pituitary, involved in milk production and endocrine function. Unlike most pituitary hormones, prolactin is under negative hypothalamic control via prolactin inhibiting factor. When seizure activity influences the hypothalamic-pituitary axis, prolactin inhibiting factor is presumed to be inhibited itself, and prolactin is released into the circulation. Trimble (105) first showed that serum prolactin rises with generalized epileptic seizures, but not with psychogenic seizure-like episodes. Complex partial seizures can also raise serum prolactin. Sensitivity is approximately 90% for tonic-clonic seizures and 70% for complex partial seizures (106). Complex partial seizures originating in the frontal lobes rarely elevate serum prolactin (89,90), again emphasizing the difficulty in diagnosis of frontal lobe epilepsy. Several conditions can generate false-positive elevations of serum prolactin (see Chapter 5), including: stress, surgery, general anesthesia, strenuous exercise, sleep, orgasm, breast stimulation, estrogens, endometriosis, primary hypothyroidism, prolactin secreting pituitary adenomas, multiple sclerosis, phenothiazines and butyrophenones, opiates, L-DOPA, bromocriptine, other ergots, apomorphine, metoclopromide, and some antiepileptic drugs. Therefore, acute rises of two to three times the baseline levels are more specific for the diagnosis of a seizure than is an elevated single serum level (106).

Serum prolactin elevations reach a peak 10 to 20 minutes after a seizure and return to baseline by 60 minutes after a seizure (107). This imposes a practical limit on the use of prolactin to diagnose epilepsy, because most spells occur away from a medical setting. We have shown that prolactin accurately can be assayed by pricking the finger and applying capillary blood to filter paper (108). The specimen is stable at room temperature for a week and may be analyzed at leisure. This finding opens the possibility of using a suitable kit in the

home or work setting to determine if infrequently recurrent spells are seizures. One remaining limitation of prolactin for diagnosis is a lack of available data on prolactin levels after several of the imitators of epilepsy, including cerebrovascular ischemia or migraine.

Electrodiagnostic Monitoring

The routine EEG is useful for diagnosing spells, but the interpretation of the EEG must be cautious. Many normal variants, such as asymmetrical vertex waves, wicket spikes, small sharp spikes, 14- and 6-per second positive spikes, and rhythmical temporal theta bursts of drowsiness (formerly called psychomotor variant), can be mistaken for interictal spikes and sharp waves (109; and see Chapter 1). Additionally, a few percent of the normal American population exhibit interictal epileptiform discharges in a baseline EEG (110,111). The combination of an ambiguous history for a seizure and normal variants in the EEG can be an invitation to inappropriate treatment. Conversely, many individuals who have epilepsy lack abnormalities on an interictal EEG (112). Repeat EEGs to a total of about four EEGs may increase the yield (113). Other procedures useful for eliciting abnormalities in the EEG are activating procedures such as sleep deprivation or use of extra scalp (114) or sphenoidal electrodes (115). Prolonged digital EEG recordings may be performed in the ambulatory setting (116). Ambulatory EEGs are useful in capturing spells, but care must be taken in interpretation, because they are very subject to movement artifact.

As discussed in Chapter 16, sleep studies are of value when the history suggests hypersomnolence as a possible etiology of an episodic disorder of consciousness (18–19). A sleep disorder mimicking epilepsy should not be mistaken for a seizure disorder linked to the sleep cycle (117,118).

Inpatient video-EEG monitoring is one of the most powerful methods for diagnosis of spells with altered neurobehavioral function (119–121). Such monitoring extends the eyes and ears of the clinician. Depending on the question being asked, long-term epilepsy monitoring can be helpful in establishing a diagnosis, in seizure classification, in the localization of seizure foci in presurgical evaluations, and in quantification of seizure activity(121). However, in monitoring units, EEG changes rarely provide a diagnosis for the many imitators of epilepsy.

PITFALLS IN DIAGNOSIS OF EPILEPSY

When epilepsy presents in a classical fashion, with recurrent complex partial or tonic-clonic seizures, accompanied by interictal epileptiform EEG patterns, the diagnosis is easy. Unfortunately, the history may be incomplete, or other medical conditions may confound the clinical picture. In these circumstances, the diagnosis of epilepsy depends on the clinical judgment and experience of the practitioner. Several potential diagnostic pitfalls are to be avoided (Table I-4).

TABLE I-4
Pitfalls in Diagnosis of Epilepsy

Obtaining an inadequate history
Overemphasizing the rare and obscure
Leading the patient to an inaccurate history
Mixed seizures and psychogenic seizures
Over-reading the EEG
Overinterpretation of a therapeutic trial
Incorrect attribution of causation

The cardinal error is obtaining an inadequate history. Observers of spells should be queried directly. "Dizzy spells" without loss of consciousness may be revealed by co-workers to be full tonic-clonic seizures. Diagnosticians should not train patients to give a textbook seizure history. By the time multiple physicians have asked a patient if they have ever experienced an odor "like burning rubber" at the start of their seizure, most patients have convinced themselves that they have.

The improper interpretation of an EEG can cause great harm. Many benign and normal variant patterns can be mistaken for epileptiform discharges (109). The combination of a shaky history and an overinterpreted EEG is especially pernicious. The diagnosis of epilepsy may suffer from incorrect attribution of causation. Focal seizures can cause a postictal transient hemiparesis (Todd's paresis) (92,93), but cerebrovascular insufficiency can directly cause hemiparesis and a seizure (122). Bilateral carotid occlusive disease can cause brief loss of consciousness (123). Distinguishing primary epilepsy from epilepsy secondary to cerebrovascular disease can be difficult. A setting conducive to cerebrovascular disease is influential, as is rate of recovery (more rapid after seizures), a history of prior seizures, TIAs, or strokes. Similarly, seizures can induce cardiac arrhythmias (124), as well as result from them (125).

The novice diagnostician tends to overemphasize the rare. Most staring spells are simple daydreaming. Most explosive outbursts in children are temper tantrums. Most episodes of a previously well person losing consciousness and falling to the ground are syncope. The diagnostic probabilities are altered when it is known that an individual suffers from epilepsy. As an example, temporal lobe seizure (78,126) should be considered as an etiology of loss of consciousness in a per-

son with known complex partial epilepsy; however, it should be far down on the differential diagnosis of syncope in a person with no prior history of seizures. Primary pain is a rare symptom of epileptic seizures (127–129), and seizures should not be on the usual differential diagnosis of pain.

The most difficult diagnostic cases tend to be those with mixed disorders. A certain percentage of individuals with documented psychogenic seizures may, at other times, exhibit epileptic seizures. The incidence of mixed epileptic and nonepileptic events has been estimated, at times, to be as high as 37% (130) but is more likely 10% or less (131,132). In these cases, it may be that the epileptic seizures and their aftermath somehow became a "template" for subsequent nonepileptic spells. By documenting lack of EEG changes during a generalized seizurelike episode, video-EEG monitoring can show that the episode under observation is nonepileptic in etiology, but it can never prove the etiology of prior episodes. Inference by analogy is imprecise. Even after establishing a diagnosis of nonepileptic attacks, the experienced clinician remains vigilant for the possibility of a mixed disorder. As a practical matter in this circumstance, it often suffices to remove anticonvulsants with the understanding that epileptic seizures may emerge and require reevaluation.

The improvement of spells with anticonvulsants gives incomplete testimony as to the nature of the disorder. Placebo effects are significant in any medical disorder, and especially in those with psychogenic components. The efficacy of antiepileptic drugs is not limited to seizures. Carbamazepine and sodium valproate have long been recognized as useful mood stabilizers (133,134). Of the newer antiepileptic medications being used for mood stabilization, evidence is available for lamotrigine (135–137). Limited supportive information is available for topiramate, oxcarbazepine, zonisamide, and tiagabine (137), while gabapentin has mixed reviews (138,139) for mood stabilization. Phenobarbital and benzodiazepines are effective both as anticonvulsants and as tranquilizers. Phenytoin can suppress ventricular arrhythmias. When a positive response to an antiepileptic agent is encountered, the clinician should consider what else besides epilepsy might be under treatment. Conversely, some patients with presumed epilepsy worsen with increasing doses of antiepileptic drugs. This can be a clue to underlying psychogenic seizures (140).

CONCLUSION

The diagnosis of a patient with "spells" usually can be obtained with a careful review of the history, physical examination, and judicious use of testing (141). The key is an awareness of the types of conditions that can imitate epilepsy and their presentations. The nature of precipitating factors and the detailed appearance of the episode narrow the differential diagnosis. Occasionally, physical findings and laboratory tests, such as routine or special EEG studies, are of value, but they should be employed selectively and in the clinical context. A careful ear, an observant eye, an open mind to multiple possibilities, patience, and good clinical judgment usually lead to the correct diagnosis.

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1 Electroencephalography in the Diagnosis of Nonepileptic and Epileptic Conditions

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This chapter reviews data pertaining to the place of scalp electroencephalography (EEG) in the diagnosis and differential diagnosis of paroxysmal conditions—epileptic and nonepileptic—affecting central nervous system (CNS) function. The prominence of this role hinges on the relative advantages and disadvantages of EEG and the appropriateness of its employment.

EEG discloses function and dysfunction directly, as opposed to neuroimaging, in which dysfunction is only implied from structural abnormalities. Also, the acuteness or chronicity of a process may be reflected in the presence or absence of prominent arrhythmic focal delta, "projected delta," repetitive or periodic discharges, and recorded clinical or subclinical seizures. In addition, EEG can monitor activity in areas possibly occult to clinical examination such as much of the frontal and parietal cortices. EEG particularly clarifies ongoing or intermittently occurring processes because it is repeatable, accessible, and affordable.

However, abnormalities on occult—medial or inferior—cortical surfaces and spatially limited dysfunction may not be detected on scalp EEG. Stable or very slowly progressive larger lesions may perturb the EEG minimally or not at all. Sporadically occurring or specifically precipitated events may not appear on routine recordings, although specially designed, repeated, or prolonged recordings may overcome this impediment.

Organized into three major components: EEG in diagnosis of epilepsy, EEG in principal epilepsy mimics, and some pragmatic points, this chapter addresses the usefulness and limitations of this time-honored yet thoroughly modern procedure.

EEG AND THE DIAGNOSIS OF EPILEPSY

Sensitivity and specificity data indicate that EEG can provide valuable assistance to the physician in determining whether a paroxysmal clinical event represents an epileptic seizure.

Moreover, as ictal semeiology and EEG define epilepsy syndromes, and as syndrome determination is the best guide to management and prognosis, the EEG is clearly the most useful laboratory test for epilepsy. Thus, it is prudent for the user to be aware of EEG's limitations and advantages.

Biophysical Properties

Compared to larger electrical potentials with which they must compete for recognition, EEG electrical signals are small. Moreover, the convolutional structure of the cortex and structures interposed between signal

FIGURE 1.1

Wicket spikes. These apiculate rhythmic waves over the left temporal (F7–T3) region are normal phenomena that emerge gradually from the background and thus are not spikes.

generators and electrodes may distort the signal and its location and will diminish its amplitude.

EEG signals can be measured best at a considerable distance from their source if the neurons are arranged in parallel and perpendicular to the recording surface, and if they are synchronously depolarized or hyperpolarized. This arrangement applies to some neocortical neurons and those of the hippocampus create *open fields* (1). Potentials generated in structures with a circular arrangement, such as the small nuclei of the amygdala, create *closed fields* that do not effectively summate and therefore are difficult to detect. Additionally, the convoluted arrangement of the neocortex distorts the depiction of fields on the scalp so that the potential difference between two points depends as much on the orientation and configuration of the field as on the proximity of any generator (1).

The inhomogeneity of the several layers interposed between cerebral current sources and scalp electrodes alter the recorded signal (1,2). The high resistance of the skull decreases cortical potentials and extends their fields horizontally (2). Thus, Blume and Lemieux (3) found that spikes recorded on the scalp were 1/5th to 1/6th the amplitude of the same spikes recorded directly from the cortex. Natural or artificially placed holes in the cortex (ears, eyes, surgical) draw current toward them and distort the field (2). The orbits and auditory meati draw current anteriorly and inferiorly (4).

The relatively small cortical potentials can be obscured by larger ones produced by scalp muscles, cornea, tongue, and heart. Some of these may become particularly active at pivotal points of the EEG, such as at the onset of a clinical seizure. In recent years, such practical considerations have augmented the considered value of interictal potentials in assessing seizure origin.

Interictal EEG Potentials and Epileptogenesis

Although a distinctly appearing EEG-recorded clinical seizure is a most useful event for the clinician, in practice interictal epileptiform potentials are far more commonly encountered. These, therefore, have demonstrated principal usefulness in the diagnosis and classification of an epileptic condition. The usefulness of such interictal spikes has several requisites: i) they must occur, ii) the recording apparatus must be able to detect them, iii) visual or automated means must recognize them, iv) they must be distinguished from other paroxysmal apiculate phenomena, and v) their clinical significance must be understood.

Sharply Contoured (Apiculate) EEG Wave Forms The practicing electroencephalographer must consistently scan a minefield of potentials resembling epileptogenic spikes, many of which do not represent the abnormal discharge of neurons. Artifact is the first of these to be considered. Electrode, muscle, cardiac, and metals artifacts are those most resembling spike discharges (5).

The superimposition of wave forms also commonly results in a sharply contoured appearance that resembles spikes (6,7). Mu rhythm, wicket spikes (Figure 1.1), and "psychomotor variant" are examples.

FIGURE 1.2

Alpha. Similarly, apiculate but normal background alpha activity.

Normal potentials, such as V-waves and lambda and even alpha waves, may be strikingly apiculate (Figure 1.2). Other potentials are classified as "spikes", but have no epileptogenic significance, such as 14- and 6-sec positive spikes and small sharp spikes.

Overall Specificity and Sensitivity of Spike Discharges for Epilepsy

Binnie and Stefan found spikes in 4 of 1,000 healthy adults (8), whereas Ajmone Marsan and Zivin found a 2 to 3% incidence among a patient population without a history of epilepsy (9).

The value of interictal spikes is suggested by a perceptive statement by Dreifuss that "A person who is epileptic all the time does not manifest seizures all the time" (10). The consequence of this truism is that interictal spikes play a greater role in determining and defining epilepsy than do recorded seizures.

The proportion of patients with epilepsy who have spike discharges on single EEGs varies considerably among patient populations. The initial EEG may disclose spikes in 30 to 50% of patients evaluated at epilepsy centers (8,9,11,12). However, as spikes by their nature occur intermittently, two EEGs will ultimately show spikes in 80 to 90% of such subjects (8,9,12). About 12 to 50% of patients with milder epilepsy, such as those with single seizures or in whom antiepileptic drugs may be discontinued, have spikes (13). Subsequent EEGs in such mild cases may increase this total. Additionally, epileptogenic zones remote from recording electrodes, such as the basal frontal or mesial regions, may not have interictal spikes on surface EEG. Interictal spikes appear more commonly in adults when the seizures arise in the temporal lobes (9,14).

The proportion of patients with epilepsy exhibiting spike discharges can rise to 80 to 85% on single

recordings if sleep is included (8). Among patients with generalized epilepsy, hyperventilation will elicit generalized spike–wave complexes in 50 to 80% of patients. Photic stimulation will do so in about 10 to 50%, depending on the syndrome (15–19).

Nonetheless, spike discharges may not appear on an EEG because of their rarity in some patients, involvement of a very limited or occult area of the cortex, and the effect of antiepileptic medication.

Interictal spikes do not always reflect a current or future seizure tendency. Although multiple independent spike foci and frontal and anterior temporal spikes correlate highly with a seizure disorder (20–23) only about 40% of patients with Rolandic spikes have epileptic seizures (24). Nonepileptic patients with visual abnormalities since infancy may have occipital spikes (25,26). A metabolic encephalopathy may be associated with epileptiform discharges without epilepsy (27). Low-grade brain tumours may produce spikes with or without seizures (28).

EEG and Types of Epilepsy

The ictal semeiology of some patients contain features common to both focal and generalized epilepsies. For example, temporal lobe seizures without warning and with rather abrupt losses of awareness and emergence therefrom may closely resemble absence. Fortunately, EEG phenomena with each are distinct. Second, whether generalized motor seizures are primary generalized or originate from a frontal focus may require EEG to determine whether primary or secondary bilateral synchrony is present (29).

Rapid propagation of epileptic seizures may create semeiology that reflects the propagated lobe as opposed to the originating lobe. An occipital to temporal propagation is a common example. Abnormalities of posterior background activity, occipital spikes, and occipitally originating seizures may all distinguish this circumstance from temporally originating seizures.

Generalized Epilepsies

Four series of patients with generalized spike–wave discharges have found generalized seizure disorders in 97 to 98% (30–33) of patients. Similarly, seizures occur in about 98% of patients with slow spike–waves (34,35). The 6 per second spike–wave phenomenon may occupy an intermediate position in epileptogenecity: Thomas and Klass (36) found epilepsy in 36% of patients with the 6 per second spike–wave phenomenon as compared to 21% of their laboratory population (Figure 1.3).

EEG plays a crucial role in distinguishing secondarily generalized epilepsy from Lennox-Gastaut syndrome (37,38).

Temporal Lobe Epilepsy

It is likely that interictal spikes appear more commonly in patients with temporal lobe epilepsy as compared to epilepsy arising in other lobes (9,39). Temporal lobe spikes have been described in 60 to 75% of such patients adequately controlled with medical therapy (40,41). Studies of patients with presumed refractory temporal lobe epilepsy report higher instances (82–91%) (42,43). The side of most temporal lobe spikes correlates with that of seizure origin in 90 to 95% of patients (42,44). Lateralization of temporal delta activity also correlates highly with that of seizure origin (42,43). However, because such delta appears frequently in association with focal temporal spikes, the independent yield of temporal delta may be small (45). Independent bilateral spikes appear in 20 to 56% of temporal lobe epilepsy patients undergoing long-term monitoring (42,45). However, 78 to 98% of patients in whom ≥75% of spikes occur on one side have their seizures arising ipsilaterally (45).

The high prevalence of temporal lobe spikes among patients with temporal lobe epilepsy suggests that a lack of such spikes should raise the possibility that the attacks represent epilepsy from another region, such as the orbital frontal cortex, or that they are nonepileptic in nature. In addition, resective surgery becomes an attractive therapeutic option in patients whose temporal interictal spikes consistently (over several recordings) collateralize with any temporal lobe MRI abnormality (44,46,47).

Neocortical Epilepsies

The incidence of interictal spikes and the lateralization of ictal potentials may be less in neocortical epilepsies than in temporal lobe epilepsy. However, valuable clues to epileptogenesis may be available to the perceptive electroencephalographer. First, unilateral distortion or reduction of normal EEG phenomena may help lateralize or localize epileptogenesis; such phenomena include alpha and beta activity during awake periods, and spindles and V-waves in sleep (28,48–50). Second, focal delta may help: two studies (51,52) showed that it had at least lateralizing value for epileptogenesis among children in 70 to 90% of patients. Although such delta activity in itself does not localize epileptogenesis, it cannot be ignored in this assessment.

As intractable frontal lobe epilepsy often arises from orbital or mesial surfaces, the lateralizing value of

FIGURE 1.3

6-Sec spike–wave, an epileptiform phenomenon possibly not representing a seizure disorder. Lower voltage and more posteriorly situated, these paroxysms can be easily overlooked, especially using bipolar montages.

interictal spikes and even their incidence is considerably less than in temporal lobe patients. Lack of interictal or ictal potentials in a monitored epilepsy patient with frontal lobe semeiology lowers the chance that seizures arise from a frontal convexity and augments the likelihood of a mesial or orbital origin. Frontal lobe spikes are less often focal and more likely bilaterally synchronous or lobar (53).

Although Williamson et al. (54) found occipital spikes on scalp EEGs of only six (24%) of twenty-five patients, in our series (55) the most active interictal spike focus identified the epileptic occipital lobe in fifteen of nineteen patients (79%).

The localizing value of ictal phenomena of extratemporal seizures is less than that of temporal lobe epilepsy (56). Unfortunately, a majority of focal

TABLE 1.1
Seizurelike Phenomena and Possible Interpretations

False Seizure Interpretation	Seizurelike Events
Temporal	Diurnal microsleep, narcolepsy, night terrors, panic attacks, fugue states, transient global amnesia, pseudoseizures, hyperventilation
Focal sensory	TIAs, hyperventilation
Focal motor	Pseudoseizures, TIAs, movement disorders
Occipital	Migraine
Absence	Diurnal microsleep
Atonic	Syncope, cardiac arrhythmias, cataplexy, TIAs, hyperventilation
Myoclonic	Syncope, cardiac arrhythmias
Generalized motor	Pseudoseizures, syncope, hyperventilation

TIAs = transient ischemic attacks

TABLE 1.2

Seizurelike Events	EEG
Diurnal microsleep	Loss of alpha; emergence of theta, beta, sporadic V-waves
Narcolepsy	As for diurnal miscrosleep; rapid eye movement (REM) onset sleep
Panic attacks, fugue states	No specific EEG change
Transient global amnesia	Normal or mild nonepileptiform, nonspecific abnormalities
Psychogenic seizures	Normal EEG with superimposed movement and muscle artifact
Hyperventilation	Diffuse theta or delta
Transient ischemic attacks	Transient focal delta or theta
Migraine with aura	Attenuation of background activity, then delta, theta during attack Normal or sporadic theta between attacks

seizures of extratemporal origin produce no visually apparent electrographic change (57). This may relate to the inferior surfaces of many frontal and occipital seizure origins and the presumed horizontal dipole orientations to surface EEG in mesial frontal and parietal epilepsies.

Although invasive recordings may be required to localize extratemporal epileptogenesis, hypotheses must be developed in planning invasive electrode placement. Ictal semeiology, together with normal and abnormal scalp EEG data, play essential roles in developing such hypotheses.

EEG Monitoring in Epilepsy

Monitoring may ultimately prove unnecessary for a temporal lobe epilepsy patient whose magnetic resonance imaging (MRI) study shows a unitemporal lesion ipsilateral to consistent interictal EEG abnormalities. It is possible that such monitoring will not achieve more reliable lateralization than neuroimaging alone (58). However, several relatively recent studies have shown that ictal semiology also has reliable lateralizing value in temporal lobe epilepsy (59). Therefore, video-EEG monitoring acquires clinically valuable clinical data as well.

Many temporal lobe patients do not achieve complete congruity of data implicating the epileptogenic region, and yet these cases may be good surgical candidates, even when bilateral electrographic and structural abnormalities are present (45). Noninvasive and invasive monitoring may be necessary in these instances.

Ambulatory Electroencephalography

Clinical description and outpatient EEGs may rarely fail to discern the nature of paroxysmal events. Moreover, such events may be precipitated by certain settings or activities (60). Ambulatory monitoring (AM) permits extended monitoring while the patient carries out his usual activities at home. Electrode and movement artifact, long the limitation of AM, may be overcome with advances in electrode manufacture and application (61). Sixteen to thirty-two channels are now possible (62), including audio, video, heart rate, and pulse oximetry. Automated seizure detection and pushbutton alarms reduce the data quantity.

AM detected an increased proportion of patients with interictal spikes and recorded seizures when compared to standard awake and sleep EEG in one study (63). Another study (64) found a clinically useful result

in 74% of outpatients. Thus, AM may help determine seizure frequency and response to therapy (65).

Although the theoretical advantages for AM abound, evidence-based comparisons between clinical judgment plus outpatient EEGs versus AM are required to determine the amount of healthcare resources that AM merits as well as the circumstances of its implementation.

EEG IN SOME EPILEPSY MIMICS

In distinguishing epilepsy from conditions that resemble it, a knowledge of EEG abnormalities of these entities is useful. Tables 1.1 and 1.2 summarize EEG findings in the more common of these disorders.

Migraine

EEG changes may occur during and after migraine attacks. Unfortunately, the literature is beset with frequent imperfections that may mislead the unsuspecting reader. This consists of the grouping of dissimilar patients, the lack of adequate controls, and vague definitions of what constitutes an EEG abnormality.

Phenomena consistent with spreading depression and alterations of cerebral blood flow underlie the acute-appearing EEG abnormalities that occur principally, if not exclusively, in patients with migraine with aura. Several studies of migraine have employed a variety of methods to measure cerebral blood flow including single photon emission computed tomography (SPECT) scan, transcranial Doppler, and perfusion weighted imaging studies. Unilateral or bilateral hypoperfusion have been noted during these attacks (66–71).

Hyperperfusion has been found in a minority of patients, usually following an episode of hypoperfusion (67,68). Spreading depression has been considered a likely mechanism of migraine with aura. This consists of a depolarization wave moving across the cortex at 3 to 5 mm/minute, preceded by a brief excitatory phase followed by nerve cell depression. During the sequence, an efflux of excitatory amino acids occur whose receptor is primarily nMDA (72). A positron emission tomography (PET) scan study by Diener (73) found no change in cerebral blood flow in patients with common migraine. Hyperperfusion of the involved hemisphere has been found in alternating hemiplegia of childhood (74). Similarly, Olesen et al. (75) described hyperemia then oligemia spreading across the cortex at about 2 mm/minute and resembling spreading depression.

Although Hooker and Raskin (76) found neuropsychological impairments in patients with migraine with and without aura as compared to controls, Wray et al. (77) found normal visual processing in migraineurs.

From the foregoing, it is understandable that most of the EEG abnormalities with migraine have occurred among patients with migraine with aura and those in whom the EEGs were performed during or soon after the occurrence of prodromata. Acutely, a decrease in the amplitude of normal rhythms, such as alpha and spindles, occur together with focal delta and theta activity. These phenomena decline within days after the headache but outlast them in milder form by days or weeks (78). Subsequently, bursts of such theta and delta activity may persist intermittently for 1 year or more. Wessely et al. (78) also found spike discharges in 8% of migraine subjects. Smyth and Winter (79) found abnormal EEGs in 45% of patients with migraine; these appeared as bursts of slow waves or "sharp transients."

A curious phenomenon of photic driving above 20 flashes per second, described by Golla and Winter (80), has been considered specific for a migraine tendency by Smyth and Winter (79). They found this abnormality in 95% of migraineurs as compared to 20% of patients with other conditions ($p < 0.0001$, Fisher's exact test).

Possibly triggered by the above-mentioned excitatory amino acid release during migraine aura, a number of syndromes associating migraine and epilepsy have been described, principally by Andermann and Lugaresi (81). Among these, children with migraine with seizures during the aura and those with basilar migraine appear to have the more commonly described EEG changes (82). These consist of occipital-posterior temporal focal spikes and/or delta and generalized or posteriorly accentuated spike–waves. Hyperventilation may increase such epileptiform activity, whereas eye opening may attenuate or abolish it. Less common is migraine with or without aura progressing to temporal lobe epilepsy, in which both posterior temporal occipital and anterior temporal spikes may appear.

Patients with hemiplegic or aphasic migraine have unilateral delta and theta activity acutely, with minor hemispheric abnormalities persisting subsequently (83–85).

Discussing EEG in the evaluation of childhood headache, the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society concluded "EEG is not recommended in the routine evaluation, as it is unlikely to define or determine an etiology or distinguish migraine from other types of headaches. In those children undergoing evaluation for recurrent headache found to have paroxysmal EEG, the risk of future seizures is negligible…" (86). A similar conclusion can be drawn for adults.

Transient Global Amnesia

Originally described by Bender (87) and by Fisher and Adams (88), this disorder may reflect vertebrobasilar artery insufficiency associated with hippocampal ischemia, which produces a retrograde amnesia without other cognitive deficit lasting several hours to a few days.

Among the largest and most thorough studies of this condition is that of Miller et al. (89), who found normal EEGs in eight of thirteen patients during an attack, with mild nonepileptiform abnormalities in the remainder. Of ninety-six patients recorded between attacks, 60% were normal and the remainder had mild diffuse abnormalities without spikes. Similarly, Jaffe and Bender (90) reported normal EEGs in twenty-six of twenty-seven patients.

Acute confusional migraine in children may be an analog of transient global amnesia (91). Diffuse or posterior delta may occur during the episode.

Therefore, in these conditions, EEG serves to exclude items of the differential diagnosis such as temporal lobe or absence status epilepticus.

Syncope

Syncope is often mistaken for generalized tonic-clonic seizures because of the prominent motor manifestations that may occur in the midst of the attack. Distinguishing features include the initial syncopal symptoms, facial pallor, and prompt recovery.

The sequential EEG changes during a syncopal attack consist of alpha suppression, low-voltage beta activity, diffuse theta increasing in voltage, then high-voltage delta that gradually decreases in amplitude followed by diffuse attenuation (suppression). Tonic and then clonic activity may accompany the decreasing delta and attenuation phases (92). As cerebral blood flow regains its normal quantity, brain waves reappear in reverse order of disappearance. More abbreviated sequences may accompany relatively minor attacks. Breathholding spells produce a similar sequence of changes (92), as may the apneic spells induced by crying in children (93). Because the semeiology of such spells is far more diagnostic than the electroencephalogram, any interparoxysmal EEG abnormality in either children or adults is very likely irrelevant (94).

Psychogenic Events

Several complexities surround the evaluation of patients whose paroxysmal events may not represent true epileptic seizures. An increasing access by the public to medical information has produced a greater variety of nonepileptic attacks, as compared to heretofore when almost all such attacks resembled generalized tonic-clonic seizures. Now several features of true epileptic seizures, particularly those arising from the frontal lobe, are shared by psychogenic seizures, although the latter may last longer than the former. Additionally, true epileptic seizures may coexist with psychogenic seizures: Krumholz and Niedermeyer (95) have found that eighteen (37%) of their forty-four patients with psychogenic seizures had true epileptic seizures. However, the majority of patients with psychogenic seizures have no evidence of epilepsy.

Studies have found epileptiform discharges in 10 to 12% of patients with psychogenic seizures (96,97). Nonetheless, these percentages are higher than the 2 to 3% incidence found by Ajmone-Marsan and Zivin (9) in a patient population without a history of epilepsy. Nonspecific EEG abnormalities occur commonly among these patients, as found in about half of patients with psychogenic seizures and no epilepsy in one study (98).

Even with a full complement of electrodes and 24-hour telemetered video-EEG, some EEG limitations in distinguishing epileptic from psychogenic seizures pertain: i) the spatial extent of some focal seizures may be insufficient to be detected by EEG, ii) seizures, particularly those arising from the frontal lobe, may occur in occult regions such as the inferior or mesial surfaces, and iii) movement or muscle artifact may obscure or complicate the display of ictal potentials.

True epileptic seizures are electrographically characterized by a morphological and/or frequency evolution of rhythmic waves or sequential epileptiform potentials followed by postictal attenuation (99). Such potentials should obey topological or physiological principles. In contrast, psychogenic seizures: i) often lack evidence of progression, ii) have potentials generated by attendant muscle, movement, or electrode artifacts that are topologically erratic, and iii) postictal delta or attenuation do not occur. Intraictally, alpha and other normal background potentials may be perceived among muscle, movement, and other artifacts.

Some laboratories apply an event-inducing stimulus such as a tuning fork. However, this may risk losing the patient's confidence in the medical team. Ambiguous or false positive responses may be evoked in patients without psychogenic seizures (100). Instead, clinical and EEG analysis together with MMPI-II data (101) usually establish the diagnosis without this measure.

Closely allied to psychogenic seizures is psychogenic unresponsiveness, identified by lack of any reaction to an afferent stimulus in the presence of a normal awake EEG. EEG helps to distinguish this phenomenon from absence and temporal lobe status epilepticus.

Sleep Disorders

Nocturnally occurring seizures may resist antiepileptic therapy. Both seizure-related sleep disruption and antiepileptic drugs may produce excessive daytime sleep and mental sluggishness. Several nonepileptic parasomnias share features with epileptic conditions by interrupting sleep. These also lead to daytime fatigue and sleepiness, possibly compounded by unnecessary antiepileptic medication. Sleep deprivation from parasomnias could aggravate a true epileptic tendency. The foregoing considerations require that the investigation and management of possible seizure disorders include a description of such somnogenic events and scrutiny for symptoms of sleep deprivation (see also Chapter 16).

Broughton (102) described three phenomena that superficially resemble dyscognitive (formerly known as complex partial) seizures: confusional awakenings (CA), sleep terrors (ST), and sleep walking (SW). CA develop from sleep stages 3 or 4 in the early night (103). The EEG consists of diffuse medium voltage theta, possibly with V-waves superimposed, or unreactive alpha. Arousal from rapid eye movement (REM) sleep may be accompanied by a visual hallucination, a possible dream remnant. ST principally afflicts children, developing in stages 3 or 4 of non-REM sleep. Inconsolable anxious behavior occurs, occasionally with screaming and subjective "single frame" imagery. The EEG during such an event depicts a transition from stage 3 to 4 non-REM sleep to low-voltage, high-frequency nonepileptic activity. SW, manifested by stereotyped behavior, such as dressing or eating while remaining inattentive to stimuli, also emerges from non-REM sleep in otherwise normal children. Diffuse theta or nonreactive alpha appear on EEG.

Emotional stress, alcohol and drugs (prescription or illicit), depriving the subject of sleep may evoke REM rebound on a succeeding night, thus producing terrifying dreams. REM-onset sleep or a higher than normal REM sleep proportion is the EEG reflection of this circumstance.

REM sleep without atonia may develop in the elderly or in disease states, allowing kicking, diving from bed, punching, or rapid walking to occur in the second half of the night, presumably in response to dream content. The EEG discloses REM sleep and low-amplitude patterns that may evolve to features of wakefulness.

Nocturnal enuresis, head banging, and hypnogenic paroxysmal dystonia are other nonepileptic parasomnias.

If not unraveled by a careful history, nocturnal polysomnography may disclose the patterns described above and thus yield a diagnosis. The unlikely possibility of epilepsy lurking in an occult frontal lobe surface may linger. However, untreated, the occurrence of a secondarily generalized tonic-clonic seizure would ultimately unravel the mystery.

EEG IN EVALUATION OF AMBIGUOUS DISORDERS: VARIOUS PRACTICAL POINTS

The following pragmatic thoughts may assist in the evaluation of ambiguous disorders:

- An incomplete or inexact description of spells by patients or observers may erroneously mark these spells as factitious. Generalized seizures with incomplete impairment of awareness may superimpose usually unconnected symptoms and signs (104). One or two EEGs or even inpatient video monitoring may be necessary to unravel the significance of such disparate data.
- Metabolic, toxic, or vascular mechanisms may produce nonepileptic spells. Diffuse or focal nonepileptiform EEG abnormalities may appear.
- Diffuse EEG abnormalities may simply reflect drug excesses and not a chronic encephalopathy.
- EEGs are more commonly over-read for abnormality than under-read, possibly reflecting a greater fear of missing a clinically significant abnormality than artificially creating one. This adds to the concept of low specificity, harbored by many practitioners who do not read EEGs.
- Some nonspecific, nonepileptiform phenomena may indicate that lurking epileptogenesis may appear on subsequent records. Anterior or posterior rhythmic delta (105) (Figure 1.4), delta gradually disappearing over the course of a recording, and posteriorly situated arrhythmic delta in an awake child have this implication (Figure 1.5).
- Never allow a patient to be sent home without medical review if an EEG shows frequent "projected" delta activity or repetitive (quasiperiodic) epileptiform or nonepileptiform events. Each may represent an evolving CNS process (49,106,107).
- Read a patient's EEG for the first time with him present, giving the patient a glimpse of your thought processes, not just the conclusions. Such EEG review is preceded by indicating i) your reasons for performing the test, ii) possible results and how they will affect management, and iii) a warning about irrelevant data, such as Rolandic spikes in a child with temporal lobe epilepsy.
- If incongruent data occur (right temporal spikes when semiology suggests left temporal seizure origin), educate the patient about the sometimes baffling complexities of the nervous system and your nonplussed approach to their ultimate solution.
- Make no compromise with avoidable technical imperfection.

FIGURE 1.4 ***(opposite page)***

(a) **Rhythmic delta. A nonepileptiform phenomenon with possible epileptogenic significance.** Although these rhythmic waves may be normal phenomena in themselves, they may lead to spike–waves, as shown minimally here and in the next segment. (b) **Rhythmic waves leading to generalized spike–waves.**

FIGURE 1.5

Posterior arrhythmic delta in childhood: A nonepileptiform phenomenon possibly representing a recent epileptic seizure. The quantity of posteriorly situated delta (01,2 and T5,6) exceeds normal for this awake 2-year-old. The most common causes of such delta are a recent seizure or mild head trauma; it rarely represents a posterior lesion.

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2 Anatomical–Clinical Localization of Ictal Behavior

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Abnormal behavior during epileptic seizures was recognized as a brain disorder since antiquity, as noted by the school of Galen (129–216 A.D.) (1). However, it was not until the later parts of the nineteenth century that ictal behavior was anatomically correlated to certain brain regions. Jackson and Gowers established an anatomical–clinical correlation by repeated observation of epileptic seizures in patients with obvious brain lesions, often found on autopsy (2,3). In retrospect the observational skills of clinicians at that time were outstanding. In the absence of advanced technology, descriptions of ictal behavior and the anatomical location thereof were made with much the same accuracy as clinical observations obtained using video-electroencephalographic (EEG) monitoring and magnetic resonance imaging (MRI) techniques (4,5). Their findings are still valid.

As ictal behavior is intermittent, anatomical–clinical correlation is harder to establish than in lesional neurology, where a persistent deficit can be more easily correlated to an obvious brain lesion. With the introduction of EEG by Berger in 1929, it was possible to correlate ictal behavior with areas of abnormal electrical cortical activity. Ajmone-Marsan used the seizure-inducing agent pethylenetetrazol (Metrazol) to induce repeated seizures. He standardized ictal behavior and correlated it to scalp EEG (4).

Penfield, at the Montreal Neurologic Institute, did further pioneering work using direct brain stimulation in patients undergoing electrocorticography under local anesthesia (6). With the help of intraoperative EEG recordings, he was able to localize clinical manifestations to cortical regions. If the patient remained seizure free after surgery, this gave further proof that some of the ictal behavior probably originated in the resected area. Similar experiments were performed by Bancaud and Talairach (Figure 2.1). After initial pioneering work, intracranial EEG recordings were also used outside the operating room during long-term EEG-monitoring. Multiple centers around the world are now using larger numbers of grid and strip electrodes to localize ictal behavior. Cortical electrical brain mapping gained increasing value to localize ictal behavior and cortical functions. Newer technologies like structural and functional MRI, ictal single photon emission computed tomography (SPECT), and positron emission tomography (PET) are now supplementing previous studies and allow further insights to localize certain behaviors (7–9).

This chapter describes typical epileptic ictal behavior and the anatomical localization thereof. This knowledge

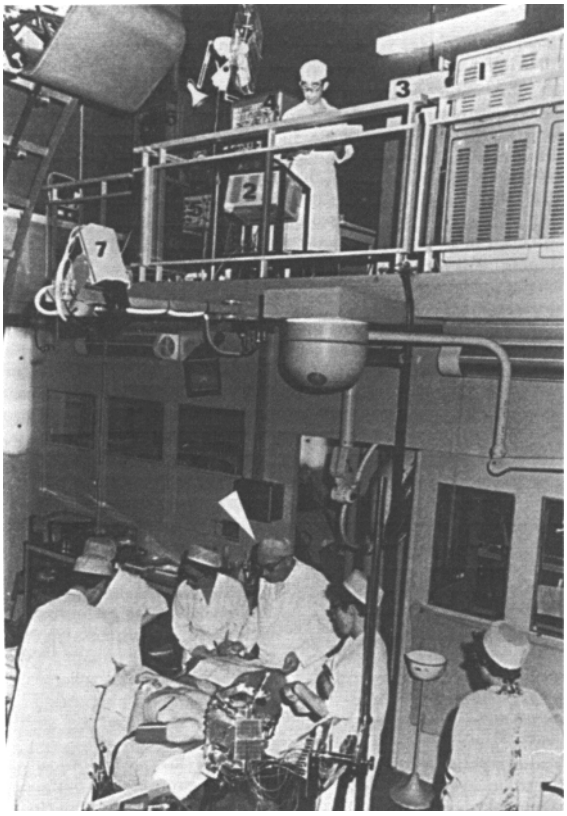

FIGURE 2.1

View of the operating room of Saint Anne, Paris. White arrow: J. Bancaud. On the balcony: EEG recording apparatus. From Talairach J, Bancaud J, Szirka G et al.: Approche Nouvelle de la neurochirurgie de l'épilepsie. Méthodologie stéreotaxique et résultants thérapeutiques. *Neurochirurgie* 1974 20 (Suppl 1).

about brain function has been derived by the following basic principles:

- Ictal behavior was correlated to an obvious brain lesion, which was thought to be the origin of the seizure.
- Ictal behavior was correlated with scalp and intracranial EEG findings.
- Stimulation experiments were performed, and stimulation sites were correlated with epileptic behavior that was induced by the stimulation.
- Patients with certain ictal manifestations underwent epilepsy surgery and became seizure free thereafter, which suggests that the ictal behavior originated in the resected area.

All the above methods have their limitations. A large systematic error is introduced by the fact that clinical manifestations may be a result of the propagation of epileptic activity beyond the functional origin and may not originate in the area of the lesion or the resection. Furthermore, seizures originating in certain regions of the brain may remain subclinical, because many areas of the brain are clinically silent. Scalp EEG recordings have been shown to be falsely localizing multiple times (10,11). Thus, the effects of stimulation experiments may not be a complete semiologic match for spontaneous seizure activity. Although our knowledge about the anatomical correlation of seizure activity is greatly enhanced compared to two hundred years ago, there still remains much uncertainty about various ictal behaviors.

In clinical practice, it is crucial to recognize certain behaviors as epileptic and localize them to certain areas of the brain. Misdiagnosis has great implications with respect to the possibilities for surgical treatment. A correct diagnosis of nonepileptic events may protect the patient from significant and unnecessary side effects attributable to antiepileptic medication. Conversely, patients with epileptic seizures may respond to appropriate medical and surgical treatment if the appropriate diagnosis is established. To distinguish nonepileptic events from epileptic seizures it is necessary to recognize certain behaviors and patterns as epileptic, by clinical description and observation. Knowledge of epileptic syndromes and associated seizure types enhances the recognition of epileptic versus nonepileptic events. However, certain behaviors can only ultimately be verified by video-EEG monitoring if the diagnosis is uncertain or the patient does not respond to treatment.

In some patients, even video-EEG monitoring is misleading. For example, frontal lobe seizures originating at the mesial surface may show no electrical abnormalities on scalp EEG. If events are highly stereotypical and brief in duration, the diagnosis of an epileptic seizure should always be considered even if symptoms seem unusual or bizarre. The role of video-EEG monitoring to diagnose the etiology of any type of bizarre episode cannot be overemphasized.

MANIFESTATIONS AND LOCALIZATION OF ICTAL BEHAVIOR IN FOCAL PARTIAL SEIZURES

Partial or focal seizures involve only certain parts of the brain and often lead to distinct clinical manifestations. These seizures provide the best information about the anatomical location of ictal behavior.

Ictal Behavior Originating in the Frontal Lobes

Frontal lobe seizures are frequently mistaken for psychogenic seizures as they do not necessarily impair consciousness and often have very emotional or sexual

FIGURE 2.2

Lateral anatomy of the brain with correlation to certain seizure types.

content (12–14). Early descriptions of frontal lobe epilepsy often included patients who were psychiatrically treated for years (13,15).

Functionally and anatomically, the frontal lobes are often divided into the following regions (Figures 2.2 and 2.3): primary motor cortex (precentral gyrus), supplementary motor area, anterior mesial frontal lobe including the cingulate gyrus, dorsolateral frontal convexity, orbitofrontal cortex, and the opercular region. All regions anterior to the primary motor cortex and the supplementary motor area are often referred to as the *prefrontal cortex*.

As the prefrontal cortex is responsible for executive function, it is often difficult to localize ictal behavior, as the onset of the seizure may be clinically silent, and the final seizure manifestation may be entirely the result of seizure propagation.

Currently, the most common and best described seizures originating in the frontal lobes are focal clonic seizures (2), complex partial seizures of frontal lobe origin (13,16–18) and supplementary motor seizures (18–21). Masticatory seizures (14,22,23) and frontal lobe absence seizures (14) are less common.

Typical Seizures Originating in the Frontal Lobes

Focal Clonic Seizures

Focal clonic seizures consist of the rhythmic jerking of unilateral muscle groups without impairment of consciousness. Clonic motor seizures originate in the primary

FIGURE 2.3

Mesial anatomy of the brain with correlation to certain seizure types.

motor cortex (Brodmann area 4) contralateral to the motor activity. The muscle groups that are involved strictly follow the cortical motor representation (homunculus, Figure 2.4). As face and hand have the biggest cortical representation, they are the most commonly involved muscle groups. If a seizure begins in the hand area, there may be spread of epileptiform activity rostrally and caudally. This translates clinically into a seizure that begins with clonic movements of the hand, with later involvement of the face and the leg as electrical spread occurs rostrally and caudally.

Focal clonic seizures are said to exhibit jacksonian march (2) if the seizure activity spreads clinically to follow the anatomical representation of the homunculus. When seizures continue for extended periods of time, without impairment of consciousness, this is referred to as *epilepsia partialis continua*. These motor seizures can last days, months, or even years.

Clonic motor seizures can occur with lesions in the primary motor cortex and can be refractory to antiepileptic medications. They are typical for benign epilepsy with centrotemporal spikes (benign Rolandic epilepsy) and Rasmussen's encephalitis. Benign child-

FIGURE 2.4

Cortical motor representation. From Penfield W and Rasmussen T. 1955. The cerebral cortex of man.

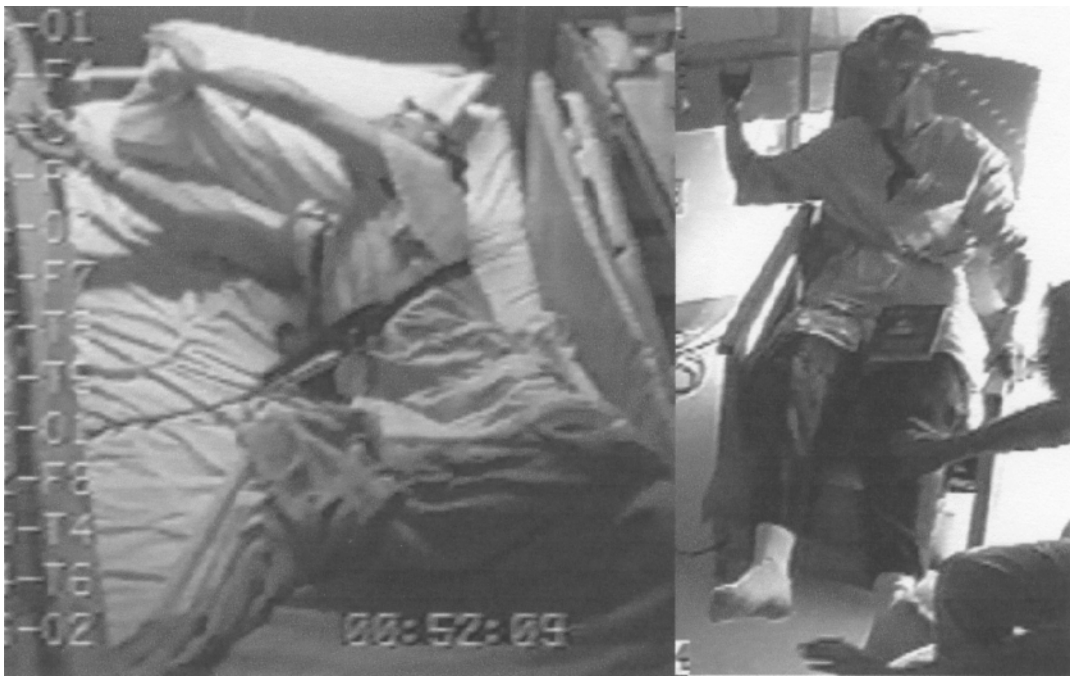

FIGURE 2.5

Typical postures of patients with SMA epilepsy. Left bilateral tonic arm extension. Right "fencing" posture.

hood epilepsy with centrotemporal spikes begins between 5 and 10 years of age (24). Patients have mainly nocturnal seizures with predominantly clonic movements of the face, throat constriction, and drooling. Occasional secondarily generalized tonic-clonic seizures occur. Seizures are often infrequent, and when treatment is indicated, responsive to carbamazepine. They remit spontanously in adolescence (24–26).

Rasmussen's encephalitis is a progressive, inflammatory, often unilateral disease of the brain, having unclear etiology (27). Autoimmune etiology has been assumed. It often manifests itself with prolonged focal clonic seizures, which may last for hours, days, or months (epilepsia partialis continua) and are contralateral to the affected hemisphere. Patients have completely preserved consciousness. With progression of the disease, atrophy of the affected hemisphere occurs and the patient becomes more cognitively impaired due to continuous seizure activity and progressive diffuse brain disease.

Supplementary Motor Area Seizures with Asymmetric Tonic Posturing

The supplementary motor area (SMA) is located at the mesial side of the frontal lobes adjacent and anterior to the primary motor cortex (Brodman area 6), superior to the cingulate gyrus. Unilateral as well as bilateral tonic posturing as an ictal phenomen is thought to originate in this area. Seizures originating in the SMA are explosive in onset. The patient may suddenly involuntarily posture an arm or leg, with preserved consciousness and at times with preserved motor function of the ipsilateral side. The patient may try to catch or hold down his tonic extremity with his uninvolved arm. If neck muscles are involved there will be head turning toward the extended arm with the patient assuming a typical "fencing" posture (Figure 2.5). Seizures are brief, often nocturnal, and may occur in clusters (28–30).

The tonic posturing of an arm or leg or both occurs contralateral to the side of SMA-seizure origin. Penfield, in his stimulation experiments, identified a somatotopic representation within the supplementary motor area comparable to the primary motor cortex (31). This was confirmed in later studies (30,32). The face representation is located most anterior, the leg representation posterior, and the arm representation in between the face and the leg area. Bilateral tonic extension could be due to a rapid involvement of the contralateral side, but stimulation experiments have shown that both extremities are represented in the each SMA area (32). Head turning usually occurs to the contralateral to the side of seizure origin (33,34).

Sometimes, seizures originating in the SMA are preceded by an aura of a somatosensory sensation that

TABLE 2.1
Differential Diagnosis of Frontal Lobe Complex Partial Seizures with Hypermotor Automatisms

	Frontal Lobe Complex Partial Seizures with Hypermotor Automatisms	Nonepileptic Psychogenic Seizures	Tourette's Syndrome
Duration	Brief (<60 sec)	Variable	Brief
Frequency	Frequent, in clusters	Variable, commonly clusters	Variable, can be continuous
Time of occurrence	Nocturnal preponderance, often out of sleep	Out of wakefulness	When awake, disappears during sleep, worsens with attention
Motor manifestations	Bizarre but stereotyped	Variable: shaking, jerking common	Simple and complex motor tics, verbal tics, variable location
Speech	Violent vocalization or speech arrest	Slurred speech	Echolalia, echopraxia
Consciousness	Preserved	Confusion and altered consciousness common, waxing and waning	Preserved
Associated features	Secondary generalization possible, clonic or tonic features	Pain syndromes, psychiatric disease especially PTSD	Obsessive compulsive disorder
Age of onset	Childhood and adolescence	Adulthood >> childhood	Childhood
Spontaneous remission	Uncommon	Possible	Common
EEG changes	Common but may lack	Normal	Normal
MRI imaging	Possibly epileptogenic lesion	Normal	Normal

can be bilateral, widespread, and proximal, indicating that there is also somatosensory representation within the SMA (30,31).

SMA seizures are often mistaken for nonepileptic events as the patient may have bilateral motor activity with preserved consciousness and no EEG changes. However, familiarity with these seizures makes them readily recognizable as epileptic events.

SMA epilepsy is observed with SMA lesions such as tumors or cortical dysplasias.

Complex Partial Seizures of Frontal Lobe Origin with Hypermotor Automatisms

Complex partial seizures of frontal lobe origin have complex, behavioral manifestations. These were initially recognized by the French school (15,35), later described by Williamson (13), and shortly thereafter also by Waterman (17). They described behavior that was bizarre and explosive. Because the behavior is so peculiar and emotional, this type of seizure is frequently mistaken as nonepileptic or psychogenic seizures. In childhood, other diagnoses, such as Tourette's syndrome, are frequently considered as differential diagnoses (Table 2.1) (see also Chapter 12).

Complex partial seizures of frontal lobe origin begin suddenly or explosively with bizarre automatisms. Automatisms may consist of stepping, bicycling, jumping out of bed, running around, pounding, or rocking. These automatisms involve the upper and lower extremities and always involve complex movements. This behavior is frequently accompanied by violent yelling and shouting, which gives the seizure an even more bizarre appearance. Vocalization is often understandable and may have emotional contents. It can be formed (swearing, shouting) as well as unformed (production of sounds such as growling or grunting). The patient often has preserved consciousness, which makes these automatisms peculiar, as the patient has no control over his motor behavior, but is fully aware of the seizures. The seizures often have a nocturnal preponderance and occur in clusters. However, behavior throughout these seizures is stereotyped and seizures are very brief, which distinguishes them from nonepileptic events. The patient often returns immediately back to normal without apparent postic-

TABLE 2.2
Diffential Diagnosis of Masticatory Seizures, Vocal Tics, Tardive Dyskinesia, and Syndenham's Chorea

	Masticatory Seizures	Vocal Tics	Tardive Dyskinesia	Syndenham's Chorea
Duration and frequency	Brief, intermittent, frequent	Brief, intermittent, frequent, worse with attention	Continuous	Continuous, lasting several weeks then disappearing
Motor manifestations	Stereotyped mouth movements	Vocalization of sounds, tongue protrusion, can be variable in appearance	Orolingual and masticatory movements	Chorea of multiple muscle groups, including face and extremities
Speech	Speech arrest	Echolalia, production of sounds	No major speech impairment	Only impaired if involvement of orolingual muscles
Associated features	Tonic mouth movement, salivation, throat constriction	Tongue protrusion	Previous intake of neuroleptics	Previous streptococcal infection
Age of onset	Childhood and adolescence	Childhood	Adulthood	Between 5–15 years of age
Spontaneous remission	Uncommon	Common	Uncommon	Always
EEG changes	Common	Normal	Normal	Normal

tal confusion after this typically brief (15–30 seconds) seizure (16). Ictal EEG may not always be helpful in distinguishing between epileptic and nonepileptic events, as scalp EEG recordings can show very little epileptiform activity during these seizures, especially if they originate on the mesial surface of the frontal lobes.

Complex partial seizures of frontal lobe origin were localized to various areas in the prefrontal cortex, namely the dorsolateral cortex, the orbitofrontal region, and the mesial frontal cortex (14,15,17). Currently, no definite localization within these areas of the frontal lobe can be made since large areas of the prefrontal cortex are clinically silent (12). The clinical characteristics represent the overall spread pattern, possibly as a release or disinhibition phenomen. For that reason, it is more difficult to identify the seizure origin unless there is a definite abnormality on imaging studies. Epilepsy surgery can be successful even in the absence of an obvious lesion (12).

Masticatory Seizures

Masticatory seizures consist of involuntary mouth movements with salivation and tongue protrusion. The patient is completely conscious and unable to speak due to motor aphasia. They originate in the frontal operculum, including Broca's language area (22,23). Masticatory seizures can occur in benign epilepsy with centrotemporal spikes, but are also seen with neoplastic lesions or cortical dysplasia.

Masticatory seizures must be distinguished from other disorders having involuntary mouth movements and preserved consciousness like tardive dyskinesia, tics, or Syndenham's Chorea (Table 2.2). As these seizures originate at the lateral surface of the frontal lobes, EEG changes are usually obvious (36).

Frontal Lobe Absence Seizures

Seizures originating in the frontal lobe can resemble absence seizures with minimal motor involvement (37). The patient has altered consciousness but may partially respond to his environment. These seizures may last for extended periods, representing a form of nonconvulsive status epilepticus. They have been associated with mesial-frontal (14) as well as frontopolar seizure onset (37).

These seizures can be clinically indistinguishable from dissociative episodes or alteration of consciousness due to psychiatric disease. However, during frontal lobe absence seizures usually obvious EEG changes occur, which are clearly epileptiform in the form of irregular diffuse sharp slow complexes (38). This again stresses the necessity of video-EEG monitoring to assure the correct diagnosis.

Other Clinical Seizure Manifestations Associated with Frontal Lobe Origin

Sexual Automatisms

Sexual automatisms were not recognized as an epileptic phenomen until recently (39). They may consist of pelvic thrusting and genital manipulation. Because of their sexual content, they are often mistaken for psychiatric disease and, in fact, in nonepileptic or psychogenic seizures, pelvic thrusting is frequently observed. However, epileptic sexual automatisms have a very stereotyped appearance, and other epileptic motor manifestations, such as manual automatisms or clonic activity, are usually associated with sexual behavior. Seizures are relatively brief. Epileptic sexual automatisms are thought to originate in the prefrontal cortex and are associated with frontodorsal, frontopolar, or orbitofrontal seizure onset (39).

It has not been systematically examined whether sexual automatisms are associated with a postictally increased prolactin level. Prolactin seems to be elevated after generalized convulsions and 60% of complex partial seizures (40). A high frequency of falsely positive elevated prolactin level occurs, therefore the use of prolactin as a measure to distinguish nonepileptic from epileptic seizures is limited.

Sexual automatisms differ from orgasmic epilepsy, where a patient may have an orgasmic sensation at the onset of a seizure. These sensations seem to originate in the right hemisphere (41) and were previously localized to the right parietal parasagittal area (42).

Urinary Incontinence

Urinary incontinence can be seen in frontal lobe seizures if the frontal cortical representation of the bladder is involved in seizure activity. This can occur without secondary generalization, but does not have a definite localizing value, because this may also be seen in temporal lobe seizures. Urinary incontinence is not a definite proof of an epileptic event, because 44% of patients with nonepileptic psychogenic seizure reported urinary incontinence with their events (43). Ictal urinary urge was also shown to localize to the nondominant hemisphere (44). Stool incontinence is exceedingly rare as a manifestation of epilepsy and could suggest other origins for the patient's episodes.

Eye Deviation

Eye deviation is not a definite localizing sign, but is often seen contralateral to the involved frontal cortical eye-fields, as often noted in epilepsy originating in the supplementary motor area (45). However, it can be false lateralizing, possibly suggesting an origin in deeper brainstem structures (16,45,46).

Ictal and Postictal Paralysis (Todd's paralysis)

Postictal paralysis is fairly common after epileptic seizures, and it occurs contralateral to the seizure onset (4). Postictal paralysis is more commonly seen with frontal and parietal seizure onset than with temporal lobe seizure onset (47–49). The paralysis resolves over minutes if it occurs after a single seizure and may be prolonged after focal status epilepticus. It always occurs immediately after a seizure.

Ictal paralysis as hemiparesis during an electrical seizure has been described but is not very common (50,51). This clearly needs to be distinguished from postictal paralysis. Ictal paralysis was observed with seizure onset within the perirolandic area (52) and, if it occurs, it is usually short in duration.

ICTAL BEHAVIOR ORIGINATING IN THE TEMPORAL LOBES

Epileptologists often divide the temporal lobe into the mesial temporal structures, the lateral neocortex, and the insula. The mesial temporal structures include the hippocampus proper, the amygdala anterior to the hippocampus, the uncus, and the parahippocampal gyrus (Figures 2.3 and 2.6). The lateral temporal cortex includes Heschl's gyrus as the primary auditory area and Wernicke's language area, responsible for receptive language (Figure 2.3). The insula is usually not accessible to epilepsy surgery, therefore seizure manifestations originating in the insula are less well defined than mesial and lateral temporal lobe seizures. The insula is essential for gustatory and autonomic function (53).

TYPICAL SEIZURES ORIGINATING IN THE TEMPORAL LOBES

Mesial Temporal Lobe Seizures

Mesial temporal lobe seizures are by far the most common seizures originating within the temporal structures and are the single most common seizure type seen in the adult population. They represent the typical complex partial seizure.

Mesial temporal lobe seizure are often preceded by an aura, which not uncommonly also occurs in isolation (54,55). The most common aura are epigastric sensations or abdominal auras, which the patient often describes as a rising sensation, nausea, "butterflies in the stomach," or a feeling like being in an elevator (54,56,57). This type of aura is highly correlated with mesial temporal seizure

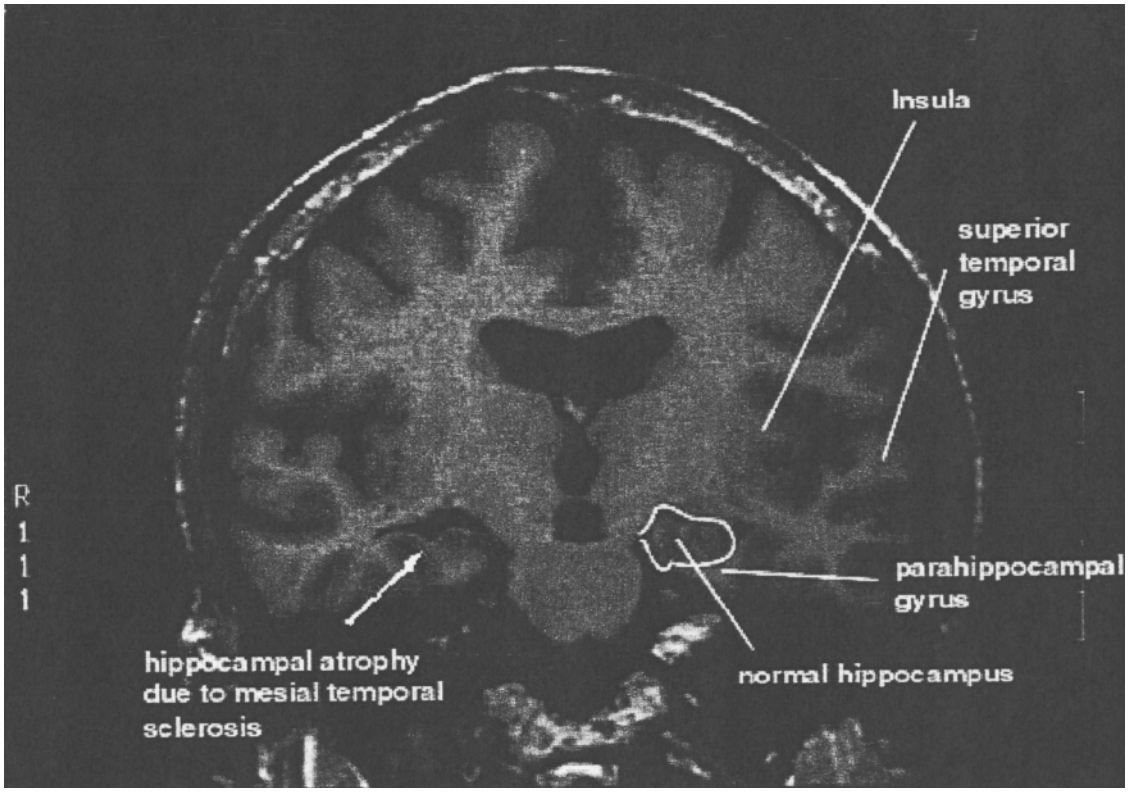

FIGURE 2.6

Anatomy of the temporal lobe shown on MRI. Typical finding of hippocampal atrophy on the right.

onset; however, exact localization within the mesial temporal structures is still controversial (56,58–60). Other auras associated with mesial temporal seizure onset include olfactory sensations, gustatory sensations, ictal fear, déjà-vu, and jamais-vu sensations.

Olfactory sensations can be pleasant or unpleasant (e.g. the smell of burned rubber). They are thought to be associated with seizure onset in the amygdala (61). Gustatory auras are usually described as an unpleasant taste and are associated with insular seizure onset (62) (see also Chapter 10). Ictal fear occurs most often in temporal lobe epilepsy, but is also described with frontal seizure onset (12,63,64). Intracranial EEG recordings and volumetric MRI measurements suggest major involvement of the amygdala in the generation of ictal fear (65,66). However, intracranial EEG recordings have shown that orbitofrontal networks may also play a role (67). Ictal epileptic fear can easily be mistaken as a psychiatric disorder, and the definite relationship to panic disorders remains undefined. It has been reported that a patient with temporal lobe epilepsy have a definite increased incidence of panic disorders (68).

Déjà-vu and jamais-vu sensations are other experiental auras associated with temporal lobe epilepsy. Déjà-vu sensations consist of a strange feeling of familiarity (69). The patient feels like he has lived through the same scene or situation previously. He may describe an intense feeling of familiarity with the situation or a scene. The exact localization of déjà-vu sensations within the temporal lobe remains still controversial, but the parahippocampal gyrus and the neocortical connections were suggested as the generators (70). Some intracranial electrical studies suggest an origin of the lateral temporal neocortex with spread to the mesial temporal structures (69). Other suggest pure mesial temporal onset (71). To distinguish epileptic déjà-vu from psychogenic phenonema, it is often helpful to obtain a clear and definite description from the patient about his sensations. Quite frequently, patients with psychogenic nonepileptic seizures are aware of déjà-vu sensations and list them as one of their symptoms. But they are unable to describe their sensations, or they give descriptions of other sensations. Jamais-vu sensations are related feelings of a sense of unfamiliarity or strangeness in a familiar situation. This is overall a rare occurrence in epileptic disorders. It probably localizes to the same brain structures as déjà-vu sensations.

A typical mesial temporal lobe seizure after an aura progresses to altered consciousness and behavioral arrest. The patient may be partially responsive, but is usually amnestic afterwards. Oroalimentary automatisms consisting of chewing, lip smacking, and lip pursing are common. Manual, semipurposeful automatisms, if unilateral, occur ipsilateral to the side of seizure origin (72). The hand contralateral to the seizure focus may assume a dystonic posture (72,73). Manual automatisms consist of semipurposeful fumbling, picking, or rubbing movements of the hands. Dystonia refers to a forced posturing of the hand with a clear tonic component. Autonomic changes, most often pupillary dilation, may occur. The pupil ipsilateral to the seizure focus is dilated and unresponsive (72). Vocalization is frequent. Vocalization originating in the temporal lobes is less dramatic and emotional than that vocalization originating in the frontal lobes. The patient mumbles or talks without making sense ("gibberish"). Postictally, the patient is confused, and if the seizure originates in the dominant hemisphere, postictal aphasia can be demonstrated. With right temporal seizure onset, the patient can relatively rapidly speak again. With left-sided seizure onset, the patient may, for example, be able to show the purpose of tools or items but is unable to name them. Seizures can secondarily generalize, often out of sleep (34), and have a mean duration of 70 to 90 seconds (72).

Whereas many different lesions in the mesial temporal structure can give rise to mesial temporal lobe seizures, mesial temporal sclerosis is the most commonly observed pathologic finding. Pathologically, pyramidal cell loss occurs in the CA1 and CA3 region of the hippocampal structures, the origin of which is unclear (74). Patients with mesial temporal seizures have similar risk factors for epilepsy, specifically prolonged febrile seizures in early childhood and similar MRI findings. MRI reveals hippocampal atrophy with the affected hippocampus being significantly smaller than the unaffected (Figure 2.6). Temporal lobe seizures associated with mesial temporal sclerosis are considered a specific epilepsy syndrome, referred to as mesial temporal lobe epilepsy (MTLE), and are amenable to epilepsy surgery (75).

Clinically obvious mesial temporal lobe seizures are fairly distinct in their clinical presentation and are highly stereotyped. Therefore, they are easily distinguishable from nonepileptic seizures or other psychiatric disease such as panic attacks. On ictal EEG, a clear build-up of rhythmic theta activity occurs over the affected temporal lobe, so they are unequivocally distinguishable from nonepileptic events. However, differentiation between isolated epileptic auras and panic attacks can be more difficult, because the patient is merely describing subjective sensations, and ictal EEG can be completely normal during epileptic auras. However, auras in isolation as pure manifestation of temporal lobe epilepsy are uncommon and often progress to clinically manifest temporal lobe seizures.

Mesial temporal lobe seizures are also observed with seizure onset in the medial, posterior, orbitofrontal region. This orbitofrontal region is anatomically connected to the mesial temporal structures, and clinical manifestations reflect ictal spread to the mesial temporal structures. It has been shown that the orbitofrontal region may remain clinically silent until spread occurs to the mesial temporal structures (16,76).

Lateral Temporal Neocortical Seizures

Attempts have been made to clearly distinguish temporal neocortical seizures from mesial temporal seizures (77,78). Mesial temporal and lateral temporal seizure may look alike insofar that altered consciousness, oroalimentary automatism, manual automatism, and dystonia occur in both types of seizures. They may only differ in their initial aura. Epigastric auras are uncommon in lateral temporal lobe epilepsy, and automatisms also seem to occur later into the seizure (77).

Auditory hallucinations point to a temporal neocortical onset. Auditory hallucinations consist most frequently of simple sounds and are thought to be generated in the primary auditory cortex in Heschl's gyrus. Onset is more difficult to identify and may require intracranial EEG monitoring if there is no clear lesion identifiable on MRI.

Other Ictal Manifestations Associated with the Temporal Lobes

ICTAL VOMITING. Ictal vomiting or retching is sometimes observed in temporal lobe epilepsy. It is rare that it occurs in isolation, and it is usually associated with other seizure manifestations such as oroalimentary automatisms or manual automatisms. It is not associated with nausea, and the patient is often unaware of the vomiting (79). Therefore, it is distinguishable from nonepileptic causes. It has been associated with right temporal seizure onset (80) but there are also recent reports of involvement of the left temporal lobe (81).

POSTICTAL NOSE WIPING. Postictal nose wiping was only recently described as a sign of temporal lobe epilepsy. The hand ipsilateral to the side of seizure origin is most commonly involved (82).

ICTAL AND POSTICTAL APHASIA. Aphasia as an ictal phenomen is rare, which may only reflect the fact that it is difficult to demonstrate during a seizure. Ictal

aphasia lateralizes to the language-dominant hemisphere, but must be clearly demonstrated using appropriate testing of naming and language during seizures.

Postictal aphasia is commonly seen after mesial and lateral temporal lobe seizures and has lateralizing value. A definite postictal aphasia with unequivocal paraphasias points to involvement of the dominant temporal language areas.

Pure speech arrest can be seen with involvement of the temporal lobes, but also occurs with seizure onset in the SMA (83). Therefore, speech arrest is not a clearly lateralizing sign, but usually originates in the language-dominant hemisphere (46).

Abnormalities of speech are commonly observed during nonepileptic seizures. Most commonly, patients present with slurred speech or stuttering. If definite aphasia with paraphasias and expressive errors is demonstrated, an epileptic event is highly likely.

ICTAL BEHAVIOR ORIGINATING IN THE PARIETAL LOBES

Parietal lobe seizures are less common than seizures originating in the temporal or frontal lobes. The postcentral gyrus represents the primary sensory area; the secondary sensory area is located at the superior bank of the Sylvian fissure (Figure 2.2). The remainder of the parietal lobes is involved in higher cognitive abilities like visiospatial function and praxia. Therefore, seizures originating in these more silent areas are harder to identify. Parietal lobe seizure were often described in the setting of lesional epilepsy.

Typical Seizures Originating in the Parietal Lobe

Somatosensory Seizures

Parietal lobe seizure can be preceded by an aura of somatosensory sensations. These consist usually of tingling or numbness, or at times as a sensation of movement (6). More complex sensory sensations are rare. The somatosensory sensation is generated in the postcentral gyrus (Brodman areas 1,2,3) and follows a somatopic representation comparable to the somatotopic representation in the precentral cortex.

The somatosensory disturbance occurs contralateral to the side of seizure origin (47,84) but may also occur ipsilaterally in some cases (84). After a somatosensory aura, the seizure may progress to a tonic seizure if it involves the SMA area, a clonic seizure if it involves the primary motor cortex, or even to a temporal lobe type seizure depending on seizure propagation (85,86).

If ictal activity originates in the secondary sensory area, the peripheral extremities and the face are involved, with sparing of the proximal extremities. This was demonstrated in stimulation experiments by Penfield and Jasper (6) and confirmed by Lüders (87). Somatosensory sensations were also elicited with stimulation of the SMA, but these are often bilateral, widespread, and more proximal (32).

Painful Seizures

Ictal pain has been recognized as a manifestation of seizure onset within the parietal lobes (88–92). If ictal pain occurs unilateral in a dermatomal distribution, it localizes to the contralateral postcentral area (88,92). Ictal pain not uncommonly also occurs in the abdominal region (92). Pain can be the only manifestation of seizure activity (90), but it is usually a distinct, brief, and localized sensation. Pain was frequently noted in nonepileptic seizures in the Cleveland Clinic series, but seemed to be more localized to the head, chest, or entire body (93).

Pure somatosensory or painful seizures are difficult to recognize if there are no other objective seizure manifestations such as automatisms or motor activity, because they can be purely objective. Somatosensory seizures may be recognized by their typical spread pattern—from initial involvement of the hand and subsequent simultaneous spread to the face and leg. They are episodic and brief. Not infrequently, somatosensory seizures are mistaken for transient ischemic attacks, especially in the elderly population. Painful seizures are brief, the pain is intense and intermittent (92). To the contrary, nonepileptic seizure patients usually describe diffuse aches and pains (93).

ICTAL BEHAVIOR ORIGINATING IN THE OCCIPITAL LOBE

The occipital lobe is the major site of the cortical visual system. The primary visual cortex is located superior and inferior to the calcarine sulcus in Brodman's area 17 (Figure 2.3). Much of remaining occipital cortex has been identified as visual association areas; the visual association area overlaps into the posterior temporal and parietal areas.

Typical Seizures of Occipital Lobe Origin

Visual Seizures

Because most of the occipital lobe is involved in visual function, occipital lobe seizures are frequently preceded by a visual aura. Visual auras include ictal amaurosis or hemianopsia, elementary or complex visual hallucinations, and visual illusions (85,94).

Ictal amaurosis describes ictal blindness and is uncommon. It may be preceded by ictal hemianopsia. If hemianopsia occurs, it has lateralizing significance to the contralateral occipital lobe. Ictal amaurosis lasts seconds to minutes and may be the sole manifestation of an occipital lobe seizure (95). It can be described by the patient as a whiteout or blackout. There may be initial blurring (96). Ictal blindness has been associated with the visual association cortex rather than with the primary visual cortex (97). Elementary visual hallucinations are images of shapes, colors, patterns, or waves that may have a flickering component (6,98). These can occur in one hemifield and, if so, they lateralize to the contralateral hemisphere. Elementary visual hallucinations are associated with the primary visual cortex. It has been shown that if elementary visual hallucinations are stationary they originate in area 17. If movement of the phosgens is present, they may originate in area 18 or 19 (6,99).

Complex visual hallucinations include a variety of images, which includes scenes, persons, animals, and material items. The images are usual uniform and stereotyped but patients with variable hallucinations are reported (100). Formed and complex visual hallucinations suggest involvement of visual association cortex.

Visual illusions include macropsia, micropsia, metamorphopsia, and pallinopsia. Patients with macropsia perceive an object bigger than its actual size. Patients with micropsia perceive an object smaller than the actual size. Metamorphopsia presents as distortions of form, size, or color. Pallinopsia is a visual preservation of an image long after the cessation of the visual stimulus (101). Visual illusions are thought to orginate in the visual association cortex, therefore the temporoparietal junction may also be involved. Distortions of body image have been described with parietal lobe seizure onset (47); however, this most likely is a disturbance of self perception rather than a visual illusion.

In occipital lobe seizures, a pulling or moving sensation in the eyes has been reported without detectable movements (94,102). Penfield observed eye fluttering with stimulation of the occipital lobe (6). Bilateral rapid eye blinking as a manifestation of occipital lobe seizures was confirmed with intracranial studies (94,103).

Ictal nystagmus is a rare seizure manifestation and has been associated with occipital seizure onset. Horizontal nystagmus has been reported in several patients with epileptic involvement of the cortical saccade region, and lateralization of the slow phase to the contralateral side has been demonstrated (104).

In a previous study, contralateral eye deviation was observed in thirteen of twenty-five patients with occiptal seizures onset; however, ipsilateral eye-deviation was observed in three (94). Eye deviation was also frequently observed in children with occipital lobe seizures (105). Ajmone-Marsan proposed three propagation patterns of occipital lobe epilepsy: mesial suprasylvian, lateral suprasylvian, and infrasylvian (4). In mesial suprasylvian spread, bilateral or unilateral tonic posturing may be observed due to the involvement of the SMA. Lateral suprasylvian spread results in clonic motor activity due to the involvement of the motor cortex, and infrasylvian spread may resemble a temporal lobe seizure. Ajmone-Marsan's description of spread patterns was later confirmed by intracranial EEG studies (94,106–109). Often patients are amnestic for the initial aura or symptoms; therefore, occipital lobe seizures can be mistaken easily as seizure either of temporal or frontal origin.

Seizures originating in the occipital lobe occur most commonly in benign childhood epilepsy with occipital paroxysms (110). Seizures begin with visual symptoms (as described earlier) and may progress to head turning, eye-deviation, vomiting, and hemiconvulsions following the described electrical propagation patterns.

Benign childhood epilepsy with occipital paroxysms manifests itself in childhood and is characterized by mainly nocturnal seizures.

Occipital lobe seizures may also be caused by lesions or cortical dysplasias, but are more difficult to recognize if they do not clearly present with visual symptoms.

Migraine is associated with visual scotoma that may resemble the elementary visual hallucinations as seen in occipital lobe seizures. It has been suggested that epileptic visual hallucinations are colored and migraine scotoma are black and white (111). However, because occipital epilepsy can be accompanied by vomiting and headaches, clinical distinction between epilepsy and migraine can be difficult without additional testing (refer to Chapter 9).

SEIZURES ORIGINATING IN THE DEEPER STRUCTURES OF THE BRAIN

Until now, the exact role of the deeper structure of the brain as the site of seizure origin remains unclear. In some seizures, there is a definite involvement of the thalamocortical networks (112), but until now only gelastic seizures due to hypothalamic hamartomas have been clearly identified as seizures originating in deeper brainstem structures.

Gelastic Seizures or Ictal Laughter

Gelastic seizures are typically associated with hypothalamic hamartomas (113), but may also arise from temporal lobe or mesial frontal foci. The patient may laugh involuntarily, and the seizures are often associated with

TABLE 2.3

Clinical Signs and Symptoms	Localization
Clonic activity of limbs, face	Primary frontal motor cortex (precentral gyrus)
Throat constriction, masticatory movements, drooling	Frontal operculum
Unilateral or bilateral tonic posturing	Mesial frontal lobe; supplementary motor area
Explosive, peculiar, and emotional automatisms such as stepping, cycling, rocking, jumping, running around, pounding, violent yelling, shouting, swearing, growling, grunting; often with preserved consciousness	Dorsolateral frontal cortex, orbitofrontal and mesial frontal cortex
Pelvic thrusting and sexual automatisms	Dorsolateral frontal cortex, orbitofrontal and mesial frontal cortex
Eye-deviation	Contralateral frontal eye-fields; deep brain stem structures; can be false lateralizing
Versive head deviation	Supplementary motor area
Limb paralysis	Perirolandic frontal or parietal area
Rising epigastric sensation, olfactory sensations, gustatory sensations, ictal fear and panic	Mesial temporal structures
Auditory hallucination	Superior mesial temporal cortex
Oroalimentary automatisms, manual automatisms (picking, fumbling), pupillary dilatation	Ipsilateral temporal lobe
Dystonic hand movements	Contralateral temporal lobe
Ictal vomiting/ictal spitting	Right (nondominant) temporal cortex
Postictal nose wiping	Ipsilateral temporal
Aphasia	Dominant temporal lobe
Speech arrest	Temporal lobe or supplementary motor area
Limb tingling or numbness, sensation of movement	Ipsi- or contralateral parietal lobe
Dermatomal or abdominal pain, chest pain	Parietal lobes
Visual aura, ictal amaurosis, hemianopsia, elementary visual illusions	Occipital visual cortex (Brodman areas 17,18,19)
Visual images, scenes, micropsia, metamorphopsia, pallinopsia, eye-fluttering, pulling or moving sensation in the eyes, nystagmus	Mesial suprasylvian, and infrasylvian occipital cortex
Gelastic seizures or ictal laughter	Deeper brain stem structures (hypothalamus, also involving frontotemporal cortex, cingulate gyrus, and basal temporal cortex)

bilateral tonic arm elevation. The laughter is usually not associated with a feeling of happiness or mirth. Seizures are very brief. The typical syndrome associated with hypothalamic hamartomas includes precocious puberty, endocrine abnormalities (114), and developmental delay. Removal of the hamartoma can render patients seizure free (115), but other alternative approaches using radiosurgery have recently been successful in eliminating seizures (116). Intracranial EEG studies have shown that epileptiform activity originates in the area of the hamartoma (117). Involvement of frontotemporal cortex has been suggested in the generation of ictal laughter (118,119). It was suggested that seizures originating in the cingulate gyrus generate laughter without the feeling of mirth, while seizure involving the basal temporal cortex also involve mirth (118). Laughter is an uncommon symptom associated with nonepileptic seizures.

CONCLUSION

Epileptic seizures of partial onset can manifest themselves with various signs and symptoms that are distinct from nonepileptic events (Table 2.3). The anatomical correlation of seizure onset is only one of many factors that determine the clinical presentation of epileptic

seizures. The anatomical correlation of clinical seizure semiology can be revealing in localizing seizure onset, but it can be falsely localizing due to electrical seizure propagation and the rapid spread of seizure activity.

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3 Curious Epileptic Seizures That Don't Resemble Seizures

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The word "seizure" typically invokes a mental picture of a confusional or tonic-clonic event. However, a myriad of epileptic seizure phenotypes are not easily identified and often misdiagnosed as nonepileptic events. These epileptic seizure manifestations involve the motor system (having bizarre postures or stereotypies), the autonomic system, the somatic and special senses, and the cognitive and psychiatric domains. The stereotyped nature of these events and a high index of suspicion can help lead the treating neurologist to the appropriate diagnostic and therapeutic modalities. These isolated, unusual manifestations can occur in complex partial or simple partial seizures. This chapter discusses unusual epileptic events across the lifespan by grouping them by their semiology. This may alert the clinician to the possibility of seizures masquerading as other disorders. We indicate the terminology recently recommended by the International League Against Epilepsy (ILAE) (1) in italics. We start with the epileptic seizures of childhood. Although recent reports show that pediatric epileptic seizures can be classified with a nomenclature similar to that used for adults (1), neonatal and infant patients with epileptic seizures can present with some unusual symptoms.

SEIZURES THAT DON'T RESEMBLE SEIZURES IN NEONATES

The typical tonic clonic seizure is not described in the neonate, possibly because of incomplete neuronal networks. Instead, neonatal seizures encompass a rich variety of semiology including autonomic phenomena, eye movements, postures, stereotypies, and tremors. Not all of these events are accompanied by electroencephalographic (EEG) changes, but they continue to be classified as neonatal epileptic seizures. These seizures are thought to be subcortical in origin, the so-called *brainstem release phenomenon.* Partial or generalized increases in muscle tone, followed by clonias, hypotonias, and other subtle features are common (2).

Abrupt changes in autonomic nervous system (ANS) function include changes in heart rate, respiration, blood pressure, and vasomotor changes such as flushing, papillary dilatation, and excessive salivation

(3). These occur in isolation or with other motor symptoms. Apnea as an epileptic seizure manifestation may rarely occur alone, even unaccompanied by bradycardia (4). Ocular manifestations vary from sustained eye deviation to random and roving eye movements or nystagmus. Motor phenomenon include oral buccal-lingual movements such as chewing, sucking, and tongue protrusions. Rowing or swimming movements of the arms, and pedaling movements of the legs are also seen in neonatal seizures. Some of these motor phenomenon may be provoked by stimulation and suppressed by restraint or repositioning (5–6) (see also Chapter 6).

SEIZURES THAT DON'T RESEMBLE SEIZURES IN INFANTS

Epileptic seizures in the preverbal infant remain difficult to recognize because of the lack of a verbal description and the lack of reliable identifiers to assess consciousness. Therefore, correctly classifying focal seizures as simple or complex remains a nearly impossible task. Infantile seizures that prove particularly challenging to identify include astatic or atonic seizures that encompass sudden loss of posture, which is typically a brief head drop. *Hypokinetic seizures (1.2.6)* often arise in the temporal lobe in infants, and may manifest as a subtle pause in activity accompanied by paleness or mild perioral cyanosis (7–9).

> A 4-month-old girl was admitted for video-EEG monitoring after two tonic-clonic events. One event was recorded manifesting as arousal with brief eye opening and an occasional, isolated, small amplitude left upper extremity jerk. EEG showed left hemispheric semirhythmic activity with intermixed sharp waves. After the event, normal infantile movements resumed.

Even if appreciated, these events may be attributed to another cause such as gastroesophageal reflux. This pause in activity should also be distinguished from breath holding spells, which are typically preceded by pain or crying.

Other seizures that are often initially overlooked are the cluster, "twitches," or "hiccups" that are infantile spasms *(epileptic spasm, 1.1.1.1)*. Using EEG, these spasms are easily distinguished from benign nocturnal myoclonus.

Other paroxysmal nonepileptic disorders include benign paroxysmal torticollis or cervical dystonia lasting 4 to 6 months. Infants, especially girls, may be brought to attention for rhythmic contraction of legs, and adduction of the thighs with flushing and perspiration. Unlike epileptic seizures, the child resists being interrupted during these masturbation-like episodes.

SEIZURES THAT DON'T RESEMBLE SEIZURES IN OLDER CHILDREN AND ADULTS *(1.0 MOTOR)*

Negative Epileptic Seizures

Negative seizures *(Negative myoclonic–1.1.2.1; atonic–1.1.4; astatic–1.1.5)* are clinically defined as a lapse in activity including attention, tone, speech, and sensation (10). Negative seizures characterized by a fall or a head drop, in the absence of a motor phenomenon such as a convulsion, are broadly classified as falling seizures, drop attacks, or by the terminology proposed by the ILAE (1). These can be of partial or generalized onset and have been given many terms in the literature including astatic, akinetic, tonic, and drops. To better characterize and prognosticate, electromyographic (EMG) recordings of the involved muscles during video-EEG can help assess tone fluctuations and distinguish tonic from atonic seizures. Drops of epileptic origin should be distinguished from other causes including syncope, cataplexy, and vestibular disease. The boxed case study #1 is an example of a falling seizure.

> ***Case Study #1.*** A 6-year-old boy was brought to medical attention for balance difficulties. On further questioning, his mother reported "knee buckling" leading to stumbling and falls. Scalp EEG showed brief bursts of spike and wave discharges, maximal in the right parietal region during each "buckling" episode.

An example of a negative focal motor seizure is illustrated by case study #2.

> ***Case Study #2.*** A 16-year-old female presented with episodic right hand weakness resulting in the dropping of objects. Initially this was thought to be a transient ischemic attack (TIA). An EEG later showed concomitant midline epileptiform discharges. Strength improved with resolution of each seizure (Figure 3.1.)

Hyperkinetic Seizures

Video-EEG has familiarized most neurologists with the fencing or "M2e" postures of supplementary motor

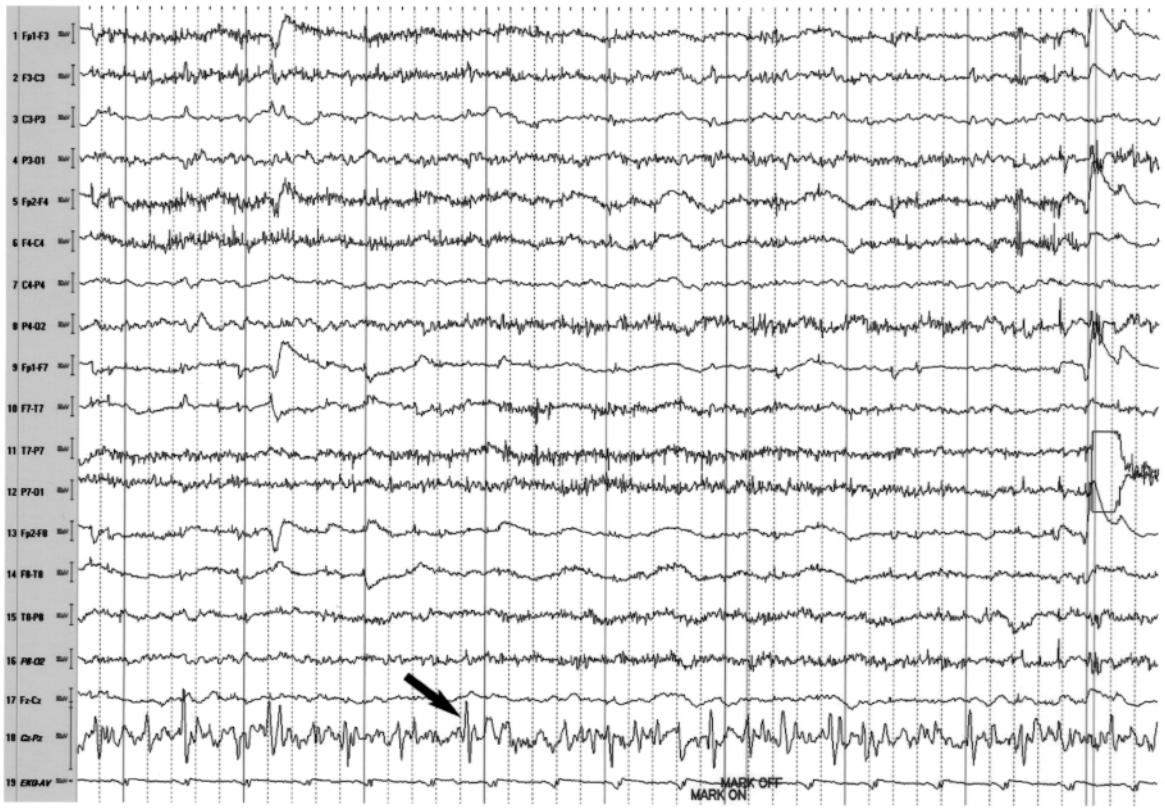

FIGURE 3.1

The figure demonstrates a young girl who loses motor control of her right hand during seizures (reproduced from video). The EEG of the event (indicated at vertical line) did not show a clear ictal build-up but demonstrated epileptiform potentials at Cz-Pz (arrow) during the event. On this and subsequent EEG figures, the calibration bar indicates 50 μV, the green vertical line corresponds to the time of the video picture, the dashed vertical lines are 200 msec, and the solid vertical lines are 1 sec. LFF = 0.1 Hz; HFF = 50 Hz.

seizures (head and eyes looking at the elevated arm on an abducted shoulder (11). We also appreciate the frenetic automatisms of the *hyperkinetic seizure (1.2.5),* which can be pedal, manual, or bimanual/bipedal (12–15). These seizures typically begin with wild automatisms such as rocking, bicycling, kicking, thrashing, pelvic thrusting, and arm waving. These are sometimes semipurposeful, accompanied by grunts, groans, screams, or animal noises. The subject may appear to do karate, direct an orchestra, or cast for a fish. They typically originate from ventral prefrontal lobe and/or orbital frontal complex, or deep mesial frontal [supplementary motor area (SMA) and cingulate; 12–17)], although they can emit from the parietal operculum with anterior propagation (12).

Case Study #3. A 23-year-old male with seizures since age 12 years was studied. His seizures began with an angry stare and deep inspiration followed by a barking noise and then by rocking, grunting, and banging his legs on the bed rails. His movements were so violent that he broke out of a posey, and at home, his mother reported he once tore down the curtains in his room. On depth record-

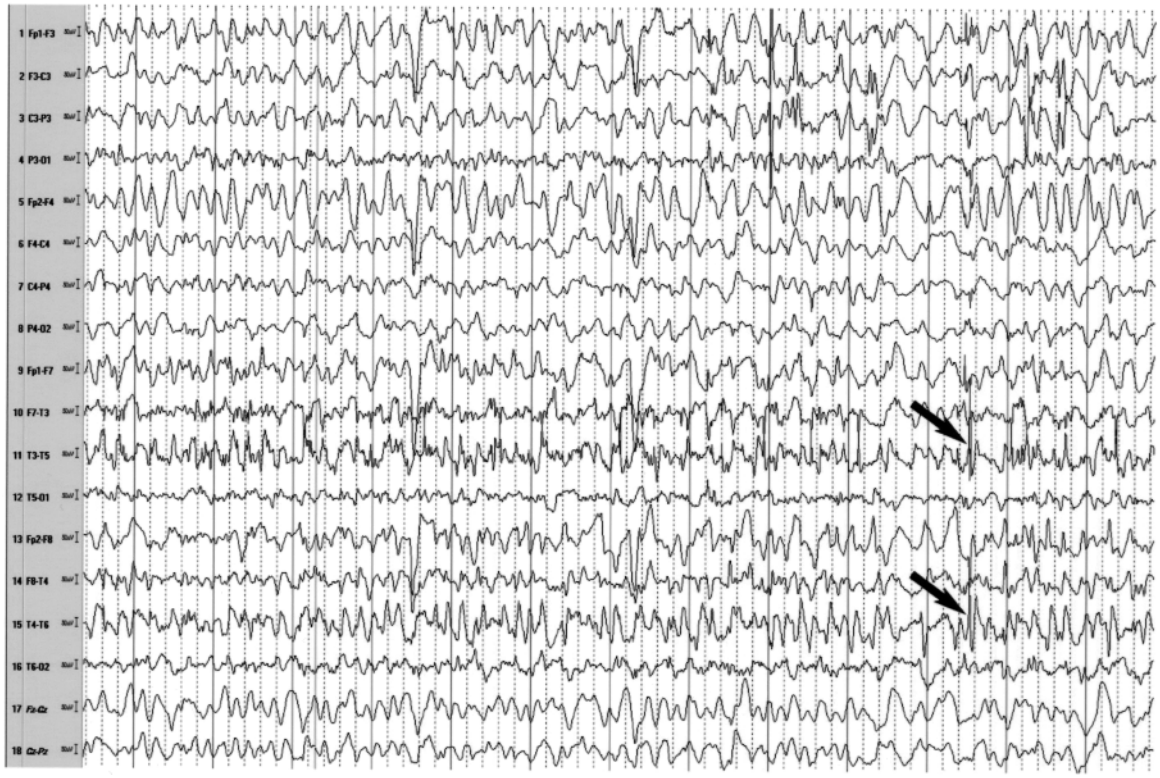

FIGURE 3.2

This female is demonstrating an angry facial expression and rotatory movements of the right arm with that hand in a fist while the left arm extends beside her as she looks to the left. The semeiology is consistent with a right-sided seizure, possibly temporoparietal (reproduced from video). The EEG at the time of the picture (green vertical line) shows a clear ictal pattern without clear localization, maximal in the temporal regions (arrows). LFF = 0.1 Hz; HFF = 15 Hz.

ings, ictal onsets were located at the left ventral premotor and prefrontal region (12).

Although the automatisms may appear "violent," directed violence occurs rarely—5% in a large series of video-EEG-documented seizures (18). Violent behavior typically is resistive, at the end of a seizure, can include throwing things or self-pugilism (19), but never occurs as part of a coherent plan of action against an individual (18). Therefore, no seizures are classified or described as "violent." Other automatisms of the arms may arise from the posterior temporal cortex or temporo-parietal junction.

Case Study #4. A 13-year-old female had complex partial seizures beginning with eye blinking and a threatening facial expression. Subsequently, fast and repetitive rotatory right arm movements occurred with a clenched fist. EEG showed widespread rhythmicity, maximal in the temporal regions (Figure 3.2a and b).

Ambulatory epileptic seizures, also called *wandertrieb* or *poriomania* (compulsive, aimless wandering) can be mistaken for psychic fugue states as they can be accompanied by depression, irritability, and dizziness (20–22). These may represent a special case of the hyper-

kinetic seizure, although it is not known if this behavior is truly ictal or is postictal. Bitemporal discharges have been associated most frequently with this semiology.

Opisthotonic posturing may occur in the context of a hyperkinetic epileptic seizure or as an isolated seizure. It has been ascribed to deep mesial frontal structures and may occur with or without loss of consciousness (12,17). Odd postures can resemble certain types of catatonia, as is illustrated in the upcoming psychiatric manifestations section.

Sensory Seizures

Sensory seizures *(2.2; Non-Motor – 2.0)* are difficult to define in children because of lack of overt ictal behavior and a child's often limited ability to communicate the experience. Patients may complain of tingling, numbness, pain, heat, cold, or electric shock sensations. The case illustrates a simple partial seizure initially thought to be a migraine variant and subsequently attention-seeking behavior.

Case Study #5. A 6-year-old boy complained of "pulsations" in his head up to several times a day. He paused briefly with a frown or more typically continued with his routine and would later report "I just had one." EEG showed seizure onset for the left parietal region, maximal at P3 electrode.

The classic "march" of a primary tactile seizure is well-recognized in adults and older children, but other variants are not. A simple sensory symptom may occasionally occur in isolation for years before declaring itself as an ictal variant. Episodic anesthesias or parasthesias, sometimes of a superficial, burning nature, have been reported from the sensory association cortex (22), and painful posturing can occur with lateral premotor seizures (23,24). In one large seizure study, pain occurred in 3% of all subjects with seizure (25). A headache is a frequent postictal complaint of any tonic-clonic seizure, but rarely may be the only symptom of an unrecognized complex partial seizure, often of occipital origin (26,27).

Vestibular-type sensations have been reported. These are unprovoked complaints of dizziness or even vertigo but are rarely directional. Vertigo may accompany visual disorientations, or sensations of ocular or whole body oscillations (20,28). The central representation of the vestibular system occurs bilaterally in the region of the superior temporal gyrus and Sylvian fissure, probably anterior to the primary auditory cortex (Heschl's gyrus) but is less precisely understood than audition (29,30). Auditory, visual, and gustatory hallucinations are discussed later under Psychic Seizures.

Changes in vision, varying from visual field cuts to complete loss of vision, have been reported as an ictal or postictal event (31,32). Differential diagnoses includes migraines and strokes or transient ischemic attacks (TIAs). Sensory agnosia of a body part (failure to recognize that it belongs to the owner) or phantom sensations (sense that a limb is in a particular position which, in fact, it is not) can also occur.

Autonomic Seizures

Autonomic epileptic seizures *(non-motor, autonomic – 2.2.1.8 and 3.0 – autonomic events)* are probably the most common of the "seizures that don't look like seizures." Fortunately these phenomena usually occur during the course of a complex partial seizure or as a prelude to a generalized tonic-clonic seizure. The pathways involved can be afferent or efferent (33). Once more, in the absence of another etiology, any isolated, recurring, paradoxical autonomic complaint should be investigated as a possible ictal manifestation. Effects on the heart have been best studied, with tachycardia occurring in a large percent of complex partial seizures (CPS) or generalized tonic-clonic (GTC) seizures (34). Tachycardia has been reported in 92 to 96% of seizures (35). A recent report on temporal lobe epilepsy (TLE) found that the percentage was highest in mesial temporal epilepsy (92%) and lowest in nonlesional cortical temporal epilepsy (77%; 35a). One early study suggested that tachycardia and pressor responses were more commonly produced by left-sided insular stimulation, with bradycardia and hypotension more common with right-sided stimulation (36). One review of ictal bradycardia reported that 76% of sixty-three reported cases were associated with frontotemporal epilepsy with left-sided ictal predominance, and that the condition is potentially lethal (37). It occurred only 1.4% of the time in a recent report on TLE. Other arrythmias have been reported, such as ventricular ectopy, Atrioventricular nodal escape, and ventricular tachycardia (38). No precise cerebral location exists for these changes although the paralimbic or limbic cortex is generally implicated (39). Stimulation of either the cingulate gyrus or the insula can produce heart rate and blood pressure changes (37,40).

Chills and pilomotor erection are a common accompaniment of temporal lobe seizures but occur rarely in isolation (41) and can eminate from hippocampus, amygdala, or insula (42,43). A single case of unilateral flushing has appeared (44). Pallor or rubor can accompany temporal limbic seizures (45,46).

Pupillary dilatation is common in partial complex or generalized seizures. However, this can be asymmetric or unilateral, with the enlarged pupil appearing

contralateral to a frontal source or spread pattern and can occur in isolation (47,48). Urinary incontinence is also common in generalized seizures, where it occurs due to the relaxation of the external sphincter (49). In absence seizures, it occurs (albeit infrequently) due to increased bladder pressure (50). Urinary incontinence is exceedingly rare in isolation, but one case is described in the text.

Case Study #6. A 15-year-old boy was admitted for uncontrolled seizures of several types. On video-EEG he was seen to stop his activity (writing) and look thoughtful, then abruptly to push his chair away from the table and look down at his lap in surprise. He called the nurse to say "I had a little flash." When asked what he meant he reported that he had had a seizure and wet himself. The origin of this patient's epileptic seizures was widespread areas of the frontal lobe, including some clearly starting in the cingulate gyrus. Isolate enuresis was not recorded on intracranial monitoring (51).

Gastrointestinal symptoms are also common ictal phenomena. These include flatulence, epigastric rising sensations, borbyrigmy, nausea, and emesis (52–56). These symptoms are frequently isolated in children. Ictal emesis, in particular, has been described from the insula, the frontal operculum, and in benign occipital epilepsy. Ictus emeticus can occur without impairment of awareness and in isolation (57). Rectal pain and burning may occur in an epileptic seizure and can be triggered by a bowel movement (58).

Respiratory symptoms are also common. These can include hyperventilation during CPS and hypoventilation during or after generalized tonic-clonic seizures (59). However, difficulty breathing, choking, stridor, and apnea can also occur (60–62). Stimulation of the temporal lobe, insula, hippocampus, anterior cingulate, amygdala, and lower motor cortex have been shown to induce respiratory inhibition (46,63,64). The differential diagnoses of autonomic phenomena includes gastrointestinal disease, endocrine diseases such as pheochromocytoma, cardiac disease, and psychiatric disease especially panic attacks (65).

Genital sensation with sexual content and sexual auras arise more commonly from limbic or temporal lobe regions (66). Ictal orgasm or priapism have also been reported (67). Other types of sexual automatisms have been described (68,69). These are motor automatisms (pelvic thrusting) from the frontal lobe and genital sensations (from parietal or limbic structures).

Dyscognitive Seizures

Time distortion, depersonalization, and disorientation are types of cognitive seizures or dyscognitive seizures *(2.3)* that have all been ascribed to the parahippocampal or fusiform gyri (70). Forced thoughts of a repetitive nature, with or without pressured speech, can be seen in some frontal lobe seizures (71). In this section, we deal with those seizures affecting attention and language. Seizures involving mood or affect *(affective; 2.2.2.1),* memory *(mnemonic; 2.2.2.2),* or distorted perceptions *(illusory – 2.2.2.4)* are dealt with under the section on Psychic Seizures. These are all listed under *experiential (2.2.2)* in the newly proposed ILAE classification (1).

Attention

Lapses of attention can be seen with absence seizure or CPS. The former is not associated with a prodome or postictal phase, lasts seconds, and is accompanied by loss of consciousness. Such epileptic seizures can be of temporal lobe origin. An example of the "dreamy state" of a temporal lobe complex partial seizure is described in case study #7.

Case Study #7. A 53-year-old man presented with complaints of intermittent problems with concentration, memory, and sensations of being in an unusual state. He had been admitted 3 years prior for new onset tonic-clonic seizures, believed to be secondary to an (undiagnosed) encephalitis, which quickly resolved, although a visual field cut had been present at the time. A previous video-EEG had not been definitive, and nonepileptiform events were suspected. However, on re-examination, clear CPSs with only slowing of responsiveness were observed (Figure 3.3a and b).

It is difficult to distinguish a true absence seizure (72) from a "pseudo-absence" seizure of frontal origin (73). CPS are often longer, and often, but not always, an aura, simple partial seizure, and a postictal phase are present.

Case Study #8. A 23-year-old male had seizures since the age of 13 years (GTC), which were controlled. However, he came in with complaints of increasing difficulty with school and work performance, felt to be due to possible antiepileptic drug toxicity. Prolonged frontal epileptic seizures were recorded, undetected by the patient or his family (Figure 3.4a and b).

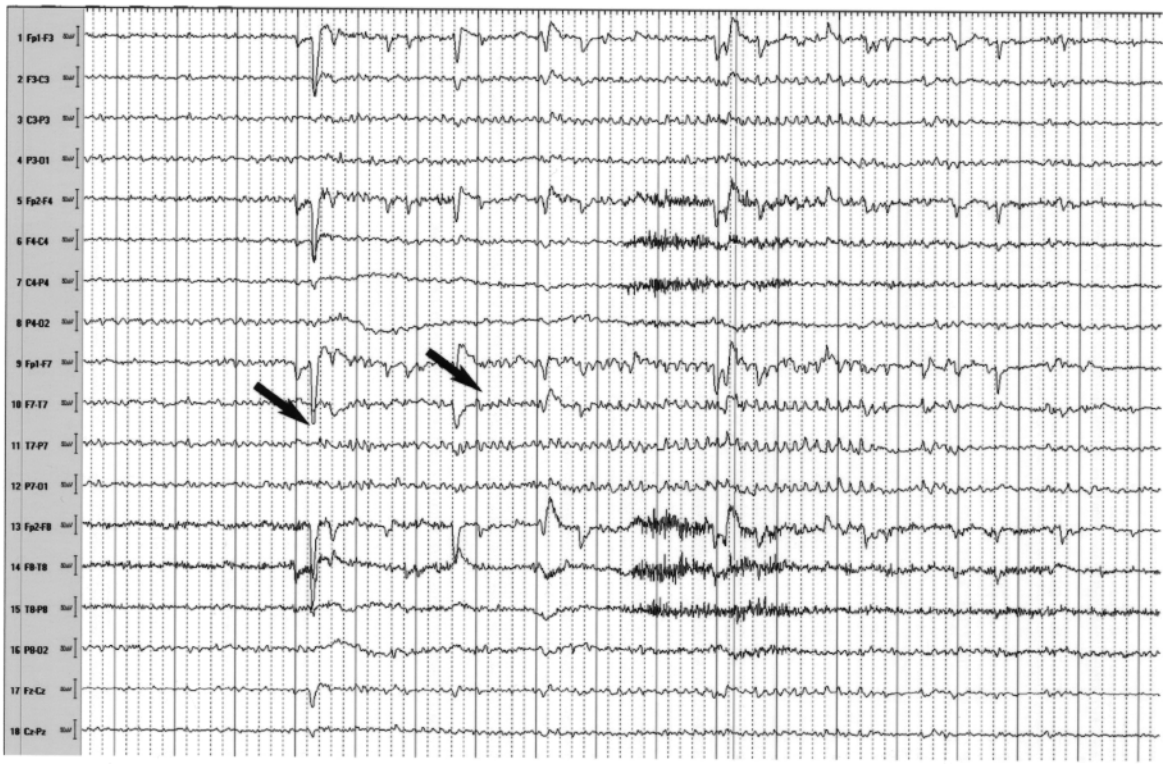

FIGURE 3.3

This patient presented with problems with memory and concentration. Here a typical seizure occurs while he is reading a book. He continues to appear as if he is reading, but does not recall later what he did at that time (reproduced from video). The EEG of the patient shows a clear ictal pattern on the left, phase reversing at F7 (arrow). LFF = 0.1 Hz; HFF = 30 Hz.

Either CPSs or true absence can be accompanied by automatisms such as eye fluttering, lip smacking, or hand wringing (72,74). In children, these epileptic seizures, especially absence, may be difficult to distinguish from lapses of attention commonly seen with attention deficit disorders (ADD/ADHD).

This presentation of nonconvulsive status is especially common in the elderly, where it can reflect a frontal lobe lesion or a history of childhood absence (73,75). It can be seen in younger persons as well. It will only be diagnosed in a timely fashion if the clinician has a high index of suspicion. Nonconvulsive status can be the initial presentation of juvenile myoclonic epilepsy (76). A history of morning jerks in a pubertal individual helps to confirm this diagnosis (77).

Language

Speech arrest as an ictal phenomenon can be a part of benign Rolandic epilepsy (77). A seizure of this childhood syndrome may involve movements of the mouth, trembling of the chin and tongue, decreased swallowing with drooling, or difficulty in moving the tongue. Speech arrest may begin at seizure onset or evolve after the utterance of a few words. This can more often reflect a simple motor phenomenon than a language involvement.

Speech can also be affected in other childhood epileptic syndromes such as Landau-Kleffner syndrome and the syndrome of continuous spikes and waves during slow wave sleep (CSWS). Whereas the latter manifests as widespread regression, the former typically begins with auditory verbal agnosia (a *dyscognitive*

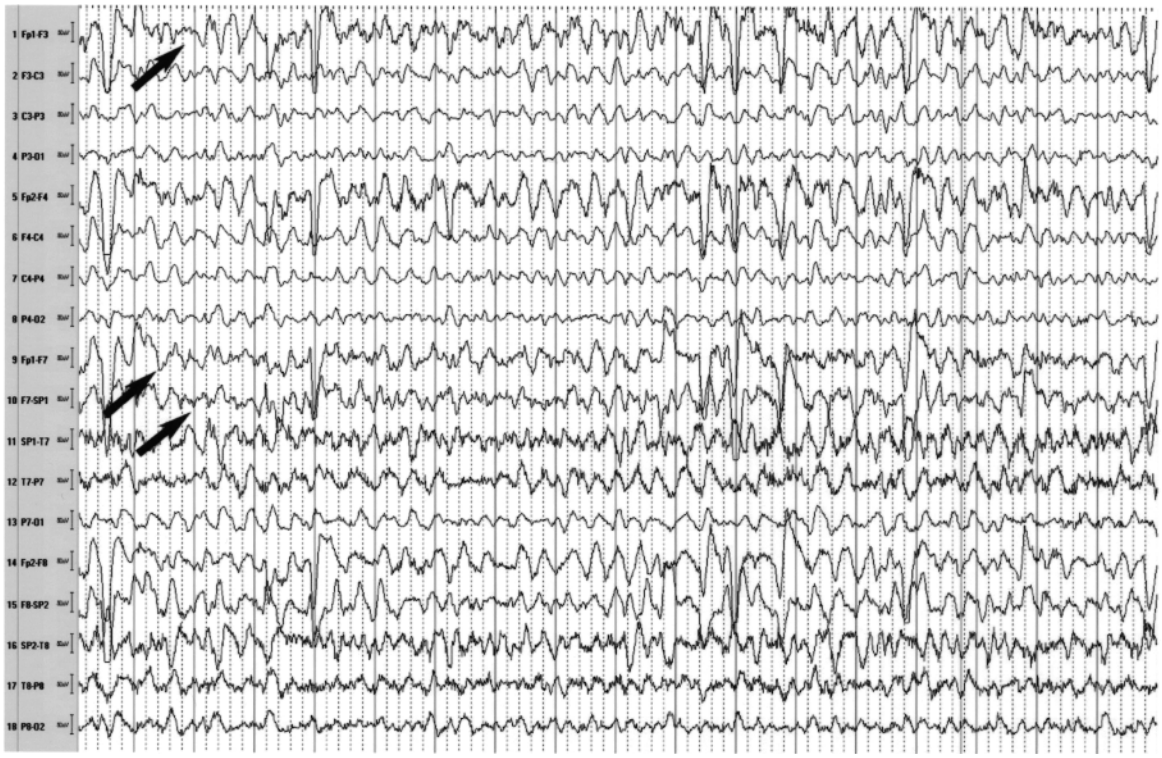

FIGURE 3.4

A frontal "pseudo-absence" epileptic seizure. The patient is seen twisting a bottle cap on and off again. He was able to nod and smile or look around appropriately during the seizure. Several subclinical seizures of this nature were recorded lasting 8 to 10 minutes (reproduced from video). The EEG corresponding to the Figure in 4a (at green vertical line) is shown. This seizure started with 10 Hz activity on the left, at Fp_1-F_7, followed by rapid propagation to the right frontal lobe and left temporal lobe. A dipole source analysis of single spikes suggested a primary focus in the deep left medial frontal region, with a secondary focus that includes the right cingulate providing a better fit in flurries of spikes. LFF = 0.1; HFF = 30 Hz.

seizure). The language disorder may be steadily progressive or become incrementally severe with relapses. The child may be misdiagnosed as hearing impaired or autistic (77).

Sometimes, speech involvement can be quite subtle, as case study #9 illustrates.

Case Study #9. A 9-year-old boy with a previous history of complex partial seizures was brought for evaluation of new onset stuttering. Initially, the differential diagnosis included antiepileptic medication effect, developmental language disorder, or parental anxiety. An EEG was subsequently performed. Bisynchronous centrotemporal spike and wave discharges of 1 to 2 sec duration were correlated with stuttering. Speech returned to normal in-between discharges.

Aphasic epileptic seizures, which can eminate from either Broca's or Wernicke's area have been described in adults, mistaken initially for TIAs or strokes (78–82). Once again, this may be the only manifestation of a seizure.

On the other hand, phonatory seizures *(vocal – 1.1.11)* can also rarely occur in isolation. This can take the form of speech automatisms. Pallilalic vocalizations, primitive sounds, or single repeated words can arise from frontal or cingulate seizures (64,71). Nonfluent vocalizations can arise from the dominant or nondomi-

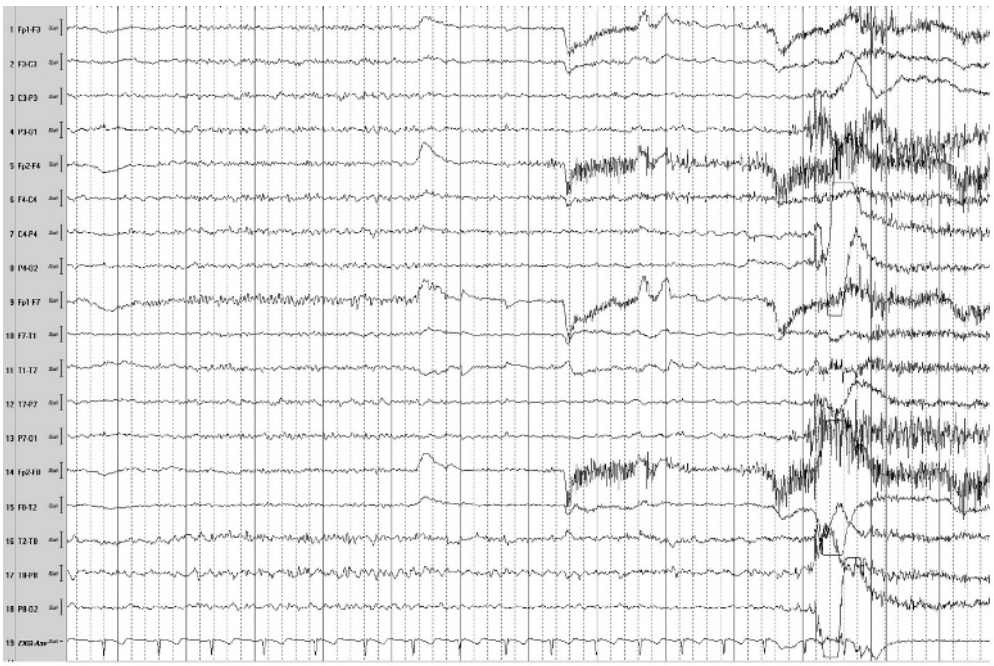

FIGURE 3.5

This patient with hypermotor seizures including pallilalic vocalizations is seen as she begins to cry out and thrash about (reproduced from video). This seizure began with rhythmic, low-voltage, fast activity in the left frontal area with rapid bilateral propagation. The video picture was taken at the green line.

nant cortex (80), and neologisms can occur (81). If the speech is of a generally fluent nature, the nondominant hemisphere is implicated (24).

Case Study #10. A 55-year-old woman had a history of epileptic seizures controlled since age 35. She also carried a diagnosis of chronic schizophrenia, although she had married, had children, and worked successfully for years before the appearance of a new seizure type. These events, characterized by grabbing her head in her hands, calling out "Oh my, oh my," or other phrases repetitively, and thrashing about were felt to be consistent with nonepileptiform seizures. Video-EEG revealed their true epileptic nature (Figure 3.5a and b).

REFLEX EPILEPSIES

Reflex epilepsies are usually discussed in association with unusual epileptic seizure types. However, the seizures themselves are less unique than the fact that specific stimuli trigger them. If seizures do not exist in the absence of the triggers, some argue that these are not real epilepsies (82), but rather, that the term "reflex" should be considered a seizure modifier. An example of a reflex epilepsy is musicogenic epilepsy (83–85), in which music may trigger a seizure with musical hallucinations (85). Bathing epilepsy has been described, a particularly hazardous trigger (86). Other stimuli are startles by loud noises, somatosensory stimulation, proprioceptive stimulation, voices, eating, sounds, and language functions (87–89). A special case of the latter, reading epilepsy, can have jaw deviations, sensation, or clonae associated with it (89).

PSYCHIC SEIZURES

Psychic epileptic seizures involve purely sensory or subjective symptoms with retained memory for the ictus. These seizures do not involve loss of consciousness. They do not have a motor component. Thus, some psychic seizures have been previously covered in the sections on sensory symptomatology and dyscognitive

seizures. In this section, we discuss ictal symptoms including hallucinations of all modalities, illusions involving distortions of existing objects, dysmnesic symptoms involving distortions of time, and intellectual symptoms with alterations in thought content. Psychic seizures must be distinguished from the psychiatric illnesses that they may closely resemble.

Affective Seizures

Any emotion can be expressed during the course of an epileptic seizure *(2.2.2.1)*. Irritability, anxiety, and anger can occur from amygdalar seizures or stimulation (46,48). Fear is commonly a component of hippocampal seizures (90). It is often without content and thus takes on the perception of unreality (91). An affectless expression of fear can occur with cingulate seizures, as can a feeling of happiness (64,71). Auras may involve the sudden onset of overwhelming fear without dependence on the patient's mood or thoughts (92), and ictal episodes of isolated fear may be confused with psychiatric illnesses of paranoia or panic disorder.

Case Study #11. A 55-year-old man was noted to have a change in mood over 3 years, from placidity to increasing spells of irritability. He was increasingly suspicious, with brief episodes of inexplicable severe fright. He had short episodes of unnatural aggressiveness lasting from a few seconds to half a minute. An EEG showed high-voltage 2 to 3 per-second waves in the right temporal area. An inoperable glioma was found in the right temporal lobe (93).

Gelastic (laughing) or *dacrystic* (crying) epileptic seizures can occur; even in the same individual.

Case Study #12. A 35-year-old had epileptic seizures since the age of 5 years. Her current seizures consisted of simple laughter, often preceded by a feeling of euphoria. These did not respond to high doses of several antiepileptic drugs, and routine EEGs were normal. Video-EEG recorded numerous episodes of laughter and/or crying accompanied by midline to right temporparietal region rhythmic theta activity. She was able to speak during the events but was amnestic afterwards.

These affective epileptic seizures may emanate from the frontal lobe or temporal lobe, but the gelastic seizures are best known in association with hypothalamic hamartomas, which appear to be the seizure source, possibly through connections to the anterior thalamus and on to the cingulate cortex (94–95).

Dysmnestic Seizures

Dysmnestic seizures are another category of cognitive seizures. The perception of memory is distorted in dymnesic seizures. Two types are commonly reported. *Déjà vu* is the false sensation that life is repeating itself. *Jamais vu* is the false sensation that familiar objects, persons, or situations have never been encountered before. The déjà vu of temporal lobe epilepsy is well known; it has been described following stimulation of either the hippocampus and surrounding regions, or the parietotemporal neocortex (96–98). Jamais vu is less well studied, but may involve the same structures with a different emotive component. Some subjects describe a sense of "wanting to remember" as an aura phenomenon (70). These dysmnestic affections have been reported with both right- and left-sided seizure foci. Rarely, a Klüver-Bucy syndrome having auditory and visual agnosias, hyperorality, hypersexuality, and emotional blunting has been described with ictal involvement of both temporal lobes or as a postictal phenomenon (99).

Gloor reported the case of a 39-year-old man with two types of seizures. One type originated from the left temporal lobe and caused loss of awareness, automatisms, and aphasia. His more common type arose from the right temporal lobe and started with unpleasant churning in the stomach, pounding headache, and a sudden feeling of déjà vu associated with a feeling of prescience. During one episode the patient reported, "In a minute there will be more people, as if it all happened before, just reliving all of this. The more I know what is going to happen, the farther it goes and the dizzier I feel…" Typical events proceeded to anguish and depressed mood. The latter epileptic seizures were reproduced with electrical stimulation of the right limbic structures (97). Real memories can be experienced as well. One of our patients had a distinct aura of "seeing her mother's purse" from when she was a child, just before a seizure. Later this was replaced by seeing the door to her gym as an aura.

Hallucinations

Epileptic hallucinations of all modalities have been reported, including olfactory, visual, auditory, and gustatory (103). Pungent odors classically, although not commonly, present as the initial symptoms of temporal lobe seizures (uncinate fits, 100). Sometimes

these auras may comprise the only symptoms. Macrae reports the case of a 44-year-old woman whose frequent attacks consisted of 1 minute of intense fear followed by the hallucination of "a horrible smell—not a real smell—somewhat like the smell of burning hedges" (91). After a few more seconds, she would feel that she was being choked by the smell and would slowly sink to the ground but would not lose consciousness. Scalp EEG showed a right temporal focus. These seizures were eliminated by the removal of a right-sided meningioma. The first such description was by Hughlings Jackson (100). One case, on depth recording, is reported of olfactory hallucinations from the orbitofrontal cortex; this patient was cured by surgery (101), although this case does not exclude a propagation out of the orbital cortex as the explanation for the symptomatology, as noted by Munari and Bancaud (16).

Paradoxical odors are more commonly due to aberrations in the nasal mucosa or psychiatric hallucinations than to actual epileptic seizures. The olfactory hallucinations associated with psychogenic seizures frequently are reported as pleasant. These pleasant olfactory hallucinations have been described as the smell of perfume, food, or pure oxygen (103, 104). This is in contrast to the ictal olfactory hallucinations of temporal lobe epilepsy, which are generally unpleasant, although one patient described her aura as "the smell of water," which was neither unpleasant or pleasant.

Epileptic visual hallucinations may be simple or complex. Simple visual hallucinations consist of phosphenes, sparks, or flashing lights. Complex visual hallucinations are formed images frequently with relevance to the patient's past experience. In a series of 144 consecutive adult patients with medically refractory simple or complex partial seizure disorders, 8.3% reported "elementary visual" auras (105). These simple visual auras were twice as prevalent in seizures having nontemporal foci than temporal foci. The visual hallucinations were the sole ictal manifestation in 3.6% of seizures. Rarely, visual auras may arise from a frontal focus (106), presumably from the direct and reciprocal occipital to frontal eye-field pathway. Complex visual hallucinations have been categorized as experiential auras and are found more often in seizures having temporal lobe foci (98). Penfield and Jasper localized these to the parietotemporaloccipital cortex (30).

Some epileptic complex visual hallucinations are so intense they may be confused with psychiatric illness. Gloor reported the case of a 19-year-old woman who had seizures consisting of intense fear, loss of consciousness, automatisms as if in intense terror, lower extremity numbness, and visions of crocodiles trying to bite her legs. Depth EEG showed ictal activity arising from the right temporal lobe (97). The visual hallucinations of drug withdrawal and psychiatric disorders are commonly well-formed as well. These can be distinguished from ictal phenomena by their greater variability in features and longer duration—hours to days—in contrast to minutes with epileptic symptoms (107).

Epileptic auditory hallucinations may be elementary or complex. Elementary auditory hallucinations are simple noises such as ringing, buzzing, or hissing and more commonly arise from foci in the temporal lobe, presumably in or near Heschl's gyrus, the primary auditory cortex. In patients with temporal lobe epilepsy, 2.6% reported elementary auditory auras in a series of 144 patients with refractory disease (105). Auditory distortions (hyper- or hypoacusis) and even deafness can occur rarely (98,104). Complex auditory hallucinations are frequently accompanied by visual images but may be isolated events. One patient with complex partial seizures reported events that started with nausea, then an illusion of voices getting louder, and finally a hallucination of music of various styles, including rock and classical. His EEG showed seizures with nonfocal right hemispheric onset or onset at the right sphenoidal electrode (108).

Auditory hallucinations are also frequently found in schizophrenia. The variability and duration of symptoms can be used to distinguish psychiatric illness from ictal auditory hallucinations.

Gustatory hallucinations are often a symptom of parietal, temporal, and temporoparietal seizures. Taste is also not well localized but appears most likely to be at the parietal operculum, posterior to the primary sensory strip (109). Seizures from this area can give rise to unusual tastes or be triggered by particular tastes.

Interestingly, the same aura preceded seizures of either parietal or temporal origin in this patient.

Case Study #13. A 32-year-old male experienced uncontrolled epileptic seizures following a head injury at age 23 years. He described an aura of a taste "like orange juice" in his mouth prior to the seizures and stated that pizza or orange juice would sometimes trigger seizures. He was taken off antiepileptic medication for purposes of intracranial video-EEG documentation, but had had no seizures for several days. An attempt at seizure induction was made with orange juice and pizza. This did trigger an epileptic seizure from the region of the right parietal operculum, which propagated to the right lateral-medial temporal complex.

In a detailed stereo-EEG study, Hauser-Hauw and colleagues (108) were able to induce a brief isolated gustatory hallucination by electrical stimulation of the parietal or Rolandic operculum in patients with gustatory seizures. Gustatory manifestations are commonly associated with elements such as staring reactions, clonic contractions of the face, deviation of the eyes, and salivation in parietal seizures, and oral movements, autonomic disturbances, and epigastric symptoms in temporal lobe seizures. Stimulation studies locate these findings to the temporal operculum or superior circuminsular region (111,112).

Illusions

Unlike hallucinations, which are perceptions of objects in their absence, illusions are misperceptions of objects or sensory phenomena that are present in the ambient environment. Visual illusions have been reported as auras in patients with partial seizures involving both the occipital and temporal lobe. These illusions comprised diffuse distortions of the object's size, color, or shape. One patient reported seeing the color of printed material change to a scarlet red or kelly green (112). Other distortions can occur. For instance, objects may appear to move further away or closer, to shrink or grow, so-called metamorphopsia. Polyopia or pallinopia (an image repeated upon itself in a series) can occur and can be monocular. Complex auditory hallucinations have been reported to be of medical or lateral temporal involvement (96–98).

In one patient with right temporal lobe epilepsy undergoing cortical mapping with subdural electrodes, "out-of-body" experiences were induced by the electrical stimulation of her right angular gyrus (112). The "out-of-body" experience comprised the sensation that her consciousness was detached from her body and floating overhead. She reported seeing her legs and trunk lying below her in bed. When asked to watch a specific limb during the stimulation, she reported distortions in the size of her limb or the sensation that the limb was rapidly moving toward her. The epileptic focus was located 5 cm anterior to the site of stimulation. "Out-of-body" experiences were not part of her usual seizures. Other cases from our experience suggest a parietal origin as well.

Case Study #14. A 20-year-old woman had nightly epileptic seizures since the age of 12, which became diurnal later in life. These were hyperkinetic in semeiology but began with an aura of "things appearing somehow strange or different, not the same." This aura was the only clue directing subdural coverage of the right mid-parietal area (other evidence had pointed to the frontal lobe). The parietal lobe was indeed the focus. (113).

Intellectual Symptoms

Psychic epileptic seizures may involve cognitive symptoms, such as the sensation of forced, racing, or perseverative thoughts. These have been ascribed to the frontal pole (16,71). Other descriptions include the sense of watching oneself from the outside, which can occur with temporal or frontal foci (114,115).

SEIZURES WITH PSYCHIATRIC SYMPTOMATOLOGY

Signs and symptoms of mania, catatonia, ideas of reference, panic, paranoia, and fear may be present in seizures. The cause of these symptoms may be mistaken for a psychiatric etiology.

Mania

One patient with a clinical picture of mania was treated with haloperidol and lithium until an EEG indicated a diagnosis of photoconvulsive epilepsy. Subsequent treatment with carbamazepine led to long-term remission of her symptoms (116). A 33-year-old woman presented with disinhibited speech, hyperactivity, generalized amnesia, auditory hallucinations (God was talking to her), visual hallucinations, grandiosity, and complete insomnia 1 week after a skiing accident in which she had lost consciousness. The initial EEG showed bursts of spike waves over the left frontotemporal region. A computed tomography (CT) scan showed a right frontal subdural hematoma. The EEG normalized after treatment with phenobarbital, but symptoms of mania persisted, despite chlorpromazine, until her third session of electroconvulsive therapy (ECT). She completed six sessions of ECT and was free of symptoms for 3 years. She had two additional episodes of mania and complex partial status, each time with a similar course, each time after 3 years of well being (117).

A study of twenty-seven patients with complex partial seizures, using intracranial electrodes, found that lateral temporal lobe seizures were more likely to lead to an initial facial expression of happiness or sadness at seizure onset. These lateral temporal lobe seizures were more likely to have psychic or sensory features (118). Mesial temporal lobe seizures were more likely to lead to an expression of disgust and occur with autonomic symptoms.

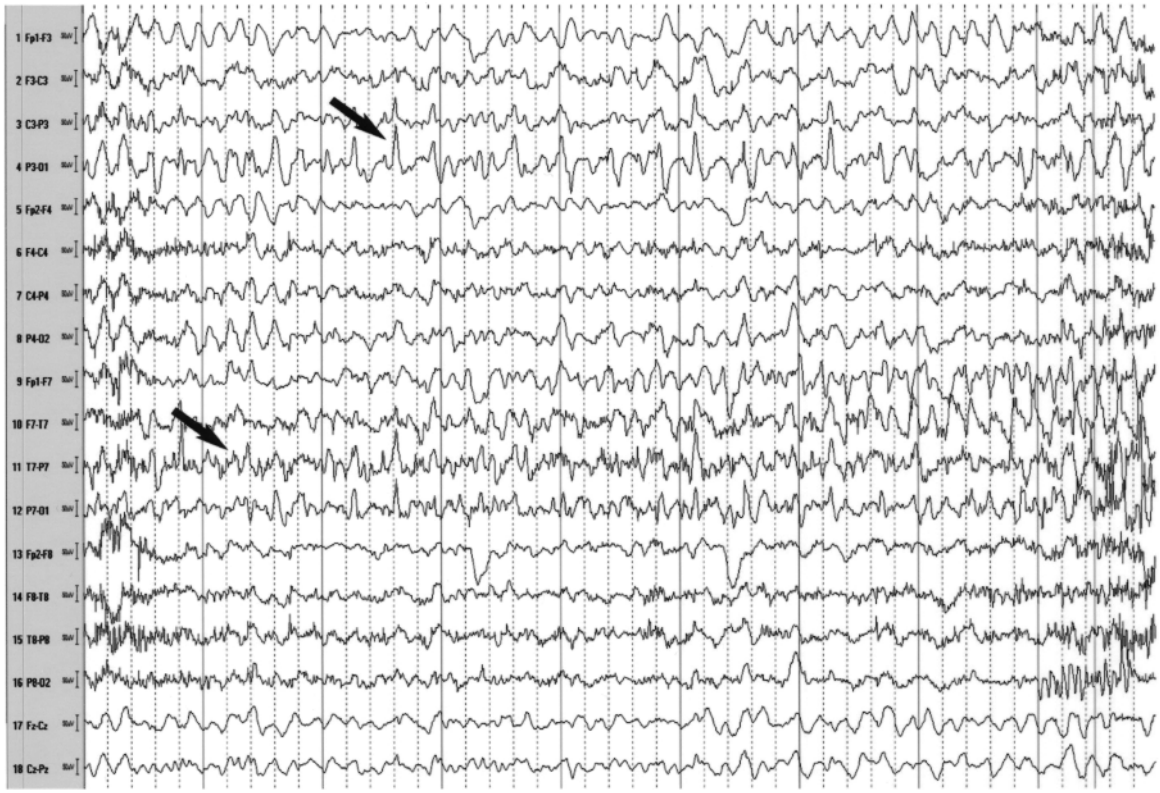

FIGURE 3.6

This patient with catatonic seizures is shown with his left arm raised and immobile (reproduced from video). The EEG shows bilateral posterior and left temporoparietal rhythmic activity. LFF = 0.1 Hz; HFF = 30 Hz.

Catatonia

The diagnostic criteria for catatonia are waxy flexibility, mutism, negativism, and cataplexy (DMSV; 119). These symptoms may be mimicked by the ictal state.

Case Study #15. The patient in Figure 3.6 is a 17-year-old male admitted for video-EEG monitoring for paroxysmal episodes of darkening of vision, red or bright flashes, and amnesia. Video-EEG showed concomitant eye fluttering, lip smacking, and catatonic posturing with the left arm flexed and raised in the air as if being held up with the right arm. Attempts to straighten his arms were minimally and only temporarily successful. EEG showed seizure onset in the left temporal occipital region with anterior spread.

Affective symptoms have been already discussed, however, the clinical picture of a psychic aura may also closely resemble panic disorder. One patient had brief spells of intense fear lasting only a few seconds for which she had no accountable reason. In the absence of any physical signs, a psychogenic cause was considered. Later, she developed brief attacks of aphasia. Two years after the onset of her symptoms a large malignant glioma was discovered in her left temporal lobe (91).

CONCLUSION

Any conceivable symptom may be a sole manifestation of a seizure or may be incorporated with a constellation of symptoms in an epileptic seizure. Because of the rich gamut of manifestations, epileptic seizures can often be misdiagnosed, as richly illustrated in the other chapters of this book. However, their paroxysmal, stereotyped, and episodic nature (no matter how unusual or atypical the symptoms) is a hallmark and can lead the clinician down the appropriate diagnostic path. A high index of suspicion and the availability of video-EEG are the principal tools to the correct diagnosis.

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4 Convulsive Nonepileptic Seizures

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A convulsion is defined as "an involuntary contraction or series of contractions of the voluntary muscles" (1). Convulsive epileptic seizures refer to epileptic seizures that are characterized by vigorous muscle contractions. Using this definition, convulsive epileptic seizures may include generalized tonic-clonic (GTC) seizures, generalized tonic seizures, generalized myoclonic seizures, and partial seizures in which there is prominent tonic or clonic activity.

In this chapter, convulsive nonepileptic events refer to nonepileptic events that have vigorous motor activity and thus may be confused with convulsive epileptic seizures. It is often difficult to differentiate convulsive nonepileptic events from convulsive epileptic events, and it is common for patients with convulsive nonepileptic events to be diagnosed with epilepsy. Many of these patients are treated with antiepileptic agents for years, and some may be referred for evaluation for epilepsy surgery. Because an accurate diagnosis is essential for the appropriate management of these patients, a vigorous effort should be made to establish a correct diagnosis.

To allow comparison of convulsive nonepileptic events with convulsive epileptic events, this chapter begins with the description of a patient who had GTC seizures. The case description is followed by a brief discussion of the phenomena of GTC seizures and of a recent study concerning the mechanism of epileptic clonic activity. The next two sections consist of case descriptions and discussions of the two most common types of events that mimic convulsive epileptic seizures—convulsive syncope and psychogenic seizures or pseudoseizures. These discussions include the clinical features, mechanism, etiology, work-up, and management of these events. The behavioral phenomena of each type of event and its differentiation from an epileptic seizure are emphasized.

The final three sections discuss three other types of events that may result in vigorous motor activity and thus may mimic convulsive epileptic seizures. These include paroxysmal dyskinesia, periodic limb movements of sleep (PLMS), and REM sleep behavior disorder (RBD). Each patient described in this chapter underwent monitoring in the Medical College of Georgia (MCG) Epilepsy Monitoring Unit.

CONVULSIVE EPILEPTIC SEIZURES

Case study #1. Patient #1 was a 35-year-old man who had the onset of seizures at 13 years of age. He described two types of events. One was

characterized by brief jerking movements of the trunk and extremities. The jerks tended to occur early in the morning and in clusters, one or two times a month. The second type of seizure was characterized by loss of consciousness and generalized tonic and clonic activity. These episodes usually occurred either out of sleep or soon after awakening. The patient had been treated with valproate, phenytoin, carbamazepine, and phenobarbital. He continued to have seizures and was referred for video-electroencephalographic (EEG) monitoring to document the nature of his events. At the time of his admission, he was taking carbamazepine.

During prolonged video-EEG monitoring, the interictal EEG showed occasional bursts of spike and wave as well as polyspike and wave activity. He had one major seizure recorded. It was preceded by six series of brief jerks that caused flexion of the trunk and extremities. Each series of jerks lasted less than 2 seconds and was separated from the previous series by approximately 30 seconds. Thirty seconds after the sixth series of myoclonic jerks, the patient had a prolonged series of myoclonic jerks, followed immediately by a loud cry, contraction of the facial muscles, tonic flexion of the arms in front of the chest, and extension of the legs. The tonic phase lasted 15 seconds and was followed by rhythmic clonic movements of the trunk and extremities. The clonic movements were initially very rapid, gradually slowing from more than 5 per second to 0.5 per second. The clonic phase lasted approximately 25 seconds. A diagnosis of a generalized tonic-clonic seizure and idiopathic generalized epilepsy was made.

Discussion

Gastaut and Broughton have provided the most complete description of the clinical features of GTC seizures (2). GTC seizures are characterized by two primary phases—the tonic phase and the clonic phase. The tonic phase begins with flexion contraction of axial muscles (primarily face, neck, and trunk) that spreads to the limb girdle muscles. This causes the arms to abduct and elevate above the shoulders. At this stage, the elbows are usually held in a semiflexed posture. The tonic flexion phase is followed by a tonic extension phase that results in extension of the neck, back, and lower extremities. The tonic phase usually lasts from 10 to 20 seconds.

The transition from the tonic to the clonic phase is characterized by recurrent muscle contractions at a rate of 4 to 8 per second that may resemble trembling (2). The clonic phase is characterized by recurrent flexor spasms of the entire body, alternating with periods of muscle relaxation. The spasms gradually slow in frequency, ending with a final myoclonic contraction occurring from 20 to 50 seconds after the onset of the clonus.

At the beginning of the tonic phase of the seizure, there is loss of consciousness, opening of the eyes, upward deviation of the eyes, and contraction of the muscles of mastication resulting in partial opening of the mouth (2). During the latter part of the tonic phase, the mouth may snap shut resulting in tongue biting. During this phase, there may be an "epileptic cry" secondary to expulsion of air across the contracted glottis.

Respiration ceases at the beginning of the tonic phase and persists throughout the clonic phase (2). The patient often becomes cyanotic. A number of other autonomic changes begin at the onset of the seizure, reach maximum intensity at the end of the tonic phase, and decrease during the clonic phase. These include increased heart rate, increased blood pressure, mydriasis, cyanosis, piloerection, and increased secretions. Urinary incontinence may occur toward the end of the seizure. Depending on the severity of the seizure, there is usually postictal stupor and a gradual return to baseline activity.

The onset of the tonic phase of a GTC seizure may be associated with adversive deviation of the eyes to one side. In our experience, as in that of others (3), this phenomenon may occur in patients who have no other features suggesting partial seizure onset and who otherwise appear to have idiopathic generalized epilepsy. Adversive deviation of the eyes may also occur in partial seizures, either with or without secondary generalization (4). There is evidence that in patients who have secondarily generalized seizures, the adversive deviation at the onset of secondary generalization is contralateral to the side of seizure onset (5).

As present in Patient #1, the tonic phase of a GTC seizure may be preceded by a series of myoclonic jerks (2,3,6). Preceding jerks are often seen in patients with juvenile myoclonic epilepsy (JME), and the resulting seizure is sometimes referred to as a generalized clonic-tonic-clonic seizure.

The pathophysiological mechanisms responsible for the motor phenomena of convulsive epileptic seizures are not completely understood. In a recent study of the mechanisms responsible for focal clonus, Hamer et al. stimulated the primary motor cortex in humans, using electrodes that were implanted for presurgical localization (7). They also stimulated the spinal cord, using epidural strip electrodes inserted at the time of dorsal rhizotomy. They found that clonus could be elicited by continuous stimulation of the motor cortex at frequencies of 20 to 50 Hz. On the other hand,

they found that continuous stimulation of the spinal cord resulted in a 1:1 relationship between stimulus and compound muscle action potentials. Thus, clonus was not produced by high-frequency spinal cord stimulation. This suggested that supraspinal mechanisms must be responsible for clonus.

Based on these and other data, they hypothesized that the recurrent muscle contractions of focal epileptic clonus result from alternating periods of the activation and hyperpolarization of cortical pyramidal tract neurons. They postulated that the recurrent axon-collaterals of activated pyramidal tract neurons stimulate gabaergic interneurons that in turn inhibit these same pyramidal cells, thus causing periods of hyperpolarization.

CONVULSIVE SYNCOPE

Case study #2. Patient #2 was a 41-year-old woman who had the onset of spells at 33 years of age. Her spells began with a feeling of nausea or a feeling that "something is going to happen." This was followed by loss of consciousness and twitching movements of the upper extremities. The frequency of events was 8 to 12 per month. The patient was not aware of precipitating factors. The past medical history was positive for Type I neurofibromatosis. At 7 years of age, she underwent resection of a posterior fossa tumor. The examination revealed the stigmata of Type I neurofibromatosis.

Soon after the onset of her symptoms, a diagnosis of complex partial seizures and generalized tonic-clonic seizures was made by her primary physician. She was treated with valproate, phenytoin, phenobarbital, and gabapentin without control. She was referred to the MCG Epilepsy Center for further evaluation.

An MRI showed changes secondary to the previous posterior fossa surgery. The interictal EEG was normal. During video-EEG monitoring, two episodes occurred. In one instance, the patient was seated and in the other, the patient was lying back in bed. At the onset of the event that occurred while she was seated, the patient appeared to lean to the side and then to slump. There was stiffening of the right arm for 5 seconds and twitching movements involving the upper extremities. She then had what appeared to be loss of tone, lying to the side on the arm rest of the couch. Between 18 and 20 sec after clinical onset, she sat back up, exhibiting myoclonic jerks on her return to the erect posture. She was able to answer questions and carry out requests within less than 10 sec. According to the patient and her family, the recorded event was typical.

The EEG was partially obscured by artifact, but no electrographic seizure was present. Thirteen seconds prior to clinical onset, the ECG lead demonstrated bradycardia, and 8 seconds prior to clinical onset, there was complete asystole. There was a return to normal sinus rhythm approximately 5 seconds prior to her sitting back up.

A cardiology consult was obtained, and a pacemaker was implanted. Following implantation of a pacemaker, the patient had no further events during 18 months of follow-up (8).

Discussion

Syncope is usually defined as a transient loss of consciousness accompanied by a loss of postural tone (9–11). This definition, emphasizing two common clinical features of syncope, allows one to develop a differential diagnosis and to pursue a work-up based on the observed phenomena.

On the other hand, Lempert defines syncope as "a transient loss of consciousness and upright posture due to global cerebral ischemia" (12). There are two major advantages to Lempert's definition: i) it limits syncope to those patients whose symptoms result from a specific pathophysiological mechanism—a global decrease in cerebral blood flow; and ii) since there is often tonic or myoclonic activity associated with these events, loss of upright posture better describes what occurs than does loss of postural tone.

For this discussion, syncope refers to the clinical manifestations that result from a global decrease in cerebral blood flow (12). In most circumstances, the patient is upright at the onset of the attack (Table 4.1). Most patients experience a subjective sensation that precedes loss of consciousness; this is often called an aura. Whereas most syncopal episodes are characterized by loss of consciousness and falling, incomplete forms do occur. In mild syncopal events, the initial subjective sensation may not be followed by either impaired consciousness or loss of upright posture. Other syncopal events may be characterized by falling, but not loss of consciousness. As demonstrated in Patient #2, a rapid return to normal consciousness usually occurs. Following the event, the patient is usually aware of the sensation experienced prior to loss of consciousness.

Benke and colleagues recently studied auras in one hundred patients with syncope, sixty with a cardiac cause and forty with a noncardiac cause (13). All forty patients with a noncardiac cause experienced an aura,

TABLE 4.1
Clinical Features of Common Convulsive Events

Clinical Feature	Convulsive Epileptic Seizure	Convulsive Syncopal Event	Convulsive Psychogenic Seizure
Position at onset	Upright or recumbent	Usually upright	Upright or recumbent
Precipitating factors	Sleep deprivation/ETOH	Fear/pain/blood	Anxiety/stress
Aura	May be present if partial onset	Almost always present	May be present
Eyes	GTCS – Upward deviation PS – may demonstrate adversive deviation	Upward deviation ± preceding downbeat nystagmus	May demonstrate eyelid fluttering or forced eye closure
Motor activity	GTCS – tonic and clonic activity PS – may demonstrate complex motor phenomena	Often demonstrates tonic activity or multifocal/ generalized myoclonus	Asymmetric movements, complex motor phenomena
Pattern of motor activity	GTCS – standard progression of tonic to clonic activity	Variable pattern of motor activity	Nonstandard progression ± intermittent motor activity
Duration	Usually 30 seconds to 2 minutes	Usually <30 seconds	May be prolonged
Skin color	Cyanosis	Pallor	Flushing or no change
Tongue biting	Common	Rare	Rare
Incontinence	Common	Rare	Rare
Ictal EEG	Rhythmic electrographic seizure or focal/diffuse slowing	May demonstrate diffuse slowing	No EEG change
Postictal prolactin	Elevated	Elevated	Normal

GTCS – generalized tonic-clonic seizure
PS – partial seizure

and fifty-three of the sixty patients with a cardiac cause experienced an aura. Many of the auras were characterized by multiple elements. The authors categorized the auras into the following groups: nausea-epigastric, vertiginous, somatosensory, acoustic, visual, cognitive, and affective.

Our experience is similar to that of Benke et al. The vast majority of patients with syncope describe an aura: the most commonly described sensations are nausea, dizziness or light-headedness, visual impairment, or "weakness." Although there are differences in the auras of epilepsy and syncope, it is often difficult to differentiate syncope from seizures based on the initial subjective experience alone. On the other hand, if there is no preceding subjective sensation, the episode is unlikely to be a syncopal event.

Lempert and von Brevern induced syncope in fourteen healthy volunteers by a combination of 20 seconds of hyperventilation, a quick head-up tilt on a tilt table, and a 10-second Valsalva maneuver (14). Thirteen patients demonstrated tonic upward deviation of the eyes. In six of these patients, the upward deviation was preceded by downbeat nystagmus. In only one patient did the eyes remain in the primary position. These data suggest that an observation of downbeat nystagmus may be helpful in differentiating syncope from an epileptic seizure. However, this phenomenon may be difficult to observe, even when using video monitoring. Since upward deviation of the eyes is seen in patients with GTC seizures, upward eye deviation does not differentiate between syncope and GTC seizures.

As implied by the common clinical definition of syncope, it is generally thought that most syncopal episodes are characterized by loss of muscle tone and a lack of tonic or clonic activity. When tonic or clonic movements have been seen, the term "convulsive syncope" has been used. However, recent studies, as well as some older studies, suggest that tonic or myoclonic movements are very common in patients with syncope

(15–17). As a result, syncope may be very difficult to distinguish from GTC seizures based solely on the presence of tonic, clonic, or myoclonic activity.

Lempert and colleagues induced syncope using hyperventilation, orthostasis, and a Valsalva maneuver in fifty-six healthy volunteers (17). Forty-two subjects developed complete syncope, defined as episodes characterized by both falling and loss of consciousness. Thirteen demonstrated falling without loss of consciousness, and one subject became unresponsive without falling. The duration of these events was brief (12.1 ± 4.4 seconds).

In this same study, thirty-eight of the forty-two subjects who had complete syncope had myoclonic jerks as a manifestation of the episode (17); 83% of the subjects fell backward; 52% fell "stiffly" with the legs extended; and 48% exhibited flaccidity of the lower extremities and flexion at the knees at the time of the fall. Unlike GTC seizures, these myoclonic jerks were usually multifocal and nonrhythmic (52%) or multifocal and superimposed on generalized myoclonus (29%). Facial muscles were involved in 58% of the subjects. Additional motor activity, including nonforced lateral head turns, versive gaze deviation, and repetitive automatisms, similar to those seen in partial epileptic seizures, were seen in 79% of the episodes. One subject had tongue biting, and no patients demonstrated incontinence.

Syncope may be caused by numerous conditions (9–11). Because of differing definitions of syncope, the classification of etiologies varies from study to study. In all studies, the cause of syncope remains undetermined in a large percentage of patients. When one limits syncope to the symptoms that result from a global decrease in blood flow to the brain, the three most common diagnoses are: i) vasovagal or neurocardiogenic syncope; ii) orthostatic hypotension secondary to neurogenic autonomic dysfunction or medications; and iii) cardiogenic, most commonly secondary to an arrhythmia. Although the clinical features of each of these categories of syncope are similar, a number of features are seen more commonly in cardiogenic syncope than in syncope secondary to other causes. These include i) syncope associated with exertion; ii) sudden loss of consciousness without aura; iii) frequent episodes or clusters of episodes, and iv) syncope in the recumbent position.

The evaluation of patients with syncope varies widely among clinicians. Linzer and colleagues reviewed studies between 1980 and 1997 to determine the value of the history, physical exam, and laboratory tests in evaluating patients with syncope (10, 18). For their review, syncope was defined as loss of consciousness accompanied by loss of postural tone. The table that lists the causes of syncope suggests that many of these patients had a clinical diagnosis of syncope that was not secondary to a decrease in cerebral blood flow. Nevertheless, the data these authors reviewed and the algorithm they developed provide a useful framework for evaluating patients with syncope.

The first step in evaluating patients with recurrent syncope is a thorough history and physical examination. Linzer et al. concluded that the history and physical exam resulted in a definitive diagnosis in 45% of syncope patients and provided information leading to additional work-up and ultimate diagnosis in another 8% (10). An electrocardiogram (ECG) provided a definitive diagnosis in another 5%. Neuroimaging and EEGs were rarely helpful.

Based on these data, a reasonable approach to the patient with syncope is to begin with a history, physical examination, and ECG. The history should emphasize the phenomena of the events, the frequency of events, precipitating factors, medication use, and the presence or absence of symptoms suggesting cardiac disease. The physical exam should emphasize the cardiac exam and evaluation for orthostatic hypotension.

Linzer and colleagues divided those patients in whom a diagnosis was not made on the basis of history, physical exam, and ECG into three major groups for further evaluation (18): i) patients with unexplained syncope and a history of heart disease, suspected heart disease, or an abnormal ECG; ii) patients with unexplained syncope and no history of heart disease or suspected heart disease; and iii) elderly patients. For the first group, echocardiography, exercise stress testing, 24-hour Holter monitoring, electrophysiologic studies, and signal averaged electrocardiography may be indicated. For the second group, long-term ambulatory loop electrocardiography, tilt table testing, and psychiatric evaluation may be indicated. For elderly patients, the authors recommend a combined approach, emphasizing assessment of situational factors, carotid sinus massage, and cardiac work-up.

The treatment of syncope depends on the underlying cause. Avoidance of those activities that may precipitate syncope is recommended for all patients. Compression stockings may be useful in some patients. A number of medications have been tried in patients with neurocardiogenic syncope who do not respond to conservative treatment. Four drugs have been shown to be effective in randomized, clinical trials (11): atenolol, midodrine, paroxitine, and enalapril.

For patients with orthostatic hypotension secondary to medications, the most effective treatment is removal of the causative agent. For those with neurogenic autonomic insufficiency, fludrocortisone (Florinef) may be used. Midodrine has been shown to

be effective in patients with orthostatic hypotension secondary to neurogenic autonomic failure (19). If syncope is of cardiac origin, specific treatment of the cardiac condition is required. As demonstrated in Patient #2, a pacemaker is indicated in some patients.

PSYCHOGENIC NONEPILEPTIC EVENTS

Case study #3. S. L. was a 24-year-old woman who had the onset of spells at 22 years of age. Episodes were characterized by a headache and tired feeling, followed by loss of consciousness and jerking movements of the trunk and extremities. Loss of consciousness lasted up to 5 min. The patient reported that incontinence occurred rarely. The frequency of episodes varied from one per week at the onset of her illness, to one per day at the time of referral. She was treated with phenytoin, gabapentin, and lamotrigine without control. Etiological factors included a motor vehicle accident that resulted in less than 5 min of impaired consciousness just prior to the onset of events. There were no neurological sequelae following the accident. The examination was normal.

Magnetic resonance imaging (MRI) studies were normal. An interictal EEG showed right anterior temporal slowing. No interictal epileptiform discharges occurred during the awake and sleep states, and there were no epileptiform discharges during a recording obtained following a night of sleep deprivation.

During video-EEG monitoring, one episode occurred. The episode began with recurrent adduction movements of both lower extremities. These began as limited movements occurring at a frequency of approximately one per second. These movements gradually increased in amplitude and frequency over a 10-second period. The adduction movements were followed by extension of the back and hyperkinetic movements of the trunk. Simultaneous with the hyperkinetic movements were alternating flexion/extension movements at the elbow and abduction/adduction movements at the shoulders; these movements were asymmetric between the two sides. Approximately 25 seconds after onset, the motor activity suddenly stopped, and the patient relaxed. The patient did not respond to the nurse for several minutes after the cessation of motor activity. On attempted eye opening at this time, there was forced closure of the eyes.

During the motor activity, the EEG was obscured by muscle and movement artifact. Prior to the onset of the motor activity and immediately following its cessation, the EEG was normal with a well-developed alpha rhythm. The EEG remained normal during the entire period of unresponsiveness. Based on the normal EEG during apparent impaired consciousness, as well as the fact that the motor phenomena did not fit a characteristic epileptic pattern, a diagnosis of psychogenic nonepileptic event was made.

Discussion

The terms psychogenic seizure, pseudoseizure, and nonepileptic seizure refer to episodes that behaviorally resemble an epileptic seizure, but are secondary to a psychogenic and not an epileptic mechanism. In this chapter, a convulsive psychogenic event refers to a psychogenic event characterized by vigorous motor activity that may superficially resemble a convulsive epileptic seizure (see also Chapter 19).

A number of observable features may assist in differentiating convulsive psychogenic seizures from convulsive epileptic seizures (20–22) (Table 4.1). When compared to generalized tonic-clonic seizures, convulsive nonepileptic events are more likely to have a gradual or fluctuating onset, prolonged duration, variation in responsiveness throughout the event, asymmetric out-of-phase clonic movements, and intermittent motor phenomena separated by periods of relative quiescence.

Gates et al. studied video recordings of twenty-five patients who had generalized tonic-clonic seizures and twenty-five patients who had psychogenic events that resembled generalized tonic-clonic seizures (21). A number of features were significantly more common in the psychogenic group than in the epileptic seizure group. These included out-of-phase clonic activity in both the upper and lower extremities; forward pelvic thrusting, and side-to-side head movements. Features more common in the epileptic seizure group included in-phase clonic movements, whole body rigidity, and unilateral head turning (21). Whereas vocalization in generalized tonic-clonic seizures consisted solely of an "epileptic cry," vocalization in psychogenic events included moaning, screaming, grunting, gagging, snorting, and retching.

Each of the characteristics described above may be helpful in differentiating nonepileptic events from GTC seizures. However, none of these characteristics is definitive. The most important feature differentiating psychogenic events from GTC seizures is that most psychogenic events do not have the classic progression of tonic and clonic phenomena as do GTC seizures (described earlier). Despite very clear differences

between psychogenic events and GTC seizures, there remain patients in whom it is difficult to differentiate psychogenic from epileptic events based on observable phenomena alone (23).

Convulsive psychogenic events must also be distinguished from complex partial seizures of frontal lobe origin (24). Williamson et al. described the clinical features of complex partial seizures originating in the frontal lobe. They emphasized that many of these patients are initially misdiagnosed as having psychogenic events. Those features of frontal lobe seizures that may be mistaken for psychogenic events include complex motor automatisms such as thrashing, bicycling, and pelvic thrusting. Vocalization is also common in both frontal lobe seizures and in psychogenic events. Unlike psychogenic events, frontal lobe seizures tend to be brief and often arise out of sleep.

Geyer et al. reported that pelvic thrusting was present in 17% of their patients with psychogenic events, 24% of their patients with frontal lobe seizures, and 3% of their patients with temporal lobe seizures (25). These data suggest that pelvic thrusting is not very useful in differentiating psychogenic events from partial epileptic seizures.

Rowan recently reviewed the diagnostic work-up of patients with nonepileptic seizures (26). Unless the diagnosis is clear from the description, most patients require an imaging study and an EEG. It is important to remember that patients with psychogenic events may also have epileptic seizures. Thus, epileptiform discharges during an interictal EEG do not rule out the possibility of psychogenic events. Ambulatory EEG monitoring may be useful in many patients. Most patients referred to medical centers undergo video-EEG monitoring. In addition to recording both the video image and the EEG during an event, inpatient monitoring is sometimes useful in gathering information concerning the patient's behavior between episodes.

The EEG during a convulsive psychogenic seizure is often obscured by muscle, movement, and eye blink artifacts. When interpretable, the EEG is usually normal. If hyperventilation is a significant part of the event, there may be diffuse slowing of the background. However, EEG slowing is not common. Since a psychogenic event is not the result of an epileptic seizure, an electrographic seizure is not present. If an EKG channel is included, an increase in heart rate may be observed.

In differentiating psychogenic events from epileptic seizures, the EEG is especially helpful if the patient appears to be unconscious and does not respond to questioning during the episode. An EEG during an epileptic seizure in which consciousness is impaired is usually characterized by an electrographic seizure or by focal or diffuse slow activity. Thus, a normal EEG during an episode in which the patient's behavior suggests unconsciousness is evidence that the event is not an epileptic seizure.

The EEG immediately preceding and immediately following an episode may also be useful in differentiating psychogenic from epileptic events. Benbadis and colleagues used video-EEG monitoring to study preictal phenomena in patients with psychogenic seizures and epileptic seizures (27). They coined the term *pseudosleep* to refer to a state behaviorally resembling sleep—lying motionless with the eyes closed—but during which the EEG shows wakefulness. They found that ten of eighteen patients with psychogenic events demonstrated pseudosleep for at least 1 minute prior to the onset of attacks. Preictal pseudosleep was not present in the thirty-nine patients with epileptic seizures. These data suggest that the presence of preictal pseudosleep is strongly correlated with psychogenic events. On the other hand, a preictal EEG demonstrating sleep is strong evidence that the event is epileptic and not psychogenic.

Immediately following a GTC seizure, as well as following many partial seizures, the EEG demonstrates diffuse or focal slowing of the background. Since slowing does not occur following a psychogenic seizure, postictal slowing suggests that the event was an epileptic seizure.

A number of investigators have shown that prolactin concentrations are elevated 15 to 20 min following a generalized tonic-clonic seizure, but not following a convulsive nonepileptic seizure (28,29). Oribe et al. have shown that prolactin concentrations are also elevated following syncopal events (30). Based on these data, an elevated prolactin concentration during the first 30 min following an event of uncertain mechanism may be of value in differentiating an epileptic or a syncopal event from a psychogenic episode, but it will not differentiate syncope from an epileptic seizure (see also Chapter 5).

Other methods of investigation may also aid in differentiating patients with nonepileptic events from patients with epileptic seizures. These include: i) psychological testing, using the Minnesota Multiphasic Personality Inventory (MMPI) (31,32); ii) quality of life surveys, using the Quality of Life Inventory in Epilepsy (QOLIE) (32); and iii) provocation, using verbal suggestion, saline infusion, or both to precipitate an event (33). In our experience, as well as that of others, the majority of patients who have psychogenic events in an epilepsy monitoring unit have them without provocation during the first 24 to 48 hours of admission (23,34).

Very few studies provide guidance in the management of patients with psychogenic events (35). Our own approach is to provide a frank explanation of the diagnosis to the patient, emphasizing three points: i) psy-

chogenic symptoms are common in the general population, and psychogenic seizures are especially common; ii) psychogenic episodes have a favorable prognosis, and prognosis for complete recovery is good; and iii) antiepileptic agents are not required, and it is very likely that chronic medications will not be required. We do not have controlled data, but it is common that following such an explanation, the events improve markedly. When episodes persist, we refer patients to a mental health professional.

PAROXYSMAL DYSKINESIA

In 1981, Lugaresi and Cirignota described a group of patients who had brief nocturnal episodes characterized by tonic or dystonic spasms and violent movements (36). All had normal interictal and ictal EEGs, and all responded favorably to carbamazepine. The authors proposed three possible mechanisms for these events: i) pavor nocturnus; ii) epileptic seizure; or iii) paroxysmal dystonia. Similar cases, with many variations, have been described by others (37–40), usually under the moniker, paroxysmal nocturnal dystonia. Recent studies have suggested that the majority, if not all, of these patients have partial epileptic seizures of frontal lobe origin (39–41).

A number of investigators have described a group of related paroxysmal disorders characterized by movements that may in some instances be confused with epileptic seizures (42–45). To clarify the terminology and classification of these disorders, Demirkiran and Jankovic proposed a comprehensive classification system that used the term dyskinesia for the abnormal movements and used the circumstances that give rise to the movements as the major factor in classification (45). Based on this system, there are four major categories of paroxysmal movement disorders: paroxysmal hypnogenic dyskinesia (PHD); paroxysmal exertion-induced dyskinesia (PED); paroxysmal kinesigenic dyskinesia (PKD); and paroxysmal nonkinesigenic dyskinesia (PNKD).

In their study, Demirkiran and Jankovic reported forty-five patients with paroxysmal dyskinesia (45). One had PHD; five had PED; thirteen had PKD; and twenty-six had PNKD. Of the thirty-two patients whose attacks were witnessed by examiners, twenty-three had pure dystonia, and the other nine had dystonia in combination with chorea or ballism. These data suggest that dystonia is the most common type of movement in patients with paroxysmal dyskinesia.

Of the forty-five patients studied by Demirkiran and Jankovic, twenty-three had episodes lasting less than 5 min, a duration that could realistically be confused with epilepsy (45). None of these patients had known epilepsy, but 44% had a family history of epilepsy. The EEGs were normal in the thirty-four patients tested. Only one of the forty-five patients had brief events limited to sleep and thus may have had nocturnal partial seizures, as discussed earlier.

The mechanisms responsible for paroxysmal dyskinesia are unknown (45). Secondary dystonia has been associated with lesions in the putamen, caudate, thalamus, and rostral brainstem. Paroxysmal dystonia has also been associated with Behçet's disease (46), subacute sclerosing panencephalitis (47), fluoxetine toxicity (48), and on assuming the upright position (49). Studies in a mutant hamster model of PNKD suggest that the abnormal movements in PNKD may be secondary to impairment of gabaergic systems (45).

Work up for paroxysmal dyskinesa has traditionally included an MRI, and if there is a suggestion of possible epilepsy, an EEG. If the MRI and EEG are normal in patients with brief nocturnal events, video-EEG monitoring may be indicated. A secondarily generalized tonic-clonic seizure following medication withdrawal is diagnostic of epilepsy.

At this time, antiepileptic agents remain the standard form of treatment for patients with paroxysmal dyskinesia (45). Other medications that have been tried include levodopa, tetrabenazine, and trihexyphenidyl. There is some evidence that patients with PKD respond better to antiepileptic medications than patients with PNKD.

PERIODIC LIMB MOVEMENTS OF SLEEP

In addition to the nonepileptic conditions previously discussed, two sleep related conditions can occasionally be confused with convulsive epileptic seizures. These are periodic limb movements of sleep (PLMS) and REM sleep behavior disorder (RBD) (see also Chapter 16).

PLMS is characterized by recurrent muscle contractions, primarily of the lower extremities, during sleep (50–53). Simultaneous movements of the upper extremities may occur. The movements tend to occur in clusters, each movement occurring approximately 20 to 30 seconds after the preceding movement, and each cluster lasting from minutes to hours. The movements tend to be more prominent in stage I and stage II sleep and tend to occur early in the night. The movements are characterized by extension of the great toe and flexion at the ankle, knee, and hip. Patients may complain of frequent awakenings, insomnia, or daytime sleepiness, all symptoms that are commonly associated with disrupted sleep. As one might expect, spouses often complain of disrupted sleep.

PLMS is present in 80 to 90% of patients with restless legs syndrome (RLS) and in a lower percentage

of patients with other types of sleep disorders (52). PLMS may be present as a distinct disorder called periodic limb movement disorder (PLMD). In addition, PLMS may occur in patients without symptoms. Asymptomatic patients are usually discovered because of complaints by the spouse or when the patient is undergoing evaluation for other reasons. The prevalence of PLMS increases with age, being present in approximately 5% of the 30- to 50-year age group, 30% of 50- to 65-year-olds, and 30 to 45% of patients over 65 years of age.

The mechanism and etiology of PLMS are not known. Using functional MRI in patients with RLS and sensory discomfort in the legs, Bucher et al. showed that during PLMS, activation occurred in the red nuclei and brainstem near the reticular formation (54). Activation was not associated with sensory discomfort alone. Voluntary imitation of PLMS produced activation in the motor cortex and globus pallidus, but not in the brainstem areas activated by PLMS. Based on these and other data, these investigators hypothesized that PLMS may result from activation of the reticular formation that in turn produces disinhibition of spinal pathways.

The observable phenomena associated with PLMS are usually not difficult to differentiate from convulsive epileptic seizures. If primarily unilateral, PLMS could possibly mimic simple partial seizures, including epilepsia partialis continua (EPC). However, PLMS occurs at a much slower frequency—every 20 to 30 sec—than EPC. The absence of cortical discharges differentiates PLMS from myoclonic seizures. Bilateral PLMS does not mimic the normal progression of a generalized tonic-clonic or clonic-tonic-clonic seizure.

When associated with RLS, PLMS is easily diagnosed and does not require further diagnostic work up. If PLMS is not associated with RLS, the diagnosis can be made with polysomnography or with video-EEG monitoring that includes electrodes for recording muscle activity.

Treatment of PLMS depends on the severity of the sleep disturbance. Treatment is not necessary in asymptomatic individuals. The three primary classes of medications used for the treatment of PLMS are dopaminergic agents (52,55), benzodiazepines (52,56), and opiates (52). Data from one controlled, double-blind study suggests that carbidopa/levodopa may be more effective than propoxyphene in controlling the movements and symptoms of PLMS (57).

REM BEHAVIOR DISORDER

The second sleep disorder that may mimic convulsive epileptic seizures is REM behavior disorder (RBD) (58,59). RBD is characterized by recurrent episodes of vigorous motor activity occurring during REM sleep, movements that often awaken the patient or spouse. The primary presenting complaints are interrupted sleep or injuries during sleep. RBD is more common in older adults, usually beginning after the age of 50. It is two to five times more common in men than in women. It is possible that rare episodes such as these occur in a large percentage of the population. I am familiar with people who have had rare such episodes throughout their adult life.

The movements seen in RBD vary from minor movements of an individual extremity to complex behavior, such as laughing, shouting, or throwing one's self from the bed (58,59). Commonly, the movements are related to a dream the patient is having during REM sleep, and the patient is often able to describe the dream. The frequency of episodes varies from many per night to one every few weeks. If more than one episode occurs in a night, the episodes tend to occur at least 90 min apart, most likely during separate REM sleep cycles.

The exact mechanism of RBD is not known. During episodes of REM sleep in normal subjects, there is complete atonia. It is thought that RBD may be secondary to impairment of the normal inhibition of muscle activity during REM sleep (59). Consistent with this hypothesis, patients with RBD have been shown to have muscle activity present even during asymptomatic episodes of REM sleep. It is hypothesized that when the muscle activity during REM sleep is especially prominent, a clinical episode results.

RBD has been associated with brainstem lesions caused by vascular disease, trauma, and multiple sclerosis (59). In addition, RBD is common in patients with Parkinson's disease (60–62), and it has been reported in patients with narcolepsy (63). Schenk et al. followed patients who were diagnosed with RBD and found that 38% developed Parkinson's disease at an interval of 3.7 ± 1.4 years (60).

Treatment for RBD with clonazepam (0-5-2.0 mg.h.s) is successful in 80 to 90% of patients (59). Clonazepam does not completely suppress the motor activity during REM sleep, but it usually eliminates the vigorous, coordinated movements characteristic of RBD episodes. This allows the patient to sleep without disruption. If clonazepam is unsuccessful or causes drowsiness, tricyclics, levodopa/carbidopa, clonidine, or carbamazepine may be tried. Donepezil, an acetylcholinecterase inhibitor, has been effective in some patients (64).

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5 The Role of Serum Prolactin in Seizure Diagnosis

Paul B. Pritchard, III, MD

Prolactin (PRL) is a peptide secreted by acidophilic pituitary lactomorph cells under the dual control of dopaminergic prolactin inhibiting factor (PIF) and serotonergic prolactin releasing factor (PRF). Thyrotropin releasing factor (TRF) promotes the release of PRL and thryrotopin (TSH), whereas estrogen releases PRL via direct stimulation of the pituitary (1).

Normal adults exhibit little change in serum PRL during waking hours, except for brief elevations after naps (2). Multiple nocturnal PRL surges occur which, unlike growth hormone (GH), are not entrained to specific sleep stages (3). Serum PRL returns to daytime values within 90 minutes of waking.

The neonatal state is associated with high levels of serum PRL. Other physiologic elevations of PRL occur during pregnancy, preparatory to lactation, and during lactation itself. Breast manipulation during nursing or sexual activity produces a transient increase in serum PRL (Table 5.1).

EFFECTS OF DRUGS ON SERUM PROLACTIN LEVELS

Dopamine agonists (bromocryptine) lower serum levels of PRL, as do levodaopa, apomorphine, and clonidine. Dopamine antagonists raise serum PRL via various mechanisms: depletion of hypothalamic dopamine (reserpine and methyldopa) and blockage of dopamine receptor sites (haloperidol and phenothiazines) (1).

The effects of the newer atypical antipsychotic drugs on serum PRL have been inconsistently reported. A relatively high affinity for the 5-HT2 serotonergic receptor and relatively low affinity for the D-2 dopamine receptor differentiates these drugs from the phenothiazines, which are prone to produce high elevations of serum PRL and more likely to cause parkinsonism. Most studies show modest elevations of serum PRL with risperidone but no significant effects from clozapine or olanzapine (4–6).

Most antiepileptic drugs (AEDs) do not appear to have a significant effect on serum PRL, but carbamazepine (7) and phenytoin (8) may produce slight elevations of PRL. The enzyme-inducing AEDs increase sex hormone binding globulin with consequently lower serum levels of unbound estrogen and testosterone (7,9,10).

CHANGES IN SERUM PROLACTIN LEVELS WITH PATHOLOGIC STATES

Lesions of the hypothalamus block the inhibitory effect of PIF and produce resulting pathologic elevations of

TABLE 5.1
Causes of Hyperprolactinemia

- Physiologic
  - Sleep, including naps
  - Breast stimulation
  - Neonatal state
  - Pregnancy
  - Lactation
- Medical disorders
  - Skin lesions of thoracic dermatomes
  - Pituitary prolactinomas
  - Hypothalamic lesions
  - Parkinson's disease
  - Epileptic seizures
- Medical treatments
  - General anesthesia
  - Surgery
  - Drugs
    - Dopamine antagonists
      - Atypical antipsychotics
      - Phenothiazines
      - Methyldopa
      - Haloperidol
      - Reserpine
    - Serotonergic drugs
    - Antiepileptic drugs
      - Carbamazepine
      - Phenytoin
    - Estrogen

serum PRL. Pituitary tumors, such as PRL-secreting microadenomas (prolactinomas), produce sustained elevations of serum PRL. Skin lesions that affect mid-thoracic dermatomes at the level of the breasts or radicular lesions at that level may cause sustained hyperprolactinemia. Patients with Parkinson's disease sometimes experience moderate hyperprolactinemia because of the diminished dopaminergic inhibition of PRL secretion. Physical stressors, such as surgery or anesthesia, produce a transient elevation of serum PRL.

CHANGES IN SERUM PROLACTIN WITH BRAIN STIMULATION

The first recognition of episodic hyperprolactinemia induced by seizures were the observations of investigators (11) who were seeking endocrine profiles to predict which patients would benefit from a full course of electroconvulsive therapy (ECT). Although endocrine changes did not predict the likelihood of successful ECT in women with depression, reproducible elevations in serum PRL followed ECT. ECT produces similar endocrine changes in schizophrenics (12,13).

Subsequent to the ECT reports, investigators studied the effects of other methods of brain stimulation on PRL secretion. Parra (14) demonstrated a transient elevation of serum PRL with the direct stimulation of the amygdala in humans, but a subsequent study (15) of limbic and extralimbic structures showed that elevations of serum PRL occur only when stimulation evokes high-frequency, widespread limbic discharges. Thus, it appears that stimulation within physiologic ranges control prolactin release via subcortical structures other than the amygdala. Gallagher (16) confirmed that the stimulation of the amygdala and hippocampus causes elevations of serum prolactin and ACTH, but not growth hormone, only when stimuli are sufficient to produce seizures or after-discharges that last 10 seconds or more.

Transcranial magnetic stimulation produces changes in serum PRL only when the stimulus induces a complex partial seizure (17). Transcutaneous stimulation of central motor pathways produces no changes in PRL (18), nor does an evoked photoconvulsive response alter serum PRL (19).

CHANGES IN SERUM PROLACTIN ASSOCIATED WITH EPILEPTIC SEIZURES

Trimble (20) first utilized a transient rise in serum PRL to distinguish between spontaneous generalized tonic-clonic seizures (GTCS) and nonepileptic seizures (NES), thus prompting further study of various types of epileptic seizures and other paroxysmal neurological disorders (see Table 5.2).

Generalized Tonic-Clonic-Seizures

Abbott and coworkers (21) demonstrated elevations of serum prolactin and cortisol following spontaneous

TABLE 5.2
Postictal Changes in Serum Prolactin

TYPE OF EVENT	POSTICTAL ELEVATION OF SERUM PRL
Generalized tonic-clonic seizure	Virtually 100%
Absence seizure	None
Myoclonic seizure	None
Akinetic seizure	None
Complex partial seizure	Most (>80%)
Simple partial seizure	Some (10–20%)
Status epilepticus	None
Psychogenic nonepileptic seizure	None

GTCS, but only serum cortisol responded to simulated convulsive seizures. Abbott considered cortisol a nonspecific response to stress, contrasted with a specific seizure-induced rise in PRL.

Trimble's patients were not monitored by electroencephalography (EEG), but subsequent studies of monitored events confirmed his findings in 80 to 100% of patients with GTCS (22–24). Each of these investigators employed different criteria for significant PRL elevation, such as three-fold elevation of baseline levels or paired t-test comparisons. Most other studies did not include EEG monitoring.

A comparison of serum levels of neuron-specific enolase (NSE) and PRL following single GTCS and complex partial seizures (CPS) showed little change in NSE for most patients. Serum PRL displayed an 80% sensitivity in the detection of CPS or GTCS (25).

A single study examined PRL and beta endorphin in cerebrospinal fluid (CSF) after GTCS. CSF levels of beta endorphin were elevated, but PRL was normal. CSF samples were obtained up to 2 hour postictally, which may have missed changes in greater proximity to the seizure (26).

Fisher (27) demonstrated the utility of capillary blood collected with filter paper as an aid in the diagnosis of seizures. This approach lends itself to outpatient use through the collection of postictal capillary blood samples by the patient's family.

Other Generalized Seizures

Absence, myoclonic, and akinetic seizures do not produce changes in serum PRL (28,29). The lack of PRL response also applies to absence status epilepticus (SE) (28,30). A single report of two cases of gelastic seizures associated with hypothalamic hamartoma detected postictal hyperprolactinemia in each case (31).

Partial Seizures

CPS of temporal lobe origin produced postictal elevation of serum PRL in patients whose seizures were monitored by EEG (32) and in a study in which seizures were not monitored (33). In general, studies confirm postictal PRL elevation in 80 to 100% of CPS (22,24,34). In the only study that utilized intracranial monitoring of CPS, elevation of PRL occurred only when seizures were accompanied by high-frequency regional limbic discharges (34).

Meierkord's study (35) reported a divergence in the effects of CPS of frontal lobe origin and those from the temporal lobe, finding hyperprolactinemia after 75% of temporal lobe seizures, versus only one of eight frontal lobe CPS with this effect. A subsequent report, which included intracranial monitoring of CPS, found that seizures of frontal lobe (60%) or temporal lobe (67%) origin were almost equally likely to cause postictal hyperprolactinemia (36). Postictal hyperprolactinemia occurs after a small percentage of simple partial seizures (SPS) (34), but SPS has been less extensively studied than CPS.

Effects of Status Epilepticus or Repeated Seizures

In absence, complex partial, and GTC SE, Swedish investigators found uniformly normal serum PRL (30). Malkowicz and her colleagues studied CPS of temporal or frontal origin. Seizures that occurred after seizure-free intervals of 31 to 240 hours showed robust postictal hyperprolactinemia, whereas those that occurred after 1- to 25-hour seizure-free intervals had reduced PRL responses (37) (Table 5.2). Another investigation of repeated seizures did not find a declining PRL response if the initial seizure had produced an elevation (38).

TRH injected during SE produces the expected rise in serum PRL (39), which refutes the hypothesis that the decline after repeated seizures or SE is caused by cellular depletion of PRL. Similarly, intravenous metoclopramide given to patients during SE also produces at least a five-fold rise in serum PRL (40). Thus, there must be a mechanism other than cellular depletion of PRL that is responsible for the lack of response to repeated seizures or SE.

Responses in Children and Neonates

GTCS and CPS in infants and children under age 14 is as likely as adults to produce postictal elevations of serum PRL as in adults (29). Nonfebrile seizures produce a more robust PRL response than febrile seizures, versus normal PRL for normal controls, syncope, or fever alone (41,42).

Because baseline serum PRL is higher during the neonatorum, the significance of postictal PRL results in this age group is more difficult to interpret. In a group of twenty-eight newborn infants with acute encephalopathy, serum PRL results were compared for those with seizures versus those with encephalopathy alone. PRL results were higher at baseline and postictally for the seizure group, but postictal levels were not significantly higher than baseline levels. It appears that serum PRL correlates best with the severity of the brain insult, as measured by abnormality of the EEG background (43). Another view is supported by a study of nineteen neonates in whom postictal PRL levels were significantly higher than normal controls, but this study did not include encephalopathic controls. The most marked

PRL response occurred with focal tonic seizures with temporal lobe EEG changes (44).

PSYCHOGENIC NONEPILEPTIC SEIZURES

Following the initial negative report of PRL changes after nonepileptic seizures, the lack of postictal serum PRL elevation was confirmed in EEG-monitored NES (45), including convulsive and nonconvulsive NES, and corroborated by other studies (46,47). In a single study of NES (48), most of the subjects monitored by EEG noted postical elevations of PRL after ES and NES, but NES produced more modest changes. Serum cortisol increases after ES and NES (45,47).

OTHER PAROXYSMAL NEUROLOGICAL CONDITIONS

Syncope

Studies of the effects of syncope on PRL release offer mixed results. A report from pediatric patients found no change in serum PRL with syncope or breath-holding spells (42), but an emergency department study noted increased serum PRL in samples obtained 18 to 60 minutes after syncope in eight of eleven cases (49). Attacks were not witnessed by medical observers in either report, nor were the episodes monitored by EEG.

Two additional studies utilized head-up tilt (HUT) studies to evaluate the effects of syncope (50,51). When orthostatic hypotension and syncope occurred in response to HUT, serum PRL rose 2.5- to 5-fold above baseline values. Further scrutiny of the data in one of these studies (50) shows that among the eleven patients with HUT-induced syncope, three patients with the greatest increase in PRL experienced convulsive activity, and three others actually did not have a significant rise in serum PRL.

As for the neurotransmitter mediation of postsyncope hyperprolactinemia, the lack of change in TSH levels indicates that TRH secretion—which stimulates release of TSH and PRL—is not the responsible mechanism. Administration of clomipramine, a serotonergic reuptake inhibitor, increases the yield of syncope from the HUT, implying serotonergic mediation of vasovagal syncope (52). Serotonin mechanisms may also explain the purported postsyncope rise in PRL.

Movement Disorders

Data for serum PRL associated with movement disorders has been limited to the study of patients with tardive dyskinesias (TD) caused by antipsychotic drugs. One such study compared serum PRL among men and women with TD, separated into groups with severe or mild dyskinesias. All subjects were taking antipsychotic medications, and all had hyperprolactinemia. Serum PRL was higher for women with severe TD than for those with milder dyskinesias, but there was no difference in PRL levels between men with severe or mild TD (53). The effects of acute dystonias and acute unilateral dyskinesias, such as hemiballismus, have not been studied.

Migraine and Other Headache

Serum PRL measured between migraine attacks is normal in men and women (54). Endocrine challenge studies of migraineurs have shown that I-deprenyl, which increases the availability of endogenous dopamine, produces greater decrease in serum PRL in migraineurs than in normal subjects, implying increased dopamine receptor sensitivity in migraine. Simultaneous administration of TRH, luteinizing hormone releasing hormone, and insulin also produces greater PRL release for migraineurs than for normal controls, suggesting serotonergic hyperactivity in migraine (55). The effects of acute migraine attacks have not been studied.

USE OF SERUM PROLACTIN AS A DIAGNOSTIC TOOL IN EPILEPSY: PRACTICE AND PITFALLS

Serum PRL levels are a useful adjunct in the diagnosis of epilepsy if one is knowledgeable of the physiologic and pharmacologic effects on PRL release. PRL levels may be misleading in the evaluation of nocturnal seizures because of physiologic surges of PRL release during sleep. Samples taken when the patient awakes, which are paired with recovery levels 1 hour later, will show a decline in serum PRL that may be misinterpreted as a postictal effect, rather than the physiological change it actually represents.

Serum PRL increases with virtually all GTCS, the great majority of CPS, and a smaller percentage of SPS. There is no change in serum PRL after myoclonic, absence, or akinetic seizures. Repeated seizures or status epilepticus usually do not produce serum PRL elevations.

NES produces increases in serum cortisol levels, but most studies have demonstrated no effect on PRL. Thus, a generalized convulsive event that does not produce a rise in serum PRL almost always represents a nonepileptic event. A rise in PRL after a staring spell, which potentially represents an absence, complex partial, or psychogenic nonepileptic seizure, almost certainly reflects a CPS.

Criteria used to determine a significant elevation of serum PRL have varied widely. We require that

results for an acute sample obtained 10 to 20 min after the event exceed the normal age-related range and that it is 2.5- to 3-fold higher than the recovery sample obtained at least 1 hour after the event. We do not utilize serum PRL to evaluate nocturnal events, and we interpret with caution results obtained within 90 minutes of waking. The results of serum PRL are most reliably interpreted in conjunction with a description (or video recording) of the event and with the ictal EEG. Single photon emission tomography (SPECT) and positron emission tomography (PET) scans also may help validate the diagnosis.

A single study has addressed the issues of sensitivity and specificity for postictal hyperprolactinemia (56). Yerby and colleagues analyzed data from a dozen reports that addressed serum prolactin in relation to nonepileptic and various types of epileptic seizures, deriving a sensitivity of 63% and a specificity of 91% for epileptic seizures. The predictive value of significantly elevated postictal serum prolactin in the detection of NES depends on the prevalence of NES in a given population. The probability of epileptic seizure if postictal serum prolactin is elevated ranges from >99% if the prevalence of NES is 1%, versus 88% if the prevalence of NES is 50%. Tertiary care centers often find the prevalence of NES in the range of 10 to 25%, yielding a predictive value of 95 to 98% for postictal hyperprolactinemia as an indication of true epileptic seizures. In contrast, a negative serum prolactin result is not highly indicative of NES.

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6 Nonepileptic Spells in Neonates and Infants

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Neonates and infants may exhibit a wide variety of paroxysmal episodes that markedly differ from those encountered in older children and adults. These differences relate to the immaturity of the nervous system, which impacts upon the nature of the paroxysmal attacks in several ways. Neonates and infants are more susceptible to imbalances in autonomic control and may, for example, have apnea and syncope spontaneously, or in response to minor provocation. The repertoire of possible movements is constrained, so complex paroxysmal attacks, like paroxysmal dyskinesias, are rarely seen. At the same time, the simplicity and subtlety of paroxysmal attacks may make it especially difficult to differentiate nonepileptic from epileptic paroxysmal events. It is useful to keep in mind the common manifestations of epileptic seizures in neonates and infants when considering nonepileptic paroxysmal events. A brief summary of the semeiology of ictal events will follow.

NEONATES (BIRTH TO ONE MONTH OF AGE)

Neonatal Seizures

Recognition of neonatal epileptic seizures is problematic. Initially, the diagnosis and delineation of neonatal epileptic seizures was based on a clinical description of a paroxysmal event. However, subsequent studies of neonatal seizure evaluation with long-term electroencephalography (EEG) disclosed that some of these clinical "seizures" do not have a consistent electrographic ictal scalp correlate. This is particularly the case for "subtle" seizures and episodes of diffuse tonic posturing (Table 6.1) Brief descriptions of the clinical features of neonatal seizures are summarized below (1–4).

TABLE 6.1
Neonatal Seizures

Seizure Type	EEG Correlate
Subtle Events	–/+
Clonic	++
Tonic	
Generalized Tonic	—
Focal Tonic	++
Myoclonic	
Focal/Multifocal	—
Generalized	+/–

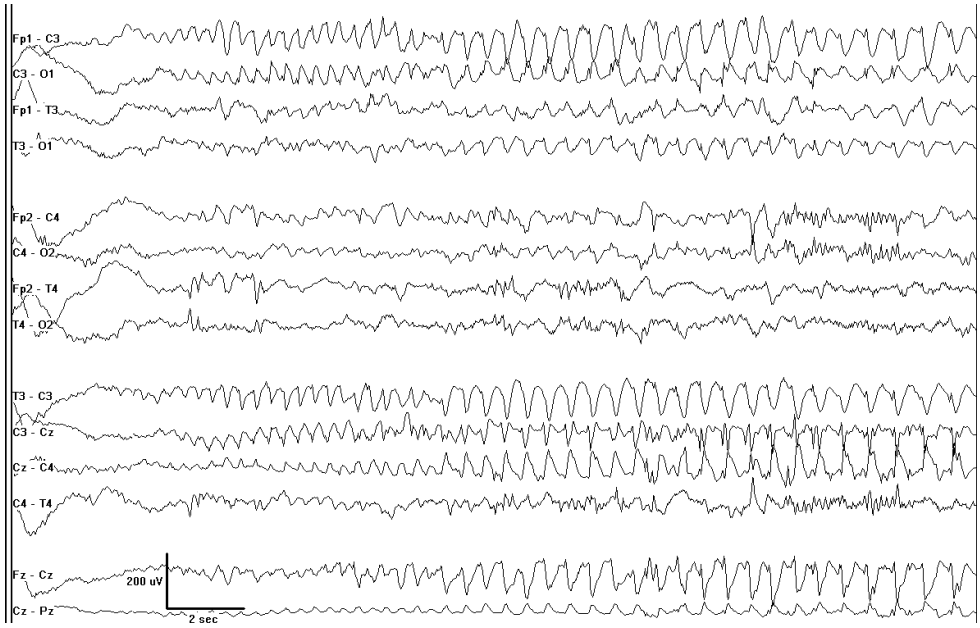

FIGURE 6.1

Neonatal epileptic seizure. 7-day-old term newborn with right arm/leg focal clonic movements. EEG shows a left parasagital rhythmic discharge in association with the clinical event.

Subtle Seizures

These events are subtle alterations in the child's behavior from either a motoric or autonomic nature; these are not clearly clonic, tonic, or myoclonic. These events have been described as including abnormal eye movements (horizontal eye deviation, sustained eye opening), oral-buccal-lingual automatisms (chewing, tongue thrusting, grimacing), extremity automatisms (pedaling, boxing movements), autonomic phenomena (increase in blood pressure, heart rate), and apnea. These clinical seizures have a variable correlation with surface EEG activity (1). In one study, up to 30% of these events had no EEG correlate. Ocular events, including horizontal eye deviation or sustained eye opening or ocular fixation, were the activity most consistently associated with EEG changes.

Clonic Seizures

Clonic seizures consist of rhythmical jerking with a slow flexion phase and a faster extension phase. These clonic jerks of the neonate are typically slow (1 to 3 jerks per second). Clonic seizures are typically focal (occurring in one area of one side of the body) or multifocal (random, migratory jerks). Generalized clonic seizures, rarely, if ever, occur in the newborn. Clonic seizures in the neonate are the seizure type that most consistently is associated with an EEG correlate (Figure 6.1).

Tonic Seizures

Tonic seizures consist of episodes of stiffening or posturing of the body, or region of the body. These episodes may be generalized or focal. Generalized tonic activity involves stiffening of the entire body with either extension of the arms and legs, or flexion of the arms and extension of the legs. These events typically (85%) do not have an electrographic correlate and may reflect some form of forebrain disconnection phenomena. The generalized tonic events that are associated with surface electrographic changes typically have associated autonomic abnormalities as well. Focal tonic events are less frequent than generalized tonic episodes. Focal tonic seizures typically involve either tonic posturing of a single extremity or asymmetric, more diffuse posturing. In contrast to generalized tonic events, focal stiffening often has an ictal EEG correlate.

Myoclonic Seizures

Myoclonic jerks are characteristically very fast movements that do not recur in a rhythmic fashion. They may be epileptic in origin, may be nonepileptic but occur in patients with severe neurologic abnormalities (pathologic, nonepileptic myoclonus), or may occur in normal patients. These jerks may be focal, multifocal, or generalized. Focal and multifocal myoclonic jerks are usually not associated with EEG changes. Generalized

TABLE 6.2
Neonatal Nonepileptic Events

Apnea
Jitteriness
Benign neonatal sleep myoclonus
Pathologic nonepileptic myoclonus
Hyperekplexia

myoclonic jerks, usually involving bilateral flexion of the upper extremities, may or may not be associated with electrographic discharges.

NEONATAL NONEPILEPTIC EVENTS

As discussed, some clinical events such as "subtle seizures," generalized tonic, and focal/multifocal myoclonic events, do not necessarily have an EEG correlate. These events may reflect brainstem-release phenomena (therefore, nonepileptic events) or may represent subcortical epileptic seizure activity. Newborns also exhibit a variety of periodic normal movements that can be readily identified by experienced observers as being nonepileptic. First-time parents may not be familiar with the character of these movements. When attacks recur frequently, parents can be asked to videotape the events. Subsequent review of the tapes can help to establish the correct diagnosis, and may also be used to reassure apprehensive parents. Some examples of common nonepileptic paroxysms include nonconjugate eye movement, sucking movements without associated eye abnormalities, and nocturnal myoclonus. Other specific nonepileptic events are described below (Table 6.2). Age ranges are somewhat arbitrary, and some of the nonepileptic events that have been classified under infancy (Table 6.3) may begin in the newborn period.

Apnea

Apnea, or cessation of breathing for greater than 15 seconds, is usually not due to an epileptic seizure, particularly if apnea is the sole manifestation, and the patient has not been already treated with anticonvulsant medication. Apnea may be secondary to centrally mediated hypoventilation or an obstructive etiology. Apnea occurs commonly in the premature child, especially during active sleep. This "apnea of prematurity" is likely to be secondary to brainstem immaturity and is typically associated with bradycardia (A's and B's). Apnea may occur in the older infant and present as an acute life-threatening event [previously called sudden infant death syndrome (SIDS)]. Since apnea may also be an important sign of neurologic diseases such as hypoxic-ischemic encephalopathy, intraventricular hemorrhage, infections, hypoglycemia, and medication side effect, an extensive search for an underlying etiology should be undertaken. If there are other concurrent manifestations, such as eye opening, eye deviation, mouth movements, tachycardia, or hypertension, an ictal etiology should be suspected (5,6).

Jitteriness

Jitteriness is a common movement phenomenon in the newborn period. Jitteriness is associated with drug withdrawal, hypocalcemia, hypoglycemia, and hypoxic-ischemic encephalopathy. Movements typically have an oscillating quality, with to and fro oscillations of equal frequency and amplitude. Jitteriness can occur spontaneously, but is also very stimulus-sensitive and can often be precipitated by touch or loud noise. In addition, the movements can be dampened by consoling the child, removing the stimulus, and relaxing the affected limb. The child is typically awake during these events and no associated autonomic activity is noted. These movements

TABLE 6.3
Infantile Non-Epileptic Events

Nonepileptoc events with excessive movements
Jitteriness*
Benign neonatal sleep myoclonus*
Pathologic, nonepileptic myoclonus*
Benign myoclonus of early infancy
Shuddering attacks
Benign paroxysmal vertigo
Stereotypies
Masturbation
Nonepileptic events that mimic tonic seizures
Hyperekplexia*
Sandifer syndrome
Dystonic drug reaction
Cyanotic syncope (breath holding spells)
Pallid syncope
Paroxysmal torticollis
Decorticate/decerebrate posturing
Nonepileptic events with abnormal eye movements
Oculomotor apraxia
Spasmus nutans
Opsoclonus

* Topics discussed under the heading of neonatal nonepileptic events.

may need to be distinguished from either clonic or repetitive myoclonic seizures. The quality of the jittery movement is different either from the two-phase movement of clonus or the quick jerks of myoclonus. The extreme stimulus-sensitivity, suppression of the movements, and lack of associated autonomic disturbances also suggest nonepileptic episodes (7).

Benign Neonatal Sleep Myoclonus

Repetitive myoclonic jerks occurring during non-REM sleep constitutes a well-described clinical phenomenon. The myoclonic jerks usually begin in the first few weeks of life and resolve by 2 to 3 months. The jerks are typically bilateral and symmetric, involving the arms and legs. However, focality and migration of the myoclonus among different muscle groups has been noted. The EEG and neurologic outcome is normal. The jerking can be significantly repetitive so as to mimic clonic seizures. Helpful features to distinguish these myoclonic jerks from epileptic phenomena include the absence of autonomic activity, no other associated seizure types, myoclonic jerks occurring only at night, and a normal neurologic and developmental examination. In addition, if the child is awakened during an episode of benign neonatal sleep myoclonus, the movements cease. It should be noted that isolated hypnogogic myoclonic jerks can occur in all age groups and is a normal physiologic phenomena (8,9).

Pathologic, Nonepileptic Myoclonus

Neonates with severe cerebral dysfunction from a variety of causes may present with myoclonic jerks that do not have an EEG correlate but are secondary to the underlying disease process (pathologic). These myoclonic jerks may be focal, multifocal, or generalized. The jerks may occur when the child is awake or asleep. This form of myoclonus is often stimulus-sensitive. Neurologic disease states associated with this nonepileptic pathologic myoclonus include metabolic encephalopathies (for example, hyperglycinemia), hypoxic-ischemic encephalopathy, cerebral vascular events, and infections. Medications may also produce nonepileptic myoclonic jerks (10).

Hyperekplexia

Hyperekplexia (stiff baby syndrome, startle disease) is a genetic disease involving an abnormal gene for a subunit of the glycine receptor on chromosome 5q. Inheritance is autosomal dominant or sporadic. The hallmark of the disease is a triad of symptoms including generalized stiffness of the baby, particularly while awake, nocturnal myoclonus, and an exaggerated startle reflex. Upon awakening or with an auditory or tactile stimulus, the neonates and infants may have a marked generalized episode of stiffening associated with apnea. These episodes can be severe and cause hypoxic brain injury. Manual flexion of the neck and hips may resolve an episode. These episodes lessen in severity as the child grows older. As adults, the subject may have a pathologic startle response to even a minor visual, auditory, or tactile stimulus. Both clonazepam and valproate have been cited in the literature as useful therapies (11,12) (see also Chapter 13).

INFANTS (ONE MONTH TO ONE YEAR OF AGE)

Difficulties arise when attempting to classify infantile epileptic seizures according to the International League against Epilepsy (ILAE) classification of seizures. In this classification scheme, partial seizures (simple and complex) are separated from generalized seizure types (absence, tonic, clonic, tonic-clonic, atonic, myoclonic). These seizure types are expected to reflect the electrographic onset of the seizure as being either from one region of the brain (focal seizures) or from the entire brain at once (generalized seizures). However, this system is problematic when applied to infantile seizures. First, the child's level of consciousness, required to separate simple from complex partial seizures, cannot be easily or reliably tested for in this age group. Second, the seizure semiology in the infant is often very subtle, with features that do not easily indicate laterality, or even permit categorization into partial or generalized types. In studies that have reviewed the electrographic correlate to the infantile seizure, it became apparent that the clinical seizure traits did not reflect whether the seizure arose from one brain region, or diffusely. For example, bilateral clonic movement may reflect either focal or generalized seizures electrographically. Finally, the seizure semiology of partial seizures is different in infants when compared to older patients. The well-described automatisms of temporal lobe seizures are often not seen in infants. Rather, a behavioral arrest from usual activities may be the most pronounced attribute of a temporal lobe seizure in an infant.

Infantile Seizures

A number of investigators have attempted to classify infantile seizures. While no universally accepted infantile seizure classification system yet exists, the unique seizure symptomotology of infants is now recognized

TABLE 6.4
Infantile Seizure Semiology

Tonic posturing
Symmetric/asymmetric
Clonic jerking
Unilateral/bilateral
Astatic seizures
Hypomotor seizures
Myoclonic jerks
Versive seizures
Infantile spasms

(Table 6.4). Infantile seizure semiology includes the following:

1. Tonic posturing. This extremity stiffening may be symmetric or asymmetric. Either type of tonic posturing may reflect either focal or generalized EEG changes.
2. Clonic jerking of one or more limbs. Bilateral clonic jerking typically does not have the synchronous rhythmicity of adult generalized clonic seizures. Although bilateral clonic movement may reflect either a focal or generalized electrographic correlate, unilateral clonic jerking of an extremity does correlate with contralateral hemispheric discharge.
3. Astatic events with loss of tone of a part or the whole body.
4. Hypomotor seizures characterized by a distinct but subtle behavioral arrest. If automatisms exist, they are typically subtle and simple, involving restless extremity movements, chewing, and lip-pursing. Complex semipurposeful automatisms are not seen in infants.
5. Myoclonic jerks (isolated or repetitive) can be seen in either a partial or generalized electrographic correlate.
6. Versive seizures consisting most notably of forced eye deviation.
7. Infantile spasms. Infantile spasms are clusters of quick extension or flexion spasms involving the neck, arms, and trunk. The spasms initially resemble a quick jerk that then sustains the posture for a few seconds. It has been debated in the literature whether these seizures should be classified as myoclonic jerks or tonic seizures. Given the distinct seizure semeiology, unique interictal electrographic appearance of hypsarythmia, and poor prognosis regarding development, a unique seizure type is proposed for these events (13–16).

Infantile Nonepileptic Events

A wide variety of events can mimic seizures in the infant. Within the first 2 years of life, while the central nervous system is maturing, children can exhibit different behaviors and events that are physiologically normal for that age, although may appear paroxysmal and unusual to care-givers. In addition, well-described paroxysmal disorders can also mimic epileptic events. The remainder of this chapter reviews spells that occur in 1-month to 2-year-old infants that may mimic myoclonic, clonic, or tonic seizures, as well as events marked by a loss of consciousness, abnormal eye movements, and unusual behaviors (Table 6.3). The following nonepileptic events are categorized as events with excessive movements, events that mimic tonic seizures, and events of abnormal eye movements. In addition, the nonepileptic events described for neonates (apnea, jitteriness, benign neonatal sleep myoclonus, pathologic/nonepileptic myoclonus, and hyperexplexia), may also occur in infants.

Nonepilptic Events with Excessive Movements

Benign Myoclonus of Early Infancy

Benign myoclonus of early infancy, also referred to as benign nonepileptic infantile spasms, is a syndrome in which infants have clinical events suggestive of infantile spasms but with a normal EEG and clinical development. The events, which begin between 3 and 8 months, resemble infantile spasms, with clusters of flexion or extension extremity movements. However, unlike spasms, both the interictal and ictal electrographic pattern are normal. Regardless of treatment, the events resolve spontaneously at 2 to 3 years of age. Head magnetic resonance imaging (MRI) and neurologic examination are normal, as is the developmental outcome. No subsequent seizures of any type are noted on follow-up (17,18).

Shuddering Attacks

Shuddering attacks may begin in infancy, as early as 4 months, or in childhood. The events consist of a rapid tremor of the head, shoulder, and trunk suggestive of the "shuddering" episodes from a chill. The duration of the events is brief, lasting only seconds, but the events may occur multiple times a day. The spells are often associated with eating and may represent a pattern of stimulation overflow in a young child. The electrographic pattern during these spells is normal. No other neurologic abnormalities are associated with these events. The spells require no treatment and spontaneously resolve by the second decade. A family history

of essential tremor has been noted for children with shuddering attacks (19,20).

Benign Paroxysmal Vertigo

Benign paroxysmal vertigo is reflected by the recurrence of events of brief dysequilibrium in young children. When the attacks occur, the child appears frightened and off balance, often reaching out to steady himself. The events may be associated with nystagmus, diaphoresis, nausea, and vomiting. These attacks occur in toddlers and young children but typically resolve by age 5 years. Neurologic examination, development, and EEG are normal. A later association with migraine has been reported (21).

Stereotypies

Stereotypic behaviors are repetitive movements such as head banging, head rolling, body rocking, and hand flapping. These behaviors can be seen in normal children but are more common in neurologically impaired infants. The behaviors may be seen while the child is awake, falling asleep, or even in early sleep stages. These behaviors are "self-stimulating" behaviors and often comfort or relax the child.

Masturbation

Infantile masturbation can present as paroxysmal episodes of rocking or stiffening. The children may be sitting or lying prone or supine with a rhythmical rocking movement. During the events, the infants are alert but may appear to have a decreased level of responsiveness or an "unusual" look on their face. The behavior can be interrupted. A careful history or a videotape of the events can distinguish masturbation from seizure activity.

Nonepileptic Events That Mimic Tonic Epileptic Seizures

Sandifer Syndrome

Infants with gastroesophageal reflux may have intermittent paroxysmal spells of generalized stiffening and opisthotonic posturing. These spells may also be associated with apnea, staring, and minimal jerking of the extremities. A careful history will reveal that these spells are associated with feedings, often occurring within 30 minutes of a feed. Sandifer syndrome can be seen in neurologically normal children as well as children with hypotonia and tracheomalacia, which may predispose the child to the acid reflux. The extreme generalized stiffening may represent a pain response to the acidic material refluxing into the esophagus. No electrographic correlate is noted with these events. If the history suggests Sandifer syndrome, a gastroesophageal work-up should ensue.

Dystonic Drug Reaction

Dystonia is a sustained abnormal posture that occurs from the contraction of both the agonist and antagonist muscle groups of an extremity. Dystonic postures may be generalized or focal. Spells of paroxysmal dystonias are difficult to differentiate from tonic seizures. In infants, a common etiology of sudden dystonia is an acute drug reaction. These reactions may manifest themselves as opisthotonic posturing, torticollis, and an oculogyric crisis. Metoclopramide, a parasympathomimetic drug often used for the treatment of gastroesophageal reflux, is a common medication used in infants that can cause this drug reaction. Other medications associated with dystonic drug reactions, such as phenothiazines and haloperidol, are used less often in toddlers.

Cyanotic Syncope (Breath Holding Spells)

Breath holding spells are common events in infants and young children age 6 months to 6 years. The attacks are precipitated by minor injury, frustration, or anger. The events are heralded by crying followed by apnea that typically occurs in expiration. The child then develops significant cyanosis. If the attacks are prolonged, the child loses consciousness and becomes limp. If significant hypoxia occurs, the child may develop tonic posturing or even a few extremity jerks that may be mistaken for seizure activity. The key to the diagnosis is the preceding crying and cyanosis prior to each event. Difficulty in correct diagnosis occurs if the onset of the attacks is not witnessed. Cyanotic syncope is presumed to be a benign involuntary development response to the injury and crying that the child will ultimately outgrow (22,23).

Pallid Syncope

Pallid syncopal events are similar to breath holding spells. Again, events are typically precipitated by minor injury, frustration, or fright. Instead of significant crying and cyanosis, the child becomes pale and then loses consciousness. If the events are prolonged, tonic stiffening may be seen. The pathophysiology is secondary to a brief bradycardia or asystole resulting in decreased blood flow and the subsequent facial pallor. Atropine has reportedly been of benefit in decreasing the frequency of these spells (23).

Paroxysmal Torticollis

Torticollis is an abnormal sustained posture of the head and neck in which the head tilts to one side and the face rotates to the opposite side. In paroxysmal torticollis, the events begin and end suddenly. The attacks can be brief or prolonged. The child is alert and responsive during an attack although the patient may appear uncomfortable and irritable. The EEG is normal during the event. The etiology of the attacks is unknown, although both a focal dystonia and labyrinth dysfunction have been suggested as the cause, as has migraine. Often a family history of migraines is noted, and children with benign paroxysmal torticollis may develop typical migraines later in life. Paroxysmal torticollis usually begins in the first few months of life, and resolves by age 3 years. No treatment is required (24).

Decorticate/Decerebrate Posturing

Decorticate and decerebrate posturing can mimic tonic seizures. Decorticate posturing refers to flexor posturing of the upper extremities and extensor posturing of the lower extremities. In decerebrate posturing, both the upper and lower extremities show extensor stiffening. Both events can occur suddenly from a severe brain injury affecting the brainstem level. This posturing can be seen bilaterally or unilaterally in different herniation syndromes. Possible impending herniation should be considered in a comatose patient exhibiting sudden tonic stiffening (25).

Nonepileptic Events of Abnormal Eye Movements

Oculomotor Apraxia

Oculomotor apraxia is a condition in which the child has impaired saccadic eye movements. The child appears to have fixed eye positions although the visual system and eye movement ability are normal. Therefore, in order to view an object, the child will turn his head suddenly so as to move the direction of gaze. These peculiar head thrusts may be confused for epileptic seizures. The idiopathic congenital form of this apraxia is called Cogan's oculomotor apraxia. However, oculomotor apraxia can also be seen in ataxia telangiectasia and lysosomal storage diseases.

Spasmus Nutans

Spasmus nutans consists of a triad of symptoms including nystagmus, head nodding, and head tilt. The symptoms can wax and wane during the course of the day and, therefore, be confused with epileptic seizures. The onset of the symptoms is usually during the first few months of life. The etiology of this disorder is unknown, although the triad has been associated with mass lesions at the optic chiasm or third ventricle. A head MRI scan should be obtained in these infants. If no abnormality is revealed, no further work-up or treatment is required. The symptoms usually resolve by age 5 years.

Opsoclonus

Opsoclonus consists of random, erratic, conjugate oscillation movements of the eye ("dancing eyes"). These movements usually occur continuously including sleep, although they may wax and wane in intensity. In mild opsoclonus, a brief stable fixation on an object may be seen. These eye movements are usually seen in association with myoclonus and ataxia. Opsoclonus can be seen in children with an occult neuroblastoma, encephalitis, or without an identifiable cause (27).

CONCLUSION

Numerous and varied paroxysmal spells in neonates and infants may be nonepileptic in nature. The knowledge of typical epileptic and nonepileptic events in neonates and infants will aid the clinician in the correct diagnosis. The most important tool in determining epileptic from nonepileptic events is a careful clinical history. However, if the history does not disclose the diagnosis, a videotape of the event or a concomitant video-EEG recording may be helpful (28–30).

Neonatal and infant electroencephalograms can be difficult to interpret. The EEG matures from the neonate to adolescence, with the most dramatic temporal changes occurring during the newborn period. EEG patterns that are normal for one age group may be abnormal for infants just a few weeks older. In addition, "epileptiform discharges" (spikes, sharp waves) may be a normal brainwave pattern at certain ages. For example, multifocal sharp transients are a normal brainwave pattern for premature infants, initially appearing at 29 weeks gestation, and may persist up to 40 weeks gestation, particularly in quiet sleep. However, multifocal sharp transients that are repetitive, persistently unilateral, polyphasic, occur in the term newborn during the awake state, or occur after 40 weeks gestation are considered abnormal discharges (Figure 6.2). Frontal sharp transients first appear at 35 weeks gestation and persist up to 46 weeks gestation in quiet sleep. Frontal sharp transients are usually surface negative, less than 200 msec, and have voltages between 50 and 150 v. Frontal sharp transients that are repetitive, unilateral, or occur after 46 weeks gestation are abnormal. In addition, abnormal epileptiform activity in the neonate is less an

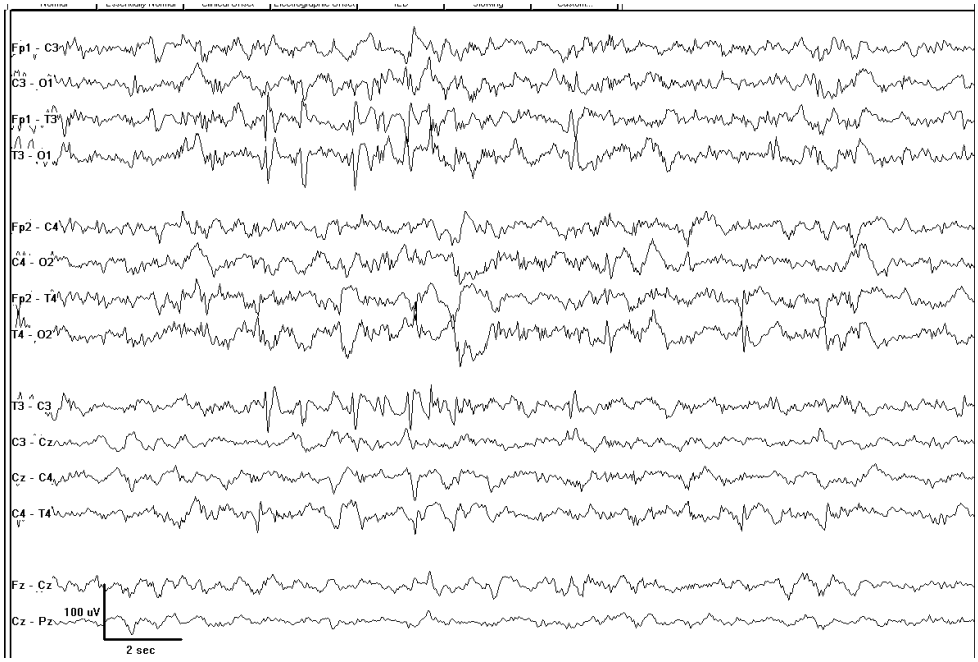

FIGURE 6.2

Neonatal EEG shows multifocal epileptiform discharges in an 8 day-old with hypotonia, apnea, and seizures. During this study, the patient was on phenobarbital.

indication of specific susceptibility to seizures ("epileptogenicity") than a measure of the underlying encephalopathy. In general, one should be conservative in using interictal spikes or sharp waves to diagnose neonatal seizures (31).

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7 Nonepileptic Seizures and Similar Phenomena in Children and Adolescents

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Most children seen by pediatricians or child neurologists in a first seizure or paroxysmal disorders clinic will not have epilepsy. The principal reason why many of these children are wrongly diagnosed as having epilepsy is a lack of time and effort spent on the difficult, lonely art of history taking. Physicians must have an equally expert knowledge of the imitators of epilepsy as they have of the myriad clinical expressions of epileptic seizures. The paramount importance of history taking is confirmed by the observation that misdiagnosis of epilepsy remains high throughout the world, irrespective of the wealth and resources available to the healthcare system. This justifies the importance of this chapter and of this book.

NONEPILEPTIC SEIZURES AND PAROXYSMAL NONEPILEPTIC EVENTS IN THE POPULATION

The diversity of nonepileptic events in childhood and adolescence is very considerable. Some of these nonepileptic events fully justify the term nonepileptic seizure (1,2). It is our impression that the most common type of nonepileptic seizure leading to diagnostic confusion in clinical practice is the anoxic seizure, or syncopal convulsion (3). This view is supported by recent observational studies (4,5).

It is also our clinical impression that misdiagnoses of epilepsy are more likely to arise when a child has more than one paroxysmal nonepileptic disorder, for example two or more of the following: psychological events, syncopes, migraine, and sleep disorders.

When children suspected of having epilepsy are studied for diagnostic purposes in tertiary monitoring units, other nonepileptic events predominate (6,7). In the study of Bye et al (6), which included children with developmental delay or mental retardation, psychological and sleep phenomena were most common, and the EEG frequently showed misleading "epileptiform" discharges. Kotagal et al (7) reported on 134 children and adolescents referred to a pediatric epilepsy monitoring unit at the Cleveland Clinic over a 6-year period. They divided their results into three age groups. In the preschool, 2-month to 5-year group, the most common diagnoses were stereotypies, sleep jerks, parasomnias, and Sandifer syndrome. In the school-age, 5- to 12-year group, the most common diagnoses were conversion disorder (psychogenic pseudoepileptic seizures), inattention or day dreaming, stereotypies, sleep jerks, and paroxysmal movement disorders. In the adolescent, 12- to 18-year group, over 80% had a diagnosis of conversion disorder (hysteria, psychogenic pseudoepileptic

seizures). A significant proportion of the children studied had concomitant epilepsy.

Although only abstracts have so far been published (8,9), the latest evidence is that the misdiagnosis rate in children with "definite" epilepsy may be as high as 40%.

CLASSIFICATION OF NONEPILEPTIC SEIZURES AND EVENTS

We classify nonepileptic seizures and events into six broad and sometimes overlapping clinical categories:

- Syncopes and anoxic seizures
- Psychological disorders
- Derangements of the sleep process
- Paroxysmal movement disorders
- Migraine and disorders possibly related to migraine
- Miscellaneous neurological events

We also mention an important and under-recognized paroxysmal phenomenon in which triggered syncopes themselves trigger epileptic seizures without (usually) the child having epilepsy. Hence a seventh additional category:

- Anoxic-epileptic seizures

DIAGNOSTIC CATEGORIES

Syncopes and Anoxic Seizures

An anoxic seizure is a consequence of a syncope, which is an abrupt cutting off of the energy substrates to the cerebral cortex, usually through a sudden decrease in cerebral perfusion by oxygenated blood (1,3). The term anoxic seizure is shorthand for the clinical or electroclinical event that occurs as a result of the cessation of nutrition to the most metabolically active neurons. Less complete, or less rapidly evolving syncope will have less dramatic consequences. For ease of reference, the syncopes have been subdivided, but it must be recognized that overlaps occur and present knowledge is inevitably incomplete. In particular, it seems likely that what we call reflex anoxic seizures or reflex asystolic syncope (RAS), breath-holding spells or prolonged expiratory apnea, vasovagal syncope, and neurocardiogenic syncope are all varieties of the same disorder, called by the adult cardiologists *neurally mediated syncope*. When parents or children are bewildered by these diagnoses, or annoyed when told that it's only breath holding or only a simple faint, then contact with a family support organization may be very helpful (http://www.stars.org.uk).

Reflex Anoxic Seizures or Reflex Asystolic Syncope: (RAS)

Gastaut (10) used the term reflex anoxic cerebral seizures to describe all the various syncopes, sobbing spasms, and breath-holding spells that followed noxious stimuli in young children. Since 1978, reflex anoxic seizure has been used more specifically to describe a particular type of nonepileptic convulsive event, most commonly induced in young children by an unexpected bump to the head (11). Although other terminology, such as pallid breath-holding and pallid infantile syncope, have been applied to such episodes (12), the term reflex anoxic seizure is now widely recognized (13,14).

Until the advent of cardiac loop recorders, direct evidence with respect to the pathophysiology of natural attacks had been very limited. Since prolonged cardiac recording has become feasible in children, many recordings of prolonged reflex asystole have been recorded and several examples published (15–18).

An extract from a letter written to a pediatrician by a consultant neurologist may give the reader some idea of the diagnostic difficulties that were commonly experienced before the phenomenon of reflex asystole was well known. He wrote:

> ***Case study #1.*** Thank you for asking me to see this 7-year-old young man. As a toddler he began to have attacks of loss of awareness, rigidity, and eye rolling which would be induced by minor knocks. This has continued and recently an episode occurred in which he had an undoubted tonic-clonic seizure with incontinence of urine. Curiously, as far as I can tell from mother's account, every attack has been triggered by a minor bump on the head, and he has never had an attack out of the blue. He had difficulties at birth. The family history is clear except for a convulsion in the mother when she was tiny, about which there is no further information. It seems to me that this boy is having a form of reflex epileptic seizure, and my inclination would have been to start treatment with sodium valproate. In fact mother told me … that he was started on Epilim just a couple of weeks ago. Even though two EEGs have been normal, I do not doubt that he has an epileptic tendency, and I am sure that he should be on treatment for at least a couple of years free from attacks.

When this boy was seen in a further consultation he was "an epileptic," his school knew about his "epilepsy," his mother was in touch with an epilepsy association, and

invalidity benefit had been applied for on the basis of epilepsy. Presumably, the difficulty here was that neither the pediatrician nor the neurologist knew that this was precisely the story of nonepileptic reflex anoxic seizures of vagally mediated cardioinhibitory type, otherwise known as **reflex asystolic syncope.** It is probable that the diagnosis of breath-holding spells had been entertained earlier, but quite rightly discarded, if only because the boy was by now over the age of 7 years. The alternative diagnosis of a primary cardiac syncope, such as is seen in the long QT syndrome (see Long QT Disorders below)—LQT—was not considered, perhaps because syncopes in LQT had not at that time been described *exclusively* as a sequel to minor bumps to the head. Since then, there has been a report of one case of LQT in which four or five syncopes, the last fatal, were precipitated by a blow to the head (19: page 94).

As children grow older, reflex anoxic seizures may cease altogether or change to more obvious convulsive or nonconvulsive vasovagal syncope in childhood and adolescence. It is possible, although proper long-term studies have not been done, that syncopes may reappear in old age.

Beyond the toddler stage, children may report sensory disturbances along with the syncopes. Most dramatic are out-of-body experiences with a dreamlike quality (17), which may include the child feeling as if he or she has floated up to the ceiling and is watching his or her body lying on the floor in a seizure (20). Night terrors (see Parasomnias below) as a sequel to the syncopal episodes have also been reported by parents.

It is often said that breath-holding spells (see Breath-holding Attacks below) or syncope caused by prolonged expiratory apnea may also occur in children who have reflex anoxic seizures. It is certainly true that in some children some episodes may be more blue or cyanotic and some more pale and blanched looking, but there are no good recordings that confirm this proposition.

It is best to try to make a precise diagnosis as to whether a convulsive syncope in a young child is cardiogenic or respiratory in origin. If it is cardiogenic, then the main differential diagnosis is a reflex anoxic seizure (reflex asystolic syncope) versus a convulsive syncope from long QT syndrome or other cardiac cause. If it appears to be a respiratory (i.e. apneic) syncope, then the differential diagnosis is breath-holding spells (prolonged end-expiratory apnea) or suffocation (in particular, from imposed upper-airway obstruction as part of Meadow's syndrome (see Suffocation below).

Vasovagal Syncope

Vasovagal syncope is the most familiar and predominant form of neurally mediated syncope. If classical reflex anoxic seizures (with reflex asystolic syncope) represent a fairly pure vagal attack, vasovagal syncope involves a vasodepressor component with variable vagal accompaniment. Episodes may begin in infancy, sometimes with reflex anoxic seizures, and thereafter are seen at all ages, becoming most dramatic perhaps in old age (21).

Tables in medical textbooks or works of epileptology tend to perpetuate gross errors with respect to the distinction between vasovagal syncope and epileptic seizures with comparable signs. This may be in part because many authors equate syncope with some sort of limp, pallid swooning in the Victorian manner. Here, for example, are the features *previously* said to distinguish between syncope and seizures:

- Posture: upright
- Pallor and sweating: invariable
- Onset: gradual
- Injury: rare
- Convulsive jerks: rare
- Incontinence: rare
- Unconsciousness: seconds
- Recovery: rapid
- Postictal confusion: rare
- Frequency: infrequent
- Precipitating factors: crowded places, lack of food, and unpleasant circumstances.

In reality the situation is different. Vasovagal syncope may occur supine, particularly in the case of venepuncture fits; though some (13) would call these reflex anoxic seizures insofar as the mechanism is strongly cardioinhibitory. Pallor and sweating are certainly not invariable, nor need onset be gradual. There is no difference between the liability to injury in convulsive syncope as opposed to a comparable convulsive epileptic seizure. Convulsive jerks are certainly not rare but occur in perhaps 50% of vasovagal syncopes (22) and more often in experimental syncope (23). Urinary incontinence is common (24), occurring in 10% of cases in one experimental study (1). Unconsciousness may be much more than seconds and recovery, although it may be rapid in mild syncope, is not necessarily complete early on (3). It is true that postictal confusion proper is rare, but it can occur (3). The frequency of vasovagal syncope may be very great, up to more than once a day. Stimuli may be very subtle, but it is true that some sort of stimulus should be detected for at least some attacks in any individual.

The setting and stimulus are indeed the most important factors in allowing the presumptive diagnosis of vasovagal syncope, together with elicitation of the warning symptoms or aura, which are commonly

present. A seizure that occurs after a bath while the child is having her hair blow-dried, or brushed, is—without need for further investigation—a vasovagal nonepileptic convulsive syncope. Premonitory symptoms are usually present in older children, even if the duration is only a second or two, but sometimes these are forgotten and only recalled when syncope is reproduced, as in the head-up tilt test. All physicians are aware of the usual symptoms of cerebral ischemia, such as dizziness and greying out of vision and tinnitus, but an important additional symptom is abdominal pain. It may be difficult to tell whether abdominal pain is a symptom or trigger of a vasovagal syncope or an intestinal symptom of a strong vagal discharge. The latter is quite common (1), and sometimes leads to confusion with the so-called epigastic aura, which may precede the complex partial component of the temporal lobe epileptic seizure. Almost all children with vasovagal syncope have a first-degree relative, commonly a parent, affected (25). It is unfortunately common [histories are included in (1)] to find that the parent who now seems convincingly to have vasovagal convulsive syncope has become irredeemably "epileptic" and too habituated (or too frightened of losing a precious driving license) to discontinue years of useless (and perhaps embryopathic) antiepileptic medication.

Such considerations have led to the use of head-up tilt testing, not only as a diagnostic aid but as a diagnostic reinforcer. If, for example, a child patient, a family doctor, and a pediatrician have all been convinced that the child has had "grand mal epilepsy" since the age of 3, then some dramatic theater may be necessary at the age of 12 to 14 years to make the switch from epilepsy to the correct diagnosis of vasovagal syncope. There are no good data on this point, but there is an impression that if the diagnosis is not properly instilled by this age, it may be too late to prevent a life of being "epileptic".

A case history illustrates the transition from reflex anoxic seizures in infancy through short latency pain-induced vasovagal syncope to blood-injury phobia (26,27) in adolescence: the history was given by the mother when her affected daughter was aged 13 years. The previous diagnoses had included epilepsy, hypoglycemia, and hysterical behavior.

Case study #2. The first episode occurred at the age of 10 months, after a very slight bump to the infant's head. The appearance of the attacks has been similar from then to now, except that severity has varied and tended to increase with the passage of time. Typically there is a latency of 10 to 20 seconds during which she may say "oh mum I've hurt myself." By this time the blood has drained from her face, she goes limp, and falls as if dead, then goes totally rigid, making a noise like a cackle or gurgle, with her hands and feet turned in and her back sometimes forming the shape of an arc. Sometimes her arms and legs jerk, but not violently, as though pedaling her bicycle, but on occasion thrashing wildly like a full seizure (as her mother describes it). Again, she looks like death and then wakes up as if coming out of a very deep sleep. She is then very disorientated, does not know what has happened or where she is, but within a couple of minutes she has come to herself and may then want to lie down again and have a proper sleep. Since about the age of 7 or 8 years she has described an aura. She hears a noise like a high-pitched screaming and sometimes hears a voice but cannot describe the voice precisely. Sometimes she sees red, a color she does not like. More recently she has had strange hallucinations during the warning period, such as seeing a train rushing towards her. The stimuli have modified over the years after the first head bump. All episodes in earlier years followed small pains like her finger being bent back. Then she developed the same reaction to seeing a minor injury such as a scab that had come off a wound, and then inevitable syncope at the sight of blood. Most recently merely the thought of self-injury was sufficient.

On the evening before the intended consultation she was told (wrongly) that her eyeballs would be pressed down (ocular compression) and within 2 minutes she was stiff and snorting. Although the mother's sister had had some type of genuine epilepsy, a family history of syncope of any kind was denied. Actually, the mother later admitted to several faints during adolescence and pregnancy, but did not mention them because she did not have a "fit." The results of a recent study suggest that adults with blood or injury phobia have a "constitutional autonomic dysregulation" predisposing them to neurally mediated syncope even in the absence of any blood or injury stimulus, and that repeated syncopes resulting from such stimuli secondarily lead to the blood or injury phobia (28).

Vagovagal Syncope

By contrast to vasovagal syncope, convincing *vago*-vagal syncope is rare. The reflex is usually triggered by swallowing or vomiting and cardiac standstill results, with a motor anoxic seizure (convulsive syncope) if the asystole is sufficiently prolonged. This is probably not a life-threatening disorder, but the symptoms can be trou-

blesome, particularly if the patient also has migraine with associated vomiting. Pacemaker therapy has been used successfully in this situation (1).

Hyperventilation Syncope

Hyperventilation in any human induces various organic symptoms that may in certain individuals stimulate further hyperventilation and exacerbation of the original symptoms. A degree of panic may be so engendered. Asking the child to hyperventilate (whether by getting the child to repeatedly blow out a candle, blow soap bubbles, blow a tissue, or to directly hyperventilate) may induce symptoms similar to those of which the child complains. Continuation of hyperventilation once the directed hyperventilation has been stopped may be of additional diagnostic value. Spontaneous hyperventilation may lead to apparent absences without spike and wave (29), but it should be remembered that a possible difficult-to-diagnose absence-like seizure may be of frontal lobe origin (30). Studies on hypocapnea and the cerebral circulation include those found in references 31 and 32.

Orthostasis

Syncope due to orthostatic hypotension secondary to autonomic failure is rare in childhood. Dopamine β-decarboxylase deficiency (33) is a possibility in such a clinical situation. The simplest way of detecting orthostatic intolerance is to stand the child on a foam mat (to avoid injury when falling) for 10 minutes with continuous blood pressure measurements; this is best done using Finapres recording from a finger with the hand secured at heart level. This method may also be used to provoke vasovagal syncope (see Vasovagal Syncope above) in young children, including those too young to tilt (34).

Chronic orthostatic intolerance can produce other symptoms, usually in addition to vasovagal syncope, these include symptoms of presyncope: lightheadedness, "dizziness," blurred vision. Furthermore exercise intolerance, chronic fatigue, migrainous headache, nausea, abdominal discomfort, chest discomfort, palpitations, shortness of breath, hyperventilation, peripheral cyanosis, sweating, and flushing on standing have been encompassed in this condition (35). Clues may be tiredness and excessive dislike of exercise. Chronic orthostatic intolerance is sometimes part of the clinical picture in chronic fatigue syndromes and it maybe helpful to consider this treatable disorder as a differential of idiopathic chronic fatigue syndrome.

One clinical picture comprising chronic orthostatic intolerance in teenagers and young adults is the postural orthostatic tachycardia syndrome (POTS) (36). Patients have symptoms of chronic orthostatic intolerance with significant daily disability, associated with a marked tachycardia on standing: a heart rate increase of >30 beats per minute or a heart rate of >120 beats per minute within 10 minutes of head-up tilt (35).

Long QT Disorders

The long QT syndromes are associated with genuinely life-threatening syncopes that may be hypotonic or convulsive. The mechanism of the syncopes is a ventricular tachyarrhythmia, normally *torsades de pointes*. As a rule, there is no great difficulty in the diagnosis of the syndrome of Jervell and Lange-Nielsen (37), in which congenital deafness is associated with an autosomal recessive inheritance. Much more difficult is the Romano-Ward syndrome (38), which is dominantly inherited but with incomplete penetrance. It has been suggested (39) that the diagnosis may fairly easily be made by asking the right question, in particular asking whether the child lost consciousness and remained completely still (like a dead body) for several seconds before having "tonic-clonic seizures." Actually what these authors describe is a cardiogenic syncope, not fundamentally different from the reflex anoxic seizure seen with reflex asystolic syncope or a convulsive vasovagal syncope in which the vagal component predominates. The observation that the child lies like a dead body is not necessarily made, and of course the nonepileptic seizure is normally not a tonic-clonic seizure but an anoxic seizure with a combination of spasms and jerks and stiffening. A degree of overlap exists between the stimuli that induce the neurally mediated syncopes and those that trigger the ventricular tachyarrhythmias of the long QT syndrome, but the most important hint in favor of a long QT disorder is the story of convulsions triggered by fear or fright and particularly in two situations:

- During exercise, especially when that exercise is emotionally charged
- During sleep

A personal example illustrates diagnostic difficulties:

> ***Case study #3.*** A 5-year-old girl presented with a history of convulsive syncope since the age of 2. At the first consultation the parents said that when she fell, not necessarily hurting herself and not necessarily falling on any particular part of her, she went gray or gray/purple around the mouth, looked faintish as if dead, went very rigid as her eyes rolled and her head flopped, she moaned, and "she was dead in my arms." One of the episodes was said to have

occurred as a splinter was being taken out of her finger by her mother. There was a positive family history in that the father had fainted on cutting his finger and the mother had faints during pregnancy. An interictal 24-hour ambulatory cassette ECG of the child had been reported as normal. A diagnosis of reflex anoxic seizures (reflex asystolic syncope) was made and it was decided that it would not be necessary to do ocular compression as a confirmatory test. Three years later the consultant pediatrician wrote again:

She had approximately 1 year without any episodes, but has had two close episodes in the last few weeks, both of which occurred during physical exertion during play. At least one of these episodes seemed to be associated with an olfactory aura, the child describing strange smells before the event. In both situations, she was found unconscious, stiff, and mottled gray but recovered fairly promptly. I guess this is still a vagally mediated event, but the parents would value further assessment and reassurance.

Review of the history revealed that although two of the episodes had originally been associated with falling when playing with a ball, other episodes had occurred when chasing a dog, trying to catch the waves at the edge of the sea, playing being chased on her bicycle, and during a hopping race. The new historical details prompted immediate measurement of her QT interval, the corrected value of which (QTc) was 479 milliseconds (normal value less than 440 milliseconds). A review of the original 24-hour ECG from 3 years previously showed that the QTc was prolonged then also at 470 milliseconds. Her mother had a marginally prolonged QTc of 449 milliseconds, whereas her father and sister had normal QTc measurements of 387 and 390 milliseconds respectively.

Long QT disorders are much less common than neurally mediated syncopes, such as reflex anoxic seizures and reflex asystolic syncope, but this diagnosis should be sought when the precipitants of a cardiac syncope are not of the typical benign reflex anoxic seizure type (that is to say, unexpected bumps to the head) and particularly when exercise or sleep are triggers. This diagnostic consideration is another reason for trying to separate by history cardiac and respiratory syncopes.

Having said this, provided that the history is *typical* of a variety of neurally mediated syncope and a careful cardiac evaluation is negative, one should be reassuring even when syncopes occur during exercise (40).

Other Cardiac Syncopes

Diagnostic difficulties do not usually arise with respect to endogenous cardiac syncopes other than those of the long QT syndromes. However, it is up to the clinician to obtain a sufficiently clear history to determine whether a seizure or convulsion is an epileptic seizure or is a nonepileptic convulsive syncope. Sometimes ventricular tachyarhythmias occur with normal QT intervals (41–44), and there are occasions in obvious congenital heart disease when, for example, paroxysmal pulmonary hypertension may have to be inferred by a precise description, indicating an anoxic seizure precipitated by exercise (1).

Breath-holding Attacks

Breath-holding spells have been described for centuries (45) but controversy as to what they are remains (46). The term "breath-holding" is not at all satisfactory (19,47). It tends to give offence to parents of affected children. It seems to imply temper tantrums and bad behavior. One imagines that many members of the public and even pediatricians actually do believe that breath-holding spells are a manifestation of a behavior disorder and, in some pediatric textbooks, breath-holding attacks are to be found in the section on psychiatric or psychological disorders. However, studies have shown that however one defines breath-holding spells, behavioral disorders in those afflicted do not differ from those in control children (48).

Breath-holding seems to imply some sort of voluntary "I'll hold my breath until I get what I want" behavior, whereas none of the behaviors so described seems to involve this mechanism. There is no difficulty nowadays in recognizing that what used to be called white or pallid breath-holding (12) has a cardiac rather than a respiratory mechanism, as discussed earlier in the section on reflex anoxic seizures and reflex asystolic syncope. The term *prolonged expiratory apnea* (49) is certainly helpful in discussing those episodes in which the mechanism is predominantly respiratory, even though the pathophysiological details may be in dispute.

One difficulty is, as with so many paroxysmal disorders, that precise detailed documentation of what happens is in short supply. Cinematographic registration has been described (50). Videorecordings—predominantly of several episodes in a single child—have been obtained (1,51) and polygraphic recordings of a few children (52), but the total information compared to the frequency of occurrence of natural episodes is very small. There appears to be a pure respiratory "breath-holding" spell or prolonged expiratory apnea, without any change in cardiac rate or rhythm (albeit information on cardiac output is not available), such

attacks being clearly cyanotic or "blue" breath-holding. There are also episodes that may be described as "mixed" breath-holding, insofar as there is not only expiratory apnea but also a degree of bradycardia or cardiac asystole (1,51).

An argument exists about the prognosis of these "cyanotic breath-holding spells" or prolonged expiratory apneas (51,52), but management of neurodevelopmentally intact children does depend on the general assumption that prolonged expiratory apnea (cyanotic breath-holding) is benign (46). The best prospective study to date is that of DiMario (53), albeit he includes pallid breath-holding spells, which may represent, in our terminology, reflex anoxic seizures or reflex asystolic syncope.

Compulsive Valsalva

Children with aberrant development, including those with autistic disorders, may have atonic or more dramatic syncopal seizures compulsively self-induced by something akin to a Valsalva or Weber maneuver (3,54). Such episodes may be very severe and, indeed, may have a fatal outcome (55). The child seems able to obstruct the cerebral circulation completely, so that an anoxic seizure results. Perhaps, because of the cerebral abnormality already present, this is one situation in which anoxic-epileptic seizures (see Anoxic-Epileptic Seizures below) may result (56–58). If the episodes are very frequent, as is often the case, detailed analysis by videorecording and polygraphic registration (55) may allow a precise elucidation of the diagnosis. Clues include the video-picture of true "breath-holding" for about 10 seconds, this time in *inspiration,* reduction of the amplitude of the QRS complexes on ECG, and then a burst of high-voltage slow waves on EEG. Sometimes, hyperventilation precedes the Valsalva maneuvre, as in Case Study 4 (see published video in [3]), and as in the experimental syncopes described by Lempert, Bauer and Schmidt (23). It is likely that many of the reported seizures in Rett syndrome are of this nature (59).

Case study #4. A boy of school age presented with an apparent recurrence of seizures. He had an early history of infantile spasms; that is, epileptic spasms with hypsarrhythmic EEG in the first year of life. The spasms remitted but he was left asymbolic—that is without the understanding of meaning—and without imaginative play or social interaction. His main enjoyments seemed to be twirling or spinning dinner plates and intermittently hyperventilating and holding his breath. He was referred back because of numerous daily tonic seizures. Videorecording demonstrated a consistent stereotyped sequence. While twirling a plate, he hyperventilated, then took a deep breath in inspiration, then made a powerful Valsalva maneuver for 10 to 11 seconds, and finally with a groan he collapsed with brief tonic extension and elevation of his upper limbs. He recovered instantly. His mother said "that's a seizure, isn't it?" It was, but an anoxic seizure, not an epileptic seizure (3).

Gastroesophageal Reflux

Much has been written about gastroesophageal reflux in infants, but cinematographic or videorecording or full polygraphic registration of a reflux-associated episode that might be described as a seizure has not been reported, though a true reflux episode associated with an epileptic seizure has been described (60). Nonetheless, there is a persuasively recognizable condition, the "awake apnea syndrome" (61). Having been fed within the previous hour, often following an imposed change of posture, the infant gasps, is apneic, stiffens, changes color, and may then look startled. A personal case is described in Stephenson (1).

Sandifer syndrome secondary to reflux is mentioned under Miscellaneous Neurological Events below.

Imposed Upper Airway Obstruction, Suffocation

An important, unusual, but difficult diagnosis relates to suffocation of a baby (usually) by the mother (62). This can be termed the active form of Munchausen syndrome by proxy, or Meadow syndrome, of the factitious epilepsy type (63) and is a classic example of fabricated or induced illness (64). In this situation, the parent repeatedly suffocates the baby by either pressing a hand or some other material over the baby's mouth, or else the mother presses the baby's face against her bosom (1) with a resultant syncope and anoxic seizure. The evolution here is *much* longer than in the usual cyanotic breath-holding spells (prolonged expiratory apnea), with a latency of something of the order of 2 minutes (65). Diagnosis may be exceedingly difficult, and depends on such factors as recognizing that the episodes only begin in the presence of the mother, although various other people, such as relatives or nursing or medical staff, observe the conclusion of the episodes (66). Definitive diagnosis may require *covert* videorecording (65,67). Transmission of the diagnosis to the family presents great difficulties. It has been found helpful to involve another experienced

pediatrician, a psychiatrist, and child protection services, before discussion with the family regarding the mechanism of induction of these truly life-threatening anoxic seizures (1).

Hyperekplexia

Hyperekplexia is a rare disorder (or group of disorders) that may include dramatic neonatal onset (68) with nonepileptic convulsive syncopes that may prove fatal. Insofar as effective treatment is possible by repeatedly flexing the baby (69), diagnostic awareness should be high. An early major paper on this topic (70) described a dominantly inherited disorder in which there were stiff hypertonic neonates with later pathologic startles. Some confusion has been engendered by the title of this first paper, which referred to hyperexplexia, whereas the proper Greek term is hyperekplexia (71). The consistent specific diagnostic sign of hyperekplexia is elicited by tapping the infant's nose (72). In a normal infant, nose-tapping produces a minimal response, whereas in affected children there is an obvious and reproducible startle response including head retraction. This startle may be induced over and over again. The diagnosis in sporadic cases in which the baby is stiff and tends to startle is not too difficult. More difficult is the situation in which the baby is not stiff but does have neonatal onset convulsions with severe syncope. These dramatic nonepileptic seizures may be induced by bathing but the nose-tap test is clearly positive. Also of diagnostic value is the EEG recording during a seizure. A series of what superficially may appear to be spikes appears on the EEG, but these are actually rapidly recurring muscle potentials from scalp muscle (synchronous potentials also are seen on the ECG channel) whose fire rate decreases *pari passu* with slowing of both EEG and ECG in the resultant severe syncope. The genetic basis for both the usual dominantly inherited variety of hyperekplexia and apparently sporadic cases is a defect in either the alpha(1) (73) or beta (74) subunits of the strychnine-sensitive glycine receptor. Whatever the variety, clonazepam remains the prophylaxis of choice (see also Chapter 13).

Familial Rectal Pain Syndrome

Although the curiously named familial rectal pain syndrome is without doubt very rare, we have had clinical contact with three families and made or seen ictal video-recordings of three children and one adult, supporting the suggestion that this unpleasant disorder is also underdiagnosed (75). Familial rectal pain syndrome is dominantly inherited, but apparently sporadic cases occur. The presenting feature is dramatic neonatal seizures. Schubert and Cracco (76) thought these might be epileptic seizures, in part because there was a favorable response to carbamazepine, but in our patients there was no independent suggestion of epilepsy, and no paroxysmal EEG discharges during many observed seizures. There were two important clues to the diagnosis. First, there were frequent striking harlequin color changes. In particular, one side of the face would turn red while the other side would turn white. Secondly, the precipitating factor for the seizures was some sort of perineal stimulation, such as wiping or cleaning. Actually the seizures appeared to be very severe syncopes, quite similar to those seen in neonatal hyperekplexia, with bradycardia and sometimes asystole, a slowing and then flattening of the EEG, and generally a life-threatening appearance. Eventually, these syncopes abated, but the adults with a similar neonatal history described continuing attacks of excruciating pain maximum in the nether regions, and precipitated by stimuli such as passing a constipated stool.

Other Syncopes and Presyncopes

All varieties of syncope and presyncope have certainly not yet been described. For example, a common variety of apparently life-threatening event consists of initial hypoxemia of entirely unexplained mechanism (77).

Psychological Disorders

Some of the disorders listed in this section may not be fundamentally different from some of the other disorders here described, particularly in the sections on vasovagal syncope and hyperventilation syncope above, but what are often called psychological mechanisms seem of more obvious importance here. A recent study (7) that looked at paroxysmal nonepileptic events (PEN) recorded on video-EEG in children and adolescents referred to a pediatric epilepsy monitoring unit found that psychological events predominated in each age group, overwhelmingly so in adolescence.

Daydreams

Episodes referred to as daydreams may be mistaken for epileptic or anoxic (syncopal) absences. There may be no fundamental difference from that described in the next subsection as gratification, but the subsequent conditions are more likely to lead to diagnostic difficulties.

Gratification (Including Infantile Masturbation) and Stereotypies

More or less pleasurable behavior, apparently similar to masturbation, may be seen from infancy onwards, more

so in preschool girls, but also in boys (78). Rhythmic hip flexion and adduction may be accompanied by a distant expression and perhaps somnolence thereafter. Manual stimulation of the genitalia does not seem necessary. The diagnosis of infantile masturbation is more difficult when the infant or young child seems unhappy during the rhythmic movements. The relative frequency of events and occurrence in specific circumstances, such as when bored or in a car seat, lends this behavior to home videotape recording. Parents prefer the term gratification (or even benign idiopathic infantile dyskinesia) to infantile masturbation, understandably. Readers are referred to Nechay et al (78) for an extensive clinical review.

Sometimes more difficult to diagnose may be the phenomenon in slightly older children, of the "television in the sky." Affected children may appear to stare into space or have unvocalized speech with imaginary individuals and perhaps seem to twitch or move one or more limbs for several minutes at a time. When there are repeated jerks or spasms, there may be confusion with epileptic infantile spasms.

Out-of-Body Experiences

In several situations children may describe experiences in which they appear to lose immediate contact with their bodies and perhaps see themselves from above. Such hallucinations have been described in epileptic seizures, anoxic seizures (20), migraine and as a "normal" phenomenon. Some of these perceptual disorders may be described as the "Alice in Wonderland phenomenon." Dissociated states have been well described by Mahowald and Schenck (79).

Panic or Anxiety Attacks

Panic attacks are well recognized in adults and criteria for their presence in children have been described and well reviewed (80). However, it is important to recognize that panic attacks may actually be manifestations of epileptic seizures (81–83). As the latter authors emphasis, long-term video-EEG monitoring may be necessary to establish the correct diagnosis and prevent inappropriate psychiatric interventions.

Conversion Disorder

Whether the term hysteria should be used is debated but self-induced nonepileptic, nonsyncopal seizures are not rare (7). Such episodes are called by various names, such as pseudoseizures, pseudoepileptic seizures, psychogenic nonepileptic seizures, nonepileptic attack disorder, or emotional attacks; none of these terms is satisfactory for every case. The sort of episodes described may crudely mimic epileptic seizures and have some resemblance to certain frontal lobe epileptic seizures but often have prominent sexual and aggressive components. They are usually recognized readily by observation and particularly by videotape observation and do not include alteration in background EEG. Some are predominantly swoons: a more or less graceful collapse without injury often into a recovery position, in some rhythmic jerking of the head, one or more limbs or trunk or pelvis predominates. In some cases incest, child sexual abuse, or other cause of posttraumatic stress disorder (PTSD) may be the etiology (84,85).

What has been called a "psychosomatic" syncope has been described in adults who collapse on head-up tilt with normal vital signs (86). This sort of response can be seen quite frequently in head-up tilt testing in children. One such child had been expelled from school because of frequent "fainting." Collapse occurred on head-up tilt without change in heart rate, blood pressure (continuously recorded by Finapres), or EEG. Simple psychotherapy was followed by prompt recovery. The differential diagnosis here includes hyperventilation syncope.

The child or teenager's insight may not be good or may fluctuate, and emotional attacks are well recognized in teenagers who also have epilepsy. The psychiatric literature has changed terms over the years (as can be seen by comparing successive versions of DSM), from hysteria to conversion hysteria to conversion disorders to dissociative states, without adding precision or clarity. A sociomedical model is useful for professionals: considering the illness "real," recognizing that it may be an inevitable response to a particular "predicament" (87,88), and allowing the patient to recover while saving face (89). We strongly recommend to readers a clear and modern view of hysteria (90).

Reassurance and encouragement, with or without simple behavioral techniques, will often work. However, in difficult cases psychiatric management should be available; even then, identification of underlying trauma or abuse is rare.

Autistic Spectrum Disorder

Because autistic children may not pay attention, they may find themselves at risk of EEG studies and a false diagnosis of epilepsy, especially if other paroxysmal phenomena such as parasomnias and syncopes coexist.

Fabricated Illness or Invention

In some families, seizures are not induced but are invented (63). This can be termed the passive form of Meadow's syndrome.

Case study #5. A preschool child was supposed to be having daily seizures. These were no longer observed after admission to the ward of a children's hospital. However, when the mother was then interviewed by an adult psychiatrist in another hospital, she affirmed that the seizures were continuing in the children's hospital with the same frequency as previously.

Derangements of the Sleep Process

While it is certain that all the funny turns that may occur in the daytime have not yet been properly described in the literature, it is even more likely that the disorders of the sleep process are by no means fully described. There are great intrinsic difficulties in readily determining what happens during sleep. Even ordinary visual observation may be difficult, whereas videorecording and even more so, polygraphic recording, may only be possible in exceptional cases, where episodes are very frequent. It is important to recognize that all parasomnias have not yet been described and to question carefully the origin of any episode that occurs only during sleep, even though some disorders previously thought to be parasomnias have now been found to be epileptic.

Sleep Disorders in General

The parasomnias and neurological disorders of sleep, such as narcolepsy, may be confused with epilepsy due to their paroxysmal nature. The difficulty in differentiating epileptic and nonepileptic events is compounded by the fact that paroxysmal nonepileptic sleep events are more common in children with epilepsy or learning disabilities than in the general childhood population (6). Sleep disorders remain a largely neglected and poorly understood area in pediatrics. However, with careful attention to the timing and semeiology of events and the use of video-EEG and nocturnal polysomnography, these conditions can be classified and distinguished from epileptic seizures (see also Chapter 16).

Parasomnias

A detailed history will distinguish most parasomnias from epileptic seizures. Parasomnias typically occur only once or twice a night. If events are occurring at a frequency of three or more times a night, the strong likelihood is that they are epileptic in nature, most likely arising from mesial or orbital frontal lobe structures. Epileptic seizures tend to occur more frequently in stage 2 sleep but may occur throughout sleep. In differentiating these events, video polysomnography is the most useful investigative tool.

Non-REM Partial Arousal Disorders, Arousal Parasomnias, Night Terrors

Brief nocturnal arousals are normal in children. They occur typically in stage 4 non-REM sleep, 1 to 2 hours after sleep onset. They vary from normal events such as mumbling, chewing, sitting up, and staring to arousals that can be thought of as abnormal because of the disruption they cause the family. These include calm and agitated sleepwalking, and a spectrum from confusional arousals to *night terrors* or *pavor nocturnus*. The child may exhibit automatic behavior, but the events are not truly stereotyped. The affected children may be very agitated and look frightened, as if they do not recognize their parents. They are in an intermediate stage between waking and sleep, so they may respond, but not normally. They look awake and may be partially responsive but in fact are still in deep slow-wave sleep (stage 4). These events typically only occur once a night, especially 1 or 2 hours after falling asleep and nearly always in the first half of sleep. Children have no memory for them. Often they are very prolonged. Typically the events last 10 to 15 minutes before the child either wakes, or settles back to restful sleep.

By contrast, nocturnal frontal lobe epileptic seizures typically last less than 2 minutes and often occur in clusters. The distinction between NREM arousal disorders and benign partial epilepsy with affective symptoms (BPEAS), (91) and a variety of idiopathic focal epilepsies like benign Rolandic epilepsy, can be more difficult. Children arouse and look similarly wild and combative. However, the epileptic seizures are, brief, may occur while awake, in sleep do not arise particularly from stage 4 sleep, and are more likely to occur towards the end of sleep, in the early morning.

NREM arousal disorders likely represent a disordered balance between the drive to wake and the drive to sleep. They are more common in toddlers who sleep very deeply, in children who are overtired because of insufficient sleep, and in those who are unwell or on certain medications. An increased drive to wake occurs if the child has an irregular sleep schedule, is unwell, or needs environmental associations to fall asleep normally. These disorders are therefore primarily managed by reassurance, explanation, and behavioral means to establish stable sleep routines and ensure good sleep hygiene. Home videotape recording is invaluable, particularly if the camera can be left running to capture the onset of the event. It is generally true that home videotape of nocturnal

events is more likely to be successful if they are nocturnal frontal lobe seizures rather than partial arousals due to the relative frequency and clustering of epileptic events.

REM Sleep Disorders

Nightmares and sleep paralysis are the principal REM sleep disorders that may be confused with epilepsy. They are both common. Ten to twenty percent of individuals have some experience of sleep paralysis. This is a frightening experience of paralysis when waking from REM sleep without abolishing the physiological REM atonia that prevents us from "acting out" our dreams. Nightmares are usually easier to distinguish from epileptic seizures than night terrors, as the child will have a memory of both waking and of the dream, and will then move into normal wakefulness rapidly. Nocturnal epileptic seizures rarely arise out of REM sleep. Behavioral management and treatment of any comorbid medical conditions are the appropriate treatment strategies. The onset of a REM behavior disorder may rarely be the first clinical sign of a brainstem lesion, and neuroimaging may be appropriate.

Sleep–Wake Transition Disorders

Rhythmic movement disorders such as nocturnal head banging *(jactatio capitis nocturna),* body rocking, and head rolling typically occur in infants and toddlers as they are trying to fall asleep. They can be present in deep sleep and in wakefulness. They are more common in children with learning disabilities. They typically remit by 5 years of age, but may persist into adult life. Management relies on good sleep hygiene and padding the headboard so the rest of the house is not wakened. Rhythmic movement disorders that are not clearly associated with the sleep–wake transition state respond less well to behavioral management techniques and (rarely) medications such as benzodiazepines may be helpful.

Benign Neonatal Sleep Myoclonus (BNSM)

The major importance of benign neonatal sleep myoclonus (92) is that it may be misdiagnosed as epilepsy and even treated with such heavy doses of antiepileptic medication that the neonate ends up in the intensive care unit on a ventilator (1). Recognition is easy for someone who has seen a videotape of the condition in which the baby has repetitive, usually rhythmic but possibly arrhythmic, jerks of one or more limbs only during sleep. In some instances, there is a report of the occasional jerk in the waking state but sometimes in very young infants it is difficult to tell whether the sleep state is actually present. A simple maneuvre to provoke BNSM has been described (93). These authors found that slow (1/second) rocking of the infant's crib in a head to toe direction would reproduce the myoclonus, which—in contrast to the situation in jitteriness—did not stop if the limbs were restrained. If there are still difficulties in the diagnosis, an EEG may have to be obtained during a period of jerking, either by prolonged recording or using the maneuvre just described. If using EEG, it is imperative to ensure that artifacts that result from the perhaps quite violent jerking are not misinterpreted as epileptic spike discharges, and collodion electrodes must be used (93). Although it is important for pediatricians or pediatric neurologists to have seen a videotape of as many of the various paroxysmal phenomena described in this chapter as possible, *it is absolutely essential for clinical staff to have seen the appearance of benign neonatal sleep myoclonus so that the misdiagnosis of epilepsy may be avoided.*

We suggest that every EEG department keep a videotape of benign neonatal sleep myoclonus so that it can be shown to worried parents whose well baby has inadvertently been referred for EEG. Technicians in our department have become skilled at recognizing these patients and will ask the neurologist to show the parents the video. This can be extremely reassuring and frequently produces what we term the *"That's it!"* phenomenon.

We mention BNSM in this chapter because 2-year-old children may present for epilepsy management, particularly if other paroxysmal events coexist, as in case study #6.

Case study #6. A 2-year-old girl was reported to have had twitching of the right hand for several weeks after the first day of life, sufficiently repetitive and vigorous to elicit treatment with phenytoin and phenobarbitone. Recent "generalized seizures" prompted referral by her pediatrician. When the mother was shown a videorecording of three other children displaying the repetitive generalized jerks of benign neonatal sleep myoclonus, she became excited and said "that's it!".

She had mentioned the right hand because it was often more obvious: the jerks had been violent, all over (four limbs) and lasting seconds. They had only been seen in sleep. The recent episodes were nonepileptic reflex syncopes (expiratory apnea or reflex asystole), but the double history had provoked the false diagnosis of secondary generalized epilepsy.

Sleep Starts

Vigevano's group (94) reported with videorecordings repetitive sleep starts in children who also had epilepsy and tetraplegic cerebral palsy. These jerks occurred repetitively at the onset of sleep, in clusters lasting several minutes, with arousal appearance on EEG but no jerk-related spike discharges. The authors emphasized the need to differentiate these sleep starts from epileptic seizures, particularly as the children also had epilepsy, so as to avoid excessive inappropriate antiepileptic medication.

Restless Legs Syndrome

We include this syndrome, though generally thought of as a condition of middle age, because it may present in childhood as an attention deficit disorder (95) and hence the possibility of misdiagnosis as absence epilepsy. Recognition is worthwhile as it tends to be exquisitely dopa sensitive (96). It is seen in children with leukemia, often as a consequence of chemotherapeutic agents, and in this situation may be responsive to benzodiazepines. In children with renal failure, it is important that iron deficiency is treated.

The Narcolepsy-Cataplexy Syndrome

Narcolepsy is a disorder characterized by excessive daytime sleepiness, cataplexy (a loss of tone in response to strong emotion, typically laughter), sleep paralysis, hypnagogic hallucinations, and disturbed nighttime sleep. A third of adults describe onset before 16 years of age, about 16% before 10 years, and around 4% less than 5 years (97). Deficiency of the neurotransmitter hypocretin (also known as orexin), produced in the hypothalamus, has recently been confirmed in human narcolepsy (98). Hypocretins help mediate arousal and project to brainstem structures involved in muscle tone. It is likely that narcolepsy is primarily an autoimmune neurological disorder due to damage to the hypocretin producing system in genetically susceptible individuals. Consciousness is maintained during cataplexy even though the eyes may be closed. Diagnostic confusion may arise if several attacks of cataplexy occur one after the other and then the individual falls asleep on the floor (99). Typically, the loss of tone spreads from the face down the body. The individual maintains a degree of control, so as they collapse this often appears to occur in a series of stages rather than a sudden fall. In a personal series of six children diagnosed with narcolepsy between 1997 and 2000, four had been given a diagnosis of epilepsy: either absences because of the excessive sleepiness, myoclonic drop attacks because of the cataplexy, or partial seizures because the cataplexy was asymmetric. One child had been treated with multiple antiepileptic medications. Diagnosis rests on the recognition of the five features of the syndrome, videorecording of cataplexy if possible and practicable, and the multiple sleep latency test, provided the child is 8 years or older (100).

Paroxysmal Movement Disorders

A complex relationship exists between epilepsy and movement disorders, the boundaries of which are difficult to define (101). They share many symptoms and are frequently confused with each other. Paroxysmal movement disorders are characterized by a variable duration of motor symptoms, usually with few if any interictal abnormalities on examination. Some children with "intermediate" exertion-related dystonia have subtle dystonia or signs of developmental dyspraxia, even on good days. The major distinguishing features between these events and epileptic seizures are the frequent presence of precipitating factors and the retention of consciousness in the paroxysmal dyskinesias and ataxias. These features may be more difficult to determine in childhood.

Historically, this group of disorders has been classified separately from the idiopathic epilepsies. Recent reports have emphasized the *co-occurrence of movement disorders and epilepsy* in the same family, thus suggesting that they both may have the same underlying mechanism (101–104). The recognition that dysfunction of ion channels leads to cellular hyperexcitability, and that mutations in these channel proteins may be associated with both epilepsy and movement disorders, may explain this relationship (105). A credible hypothesis is that mutant ion channels are expressed in variable degrees in different central nervous system (CNS) structures and that this expression may also vary with brain development. Thus, the phenotype of a genetic ion channelopathy may include partial epileptic seizures in infancy, indicating a cortical pathology, and an episodic ataxia in childhood and adolescence, suggesting cerebellar dysfunction. It is relevant to note that many antiepileptic medications are effective treatments for paroxysmal movement disorders.

The neurological CNS channelopathies comprise a large group of disorders, including epilepsy, migraine, movement disorders and hyperekplexia, which are characterized by their paroxysmal nature (106). Why the channelopathies are paroxysmal is not well understood but is likely to relate to the vast number of complex interacting influences on ion channel function (107). These include cell membrane voltage, pH, temperature, intracellular and extracellular ligands, phosphorylation of channel proteins, electrolyte status, and the relative expression of mutant and wild-

type subunits of the channel, which will vary over time.

Paroxysmal Dyskinesias

Various complex classifications have been proposed for this group of disorders [see Fahn (108) for a summary and a history of terminology]. The most clinically relevant and simplest is used here. Most of the literature describes familial cases, which are easier to diagnose (especially once one or more affected family members are known) and are possibly more interesting to report than sporadic cases. However, it is our clinical impression that most people with paroxysmal dyskinesias are sporadic, and many cases do not fit exactly into the classical descriptions outlined.

Paroxysmal kinesigenic dyskinesia (PKD). Typically, onset is in early childhood or adolescence with episodes of choreoathetosis, dystonia, or a mixed pattern. Attacks tend to become less frequent or remit totally in adult life. Attacks last seconds to 5 minutes and are precipitated by sudden movements, change in position, or change in movement velocity (109). Getting up from a chair or getting out of a car are frequent triggers. Consciousness is retained, and some individuals may have a brief nonspecific warning or aura prior to an attack. Interictal examination is normal. Diagnosis is based on history, and a videorecording of events is invaluable. Carbamazepine is often highly effective in small doses. A family history of similar events exists in about a quarter of patients, with autosomal dominant inheritance in many families. Linkage to several overlapping but distinct loci around the pericentromeric region of chromosome 16 has been reported but the genes involved have not been identified to date (110,111). In some families, the paroxysmal dyskinesia is associated with benign familial infantile convulsions (102,104). This has been reported as the infantile convulsions and choreoathetosis syndrome (ICCA). However, the movement disorder may include paroxysmal dystonia and is, therefore, better classified as a paroxysmal dyskinesia.

Paroxysmal non-kinesigenic dyskinesia (PNKD). Attacks are often longer in PNKD and may last 2 minutes to several hours or even 2 days. This type is sometimes referred to as paroxysmal dystonic choreoathetosis (PDC). The attacks are often markedly dystonic and occur spontaneously, although in adults alcohol, caffeine, and stress are frequent precipitants. Differentiation from epileptic seizures is easier and treatment with antiepileptic medications is less effective than in true epilepsies. Inheritance is usually autosomal dominant, and linkage has been reported to chromosome 2 (112,113).

Paroxysmal exercise induced dyskinesia (PED). Events occur after several minutes of exercise, usually 10 to 15 minutes or more, not at the initiation of movement, as in PKD (114). Typically, the part of the body that has been doing most exercise becomes dystonic. The abnormal movement resolves gradually with cessation of the exercise, over 5 to 30 minutes (intermediate between PKC and classical PDC). Antiepileptic medications are not generally helpful although acetazolamide has been effective in some families (114).

Benign paroxysmal torticollis in infancy (BPT). In BPT, infants have attacks of retro-, latero-, or torticollis that may last minutes to hours (115). In rare instances, they may last days. Typically, attacks begin in early infancy and remit by age 5. They may be triggered by movement, often in the early morning, and are heralded by irritability, pallor, vomiting, and in older children, clear ataxia. BPT is both a movement disorder and a migraine equivalent (116). Two patients with BPT in a recent series came from a family with familial hemiplegic migraine linked to a mutation in the voltage-gated calcium channel gene CACNA1A on chromosome 19 (117).

Benign paroxysmal tonic upgaze of childhood. Benign paroxysmal tonic upgaze of childhood (118) typically presents in infants of less than 3 months with prolonged periods (hours to days) of sustained or intermittent upgaze deviation. Later, ataxia is associated. The episodes remit with in a few years but are associated with psychomotor retardation or language delay in up to 80% of cases (119).

Episodic Ataxias

Episodic ataxia type 1 (EA1) is a rare disorder caused by mutations in the voltage-gated potassium channel Kv1.1. Affected individuals have brief episodes of cerebellar ataxia lasting seconds or minutes (120). Interictal myokymia, detected clinically or by demonstration of continuous motor unit activity on EMG, is the principal diagnostic feature. As well as this paroxysmal ataxia being confused with a partial epileptic seizure, there exists a real over-representation of epilepsy in families with EA1 (103,121). The potassium channel is expressed throughout the central and peripheral nervous system. Whether the phenotype comprises ataxia, myokymia (or neuromyotonia), or epilepsy or a combination of these seems to relate to the functional consequences of the mutation and its tissue-specific developmental expression (121).

Episodic ataxia type 2 (EA2) is less frequently mistaken for epilepsy because the attacks are longer (minutes to hours), and there may be interictal cerebellar signs including eye movement control impairments. This disorder is associated with mutations in the voltage-gated calcium channel gene CACNA1A located on chromosome 19 (122). It is allelic with familial hemiplegic migraine and spinocerebellar ataxia type 6. In their pure forms, these are distinct disorders but overlap syndromes do occur. Partial seizures have been documented in familial hemiplegic migraine families, and there is a case report of a child with a de novo truncating mutation in CACNA1A who has EA2 and absence epilepsy (123,124).

Migraine and Disorders Possibly Related to Migraine

Some authors regard migraine with aura as an important differential in the diagnosis of epilepsy (125). A number of conditions exist, ranging from undoubtedly varieties of definite migraine through migraine equivalents, probably having a migrainous origin to conditions in which the migraine link is more tenuous. On the whole, the more classical the migraine picture, the easier the diagnosis.

Familial Hemiplegic Migraine

Insofar as virtually all attacks of familial hemiplegic migraine (FHM) are associated with headache and a family history of hemiplegic migraine (126), the differential diagnosis normally should not be difficult.

Benign Paroxysmal Vertigo of Childhood

This is the most common of the migraine equivalents (116). Although affected preschool children are often referred to as having epilepsy, the characteristic history of anxious arrest of movement without loss of awareness and subjective vertigo or "drunking" makes the diagnosis easy. A related migraine equivalent, benign paroxysmal torticollis of infancy, has been discussed under Paroxysmal Disorders of Movement.

Case study #7. A 2-year-old girl had a 6-month history of episodes in which she had been dizzy, unsteady, and pale. There was no definite precipitation. She would say "Oh mummy dizzy dizzy dizzy" or "fright" and stand and cling onto her mother. At the same time something happened to her eyes. Her mother could not mime the speed of the eye movements, but recognized them as nystagmus after the child had been spun in a rotating chair (an alternative trigger would have been to elicit optokinetic nystagmus with a tape measure or drum).

Benign Nocturnal Alternating Hemiplegia of Childhood

Although perhaps even more rare than the better known alternating hemiplegia described in the next section, benign nocturnal alternating hemiplegia of childhood is more probably migraine related (127). Neurodevelopmentally normal young children experience recurrent attacks of hemiplegia arising from sleep. Attacks begin at about age 2 years and the course is benign.

Alternating Hemiplegia

The paroxysmal features and neurology of alternating hemiplegia of childhood are remarkable and fascinating. In their original report, Verret and Steele (128) described eight cases from the Hospital for Sick Children, Toronto; they regarded the condition as infantile onset complicated migraine. Casaer (129) only managed to include twelve cases in a multicenter European flunarizine trial. Since then, ten patients were reported from Montreal (130), a further twenty-two patients from Aicardi's group in Paris (131), and most recently forty-four patients from Boston (132). These and other figures suggest that the condition has in the past been both underdiagnosed and underreported.

The general features are well known to all pediatric neurologists, with attacks of flaccid hemiplegia on one or both sides, beginning in the first 18 months of life. This is associated with autonomic phenomena and the gradual appearance of developmental delay unsteadiness and a degree of choreoathetosis. Actually, paroxysmal hemiplegia is not the first symptom and usually the first hemiplegic attack is not noticed until after the age of 6 months or considerably later. The initial manifestations begin before the age of 6 months, often in the neonatal period. The earliest manifestation is commonly a disorder of eye movements, in particular nystagmus and strabismus. The nystagmus is paroxysmal and frequently unilateral. The strabismus may be paroxysmal also, and associated with signs of transitory internuclear ophthalmoplegia (133). Tonic and dystonic episodes also appear early in infancy, well before the first hemiplegic attack. These consist of predominantly brief and perhaps clustered tonic attacks that may be easily be mistaken for epileptic tonic seizures. These stiffenings are commonly unilateral, with some resemblance to the asymmetric tonic neck reflex, which may also be bilateral, with a degree of opisthotonus and updeviation of the eyes. Pallor and crying or screaming and general misery tend to accompany these attacks.

Once hemiplegic episodes begin they may affect one or both sides [or even one upper limb and a contralateral lower limb as in case 3 of Casaer (129)]. Bilat-

eral hemiplegia is associated particularly with autonomic phenomena and drooling.

Some sort of trigger precedes attacks in most affected children. Emotional factors—excitement, bright lights, and bathing, including hot baths—are reported. The frequency of bathing as a trigger (in the bathroom, not in the sea) is probably underreported—in one family [case 3, Casaer, (129)] this regular trigger was not recognized until the child was 15 years old.

Developmental delay, ataxia, and persistent choreoathetosis develop in the majority of children, and a few develop migraine with aura (case 3, Casaer [129]; Silver and Andermann [130]).

Miscellaneous Neurologic Events

Many paroxysmal disorders or episodic phenomena can be described as of neurologic origin, and these may be mistaken for epileptic seizures. Some more or less well-recognized examples are briefly described. It is not possible to give a complete picture—many types of events, fits, attacks, turns, or spells have surely yet to be described.

Tics

Tics, whether simple, complex, or as part of Tourette syndrome, do not usually pose diagnostic difficulty. However, if tics are frequent, as they usually are, the alternative diagnosis of an epileptic origin may be determined by recording an EEG during the tic, preferably with simultaneous videorecording.

Myoclonus

Nonepileptic myoclonus occurs in many situations. If there is difficulty in diagnosis, EEG will determine whether the myoclonus is epileptic or not. The EEG (preferably with surface electromyography (EMG) and videorecording simultaneously) will show obvious spike discharges during epileptic myoclonus. Mention should be made of the myoclonus–dystonia syndrome, if only to remark on the unexpected finding of mutations in the gene for ε-sarcoglycan (134,135).

Cataplexy in Neurological Disorders

Cataplexy in the narcolepsy–cataplexy syndrome was discussed in Derangements of the Sleep Process. Cataplexy is very rarely associated with acquired brain stem lesions. Cataplexy may be seen in Niemann-Pick type C, Norrie disease, the Prader-Willi Syndrome (136), and as an isolated familial trait. Recognition is based on the identification of emotional triggers, especially laughter, to the sudden loss of muscle tone. A cataplexy-like disorder is seen in the Coffin-Lowry syndrome (137) and described in the next section.

Cataplexy and Other Falls in Coffin-Lowry Syndrome

Early reports suggested that epilepsy was a feature of the X-linked but female manifesting Coffin-Lowry syndrome (CLS). Later publications (137) suggested that those with CLS did not have epilepsy but probably a cataplexy-like disorder triggered by the startle effect of unexpected sounds. Since then, others have recognized that reflex stiffenings may also occur (138,139) and even true epilepsy (140).

Case study #8. A girl with CLS but with considerably spared language ability began to have sudden collapses resembling cataplexy when she was about 7 years old. It became clear that an unexpected sound was the usual stimulus. In adulthood, the shutting of a door might only induce "cataplexy," but louder and more startling sounds also induced stiffening, sometimes prolonged. Apparently true cataplexy while telling a joke was videotaped. She also began to have nocturnal epileptic seizures without any obvious trigger.

Nonepileptic Head-Drops

Nonepileptic head drops are characterized by there being no difference in the speed of the initial flexion of the neck and the subsequent extension (141). These authors found that repetitive head-nods, which they described as bobs (in which the velocity of recovery matched that of descent) and in which the episodes were repeated (bobbing), were a consistent feature of nonepileptic head-drops. Defining epileptic nods as those accompanied by epileptic scalp EEG discharges, they found that head-bobbing did not occur as an epileptic phenomenon.

Head Tremor

Childhood head tremor (142) is unlikely to be confused with epilepsy. It is possible that the condition is heterogeneous.

Functional Blinking

Functional blinking (143) should perhaps be in the psychogenic section: it is a differential diagnosis of the epileptic syndrome of eyelid myoclonia with absences. However, it is not associated with EEG discharges. Drug treatment may abolish the absence seizures and pho-

toparoxysmal response in patients with eyelid myoclonia with absences who may then continue to have tic-like eyelid myoclonia, with or without being consciously aware of the blinking (144).

Craniocervical Junction Disorders—Chiari Type 1

Disorders of the craniocervical junction, particularly congenital disorders such as type 1 Chiari malformation, may be responsible for apparent syncopes that are distinctive in not being associated with EEG or ECG change. Clues are stimuli, such as coughing, which would be expected to increase downward brain herniation. Definitive diagnosis is by sagittal brain MRI.

Raised Intracranial Pressure Attacks

Pyogenic meningitis must be mentioned here because the tonic or vibratory nonepileptic seizures that accompany brain swelling (as in *Hemophilus influenzae* meningitis) were often misdiagnosed as epilepsy and treated with repeated injections of diazepam with disastrous results [e.g., (1), case 15.46]. Although immunization should now prevent serious hemophilus infections, the situation of brain swelling and herniation is by no means confined to this disorder and can be seen with any acute rise in intracranial pressure, as with intracranial hemorrhage or decompensated hydrocephalus.

Tetany

Aside from metabolic derangements in which the diagnosis is obvious, tetany is most often seen with hyperventilation—see vasovagal syncope, hyperventilation syncope, panic and anxiety attacks. In hypoparathyroidism, it is more usual to have some form of epileptic seizure than tetany.

Sandifer Syndrome

Intermittent contortions of the neck with marked lateral flexion are occasionally seen with severe gastroesophageal reflux, either in normal or in neurologically impaired children (145).

Tonic Reflex Seizures in Early Infancy

A recent publication (146) has highlighted the occurrence of a new form of nonepileptic seizure in the first 3 months of life. Episodes of sudden stiffening occurred in wakefulness in otherwise normal children and were almost exclusively precipitated by holding the infant upright in a vertical posture. The stiffening lasted for a few seconds and was accompanied by apnea and cyanosis, often followed by crying. Whether this is completely different from the awake apnea of gastroesophageal reflux (61) is unclear.

Benign Nonepileptic Infantile Spasms, Benign Myoclonus of Early Infancy and Shuddering

We conclude this section on Miscellaneous Neurologic Events with a disorder that is most important in the differential diagnosis of epileptic infantile spasms. We were tempted to have placed it in Psychological Disorders next to Gratification (Including Infantile Masturbation) and Stereotypies, but as we shall see there are hints that it may sometimes be a marker of deviant nervous system development, albeit to a very mild degree.

In the first description (147) and in the most recent publications (148, 149) this has been called "benign myoclonus of early infancy", but we agree with Charlotte Dravet and her colleagues (150) that a much better term is "benign nonepileptic infantile spasms". This is because the repetitive axial and limb muscle contractions last longer than myoclonus and are easily misdiagnosed as epileptic infantile spasms (149). The distinction is that in benign nonepileptic infantile spasms the EEG is normal not only interictally, but during the runs of spasms as well.

Shuddering attacks (151) have been regarded by some authors as a separate condition that may sometimes be an early manifestation of essential tremor (152), but we agree with Kanazawa (153) that shuddering attacks and benign myoclonus of early infancy and benign nonepileptic infantile spasms are all the same thing. A difficulty may be that most physicians have not seen such video recordings which have only rarely been published (148). A case study (case study 9) illustrates the emotional harm that may be done by a precipitate diagnosis of epileptic infantile spasms or West syndrome.

Case study #9. An otherwise normal male infant was referred to the authors' institution at the age of 6 months, with a 1 month history of daily episodes now increasing in frequency. Now three to four times daily he would have a series of clusters of spasmodic extensions of the upper limbs with flexion of his neck and stiffening of his lower limbs. During these runs of spasms he would seem unresponsive although his eyes were open with some upward deviation of the globes. His pediatrician witnessed an episode of serial spasms and thought the appearance typical of infantile spasms (as did renowned paediatric neurologists and epileptologists when video record-

ings were shown at international meetings in due course). West syndrome was discussed with the parents, who formed the impression that their baby's chance of eventual normal intellect was no more than 10% and were much distressed.

It was notable on detailed questioning that episodes initially occurred only when he was in his high-chair at feeding time, and later when the boy was in his car seat, sitting in a shopping trolley, or sitting on the floor. By the time of his referral to us these serial spasms occurred during every meal, at breakfast, lunch, tea, and dinner. They were never seen when he was lying in bed or standing up. His mother felt that she could prevent or stop the episodes by clapping or talking to him. She thought they were more likely if he was exhausted or exasperated or if his food did not come in time.

Video recording of episodes in his high-chair showed repeated bowing of his head with eyes up, upper limbs outstretched with fists clenched, and lower limbs rigid. The run of spasms ceased when he was given a biscuit and he smiled. Simultaneous EEG showed no ictal complexes, and interictal EEG was also normal.

Episodes gradually lessened and ceased spontaneously at the age of 13 months. Now a schoolboy of 10 years, he has no problems at all. There is no family history of essential tremor.

Of course epileptic infantile spasms may occur in the context of normal development, but the clue to the correct diagnosis of nonepileptic infantile spasms lay in the setting and provocation. Episodes in the high-chair and in the car seat closely resemble the history in cases of infantile masturbation (78) and suggest a similar behavioural mechanism, and not a precursor of essential tremor. Such subtleties add to the richness of the Child Neurologist's work, with no prospect of closure in the foreseeable future.

Anoxic-Epileptic Seizures

In the past 40 years, those who have paid close attention to the mechanisms of seizures have recognized that the common motor seizure that is a manifestation of severe convulsive syncope is a nonepileptic seizure, the so-called anoxic seizure (see Syncopes and Anoxic Seizures). Many comments in the literature suggest that it is "common knowledge" that severe anoxia produces epileptic convulsions, or even specifically tonic-clonic epileptic seizures, but, in fact, such remarks have until recently been based on a misinterpretation of the data. Indeed, there is no published, well-documented instance of a generalized tonic-clonic epileptic seizure, as currently defined, ever having been an immediate sequel of acute anoxia, either asphyxial or ischemic. Nonetheless, true epileptic seizures as an immediate consequence of syncope have now been properly described and recorded (1,57,154). We call this phenomenon of a syncope followed by an epileptic seizure an anoxic-epileptic seizure (AES).

Nature of the Syncope

Most of those reported with AES were infants or young children who also had a history of reflex syncopes without an epileptic component. Most of these syncopes were reflex anoxic seizures, with reflex asystolic syncope or reflex expiratory apnea (cyanotic breath-holding spells), or syncopes which, from the description, might have been mixed breath-holding. Compulsive Valsalva maneuvers were also responsible (56).

Nature of the Epileptic Component

To date, the reported induced epileptic seizures have been predominantly clonic or absence in type. Status epilepticus (155) is either common or a stimulus to the medical attendants to write a paper!

CONCLUSION

The differential diagnosis of epilepsy in children—from the very young to the maturing adolescent—may be difficult, but rarely is it impossible. It demands two processes: the art of history taking, and the intellectual process of diagnosis.

The history comes from an intense direct communication between pediatrician or child neurologist and child, caregivers, or witnesses. If the parents were not there at the time of an event, don't forget the school teachers. From whoever it is gleaned, the precise, detailed, consecutive, all-embracing history remains paramount. If in doubt, have someone at home, school, or outdoor activity capture an event on videotape. If that does not succeed, a useful addition to the history-gathering processes is the method of showing video-recordings of different epileptic and nonepileptic events to parents to discover which, if any, resemble their own child's attacks—the "that's it!" phenomenon.

Although the intellectual process of diagnosis normally integrates all the clinical information from history and examination with the laboratory tests, in the case of paroxysmal events, the history often stands alone. The intellectual process is then to pull together the threads of the history and weigh the probability of epileptic phenomena versus the probability of nonepileptic phenomena in the knowledge that, in total, the latter are more common than epileptic seizures and at least as diverse as the epilep-

tic events that they imitate. Not only that, but it may be more dangerous for the physician and the patient to miss the diagnosis of a syncope from a cardiac conduction defect than to miss a diagnosis of an early epilepsy.

Even when a diagnosis of epilepsy has seemed secure for many years, still be prepared to question not only the type of epilepsy or epileptic syndrome, but whether it is really epilepsy after all. As we have shown, this applies even when the original diagnosis of epilepsy was certain. Beware writing or even thinking "known epileptic" (156). To quote Stephenson (1) "'known epileptic' means nothing of the kind. Either it is not epilepsy, or the epilepsy is insufficiently understood—otherwise, why the consultation?" May the development of your understanding never cease.

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8 Paroxysmal Disturbances Resembling Seizures in the Elderly

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The diagnosis of paroxysmal events in the elderly presents particular difficulties, especially when contrasted with the problem presented by younger patients. In the first instance, the history is often difficult to obtain, vague, or not available at all. A second problem, common in the elderly, is the coexistence of multiple medical and/or neurological problems that complicate the analysis of intercurrent paroxysmal symptoms. A third factor involves the confounding results of diagnostic studies, for example, electroencephalographic (EEG) findings or the results of studies of the cerebrovascular system that either may help to elucidate an obscure event or series of events, or serve to obfuscate diagnosis.

Perhaps the best way to approach the diagnostic dilemma is to understand the general characteristics of epileptic seizures in the elderly population, and then draw a contrast with the presenting symptoms in a particular case. The most common type of epileptic seizure in the aged is the complex partial (CPS)—up to 40% of those presenting with new onset seizures (1). In some cases, the CPS is typical in its characteristics. That is, it begins with a motionless stare, followed by a period of automatisms. There is postictal confusion and perhaps reactive automatisms during the postictal state. These events are relatively easy to recognize and are usually not confused with other conditions. By contrast, the CPS often does not conform to this progression of symptoms. A period of unresponsiveness or clouded consciousness, without obvious motor activity, is common. Such events are usually short-lived, lasting perhaps minutes. A postseizure confusional state follows but may not be profound. The patient may be, and usually is, unaware of having such seizures and, indeed, may be hard to convince when the diagnosis is suggested. Table 8.1 list those imitators of epilepsy frequently occurring in the elderly population.

THE AGED PERSON FOUND UNCONSCIOUSNESS ON THE FLOOR

A common problem in the aged is an episode of unconsciousness for which there are no historical details. Typical is the person found on the floor, say beside the bed or in the bathroom. Upon discovery, there is no motor activity or other features suggestive of an epileptic attack. Usually the duration of unconsciousness is unknown, although it may be suspected, based on such factors as when the person was last seen, when there was no answer to the telephone, or when the person was known to arise in the morning. The person may be recovering when found, may or may not be confused,

TABLE 8.1

Imitator of Epilepsy	Epilepsy
Convulsive syncope	
Light-headed warning, brief LOC without achieving horizontal position, a few brief convulsive movements,little or no postictal confusion	If there is a warning, likely to be RES; LOC 1–2 min. with generalized convulsive movements, tongue bite (sometimes), postictal confusion that may be prolonged.
Memory disturbances	
Simple forgetfulness; continual memory loss without obvious fluctuation	Fluctuating memory loss; restricted duration; stereotyped; may not be aware of the occurrences
Dizziness	
Nonspecific term, may be "lightheadedness" or even vertigo; no alteration of awareness	Vertigo may be a manifestation of a seizure, followed by clouded consciousness or confusion; stereotyped events
Transient ischemic attacks	
Transient hemiparesis or hemisensory loss; may be manifested by aphasia; minutes to hours	Hemiparesis/hemisensory loss rare as epileptic manifest; aphasic seizures are described; differentiation from TIA may be difficult; EEG or video-EEG monitoring studies are required (in addition to vascular studies)
Transient global amnesia	
Memory registration intact; failure of second stage memory, able to respond and carry out complex acts;repeated questioning; duration: hours; sometimes confused with CPS	CPS duration 1–2 minutes on average; automatisms; altered awareness; often a warning (e.g., RES); postictal confusional state that may be prolonged; EEG likely to be to be abnormal with epileptiform discharges
Metabolic encephalopathies	
Altered mental status: confusion, lethargy; coma; may fluctuate; myoclonic jerks (multifocal); epileptic seizures may occur; abnormal laboratory studies; may be typical EEG findings such as triphasic waves	Nonconvulsive status epilepticus may have similar clinical manifestations; fluctuations in mental status may be more evident; seen in multisystem disease, benzodiazepine or psychotropic drug withdrawal, as a sequel to generalized epileptic seizures. EEG: generalized epileptiform activity; responds to antiepileptic drugs such as benzodiazepines (and others)

RES: rising epigastric sensation; LOC loss of consciousness; CPS: complex partial seizure

and usually has no memory of the event. Any possible premonitory symptoms may not be remembered.

In these cases, the examination may offer substantial clues. For example, is there evidence of bruising or other injury? Is there evidence of breakdown of the skin? Are there signs of fracture? Is there an apparent head injury? Could the patient have had a syncopal attack and struck his head, thus accounting for the unresponsiveness? Was she hypoglycemic? On neurological examination, there may be no focal or lateralizing findings. Conversely, there may be neurologic signs pointing to a focal brain lesion, such as a new CVA. These are only a few of the possible factors that might suggest an etiology. Clearly, a complete medical and neurological evaluation is indicated. The problem is that investigations may be unrevealing, equivocal or, as is commonly the case, reveal several concurrent abnormalities, say cardiovascular, metabolic, and neurologic.

An obvious consideration is an epileptic seizure, even though there may be no history of seizures. New onset seizures are quite common in the elderly, the majority being secondary to cerebrovascular disease including acute stroke, silent stroke, and diffuse small vessel disease (2,3). In cases without history or observation, a definitive diagnosis may be impossible. Many will rely on the EEG, which should be performed in all such cases. Discovery of a spike focus or other paroxysmal phenomena may tilt the balance toward seizure occurrence. When such are absent, however, a diligent search for another etiology is mandatory. Unfortunately, when all studies are unrevealing, the clinician may be forced to observe the patient, or treat empiri-

cally with an antiepileptic drug—not an ideal choice but one often selected.

BLACKOUT SPELLS

We frequently encounter this nonspecific complaint, and it is always difficult to unravel. The patient usually means episodes of unawareness or lack of any memory for a time. The differential diagnosis obviously must include seizures, most particularly CPS, for which the patient has no memory. The EEG may aid in making the diagnosis if there is no available history from a family member or other reliable observer. If the EEG is unrevealing, the diagnostic problem remains. Other considerations include transient global amnesia (TGA) and transient ischemic attacks (TIAs) involving the posterior circulation. One should bear in mind the possibility of alcohol or drug use. Alcoholism is more common in the elderly than usually recognized, and drug use is not rare (4,5). The elderly brain is ill-equipped to cope with the effects of substance abuse, and episodic loss of memory would be expected. Although the patient may be reluctant to reveal his use of these substances, the physician should be aware of this possibility and specifically take an alcohol and drug history.

DROP ATTACKS

Drop attacks have always presented difficulties in diagnosis, and there still is no unanimity concerning their cause (6). Such attacks are truly frightening in that the patient, usually in later years, suddenly drops to the floor without warning. The person usually is able to arise very soon after the fall and commonly denies loss of consciousness. There may or may not be a brief postevent confusional state. A common school of thought ascribes the attacks to basilar-vertebral insufficiency; that is, an acute decline in blood flow to the posterior circulation. In this formulation, the ischemia disables the reticular activating system as well as the motor system. Thus, the patient falls suddenly. Evaluation includes studies of the posterior circulation, including transcranial Dopplers, and of the cardiovascular system. Whereas arteriosclerotic disease of the vessels may be found, it may seem insufficient to explain the symptoms. Such patients may suffer from intermittent arrhythmias or even Stokes-Adams attacks, resulting in acute ischemia. In these instances, EEG studies would not contain epileptiform discharges. With these factors in mind, one may consider whether drop attacks can be epileptic in origin. The answer is yes, although an epileptic seizure characterized solely by a sudden fall with no postictal phase would be unusual. The entity known as *temporal lobe syncope* is characterized by sudden falls without significant motor activity. There is a following confusional state, suggesting an epileptic origin. The diagnosis becomes more evident if a past history of typical CPS is obtained. The EEG is likely to show a temporal lobe abnormality, supporting the diagnosis. If the EEG is unrevealing, or if the typical history is not available, the events are more likely to be ischemic in origin.

SYNCOPE

There is a tendency for non-neurologists to diagnose syncope in elderly patients who have episodes of unconsciousness. Syncope is a condition with a constellation of symptoms that differentiate it from epilepsy. Well known is the premonitory symptom of "light headedness," variously described as blood draining from the head or wooziness. The patient rapidly loses consciousness and falls to the ground. The duration of unawareness is brief, with adequate cerebral circulation being established rapidly in the horizontal position. Postsyncopal confusion is brief or absent. These features discriminate syncope from epilepsy. Note, however, that syncope is sometimes accompanied by brief clonic movements or tonic posturing—*convulsive syncope* (7). Convulsive syncope is more likely to appear if, when the patient faints, the patient remains relatively upright, for example when a faint occurs in an easy chair, or when someone nearby attempts to prevent the patient from falling. Despite the motor activity, convulsive syncope retains the other features of the uncomplicated condition. Note that patients with syncope do not have epileptiform EEG findings. The evaluation must include a detailed cardiovascular work up as well as an evaluation of the patient's medications (8,9) (see also Chapter 17).

MEMORY DISTURBANCES

Memory disturbances, especially when intermittent, present a truly vexing problem. As any neurologist or epileptologist knows, memory difficulties are one of the most frequent complaints in the consulting room. Of course, the nature of the memory complaint is key to a working diagnosis. Simply forgetting where one last placed a set of keys, or forgetting to add a loaf of bread to a shopping list, does not raise much suspicion of an ictal event. On the other hand, not recalling how one got to the parking lot from the store, perhaps a period of several minutes, or passing one's subway stop without recall, certainly would raise the question of an ictal event. Such lapses may occur without any evidence of organic disease, and only detailed neurological investigation will provide the answer.

A related episodic disturbance is the occurrence of staring spells. Yes, people stare frequently. If one

observes such staring, particularly when devoid of motor activity, it is impossible to know what is happening in the brain of such a person. Daydreaming? In thought? Tuned out? It is important to understand that epileptic seizures in the elderly not infrequently are characterized by motionless staring. The patient usually is completely unaware of being "absent," and if confronted will vigorously deny it. The key to diagnosis is stereotypy—that is, the recurrent events are similar in duration. A good observer might see some minor automatisms, less evident than in typical CPS. Again, the EEG may provide diagnostic support for CPS, and if it does, any abnormality will be focal or lateralized. If the EEG is unrevealing or nonspecific, the clinician may institute treatment on the basis of the clinical picture. Bear in mind that few neurologic conditions produce stereotyped symptoms of this type, and a diagnosis of epileptic seizures is likely.

DEMENTIA

The elderly patient with dementia presents particular and often confounding problems when it comes to episodic symptoms resembling seizures. As anyone knows who has experience with patients in nursing home care units, those with dementia exhibit many intermittent behaviors such as staring, apparent orofacial and other automatisms, temper outbursts, wandering, fluctuating confusion, and memory lapses, to name a few. All these phenomena could well be ictal events, and all could simply be related to the dementing process. Unfortunately, many nursing home facilities have a relatively limited number of visits by physicians, who generally spend limited time with individual patients and who may have limited neurologic experience. It is probable that epileptic seizures would not be a consideration to explain the episodic behaviors mentioned above. In a study of patients in three nursing homes who were receiving antiepileptic drugs, it was found that EEGs were seldom ordered (10). In fact, few EEG reports were available in the records. The answer to this diagnostic dilemma lies in an educational process to raise awareness of the possibility that some patients may suffer from seizures in a setting of dementia. More liberal use of neurologic consultations and EEG studies could result in appropriate treatment and improved quality of life for many.

DIZZINESS

This is one of the most common complaints the neurologist encounters. The problem is that there is no uniform definition of the term. In fact, each patient has his or her own experiences that lead to a complaint of dizziness. The most obvious and understandable type of dizziness is true vertigo, meaning a sudden feeling of rotation or displacement in space. True vertigo can be a manifestation of CPS, but in this setting it rarely is an isolated symptom. Nonetheless, the evaluation of a patient with true vertigo should include an EEG. More difficult to interpret are other forms of dizziness such as light-headedness, or a vague feeling in the head that the patient cannot describe. Such complaints are difficult to evaluate. Close inquiry may reveal that the patient is not "clear" with his or her thoughts, or feels a little confused. Again, the problem is determining whether the complaints are episodic or continual. In episodic cases, epileptic seizure activity is a distinct possibility. Again, one of the major problems in assessment is establishing whether there is an episodic or stereotyped pattern of symptoms. In a setting of dementia, this may be difficult. In any event, evaluation including EEG studies is indicated.

TRANSIENT ISCHEMIC ATTACKS

Transient ischemic attacks (TIAs) are sometimes confused with epilepsy, although the two conditions are quite distinct with respect to their clinical features. The transient occurrence of hemiparesis or hemisensory loss (numbness, deadness) is well known. Such negative symptoms, although not unknown, are rare manifestations of epileptic seizures. Somewhat more problematic is the transient occurrence of dysphasia or aphasia. While more likely to be a TIA than a seizure, aphasic seizures are well known (11). Generally speaking, ictal aphasia is progressive, developing over time from dysnomia or hesitancy of speech, through paraphasic errors, and culminating in a global aphasia. This process may take several minutes or even more. When the EEG discharges subside, progressive improvement occurs. Aphasia resulting from a TIA, whether complete or incomplete, tends to occur suddenly and, after a time, resolves more quickly. These features are admittedly generalizations but they can provide clues as to the true nature of the disturbance. The evaluation of episodic aphasia must include cerebrovascular studies and an EEG. If event frequency permits, video-EEG monitoring should be carried out in an attempt to record the clinical and electrographic features of the language disturbance.

TRANSIENT GLOBAL AMNESIA

Transient global amnesia (TGA) is a condition characterized by the abrupt onset of memory loss, usually in older persons. The patient is awake and able to carry out many normal activities. Memory registration

appears to be intact, thus allowing the patient to converse or carry out relatively complex acts. Such patients typically are confused to some degree and typically ask questions repeatedly such as "where are we now, where are we going?" and the like. In the past, an attack of TGA was thought to be a once-in-a-lifetime event lasting 24 hours (12). Subsequent experience has shown that multiple events may occur, and that the average duration is considerably shorter, on the order of 9 to 11 hours (13).

Over the years, the cause of TGA has been the subject of controversy. Originally thought to be epileptic in nature, this turned out not to be the case. The EEG is normal, or at least contains no epileptiform activity. In fact, an EEG recording during an attack of TGA demonstrated a normal background with no paroxysmal discharges. It is likely that most attacks of TGA are due to ischemia involving both temporal lobes. TGA has also been described in younger patients without evidence of cerebrovascular disease. In these cases a mechanism similar to migraine has been proposed (14).

The differential diagnosis of TGA includes CPS. Whereas the duration of TGA would appear to be inconsistent with CPS, the elderly often have prolonged postictal states following a brief seizure. If the seizure itself is unobserved, the postseizure confusional state with memory loss may mimic TGA. A thorough evaluation including EEG studies should settle the issue. Although not usually possible, an EEG performed while the patient is symptomatic would provide support for the true diagnosis (see also Chapter 17).

TREMOR AND CLONUS

One might think that patients with tremor or clonus would not qualify as those with paroxysmal disturbances resembling epilepsy. From time to time, however, we receive an EEG request with a brief history such as "patient with intermittent tremors, rule out seizures." Such patients usually have parkinsonism with intermittent rhythmic tremor at about 4 to 6 Hz. The EEG is devoid of epileptiform activity, but tremor artifact may be prominent, either unilateral or in the occipital regions due to transmission of the tremor to the head. Although the artifact may superficially resemble epileptiform activity, the lack of a potential field and correlation with recording from an EMG electrode will confirm the diagnosis.

In cases of referral for rhythmic motor activity due to clonus, a neurologist (who would immediately recognize the condition) usually has not seen the patient. Our technologists make the diagnosis by observation, and the EEG is nonepileptiform.

MYOCLONIC JERKS

Myoclonic jerks present difficulty in diagnosis, especially when associated with an altered mental status. In many cases, the cause is fairly clear: for example, patients with renal failure who develop multifocal myoclonic jerks. This motor activity is not epileptic in nature and reflects the metabolic encephalopathy. The clinical picture may be complicated if the patient develops a seizure. In these cases, the myoclonus may well be regarded as part of an epileptic diathesis. Seizures are not particularly unusual in metabolic encephalopathies. Moreover, the EEG may reveal some multifocal sharp waves, thus further compounding the diagnostic dilemma. These patients do not have epilepsy, and the seizure and/or the myoclonic jerks are secondary to the metabolic derangement. Nonetheless, they often are treated with antiepileptic drugs. If so, the treatment should not be continued after the patient has stabilized.

TOXIC-METABOLIC ENCEPHALOPATHIES

Although it may appear that a metabolic encephalopathy in the aged would present no diagnostic difficulties, the opposite is the case. Hepatic, renal, and electrolyte disturbances are common, as are sepsis and drug intoxications. In all these cases, the patient may present with altered mental status including confusion, disorientation, lethargy, and even coma. The changes in mental status may be continuous or discontinuous; in fact, intermittent confusion is common. For example, in cases of hepatic or renal encephalopathies, such patients are usually well known to suffer from renal or hepatic disease. Thus, when they present with increasing confusion, the assumption is that the known medical condition is the cause. Routine laboratory studies may reveal an increase in BUN/creatinine or deranged liver function tests. Conversely, there may be little change in the numbers from previous known levels. In the latter case, one may question whether another cause for mental status fluctuations exists. Here the EEG may offer important diagnostic information. Typical EEG findings are present in metabolic encephalopathy, such as background disorganization, diffuse slowing and, importantly, triphasic waves (15,16). Although triphasic waves are typical in hepatic encephalopathy, they are also found in renal and other metabolic disturbances. However, the EEG may reveal continuous or discontinuous epileptiform activity, suggesting strongly that CPS is responsible for the patient's presenting symptoms.

With respect to other systemic diseases—sepsis is a good example—the patient often presents with lethargy and confusion due to the toxic effects of the infection.

In most cases, the EEG reveals poor organization and diffuse slowing along with bifrontal delta activity. However, in others, epileptiform discharges may be recorded, suggesting the possibility of clinical epileptic seizures. The risk of epileptic seizures is likely to be increased if the patient has a pre-existing cerebral lesion, such as an infarct. Although the patient may develop obvious clinical seizures characterized by generalized or focal motor activity, the confusional or lethargic state may be a manifestation of CPS.

Mention should be made of conditions such as hypoglycemia and hypocalcemia. The patient may present with generalized tonic-clonic convulsions and even status epilepticus. In some cases, focal or even multifocal seizures may occur. Rapid correction of the metabolic defect is essential, as is the prompt administration of an intravenous antiepileptic drug. These patients, of course, do not have epilepsy, and chronic antiepileptic drug administration is not required.

Prescription drugs, such as psychotropic agents may lead to a toxic encephalopathy. The aging brain is particularly prone to medication side effects (17,18). Intoxications may be manifested by such central nervous system (CNS) symptoms as unsteadiness or dizziness. In addition, confusion and lethargy may result. Again, the EEG will be helpful in differentiating possible seizures from encephalopathic fluctuations in mental status (see also Chapters 14 and 15).

NONCONVULSIVE STATUS EPILEPTICUS

Nonconvulsive status epilepticus (NCSE) is indeed an epileptic condition and not an *imitator* of epilepsy. Thus, the reader might well be curious regarding the inclusion of this entity in this chapter. In fact, the reverse is true. NCSE is an imitator of *nonepileptic* conditions such as metabolic encephalopathies and, as such, is underdiagnosed and inappropriately treated (19). Therefore, it seems rational to include a discussion of NCSE here in order to complete the circle of "diagnostic deception" in the elderly.

There are two broad subdivisions in NCSE: absence and complex partial. Absence NCSE occurs mainly in children and is not considered in this discussion. Complex partial NCSE occurs in many settings and is not infrequent in the aged. Further, the clinical manifestations are diverse, ranging from modest confusion or personality change to apparent sleep or coma.

Situations particularly likely to reveal complex partial NCSE include:

- Failure to recover full awareness after general anesthesia
- Cerebral hypoxia
- Multisystem disease
- Infection
- Drug withdrawal (e.g., benzodiazepines and psychotropics)
- Failure to recover after a generalized tonic-clonic convulsion

In all the above conditions, the underlying condition is assumed to be the cause, and often this is true. Take the example of delayed recovery after a prolonged operation under general anesthesia. There may have been a hypotensive episode, or a particularly difficult procedure with considerable bleeding. Under these circumstances, one might not expect immediate recovery. With the passage of time and continued unresponsiveness, a neurologist may be summoned for an opinion. Examination reveals alteration of consciousness, perhaps coma. There may be little or no minor motor activity. An imaging study was probably ordered before the neurologist arrives; it is usually unrevealing. The EEG is the relevant test, and it should be ordered as soon as possible. Although the EEG may be disorganized, with the diffuse slowing compatable with a depressed state of consciousness, it reveal a picture consistent with NCSE. Prompt treatment may lead to improvement, although the extent of recovery depends on the extent of any underlying cerebral damage.

Elderly persons with multisystem disease, such as hepatic and renal failure, old strokes, electrolyte disturbances, and perhaps superimposed infection, are obviously quite ill and nearly always have a decline in their level of consciousness on these bases alone. It is unusual for the treating physician to consider any other cause for the mental status change. Nonetheless, NCSE may have intervened without obvious clinical evidence to suggest its diagnosis. As the patient begins to stabilize, and there is little change in mental status, the clinician may well call for a neurologic consultation. On examination, the patient will have a depressed state of consciousness ranging from lethargy to coma. Minor motor manifestations, such as myoclonic jerks or intermittent nystagmus, may be observed. Another clue to the diagnosis of NCSE may be an observation of fluctuation in the patient's level of consciousness. Usually an EEG will be ordered as part of the work-up, and NCSE may well be revealed at that time. Unfortunately, such patients present a difficult therapeutic problem. They are usually in the older age group, and this, in addition to their medical condition, makes them particularly vulnerable to the side effects of intravenous drugs. Hypotension resulting as a side effect of medication is most common (19). Moreover, it is common experience that good mental status will be difficult to support as long as the underlying medical problems continue or are unstable (20).

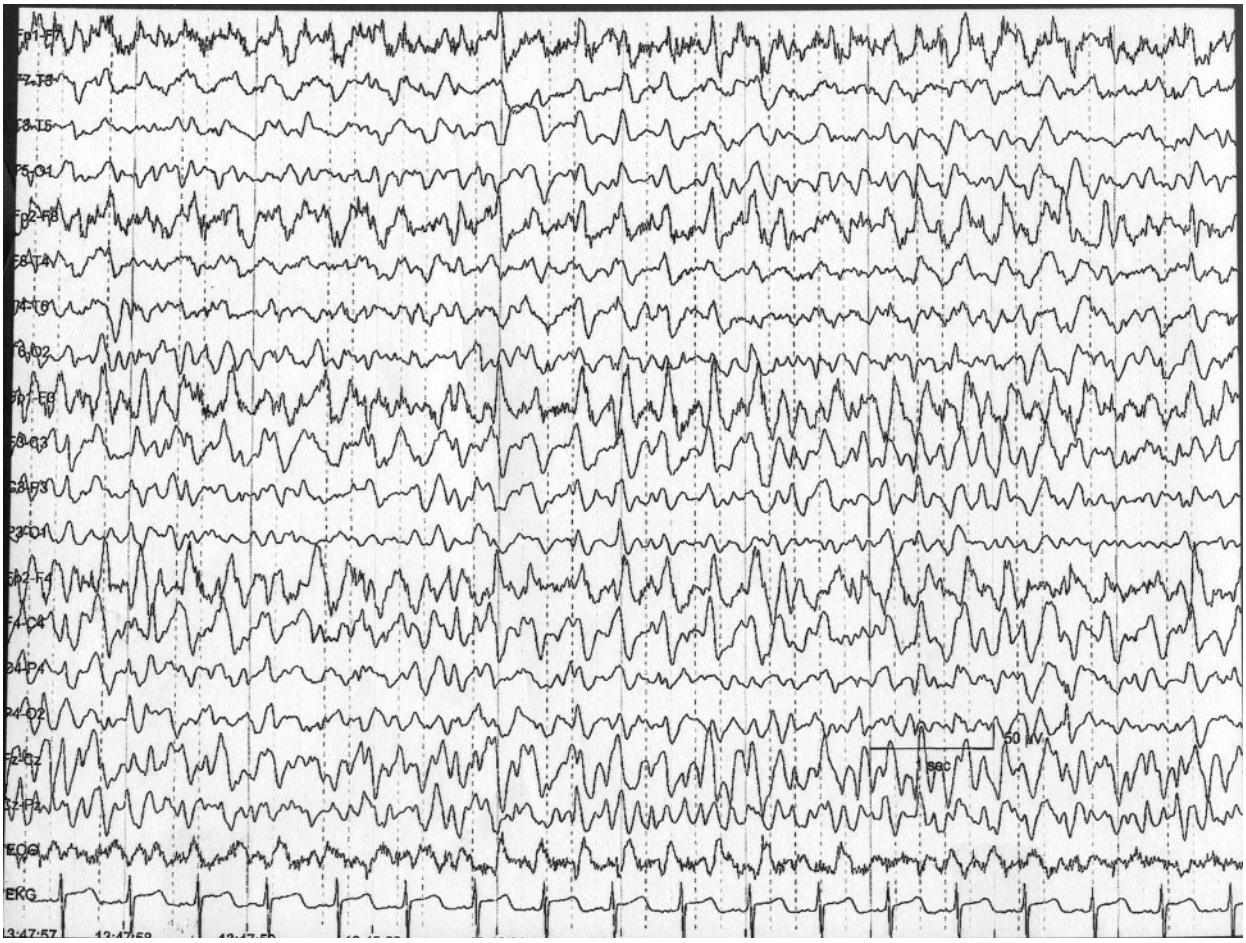

FIGURE 8.1

Nonconvulsive status epilepticus (NCSE). Note the synchronous, quite rhythmic 3 to 4 Hz sharp waves with a bifrontal preponderance. Breaks in rhythmicity occur during the first 3 and last few seconds. Some background activity is visible, and there is no lateralization.

The EEG in Nonconvulsive Status Epilepticus

EEG findings in NCSE are quite variable and, to the uninitiated, not always obvious. The principal feature is a generalized, usually rhythmic waveform with a bifrontal amplitude preponderance (21,22). In its most obvious form, the discharge is a high-voltage rhythmic sharp wave or spike. The configuration may be mono-, bi-, or even triphasic (Figures 8.1 and 8.2). In fact, differentiation from the triphasic waves of hepatic encephalopathy may be difficult. Rhythmicity usually varies; quite regular runs alternate with more irregular sequences. Random focal or multifocal sharp wave or spike discharges may occur but often are absent. In some cases, a clue to the epileptic nature of the EEG picture is the cessation of the discharges for a brief period, during which a relatively low-voltage background, perhaps consisting of theta frequencies, is revealed. Such a sequence is usually not a feature of metabolic encephalopathies.

In other cases, the discharges are not so apparent. For example, a common finding is a bifrontal slow frequency in the delta range that displays a sharp contour. The slow waves are rhythmic or quasi-rhythmic in character and indeed have the same significance as the more obvious sharp potentials. The feature that strongly suggests the diagnosis is rhythmicity, and the sharp contour to the waveform also raises suspicion. Still other patients display high-voltage paroxysms of slow or sharp activity that are frequent but not necessarily highly rhythmic. In these cases, the EEG picture, while not typical of NCSE, suggests that an epileptic contribution to the patient's depressed mental status is likely.

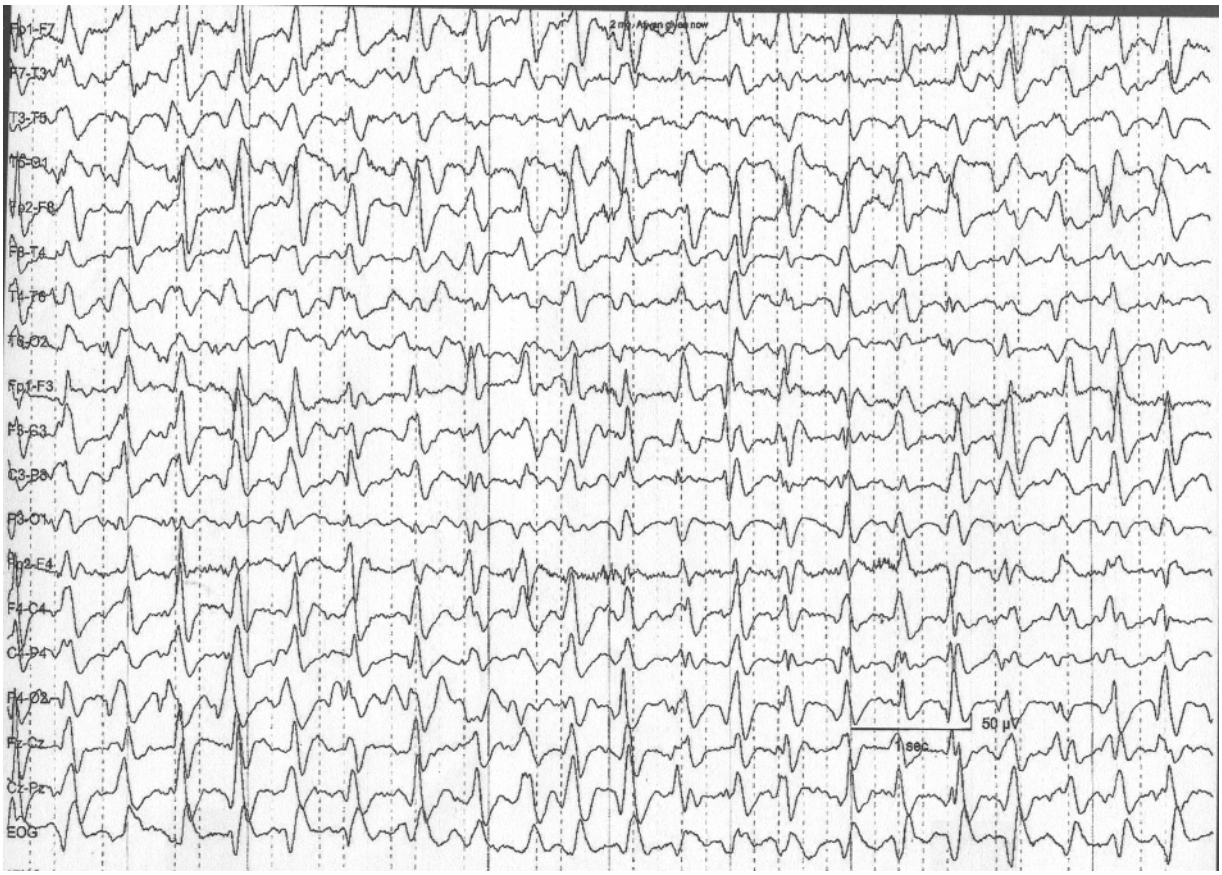

FIGURE 8.2

In this case of NCSE, the synchronous, rhythmic discharges look very much like the bi- and triphasic potentials associated with a metabolic encephalopathy.

Ideally, when the EEG shows a picture consistent with NCSE, immediately treatment with an intravenous agent should be administered under EEG control. Probably the most useful drug is lorazepam. In our laboratory, we usually give a small dose to start, either 0.5 mg or 1.0 mg IV. In many cases, a decrease in discharge frequency and rhythmicity may be observed within 2 to 3 minutes. We then may follow with a second small dose. The idea is to suppress the discharges with as little of the benzodiazepine as possible, to avoid putting the patient to sleep. This is not always possible, but we have found this a safe and often effective way to proceed. Others recommend giving valproate intravenously, which also may be effective. As mentioned above, when patients are medically unstable, it may be difficult to suppress the epileptiform activity. In such cases, we recommend that the patient not be treated vigorously, as in cases of generalized convulsive status epilepticus. Morbidity from the treatment itself may well outweigh the benefits of discharge suppression.

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9 Migraine and Epilepsy

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Migraine and epilepsy are both heterogenous families of chronic disorders with highly variable clinical features, natural histories, and patterns of treatment response (1,2). Both are characterized by episodes of neurologic dysfunction sometimes accompanied by headache, as well as gastrointestinal, autonomic, and psychologic features. Each has clear age-specific and hormone-related syndromes. Each has an internationally recognized classification system (3). One important difference is that epilepsy has a supportive test, the electroencephalogram (EEG), whereas migraine continues to be a strictly clinical diagnosis.

The International Headache Society (IHS) criteria, originally developed in 1988 and revised in 2002, divide headache disorders into two broad groups: primary headache disorders and secondary headache disorders (3). A secondary headache disorder is one in which the headache is attributable to an underlying condition, such as a stroke or a mass lesion. This group is analogous to the symptomatic epilepsies. A primary headache disorder is one in which the headache does not have an identifiable underlying cause. This group includes migraine, tension-type headache (TTH), cluster headache, and a number of rare disorders; it is analogous to the idiopathic epilepsies. (See Table 9.1).

This chapter focuses on the relationship between headache and epilepsy for several reasons. First, abundant clinical and epidemiologic data demonstrate that migraine and epilepsy are highly comorbid, and individuals with one disorder are at least twice as likely to have the other (1,4–7). Migraine affects approximately 18% of women in the United States and 6% of men (8,9). Epilepsy affects approximately 0.5% to 2% of the U.S. population (10–12), and seizures affect an even larger percentage of the population. The prevalence of migraine in patients with epilepsy ranges from 8% to 23% (13), and the prevalence of migraine is 15% to 26% for the family members of these patients (7,14,15). Second, comorbid disease presents challenges in both differential diagnosis and concomitant diagnosis (16). The clinical presentation of migraine and epilepsy may overlap, creating diagnostic difficulty. Finally, the disorders have overlapping risk factors, brain mechanisms, and treatments (16).

Case Study 1, reported by Hanson and Chodos in 1978 (17), was initially reported as epilepsy, and demonstrates the diagnostic difficulty between migraine and epilepsy.

TABLE 9.1
IHS Migraine Classification (31)

1. Migraine
   - 1.1 Migraine without aura
   - 1.2 Migraine with aura
     - 1.2.1 Migraine with typical aura
     - 1.2.2 Migraine with prolonged aura
     - 1.2.3 Familial hemiplegic migraine
     - 1.2.4 Basilar migraine
     - 1.2.5 Migraine aura without headache
     - 1.2.6 Migraine with acute onset aura
   - 1.3 Ophthalmoplegic migraine
   - 1.4 Retinal migraine
   - 1.5 Childhood periodic syndromes that may be precursors to or associated with migraine
     - 1.5.1 Benign paroxysmal vertigo of childhood
     - 1.5.2 Alternating hemiplegia of childhood
   - 1.6 Complications of migraine
     - 1.6.1 Status migrainosus
     - 1.6.2 Migrainous infarction
   - 1.7 Migrainous disorder not fulfilling above criteria

Case Study #1. A 12-year-old, right-handed boy had a mild, ill-defined illness 2 weeks prior to admission. He was then well until the day before admission, when he had an episode of vomiting and headache. The morning of admission, while taking a bath, he found himself unable to move or talk. He was aware, in retrospect, of some left-sided shaking, and he may have fallen to the ground. He claimed to have been conscious throughout. He remained paralyzed on the left side. When admitted, approximately 8 hours after onset, he was able to walk unassisted but had a clear left hemiparesis. He was fully oriented but complained of severe headache and mild lethargy.

This case was reported as epilepsy, but without electroencephalographic evidence of seizure, the clinical diagnosis of hemiplegic migraine would be an appropriate alternative to seizure with postictal Todd's paralysis.

We begin by describing the migraine attack, dividing it into traditional stages. We then review the diagnosis of migraine using the IHS criteria, emphasizing the variants of migraine most frequently mistaken for epilepsy. We discuss the pathophysiology underlying migraine and, finally, we briefly discuss pharmacologic treatment.

THE MIGRAINE ATTACK—A CLINICAL DESCRIPTION

The migraine attack can be divided into four phases: the premonitory phase, which occurs hours or days before the headache; the aura, which comes immediately before the headache; the headache itself; and the postdrome. Although most people experience more than one phase, no one phase is absolutely required for a diagnosis of migraine, and most people do not experience all four phases (18). Likewise, the epilepsy attack can be divided into phases that are closely related to those of the migraine attack, although there are distinct differences as well.

Premonitory Phase

As many as 60% of migraineurs experience symptoms, often hours to days before the onset of headache (1,2,18–20). These phenomena include psychologic (depression, euphoria, irritability, restlessness, mental slowness, hyperactivity, fatigue, and drowsiness), neurologic (photophobia, phonophobia, and hyperosmia), constitutional (sluggishness, thirst, urination, anorexia, and food cravings), and autonomic (cold sensation) features. Some patients report a poorly characterized feeling that a migraine attack is coming. Although premonitory symptoms vary widely among individuals, they are often consistent within an individual. Using an electronic diary, migraineurs who reported premonitory symptoms accurately predicted their fullblown headaches 72% of the time. The most common symptoms were feeling tired (72%), difficulty concentrating (51%), and stiff neck (50%) (21). Prodromal symptoms have been reported in about 30% of patients with partial seizures, although they are less common than with migraine and might suggest the latter diagnosis (22,23).

Aura

The migraine aura consists of focal neurologic symptoms that precede or accompany an attack and is experienced by approximately 20% to 30% of migraineurs (Table 9.2). The aura may also occur in isolation, that is, unaccompanied by headache, in approximately 20% of attacks (24). The symptoms may be either positive or negative, and are often a combination of both. Most aura symptoms develop slowly over 5 to 20 minutes and usually last for less than 60 minutes. The aura usually includes visual phenomena, but may involve somatosensory or motor phenomena, as well as language or brainstem disturbances.

TABLE 9.2
Migraine with Aura (31)

Diagnostic Criteria

A. At least 2 attacks fulfilling B.
B. At least 3 of the following 4 characteristics:
   1. One or more fully reversible aura symptoms indicating focal cerebral cortical, brainstem dysfunction, or both.
   2. At least one aura symptom develops gradually over more than 4 minutes or, 2 or more symptoms occur in succession.
   3. No aura symptom lasts more than 60 minutes. If more than one aura symptom is present, accepted duration is potentially increased.
   4. Headache follows aura with a free interval of less than 60 minutes. (It may also begin before or simultaneously with the aura).
C. At least one of the following:
   1. History, physical and neurologic examinations do not suggest one of the disorders listed in groups 5-11.
   2. History, physical, and neurologic examinations or all do suggest such disorder, but it is ruled out by appropriate investigations.
   3. Such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder.

The most common aura is the visual aura. A visual aura often has a hemianoptic distribution and includes both positive (scintillations, fortification spectra, photopsia) and negative (scotoma) features. Elementary visual disturbances include colorless scotoma, photopsia, or phosphenes. Simple flashes, specks, or hallucinations of geometric forms (points, stars, lines, curves, circles, sparks, flashes, or flames) may occur and may be single or number in the hundreds. More complicated hallucinations include teichopsia (Greek: *town wall and vision*) or fortification spectrum, which is the most characteristic visual aura and is almost diagnostic of migraine. An arc of scintillating lights classically begins near the point of fixation and may form a herringbone-like pattern that expands to encompass an increasing portion of a visual hemifield. It migrates across the visual field with a scintillating edge of zigzag or flashing lights, which are often black-and-white; on occasion colored dots appear at the end of the white stripe.

A scotoma is a negative phenomenon consisting of a blanking or graying out of vision in any field distribution including central, quadrants, or bitemporally. Scotomas are usually accompanied by positive visual display, but may occur independently. Complex disorders of visual perception include metamorphopsia, micropsia, macropsia, and zoom vision. These phenomena, which may originate in the visual association cortex, may be referred to as the "Alice in Wonderland" syndrome; they are more common in the pediatric population (25–29). Additional visual perception disorders, such as alexia, mosaic vision, achromatopsia (loss of color), cinematographic vision (illusion of motion lost), and palinopsia (persistence of visual images after the stimulus object has been removed) have been described (25–29).

Case Study #2. A 41-year-old woman with a long history of migraine recalls peculiar spells during childhood. From age 4 through 17 she would get "spells" that were entirely aural: "every sound around me—speech (her own and that of others), music, crickets, everything—would assume the same overpowering rhythm." There was nothing she could do about it. She remembers being terrified of the spells when she was very young, but she eventually got used to them and would lie down until they went away.

Her most striking spells were what she now calls the Alice-in-Wonderland syndrome. "On many occasions, particularly while reading, I would suddenly feel that my body had grown from the waist up, that I was looking down at my book from a distance of 10 feet or more. I distinctly remember this happening semi-regularly when I was about 20; it has happened since, but it is a relatively rare thing. At about the same time, I was riding my bike one day and lost half my field of vision. This never occurred again." The spells were not associated with headache. After age 20, she developed severe migraine headaches without aura.

The headaches disappeared for 5 years, until she began fertility treatments. After starting hormonal treatments, her headaches and auras returned. The auras were then typical scintillating scotomata, except they always preceded the headaches by approximately 24 hours. She would get an increase in the number of "floaters," a narrowing of the visual field, flashes of light, and wavy lines, in that order. The entire process would take hours, followed the next day by a headache (occasionally associated with ipsilateral ptosis and eye tearing) (25).

Numbness or tingling (paresthesia) over one side of the face and in the ipsilateral hand or arm are the most common somatosensory phenomena that occur. Hemiparesis and dysphasia or aphasia may develop.

Olfactory hallucinations are rare, unpleasant, and short-lived (5 minutes to 24 hours). Anxiety, déjà vu, and jamais vu have been reported as migraine auras and are presumably of temporal lobe origin (30). One type of aura may follow another: sensory phenomena may occur as visual phenomena fade, or motor phenomena may develop as sensory phenomena dissipate. The temporal characteristics of the symptoms and their complex nature and distribution can often help to distinguish the migraine aura from that of seizure and cerebrovascular disease. The most difficult to distinguish may be occipital lobe epilepsy.

Nonvisual association cortex symptoms also occur as part of a migraine aura; these include complex difficulties in the perception and use of the body (apraxia and agnosia), speech and language disturbances, states of double or multiple consciousness associated with déjà vu or jamais vu, and elaborate, dreamy, nightmarish, trancelike, or delirious states (25,30–32).

Case Study #3. A 23 year-old woman suffers from unusual seizure-like spells associated with her migraines. They can occur up to twice a day and last 20 minutes to 2 hours, but "time is meaningless; it could be a second or days." The right side of her face becomes numb ("You could stick a pin into it"), and her tongue feels very thick, as if it were filling her mouth, making it difficult for her to speak. Her eyes flutter, and her balance is off. The day before or the morning of an attack she will typically say "It's not going to be a good time today." She had at least one episode of *confusion:* while driving in the neighborhood where she grew up, she suddenly became disoriented; she had no idea of where she was or how long this spell lasted.

She had an unusual spell when she was a college student. She woke up feeling very tired and feverish. She took her temperature; it went from 99° to 104° within an hour. Four days later, she had a headache that she described as feeling as if a lightning bolt struck her or a volcano erupted inside her head, and she was unable to speak. A friend found her lying on her bed with her legs upright against the wall, and said, "You're climbing the walls!" She was able to spell out numbers on her hands but not talk.

A later episode was described as follows: "She could see her body lying like a dead weight on the bed beneath her while her mind and all that was essentially *her* was floating in the air above her body. A friend walked into the room, could not rouse her, and summoned Public Safety, the campus emergency team. When she 'awoke,' everything was blurry; the movements and expressions of the people around her seemed both slowed and exaggerated. She described a friend's smile as "ripping right across her face."

These episodic bizarre spells could be considered "migrainous" with disturbances of cognition and perception (25).

Headache Phase

The typical migraine headache is unilateral, but it can be bilateral; it is described as throbbing in 85% of patients. Headache severity ranges from moderate to marked and is aggravated by head movement or physical activity. The onset is usually gradual, and the attack usually lasts 4 to 72 hours in adults and 2 to 48 hours in children (2).

The pain of migraine is invariably accompanied by other features. Anorexia is common, although food cravings can occur. Nausea occurs in as many as 90% of patients, and vomiting occurs in about one third of migraineurs (33). Many patients experience sensory hyperexcitability manifested by photophobia, phonophobia, and osmophobia, and seek a dark, quiet room (32,34). The IHS selects particular associated features as cardinal manifestations for diagnosis (Table 9.3) (35).

TABLE 9.3
Migraine Without Aura (31)

Diagnostic Criteria

A. At least 5 attacks fulfilling B-D.
B. Headache lasting 4 to 72 hours (untreated or unsuccessfully treated).
C. Headache has at least two of the following characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate or severe intensity (inhibits or prohibits daily activities)
   4. Aggravation by walking stairs or similar routine physical activity
D. During headache at least one of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia
E. At least one of the following:
   1. History, physical and neurological examinations do not suggest an organic disorder
   2. History and/or physical and/or neurological examinations do suggest such disorder, but it is ruled out by appropriate investigations
   3. Such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder

The pain or headache phase of migraine may be comparable to the seizure in that it is the ictus, or main event, noted by the patient or nearby observers.

Postdrome

The postdrome, clinically comparable to a classic postictal state after seizure, may last hours to days, and the patient may feel tired, washed out, irritable, and listless, and may have impaired concentration. Many patients report scalp tenderness. Some people feel unusually refreshed or euphoric after an attack, whereas others note depression and malaise.

MIGRAINE VARIANTS

Some variants of migraine may present particular diagnostic difficulty due to their clinical similarity to epileptic phenomena. Migraine variants may be age- or developmentally specific, as are some forms of epilepsy. A temporal relationship may be found in some migraine variants such as menstrual migraine, perhaps comparable to catamenial epilepsy.

Basilar migraine affects all age groups and both sexes, although it typically begins in the second decade and affects women more often than men. The attack begins with visual symptoms, often a hemianopic field defect that rapidly develops into total blindness, that last less than 1 hour. This is followed by at least one of the following: ataxia, vertigo, tinnitus, diplopia, nausea and vomiting, nystagmus, dysarthria, bilateral paresthesia, or alteration of consciousness. This aura phase is then followed by severe occipital headache that lasts 1 to 3 days.

The headache of confusional migraine is characterized by aura, followed by headache and confusion. However, confusion may either precede or follow the headache phase. A profound alteration of consciousness may lead to migraine stupor, which lasts from hours to days. The episode rarely occurs more than once, but it can recur over a period of days to months and then evolve into typical migraine episodes. A history of typical migraine aura supports the diagnosis of confusional migraine, but other etiologies for this type of alteration should be investigated.

Aura without headache may be difficult to diagnose, and the diagnosis should be accepted only after a full investigation of the presenting symptoms has been performed. Late-life migrainous accompaniments are characterized by attacks of aura without headache that begin in late life (36,37). Often, patients with this disorder have a history of migraine in the past, followed by a headache-free period prior to the onset of aura without headache.

In children, migraine variants occur in which headache is not experienced. Alternating hemiplegia of childhood has a typical age of onset of 1 to 18 months. The attacks begin with abnormalities of eye movements and crying, often followed by dystonic posturing of one side of the body followed by weakness of that side. Attacks usually last hours, but this varies, and they can last minutes to days. Attacks are not accompanied by electroencephalographic abnormalities (38). In benign paroxysmal vertigo, young children experience clusters of spells, which last only minutes, in which the child will suddenly become unsteady and attempt to grab hold of objects around herself to regain stability. Often, these children develop migraine later in adolescence (39). Children with paroxysmal torticollis develop attacks of head tilt, nausea, and vomiting lasting hours to days. Cyclic vomiting, another childhood migraine variant, is characterized by attacks of severe vomiting leading to dehydration (39).

HEADACHE AND SEIZURE OCCUR TOGETHER

Many possible relationships between headache and seizure exist in the clinical setting. Migraine may trigger epilepsy (migralepsy) or epilepsy may initiate headache. Seizure and headache seem to be associated in certain syndromes, such as benign occipital epilepsy of childhood with occipital paroxysms (BOEP). Both disorders may have a common underlying cause, such as head trauma or an arteriovenous malformation. Examples of these interrelationships are found in Table 9.4.

Preictal, Ictal, and Postictal Headaches

Although headache is commonly associated with seizures as a preictal, ictal, or postictal phenomenon, it is often neglected because of the dramatic neurologic manifestations of the seizure. Patients with migraine-triggered epilepsy seek medical attention because of seizures, which may overshadow the migraine and be overlooked by the patient and physician. Headache can also be the sole or most predominant clinical manifestation of epileptic seizures, although this a relatively rare situation (40).

Palmini and Gloor (41) described auras in partial seizures. Auras were termed cephalic if the symptoms included nonvertiginous dizziness, lightheadedness, or pressure on the head; cephalic auras occurred in 22 of 196 patients. In Blume and Young's epilepsy unit, 2.8% of 858 patients had brief ictal pain, 1.3% (11 patients) had headache (42). Only two patients described the pain as throbbing; the others described it as sharp or steady. Headache preceded the seizure in eight patients

TABLE 9.4
Migraine and Epilepsy Relationships

1. *Coexisting Epilepsy and Migraine*
   Both disorders occur together at an increased prevalence, but attacks occur independently.
2. *Migraine Induced Epilepsy (Migralepsy)*
   Seizures are triggered by migraine aura
3. *Epilepsy Induced Headache* (Ictal or Postictal)
   Headache occurs as part of seizure or postictal state
4. *Primary Epilepsy-Migraine Syndromes*
   Syndromes with features of both migraine and epilepsy without a specific underlying cause
   – Occipital epilepsies (eg, Benign occipital epilepsy)
   – Benign rolandic epilepsy
5. *Secondary Epilepsy-Migraine Syndromes*
   Both migraine and epilepsy occur in the same individual with a common underlying cause
   – Mitochondrial disorders (MELAS)
   – Symptomatic (eg, AVM of occipital lobe)

and accompanied the other ictal symptoms in three; all three of these patients had partial seizures, although the nature and location of EEG abnormalities varied considerably from patient to patient.

In a telephone interview of 372 patients attending an epilepsy clinic, 45% had experienced postictal headache (PIH) and 21% always had postictal PIH. Of those who always had PIH, it was severe 39% of the time; in contrast, it was severe in only 10% of patients with occasional PIH. Twenty-seven percent of patients had independent headaches that were usually similar to their seizure-related headache. Headaches lasted less than 6 hours in 81% of patients, 12 to 24 hours in 11%, and more than 24 hours in 8% (43). The headache was throbbing in over two-thirds of patients.

Schon and Blau (44) reported on one hundred epileptic patients, fifty-one of whom had PIH either always (n=35), usually (n=5) or 25% to 50% of the time (n=11). PIH was more commonly associated with generalized tonic clonic seizures than with focal seizures; 9% of the patients had independent migraine attacks. The headaches were either bilateral or unilateral, were associated with photophobia and phonophobia, throbbing pain, vomiting, nausea, and visual aura, and lasted 6 to 72 hours. Epileptic migraineurs stated that these headaches were similar to their migraine.

MIGRAINE-TRIGGERED EPILEPSY

Niedermeyer reported eight patients in whom convulsions were usually preceded by typical migrainous visual aura and always followed by severe attacks of migraine pain. All of the patients had normal EEG and imaging. Confusional migraine may be misinterpreted as complex partial seizures triggered by migraine in some patients (10). Andermann (5) reported several epilepsy patients who had classic migraine histories and whose family members developed, variably, migraine alone or migraine accompanied by seizure. Some patients who developed seizure secondary to migraine were noted to have additional factors lowering the seizure threshold, such as sleep deprivation or alcohol use.

Migraine-Epilepsy Syndromes

BOEP is a syndrome of occipital spikes, ictal visual symptoms followed by a partial seizure, and postictal migraine. A rare syndrome of childhood (mean age of onset 7.5 years), it accounts for less than 5% of epilepsy in children (45–47). BOEP has features of both epilepsy and migraine (46,48,49). The seizures usually begin with visual symptoms, including amaurosis, elementary visual hallucinations (phosphenes), complex visual hallucinations, or visual illusions, including micropsia, metamorphopsia, or palinopsia (46,50,51). The visual symptoms are often followed by hemiclonic, complex partial, or generalized tonic-clonic seizures. Following the seizure, approximately 25% to 40% of the patients develop migrainelike headaches (49).

Mitochondrial disorders may present with multiple CNS abnormalities, including migraine and seizures. Sacconi, et al. (52) reported on a patient with a complex neurologic history that included a long history of migraine since the age of 10 and epilepsy that developed in the fourth decade of life. A mitochondrial DNA mutation was identified as the cause of this syndrome. In another well-defined mitochondrial disorder (mitochondrial myopathy, encephalopathy, lactic acidosis, strokelike episodes [MELAS]), migraine and seizures can be a prominent feature. Iizuka, et al. evaluated fourteen strokelike episodes in six patients using clinical assessment, EEG, and various neuroimaging techniques. Migrainelike headache was the most common presenting symptom of a strokelike episode; seizure was next. These patients' EEGs showed periodic epileptiform discharges, and single positron emission computed tomography (SPECT) studies revealed focal hyperperfusion in the same region as the epileptiform discharges (53).

A recently described family (54) included several members who developed a syndrome characterized by the co-occurrence of migraine, epilepsy, and ataxia. A mutation in the CACNA1A gene coding for a subunit of a neuronal voltage-gated P/Q-type calcium channel was identified.

PATHOPHYSIOLOGY OF MIGRAINE

The mechanisms of migraine pain are probably independent of the mechanism of migraine aura. Migraine aura has long been thought to be due to the human equivalent of cortical spreading depression (CSD) in the rat, first described by Leao in 1944. In migraine with visual aura, cerebral blood flow studies demonstrate a wave of oligemia that spreads forward from the occipital area, does not respect vascular territories, precedes the aura, and may persist into the headache phase (55). The rate of progression of the oligemia is the same as the rate of CSD (56). Recent magnetoencephalographic studies suggest the existence of spreading depression in humans with migraine (57,58), thus implying that spreading depression may be the mechanism that produces the aura (59–64). More recently, functional magnetic resonance imaging (MRI) studies using BOLD (blood oxygen level dependent) full imaging have shown contralateral occipital lobe changes during spontaneous human aura. Spreading hyperemia occurs during the aura phase, followed by a period of oligemia. The hyperemia in the neuronal tissue correlates to increased neuronal activity that is generating positive neurologic phenomena during the aura. The signal changes in this study traveled at 3.5 mm/min, did not respect vascular territories, and did not cross large sulci, as previously demonstrated CSD in rats (65).

The headache phase of a migraine attack is associated with the perception of pain. Pain-sensitive structures involved in migraine include the dura, the vasculature, and the trigeminal afferent nerves. The activation of brainstem centers promotes the peripheral release of neurotransmitters and neuropeptides by efferent autonomic fibers and the trigeminal system, thus leading to the vasodilation of meningeal blood vessels and extravasation of inflammatory chemicals into the dura and spinal fluid. Mechanical stimulation (stretch or distention), chemical irritation by inflammatory proteins, and neurotransmitter/receptor interactions all activate trigeminal afferents, which transmit pain signals through the trigeminal ganglion back to the trigeminal nucleus caudalis (TNC) in the brainstem. Some cells in the TNC can be modulated by descending input from higher brain structures. Repeated excitation or lack of inhibition may allow this brainstem center to continue to propagate the cascade of a migraine attack. Positron emission topography (PET) during spontaneous human migraine has revealed increased regional cerebral blood flow (rCBF) in the brainstem in the region of the dorsal raphe nucleus and locus ceruleus, thought to be involved in autonomic control of cerebral blood flow and antinociception (66). Other evidence supports various components of the proposed physiology of the migraine attack. Electrophysiologic studies have shown facilitation of nociceptive transmission in the trigeminal system ipsilateral to the migraine pain (67), and functional MRI has been used recently to demonstrate leakage of contrast from the vasculature into the subarachnoid space (68).

The mechanism by which a migraine is triggered remains less clear. A link was recently identified between the long-accepted mechanism of aura and the more recent theories regarding the mechanism of migraine pain. Bolay et al. (69) demonstrated that CSD can activate trigeminal terminals in the brain and set off a chain of events, including changes in blood flow and plasma protein extravasation, consistent with the current mechanisms thought to be involved in migraine pain generation. The cascade was prevented when the trigeminal afferent nerve was sectioned or pretreated with the serotonin receptor agonist sumatriptan.

THE EEG AND MIGRAINE

The utility of EEG in diagnosing epilepsy is undisputed, but it is much less useful in diagnosing migraine. Even EEGs recorded during migraine aura are usually normal. The Quality Standards Subcommittee of the American Academy of Neurology has reviewed EEG's usefulness in headache. They found that no study has consistently demonstrated that EEG improves the diagnostic accuracy for the headache sufferer. EEG has not been convincingly shown to identify headache subtypes, nor has it been shown to be an effective screening tool for structural causes of headache. They conclude that EEG is not useful in the routine evaluation of patients with headache. This does not exclude the use of EEG to evaluate headache patients with associated symptoms that suggest a seizure disorder, such as atypical migrainous aura or episodic loss of consciousness.

The EEG and 24-hour closed-circuit television (CCTV) EEG recording can help differentiate migraine aura and epileptic aura; these procedures can also facilitate the diagnosis of comorbid epilepsy and migraine as well as the migralepsy syndrome. Marks and Ehrenberg (70) studied patients with migralepsy using multiple 24-hour video-EEG telemetry recordings. In two patients, the entire migraine–epilepsy sequence was captured; it showed changes during the clinical migraine aura that were atypical for electrographic epilepsy. During migraine aura, bursts of spike activity may resemble the ictal EEG during an epileptic seizure. However, in most reported cases, the EEG does not show the usual temporal evolution with progressive increases and declines in the frequency and amplitude of rhythmic, repetitive, epileptiform activity typical of ictal EEGs in epilepsy. In addition, the EEG during migraine aura may show

"waxing and waning" patterns, separated by completely normal EEG activity despite the persistence of clinical symptoms.

Manzoni et al (71) and Terzano et al (72,73) coined the term *intercalated seizures* to denote epileptic seizures occurring between the migrainous aura and the headache phase of migraine. They found that 16 of 450 patients with migraine (3.6%) also had seizures. The two conditions appeared to be coincidental in four of the sixteen patients. In another five patients, the two types of attacks were quite distinct, but often an epileptic seizure was followed by a migraine attack and vice versa. The remaining seven patients had intercalated seizures. All had a family history of migraine, and two also had relatives with epilepsy. They all had visual seizures consisting of highly stylized contours of plain figures, or single or multicolored spots that often rotated. The seizures lasted for 1 to 2 minutes and came out of a scintillating scotoma, slowly developing in the visual field and evolving into unilateral or bilateral hemianopia. DeRomanis et al. (74,75) studied patients who had brief ictal visual hallucinations of "colored dots or discs" and interictal occipital paroxysms on EEG. EEG during a seizure showed that they had occipital epilepsy and not migraine with aura (76).

Striking EEG patterns have been described in specific subtypes of migraine (77). The brain regions most often involved in the published EEG samples in basilar migraine include the posterior temporal, parietal, and occipital regions. The posterior electrographic localization may not pertain to other forms of migraine (78). Paroxysmal lateralized epileptiform discharges (PLEDs) or PLED-like activity have been associated with hemiplegic migraine, prolonged migraine aura, or incipient migrainous infarction. Those patients with PLED-like activity did not have any of the usual entities associated with PLEDs, such as stroke, brain abscess, glioblastoma, or viral encephalitis; their PLEDs usually resolved within 24 hours. Certain migralepsy patients had clinical seizures when PLEDs were present on their EEGs (6). PLEDs or other epileptiform discharges have been described in association with focal hyperemia and clinical deficit in patients with MELAS. These areas also corresponded to the area of infarction on MRI or computed tomography (CT). In contrast, only rarely do the areas of infarction associated with cardioembolic stroke show epileptiform discharges on EEG (53).

PHARMACOLOGIC TREATMENT OF MIGRAINE—BASIC PRINCIPLES

There are two approaches to the pharmacologic treatment of migraine, acute and preventive, and many patients require both. Acute therapy is used to treat the pain and associated symptoms of an individual migraine attack and is most effective if used early in the attack. Agents commonly used as acute migraine treatment in the outpatient setting include over-the-counter analgesics, nonsteroidal antiinflammatory drugs (NSAIDs), and the ergots and triptans.

The goal of preventive therapy is to decrease the frequency and severity of attacks and improve response to acute therapy. The American Headache Consortium recommends the use of preventive therapy for a variety of clinical circumstances. Prevention should be used for patients in whom the frequency of attacks prohibits the regular use of acute treatment; patients who experience significant interference in daily activities despite acute treatment; patients whose attacks do not respond to acute treatment; and patients who cannot use acute therapies due to comorbid illness or contraindications, such as hemiplegic migraine. When patients must take daily medication due to comorbid disorders, a drug that will also be effective for migraine should be chosen. Cost and patient preference may also be considered when making recommendations for preventive therapy (79).

When devising a treatment plan for migraine, one should consider other comorbid disorders such as epilepsy or hypertension, which may guide treatment plans. For instance, although many antidepressant drugs are useful for migraine prevention, many also lower seizure threshold and thus may be less optimal for some epilepsy patients. Conversely, these medications may be the ideal choice for patients with migraine and comorbid depression (35).

Likewise, in devising a treatment plan for epilepsy one should consider a patient's comorbid diagnosis of migraine.

NEUROPHARMACOLOGY OF MIGRAINE TREATMENT

Several lines of indirect evidence suggest a relationship between serotonin and migraine. The 5-HT receptors consist of at least three distinct types of molecular structures: guanine nucleotide G protein-coupled receptors, ligand-gated ion channels, and transporters. There are at least seven 5-HT receptors: 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, and 5-HT_7 (80,81). In humans, there are at least five 5-HT_1 receptor subtypes: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F}. The search to characterize serotonin receptors in the vasculature led to the identification of the 5-HT_1-like receptor (82).

Headaches similar to migraine can be triggered by serotonergic drugs, such as reserpine (a 5-HT releaser and depleter) and m-chlorophenylpiperazine (m-CPP) (a serotonergic agonist) (83,84). Dihydroergotamine (DHE) (85) (an ergot derivative) and the new selective

HT-1 agonists (86–88), which are effective in the acute treatment of migraine, have variable affinity for the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors. These agents block the development of neurogenically induced inflammation in the rat dura mater, presumably by activating prejunctional 5-HT_1 heteroreceptors on the trigeminal nerve, thus blocking the release of neuropeptides, including substance P and calcitonin gene-related peptide. The NSAIDs may also block the development of neurogenic inflammation; the mechanism of this action is less certain, but may involve the inhibition of prostaglandin synthesis.

Radiolabeled DHE and most of the triptans, injected intravenously (IV) in the cat, pass through the blood–brain barrier and then label nuclei in the brainstem and spinal cord that are intimately involved in pain transmission and modulation (89). In addition, the trigeminal nucleus caudalis is activated by stimulation of the sagittal sinus, and this activity is transmitted to the thalamus (90). Both ergotamine and DHE and most triptans (except sumatriptan) surpass this activation. Sumatriptan has the same effect if the blood–brain barrier is disrupted.

Ergotamine, DHE, and the triptans exert their antimigraine effect through a receptor-mediated neural pathway in both the central nervous system and the trigeminal nerve, where they block neurogenic inflammation.

A preventive migraine drug could raise the threshold to activation of the migraine process either centrally or peripherally. Drugs could conceivably decrease the activation of the migraine generator, enhance central antinociception, raise the threshold for spreading depression, or stabilize the more sensitive migrainous nervous system by changing sympathetic or serotonergic tone. Preventive drugs most likely work by more than one mechanism.

Valproate blocks the development of neurogenic inflammation by enhancing peripheral gamma-aminobutyric acid (GABA) activity at the $GABA_A$ receptor. In addition, valproate-induced increased central enhancement of $GABA_A$ activity may enhance central antinociception. Valproate interacts with the central 5-HT system and reduces the firing rate of midbrain serotonergic neurons (91).

The gene for familial hemiplegic migraine (FHM) has been mapped to chromosome 19p13 in some, but not all, families. This region may also be involved in more common forms of migraine (92). In four families, the defect in FHM has been found to be caused by different missense mutations in a brain-specific P/Q Ca2+ channel $alpha_1$-subunit gene *CACNL1A4* covering 300kb with 47 exons. This is the same gene that is associated with episodic ataxia (93). P-type neuronal Ca^{2+} channels mediate 5-HT release. Dysfunction of these channels may impair 5-HT release and predispose patients to migraine attacks or impair their self-aborting mechanism.

Ca^{2+} channels are important in spreading depression, which may initiate the migraine aura. Impaired function of these channels may predispose to more frequent and severe attacks. Anticonvulsant medications may stabilize neuronal membranes and ion channels, thereby raising the threshold to attacks. The release of glutamate from neurons is thought to be important in CSD, and lamotrigine is a sodium channel blocker that leads to inhibition of glutamate release. In one small, open-label trial, lamotrigine was shown to decrease the number of episodes and duration of aura symptoms in patients with a history of aura (with or without migraine) (94). In another small, open-label trial, thirteen of twenty-four patients diagnosed with migraine with aura had complete resolution of attacks on this medication (95).

SOME DIAGNOSTIC DISTINCTIONS AMONG MIGRAINE, EPILEPTIC SEIZURES AND TRANSIENT GLOBAL AMNESIA

In differentiating between migraine without aura and epilepsy, the history is the most important tool (96). Although Tables 9.1 and 9.2 present the features most useful in distinguishing them, the history is the most important tool. In general, in comparison with epilepsy, attacks of migraine are of more gradual onset and of longer duration. Nausea and vomiting are more commonly associated with migraine. Prolonged confusion or lethargy after the attack favors epilepsy.

The migraine aura usually lasts longer than 5 minutes; in epilepsy less than 5 minutes (usually less than 1 minute) (97). Automatism, positive motor features, and alteration of consciousness favor an epileptic aura. A mix of positive and negative features, such as a scintillating scotoma, favors migraine (98). Colorless glittering scotomata are typical of migraine, as are black-and-white zigzag patterns that appear concentrically around the point of fixation, usually unilaterally. (These are also termed fortification lines.) Colors may be seen as well, or spots, circles, and beads with or without colors. When these occur, they are usually part of the scintillating scotoma or teichopsia and not a predominant independent feature of the migrainous visual hallucination. In contrast, visual epileptic auras are predominantly multicolored with a circular or spherical pattern as opposed to the predominantly black-and-white zigzag pattern of migraine (99). In contrast to migraine, epileptic visual auras last for only seconds (100).

The sensory auras of migraine and epilepsy also differ. In migraine, the auras are paresthesias (pins and needles) that typically begin in the hand, move up the arm, skip the shoulder, and move into the face and tongue over a period of 10 to 15 minutes. They are often associated with a visual aura (101). Sensory epileptic aura is typically briefer and is often described as burning, cramping, stinging, aching, electric, or throbbing.

Transient global amnesia (TGA) is a memory disorder of unclear etiology, with possible migrainous or ischemic etiology. Imaging studies of TGA are consistent with CSD. PET imaging, in a patient experiencing TGA, demonstrated metabolic depression in the left frontal and temporal cortices; the hippocampal gyrus was spared and CBF was preserved or slightly increased (102). CBF was increased in the left parietal cortex and reduced in the left occipital cortex, both with normal metabolism. This is similar to CSD, in which there is first a wave of decreased metabolism associated with brief hyperemia, followed by oligemia as metabolism normalizes, spreading from occipital to frontal cortex. Volpe et al. (103) demonstrated hypometabolism of the hippocampus using PET imaging in a patient with TGA, and Otsuka et al. (104) demonstrated hippocampal hypoperfusion during TGA using SPECT imaging. Their differing findings may be due to imaging at different phases of the TGA episode and therefore different stages of a CSD-like phenomenon with concomitant spread of metabolic and perfusion changes.

Strupp et al. (105) demonstrated diffusion weighted image (DWI) signals consistent with ischemia in the left mesial temporal lobe of seven patients with TGA, supporting ischemia. Saito et al. (106) reported a case of TGA in which DWI showed high signal in the left retrosplenium of the corpus callosum.

Several different mechanisms could clinically produce TGA, just as there are several mechanisms by which patients can experience paresthesias in both migraine and epilepsy.

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10 Strange Tastes, Smells, Sounds, Visions and Feelings: Nonepileptic Events that Mimic Simple Partial Seizures

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An accurate identification of epileptic seizure and epilepsy types is necessary to provide optimal treatment. The physician must distinguish between epileptic and nonepileptic events, and among epileptic events, between partial (focal) onset versus generalized onset seizure types. Further diagnostic evaluation helps determine the epilepsy syndrome, localization (if focal epilepsy), and etiology. Partial-onset seizures may begin with subjective phenomena or auras before progressing to loss of consciousness. The earliest symptoms experienced presumably arise in or near the epileptogenic zone, and provide significant clues in localizing the epileptic focus (Table 10.1). Thus, great attention must be paid to these symptoms, and the physician must carefully question the patient about them. Unfortunately, the experiences created by epileptic seizures can also be due to numerous other medical, psychiatric, and neurologic disorders or may be found in people without any pathological process at all.

This chapter reviews conditions that may be confused with *simple partial seizures* (SPS). SPS are epileptic seizures, arising from one region of the brain, which do not affect consciousness (1). "Consciousness" is a problematic term to define precisely, and is operationally defined as the "inability to respond normally to exogenous stimuli by virtue of altered awareness and/or responsiveness" (1). An SPS without motor symptoms has also traditionally been called an "aura." Aura is derived from the Greek for "breath" or "breeze." Its original use in English was for "a gentle breeze." In the seventeenth century, the aura epileptica was considered a rising breeze that caused the seizure (2). Cullen (1827) first referred to the aura specifically as a premonitory symptom in epilepsy and broadened its scope to a sensation of something moving in the body towards the head (2).

Electrographically, SPS begin in a localized discharge over the corresponding area of cortical representation. These discharges are not always recorded on the scalp. Indeed, one study with blinded reviewers found that only 15% of nonmotor SPS were associated with an ictal discharge on scalp EEG (3). The symptoms of an SPS may manifest as any of the countless perceptions, sensations, and emotions our brains can experience. Although we traditionally think of "positive" phenomena such as a hallucination or sweating, SPS can also cause negative symptoms such as a scotoma or

TABLE 10.1
Localizing Value of Simple Partial Seizure Symptoms

LOCATION	SYMPTOMS
Limbic	Olfactory Gustatory Epigastric Mnemonic Psychic-experiential
Lateral temporal lobe	Auditory Vestibular Aphasic Complex visual hallucinations
Occipital lobe	Visual hallucinations (usually unformed) and illusions
Parietal lobe	Somatosensory (contralateral) Visual Distortions of body or spatial perception
Frontal lobe	Focal motor Aphasic Forced thinking Cognitive disturbances

diminished auditory acuity. These experiences are divided into four main categories:

- With focal motor symptoms (not further considered here)
- With somatosensory or special-sensory symptoms: somatosensory, visual, auditory, olfactory, gustatory, and vertiginous
- With autonomic symptoms or signs (including epigastric sensation, pallor, sweating, flushing, piloerection, and pupillary dilatation)
- With psychic symptoms or disturbances of higher cerebral functions, affecting language, memory, cognition, affect, complex hallucinations, or illusions

As the electrophysiological epileptic seizure spreads and evolves over time, the corresponding symptomatology may change. SPS may progress into epileptic complex partial seizures (partial seizures associated with loss of consciousness) and possibly secondarily generalized tonic-clonic seizures, or they may even progress directly to the tonic-clonic seizure without a complex partial phase. SPS also typically last seconds or a few minutes, with the exception of the "aura continua" or simple partial status epilepticus. The diagnostic key to recognizing SPS is the temporal relationship to an event more clinically evident as an epileptic seizure. This relationship is not always present or readily identified in people with epilepsy. However, isolated auras or symptoms that suggest a SPS, but are never associated with focal motor features or impaired consciousness, are a red flag: they may not be caused by seizures. What is the likelihood that someone with paroxysmal subjective symptoms has epilepsy? Ardila et al. (4) surveyed 2,500 subjects in a general population sample for the presence of episodic psychic symptoms. Although some subjects had epilepsy (as might be expected in such a large group), many risk factors for such feelings were identified, including head injury, car accident, febrile illness, or birth injury. Significant correlations existed with other paroxysmal conditions such as sleep disorders, migraine, and allergies. Holmes and Dodrill (5) reviewed 379 adults who underwent video-EEG monitoring to characterize subjective events. They found in this more highly selected group that 52% had epileptic seizures, 7% had psychogenic nonepileptic seizures (NES), 1% had both, and 40% had only subjective events. Thus, nonepileptic causes of subjective events are very common and must always be considered in the differential diagnosis.

Two case examples illustrate the diagnostic difficulties in clinical practice.

CASE STUDY #1. A 25-year-old woman presented with a history of seizures since her teen years. Seizures began with several minutes of confusion or cognitive difficulty (but preserved responsiveness) before secondarily generalizing into a tonic-clonic seizure. On careful questioning, she noted that she had frequent, strong sensations of déjà vu. On the basis of this history, the diagnosis of partial epilepsy (probably temporal lobe) was made, but trials of carbamazepine and other drugs were ineffective. Video-EEG monitoring captured typical episodes: her periods of cognitive difficulty were actually frequent, brief absence seizures with a 3-Hz generalized spike–wave pattern on EEG, which evolved to a primary generalized tonic-clonic seizure. The déjà vu spells had no EEG correlate. She became seizure-free after changing medication to divalproex sodium.

CASE STUDY #2. A man in his 30s had a history of rare generalized tonic-clonic seizures, usually occurring when he was off medication. He also complained of daily episodes of difficulty thinking on awakening each day, diagnosed as complex partial seizures. Trials of multiple antiepileptic

medications increased to toxic levels and did not alleviate these latter symptoms. Video-EEG monitoring captured several typical spells: all occurred in the early morning hours, on arousal from sleep, and none showed EEG seizure patterns. The diagnosis of confusional arousal was made, allowing significant medication reduction and elimination of both toxicity and anxiety.

We approach the differential diagnosis of nonepileptic causes of SPS-like phenomena by first broadly considering some common alternative paroxysmal disorders, and then more specifically addressing the symptomatology described in the ILAE seizure classification.

NONEPILEPTIC PAROXYSMAL DISORDERS

Cerebrovascular disease often causes paroxysmal neurologic symptoms. Like an epileptic seizure, cerebral ischemia evolves over a brief period and through neuroanatomically related symptoms. Transient ischemic attacks (TIAs) may leave no permanent sequelae, either clinically or on neuroimaging, making them sometimes difficult to distinguish from seizures. This distinction may be particularly problematic in the patient with a known prior stroke (an epilepsy risk factor) and recurrent symptoms in the same region. Although the possibility of cerebrovascular disease may be more obvious in those with clear risk factors, such as age or heart disease, it can also occur in younger patients with more obscure causes of stroke, such as hypercoaguable states or vascular anomalies. The EEG may show focal slowing in patients with cerebrovascular disease, making the diagnosis even harder to distinguish from epilepsy. Stroke, like other destructive lesions, can cause "release" hallucinations. Such hallucinations have less localizing value than those due to cortical irritation (6,7). For example, visual hallucinations occur in more than half of patients with visual loss, with simple forms occurring more than twice as frequently as complex hallucinations (7). Following ocular enucleation, simple visual hallucinations may occur despite normal vision in the remaining eye (8). Simple and complex visual hallucinations also occur in patients with pseudotumor cerebri who have only slightly enlarged blind spots (7). Therefore, simple sensory deprivation cannot explain all release hallucinations. It is uncertain if the confabulatory visual reports of patients with Anton's syndrome (denial of cortical blindness) represent release hallucinations or fabrications. Patients with peduncular hallucinations experience vivid experiential phenomena (e.g., hallucination of a brightly colored parrot) and dreamlike behavior, often resulting from rostral brainstem infarction (the top-of-the basilar syndrome) (9). Peduncular hallucinosis probably occurs via a release mechanism.

Cardiovascular conditions may cause paroxysmal autonomic symptoms similar to SPS phenomena, and are discussed further below.

Migraine

Migraine is an extremely common condition that causes episodic neurologic symptoms. Migraine with aura (classic migraine) begins with one or more symptoms, such as an hallucination of flashing lights, which may progress over 5 to 30 minutes, followed by a typical pulsating unilateral headache with nausea and vomiting, photophobia, and sonophobia, lasting up to hours. Diagnostic confusion with epilepsy is possible for several reasons. The range of experiences of a migraine aura overlaps extensively with SPS symptoms. Migraine auras include i) visual hallucinations (e.g., flashing lights, wavy or zig-zag lines, spots), illusions, blurry vision, scotoma; ii) olfactory hallucinations or illusions; iii), tingling or numbness of the face or extremities, typically on the side where the headache later develops, loss of sensation or hypersensitivity to tactile stimuli; iv) vertigo, v) auditory hallucinations or illusions, or diminished or loss of hearing; vi) difficult with speech production or anomia; vii) confusion; or viii) weakness (10).

The temporal evolution of an aura usually distinguishes migraines and seizures. For example, paresthesias spreading from the fingers to the shoulder march over seconds (usually <30 secs) in a case of epilepsy and over minutes (often more than 5 minutes) in a patient with migraine. A migraine aura that evolves more rapidly may be harder to distinguish from an SPS. An SPS with or without a complex partial seizure may be followed by a postictal tension or migraine headache (11), further confounding the differentiation of seizure from migraine. *Migraine dissocié* (migraine without headache) may occur with only the aura, thus the lack of headache makes recognition difficult. Lastly, there is a high comorbidity of epilepsy and migraine, and it may be difficult to determine which symptoms are due to which condition in an individual patient (12). Patients may need more intensive diagnostic evaluations, such as with ambulatory or video-EEG monitoring, to clarify the nature of the symptoms, and particularly in determining how to treat specific symptoms in patients with both epilepsy and migraine. Several antiepileptic medications (e.g., valproate, topiramate) are effective in migraine prophylaxis, thus

allowing a simplified treatment for patients with both conditions or providing a shotgun therapy in cases that remain diagnostically inconclusive.

Sleep Disorders

Sleep disorders are common and cause paroxysmal symptoms. Feelings of altered awareness can occur in any of the hypersomnic syndromes. Hallucinatory experiences are common in narcolepsy, particularly at sleep onset (hypnogogic) but also on awakening (hypnopompic). In such cases, dreamlike experiences occur during an awake state and represent an uncoupling of the dreaming state and sleeping state.

Intoxication

Intoxication can be environmental, iatrogenic, or intentional (e.g., alcohol or recreational drug use). Although intentional substance is usually apparent in the acute setting, later aftereffects of drugs, such as flashbacks after hallucinogenic drug use (13), may occur episodically. Withdrawal symptoms may also escape detection even when toxin screens are obtained. Medication side-effects may be related to dose or blood levels, and careful questioning of the patient may reveal this relationship. Side effects of infrequently used medications are often not recognized. Further, even commonly used agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) can cause aseptic meningitis, hallucinations, and psychosis in susceptible individuals (14). A toxicity to medications may develop slowly or cause secondary problems (e.g., peripheral neuropathy that causes paresthesias). Rapid rises in the blood levels of antiepileptic drug can cause paroxysmal visual or vestibular changes. Environmental intoxications may fluctuate with location or season, and may be much harder to discern.

Infectious and Inflammatory Disorders

Viral encephalitis, most commonly herpes and Epstein-Barr, often cause focal neurological symptoms. Olfactory or gustatory hallucinations or illusions can result from the seizures that complicate encephalidites. However, these symptoms can also result from direct infection causing irritation or destruction of neurons in primary or association sensory areas for olfaction, taste, or other sensory functions. Epstein-Barr infection can cause prominent distortions of body image and visual hallucinations (Alice in Wonderland syndrome) (15).

Mycoplasma pneumoniae can also cause sensory and affective changes (16). In patients with encephalitis who are treated with acyclovir, it is important to remember that this drug can cause hallucinations and confusion when toxic levels are present, as occurs in the elderly and in patients with renal insufficiency (17). In Third World countries, rabies remains common and often presents with paroxysmal sensory hallucinations and illusions, as well as affective and autonomic symptoms. Other central nervous system (CNS) infections, such as meningitis and cerebral abscess, can also secondarily affect sensory and limbic areas and thereby evoke hallucinations, illusions, and psychic phenomena.

Many inflammatory disorders such as systemic lupus erythematosus (SLE), Sjogren's syndrome, and other autoimmune disorders can affect the brain and cause paroxysmal sensory, affective, and autonomic symptoms (18). Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections can also cause various paroxysmal motor as well as sensory and cognitive-affective symptoms (19).

Metabolic Disturbances

Metabolic disturbances can occur episodically, as with hypoglycemic symptoms in diabetes mellitus or in patients with insulinomas. Many endocrine disorders and disturbances of electrolytes can alter the sensitivity of sensory systems (e.g., increased sensory sensitivity in Addison's disease) or cause hallucinations or illusions (e.g., thyrotoxicosis). These endocrine and metabolic disorders can also exacerbate or provoke epileptic seizures. Pheochromocytomas and carcinoid tumors can cause paroxysmal autonomic, visceral, and affective symptoms (20). Attention to the general medical history and screening laboratory testing can help to evaluate these potential causes.

Multiple Sclerosis

Multiple Sclerosis (MS) can cause a wide variety of paroxysmal symptoms. Although the classic demyelinating episode produces more persistent symptoms lasting days or weeks, recurrent briefer symptoms may occur, particularly with provocative factors such as temperature elevation. Lesions at the dorsal root entry zone or other central white matter tracts can cause lancinating pain that may respond, at least partially, to antiepileptic drugs that reduce aberrant neural signals. The incidence of epilepsy is increased in MS compared to the general population, making it difficult sometimes to evaluate paroxysmal symptoms.

Intra- and Extraxial Brain Tumors

Tumors can evoke paroxysmal sensory, cognitive, and other behavioral changes that do not result from

seizures (21,22). For example, parietal tumors can cause paroxysmal pain or tactile hallucinations (23) and spinal cord tumors can cause paroxysmal limb pain (24). In addition to classical headaches, paroxysmal head pain can result from brainstem or cerebral tumors (25).

Disturbances of Peripheral Sensory Organs

Disturbances of peripheral sensory organs may produce paroxysmal sensations that can be confused with SPS. The irritation or destruction of the sensory nerves can also lead to paroxysmal hallucinations, illusions, or sensory deficits. For example, recurrent spells of rotational vertigo and postural imbalance were elicited and modulated by changing the horizontal head positions in a patient with a right cerebellopontine-angle arachnoid cyst that compressed the vestibulocochlear nerve (26). These are discussed in more detail under individual symptoms.

Psychiatric Conditions

Psychiatric conditions are another important, common category of causes for paroxysmal psychic symptoms. The Silberman-Post Psychosensory Rating Scale (SP-PSRS) assesses a variety of paroxysmal sensory, cognitive, and affective symptoms that overlap with the simple partial seizure phenomena reported by partial epilepsy patients (27,28). These symptoms are common in patients with bipolar disorder and other affective disorders but rare in healthy controls (27,28). Psychotic conditions may cause complex hallucinatory, affective, and sensory experiences. Panic attacks may produce autonomic and affective symptoms (similar to those in SPS) from temporolimbic foci. Dissociative states can cause episodic memory impairments. As in several other conditions discussed, there may be significant comorbidity between psychiatric diseases and partial epilepsy, making it difficult to assign a clear cause to an individual symptom. Careful neurologic evaluation including video-EEG monitoring may be necessary to rule out seizures, and a thorough psychiatric evaluation is necessary even in patients with known epilepsy if they present with potentially psychiatric complaints.

SIMPLE PARTIAL EPILEPTIC SEIZURES AND THEIR NONEPILEPTIC IMITATORS

Sensory Symptoms

Somatosensory

Somesthetic (haptic) hallucinations include tactile sensations as well as bodily (corporeal or internal) feelings. Corporeal feelings include muscle, ligament, joint, and bone sensations and deep pain. These internal feelings also include poorly localized symptoms such as nausea, hunger, thirst, and sexual pleasure. Haptic hallucinations pose an enormous diagnostic problem since itches, tickles, pains, aches, and other corporeal sensations cannot be consensually verified (29). Notably, sexual hallucinations can occur during or after sedation, especially with newer anesthetic agents such as midazolam and propofol (30).

Visceral hallucinations and illusions may accompany neurological disorders other than epilepsy, such as thalamic pain syndrome and multiple sclerosis, and psychiatric conditions such as bipolar and psychotic disorders. Visceral hallucinations often include poorly localized and sometimes bizarre feelings.

Tactile hallucinations are common in withdrawal states such as delirium tremens and intoxication with amphetamines, cocaine, chloral hydrate, or atropine (31). These drug-induced states may cause formications, a feeling of ants crawling under the skin. Thalamic or parietal lesions can cause unilateral formications (32,33).

Visual Complaints

Visual Hallucinations. Visual hallucinations occur in many neurologic and psychiatric disorders. These hallucinations may occur in head trauma, ischemic damage, and neurologic conditions that compromise any portion of the visual system from retina to the occipital lobe, temporal visual association areas, or limbic areas. Visual hallucinations result from destructive and irritative lesions of the visual system. Simple visual hallucinations include spots of white light, colored or geometric forms, or positive scotomas (e.g., "heat waves" surrounding a black hole). Complex visual hallucinations, such as the image of a child, can occur in a limited portion or throughout the visual field. Complex and simple visual hallucinations can occur in a clear or clouded sensorium. Photopsias, sparks, or flashes of light, are the most common simple visual hallucination. Simple visual hallucinations arise from a dysfunction in the visual pathways from the eye to the primary visual cortex or, less often, from irritative lesions of the visual association cortex and medial temporal lobe. These types of hallucinations have little localizing value, but are usually ipsilateral to lesions anterior to the chiasm and contralateral to postchiasmal lesions. Patients with homonymous hemianopia and simple visual hallucinations often incorrectly describe the image as being in the contralateral eye. If patients are uncertain about which eye is affected, ask them to test vision in each eye with the other eye closed. With

primary visual cortex lesions, hallucinations usually arise in areas of visual loss and are usually continuous and unformed. These hallucinations are often associated with an element of movement, as zigzag and weaving lights or a shower of sparks. However, interrupted flashes of light are not typical of hallucinations arising in the primary visual cortex. In any patient with the new onset of visual hallucinations, a structural lesion in the posterior cerebral cortex or other portions of the visual pathways must be excluded.

Formed or complex visual hallucinations usually result from lesions of the visual association cortices in the temporal, occipital, or parietal lobes. However, lesions in any part of the visual system can cause formed hallucinations. The images can be stationary or moving, single or multiple, or enlarged or diminished in size. Ictal visual hallucinations usually last less than 2 minutes and are often associated with illusions or hallucinations in other sensory modalities. Penfield and Perot (34) reported that formed visual hallucinations are most common with seizures arising in the nondominant temporal lobe. Multimodal hallucinations often result from systemic illnesses, hallucinogenic drugs, or alcohol withdrawal.

The Charles Bonnet syndrome is characterized by formed or unformed hallucinations in blind or partially blind persons. The hallucinations are perceived in the defective visual field and may be abolished by eye motion or closure of the blind eye. Hallucinations of color, faces, textures, and objects are correlated with cerebral activity in the ventral extrastriate visual cortex, both during and between hallucinations (35). Further, the content of the hallucinations reflects the functional specializations of the region. The rare disorder of peduncular hallucinosis was previously described. The pathophysiology of peduncular hallucinosis is uncertain, but is likely a release phenomenon, possibly resulting from a sleep abnormality that is present in most cases, and related changes in ascending cholinergic or serotonergic activity (36). Evening hallucinations in elderly subjects with cognitive deficits ("sundowning") and hypnogognic and hypnopompic hallucinations in narcolepsy may share pathophysiologic mechanisms. In all these disorders, the processes that activate dreaming during sleep may become abnormally activated during wakefulness.

Visual Illusions. Visual illusions, like visual hallucinations, are caused by destructive and irritative lesions of the visual system. In visual illusions, the image may be altered in size (micropsia or macropsia), shape (dysmorphopsia or metamorphopsia), position (telopsia), number (polyopia), color, or movement (37–39). The illusions may be restricted to areas of partial visual loss or may affect the entire visual field. In confused patients, real images may be perceived as familiar and more complex images. In alcohol withdrawal, for example, a patient may "see" a spot on the wall as a spider. Vestibular or oculomotor disorders may cause illusions with altered depth perception, tilting, and changes in shape (e.g., straight edges become curved).

Palinopsia. Palinopsia or visual perseveration, is the persistence or recurrence of a visual image after the excitatory stimulus is withdrawn (40). Palinopsia is illustrated in the words of a patient who shaved repeatedly (41): "I have shaved one side so that it is beautifully clean to my fingers. I looked back to find that the beard seemed to be still there. Because of that I sometimes shave myself twice, for no earthly reason." Palinopsia results from structural lesions of the parietal and occipital lobes of either the right or left hemisphere, but the right hemisphere is usually involved (42,43). Palinopsia can also complicate psychiatric disorders (e.g., schizophrenia, depression) and drug use (e.g., lysergic acid diethylamide [LSD], trazodone). With structural lesions such as stroke, palinopsia is usually a transient phenomenon, occurring during the progressive evolution or resolution of a homonymous visual field defect, and it appears in the area of visual loss. Rarely, palinopsia persists for years. Palinopsia may be related to the illusory visual spread, in which visual perception extends over a greater area than that which the stimulus would be expected to excite. For example, the patient looks at a clock and sees the area between 1 o'clock and 6 o'clock as being twice as large as the area between 7 o'clock and 12 o'clock (41). Palinopsia may be the result of an epileptic seizure, but is most often a release hallucination (40,43). Psychologic factors may contribute to palinopsia, as Critchley observed of such patients: "things they think about a lot do not go out of vision as quickly, as if they were slow in being switched off" (41).

Visual Synesthesia. Visual synesthesia is an optic percept induced by the stimulation of an auditory, tactile, or other sensory modality (44). For example, after feeling a specific object, a patient may see shapes or colors. Visual synesthesia can develop in both normal individuals and in patients with lesions throughout the visual pathways.

Visual Allesthesia. Visual allesthesia is the transposition of visual images from one homonymous half-field to another. This rare phenomenon usually occurs in patients with bilateral cerebral lesions, but may result from a partial seizure (45). Auditory and tactile sensations are frequently present.

Auditory Symptoms

Auditory hallucinations and illusions arise from injury to all portions of the peripheral and central auditory pathways. Auditory illusions are perceptual distortions of sounds (e.g., muffled, change in volume). Auditory hallucinations can be unformed, as in ringing, clicking, buzzing, or humming, or formed, as in voices or music. Auditory illusions, as well as both unformed and formed auditory hallucinations, can result from simple partial seizures arising in the lateral temporal lobe as well as a variety of other neurologic and psychiatric disorders (46). For example, stroke, multiple sclerosis, migraine, schizophrenia, psychotic depression, salicylate intoxication, cocaine and amphetamine psychoses, alcoholic hallucinosis, and delirium (47,48,49). The electrical stimulation of the primary auditory cortex (A1) elicits unformed auditory sensations, which may be selectively perceived in the contralateral ear (50). Lesions in the cochlea and auditory nerve cause ipsilateral auditory hallucinations, whereas cortical lesions cause bilateral or contralateral auditory hallucinations. Complex auditory hallucinations may be produced by the stimulation of temporal association or limbic areas (49,50). Musical hallucinations most often occur with nondominant hemispheric foci (49,51). Hemispheric lesions that cause auditory hallucinations and illusions are usually found in the posterior superior temporal gyrus, including A1 and the planum temporale (47). Schizophrenia is the most common cause of prolonged, formed auditory hallucinations in a clear sensorium. Typical schizophrenic auditory hallucinations include voices commenting on the patient's actions, voices discussing the patient in the third person, and voices repeating the patient's thoughts. Alcoholic hallucinosis is characterized by the abrupt or gradual onset of auditory (and occasionally transient visual) hallucinations with relatively clear consciousness. These prolonged auditory hallucinations may be persecutory, are often accompanied by paranoid ideation, and occur while the subject is, or has recently been, abusing alcohol. Recovery usually occurs within hours or days, but may take weeks or months.

Unformed and formed auditory release hallucinations are usually more prolonged than epileptic hallucinations. These release hallucinations result from destructive lesions of the auditory end-organs, nerves, or brain stem nuclei or pathways. Auditory hallucinations during SPS are almost always recognized as unreal, are paroxysmal in onset and offset, and usually last less than 3 minutes. Migrainous auditory hallucinations usually consist of hissing, rumbling, or growling noises (52). Both epileptic and migrainous auditory hallucinations are often associated with distortion or partial loss of hearing. Nonpsychotic children with a history of migraine and affective disorders may experience formed auditory hallucinations of voices (53).

Olfactory Disturbances

Alterations in olfactory sensibility include a reduction or loss of sensation, impairment of higher order of olfactory discrimination, and olfactory illusions and hallucinations. Olfactory function should be systematically evaluated in patients with olfactory symptoms and in all patients after head injury (54). Unfortunately, olfactory testing is often omitted from neurologic and neuropsychiatric evaluations, highlighted by the common shorthand "CN II–XII." Olfactory sensation can be intermittently disrupted by a physical obstruction in the nasal canal that prevents molecules from reaching the receptor epithelium; dysfunction of the olfactory receptor or cranial nerve I; or a brain disorder. The olfactory nerve delivers information to the primary olfactory cortex (pyriform cortex), secondary olfactory cortex (orbitofrontal lobe), and the medial dorsal thalamic nucleus. The vast majority of olfactory disorders result from peripheral causes.

Anosmia is the loss of smell sensation. It can be transient or permanent, most often resulting from a local nasopharyngeal condition or head injury. Recurrent anosmia is rare and is usually more prolonged than SPS symptoms, permitting easy differentiation from seizures. *Dysosmia,* an altered sense of smell, most often results from a local nasopharyngeal process such as toxin exposure, physical irritant, or medication effect; less often, it results from a direct structural or functional disorder of the olfactory bulb or central olfactory system. The abnormal smell may appear episodic, since the distorted perceptions occur only when certain airborne aromatic molecules interact with the injured receptors that detect its presence. The abnormal perception therefore appears unprovoked, random, and recurrent. This experience may be similar to an aura or a simple sensory size, in which an "unpredictable" smell of a burnt substance occurs.

Olfactory hallucinations can occur in epilepsy associated with central processes such as epilepsy, depression, or a medication effect. When related to brain dysfunction, olfactory hallucinations are primarily seen in temporal lobe disorders including partial seizures, migraine, Alzheimer's disease, and in psychiatric conditions (55,56). However, they can also occur with inferior frontal lesions that compress the olfactory bulb (e.g., orbital meningioma).

Case Study 3. An adolescent with migraine and olfactory hallucinations was found to have a tumor in the temporal lobe on MRI, emphasizing

the importance of excluding serious pathologies in patients with other etiologies (e.g., migraine) that can cause olfactory hallucinations (57).

Olfactory dysfunction is a common finding in patients with Parkinson's disease (PD). Deficits in odor identification are more frequent in advanced and treated PD patients. When these perceptions occur in uncinate or temporal lobe seizures, they may be described as an unpleasant but often unidentifiable smell. An altered mental status accompanying or subsequent to the smell sensation would suggest an epileptic etiology. Olfactory hallucinations and delusions can also occur in a transient, recurrent pattern in other neurologic conditions including depression, schizophrenia, and alcohol withdrawal. A greater variety of olfactory sensations exists in psychiatric and neurodegenerative conditions compared to the more characteristic "unpleasant" olfactory perceptions in epilepsy. In psychiatric conditions, patients often specify where the smell perceptions appear to emanate from. Patients describe intrinsic olfactory hallucinations (emanating from themselves) or extrinsic (emanating from others).

Common environmental factors include cigarette smoke and industrial toxins. Several medical treatments are common causes of olfactory disturbances including hemodialysis, radiation therapy, and specific medications.

Many drugs affect smell as well as taste sensations. Patients may report total loss of taste or, more likely, an alteration of taste sensation with or without a disturbance of smell. Cancer chemotherapy often disrupts both smell and taste perception (58). Most drug-induced smell disorders impair but do not eliminate the perception of familiar vapors (e.g., perfumes). Drugs may affect the receptors directly or indirectly by producing deficiencies of vitamins and essential elements such as copper and zinc. Zinc is critical for maintaining receptor integrity. An alteration in receptor sensitivity, inhibition of receptor turnover, and inactivation of events in the receptor-coupled second-messenger system and activation of sodium or calcium ion channels can distort sensory transmission. Drug-induced impairment of these events can impair the generation of action potentials transmitted along smell and other sensory nerve pathways to the brain.

Head trauma is a very common cause of impaired smell sensation. The incidence of olfactory nerve dysfunction in moderate head injury is 7%, increasing to 30% with severe head injuries or anterior cranial fossa fractures (59).

Recovery most frequently occurs within 3 months. However, residual deficits may remain. In some cases, olfactory hallucinations develop shortly after the transection of olfactory nerve fibers passing through the cribiform plate or can occur as a delayed phenomenon. In such cases, we have occasionally had success with gabapentin in reducing these hallucinations, possibly by reducing ephaptic transmissions.

Gustatory Disturbances

Hallucinations and illusions of taste perception can occur with disorders of the sensory end organs, peripheral nerve lesions, and brainstem, white matter, and cortical areas that represent gustatory sensibility. *Ageusia* is the loss of taste perception and *hypogeusia* is diminished taste percpetion. Gustatory hallucinations can also occur in psychiatric disorders such as schizophrenia and bipolar disorder, but neurologic and drug-induced disorders must be carefully excluded, even in patients with primary psychiatric disorders (60).

In healthy volunteers, the topical application of a tricyclic antidepressant can impair responses to a wide range of taste stimuli (61). Several other medications can deplete of vitamins and minerals and result in distortion of taste (62). Zinc depletion can occur with captopril, enalapril, and various diuretics. Penicillamine can result in copper depletion, and some cholesterol-lowering drugs decrease the absorption of fat-soluble vitamins that are needed for receptor viability, including vitamin A.

Medications that cause sodium and calcium channel disturbances in sensory receptors typically inhibit function and therefore the sensation of taste. Drugs that inhibit sodium channels are amiloride, spironolactone, and lithium. Calcium channels blockers, such as nifedipine, have similar effects.

Several studies of diagnostic tests of gustatory function reveal that none of the subjective tests are satisfactory because they produce variable responses and cannot detect psychogenic disease or malingering (63). Gustatory-evoked potential testing is an objective measure that does not require expensive equipment and can be reliable (63).

Vertigo

Vertigo is a common disorder, but rarely results from epileptic discharges. The diagnoses of epileptic vertigo (tornado epilepsy) must be made with caution. Isolated vertigo is rarely the result of a partial seizure focus in the temporoinsular or frontal cortex (64,65). In patients with known epilepsy, the vast majority of vertigo results from peripheral causes (e.g., vestibular neuronitis, Meniere's disease) or antiepileptic drug toxicity (e.g., carbamazepine or phenytoin). Other CNS causes of vertigo include migraine, and brainstem stroke or compression.

Autonomic Symptoms or Signs

Ictal autonomic events cause alterations in cardiovascular, respiratory, gastrointestinal, cutaneous, pupillary, genital, and urinary symptoms and signs (66,67). They can also elicit visceral, emotional, and sexual feelings. Ictal activation of the central autonomic network (i.e., amygdala, anterior insula, anterior cingulate, posterior orbitofrontal) often evokes hallucinations and occasionally illusions of visceral or corporeal sensations (68). These may be painful, but many are vague, poorly localized, and indescribable. When autonomic phenomena are the sole manifestation of partial seizures, the diagnosis is often delayed or missed. Generalized sensations, such as heat over the entire body, may result from the activation of areas that receive input from autonomic areas. Autonomic features such as palpitations, tachycardia, tremor, and piloerection simulate the peripheral accompaniments of "fear" and can contribute to evoking the emotion of fear during some partial seizures. Sympathetic activation predominates during most partial seizures, causing tachycardia, tachypnea, increased blood pressure, pupillary dilatation, diaphoresis, and facial flushing. However, ictal parasympathetic activation can occur, producing excessive salivation; gastric acid secretion; peristalsis; decreased heart, respiratory rates, and blood pressure; and miosis.

The differential diagnosis of paroxysmal autonomic phenomena is extensive, spanning many neurologic, medical, toxic-metabolic, and psychiatric disorders. The key elements of the diagnosis depend on the paroxysmal nature of the symptoms and their brief duration. However, when epilepsy patients present with autonomic and visceral symptoms that are are not characteristic of their usual stereotypic auras (those that occur before complex partial or tonic-clonic seizures), medical causes (e.g., myocardial infarct, gastrointestinal reflux disorder, gastritis) should be excluded. Indeed, epilepsy is the cause of autonomic symptoms or signs in less than 1% of hospitalized or outpatient medical or psychiatric populations, or in individuals without a known medical history.

Psychic Phenomena

Psychic phenomena in epilepsy include a wide range of experiential states. These states are among the most difficult to describe by patients with epilepsy. Various cognitive, linguistic, mnemonic, and affective phenomena can occur during simple partial seizures (Table 10.2). The differential diagnosis of psychic symptoms is extensive. These symptoms can occur in many neurologic disorders including transient ischemic attacks and stroke (e.g., speech arrest, aphasia, and amnesia), transient global amnesia (e.g., amnesia, confusion, altered familiarity), migraine (e.g., déjà vu, aphasia, affective changes), multiple sclerosis, and brain tumors. Differential diagnosis often relies on the paroxysmal nature of symptoms and a duration of 10 to 180 seconds in simple partial seizures, whereas most of these other disorders cause longer-lasting symptoms. Psychic symptoms can occur in many psychiatric disorders, and in intoxications and toxic-metabolic disorders.

TABLE 10.2
Psychic Phenomena in Epilepsy

Cognitive	**Mnemonic**
Dreamy state	Déjà vu
Derealization	Jamais vu
Depersonalization	Amnesia
Dissociation	Verbal
Religious	Nonverbal
Sexual	Autobiographical
Forced thinking	
Altered speed of thoughts	**Affective**
Distortion of time	Fear
Distortion of body image	Psychic phenomena in epilepsy
Language	Anger
Speech arrest	Pleasure
Nonfluent speech	Laughing (gelastic)
Anomia	Crying (dacrystic)
Paraphasias	
Comprehension deficit	
Repetitive utterances	
Dyslexia	
Agraphia	

Vasovagal and Cardiogenic Syncope

Syncope is caused by a reduction of cerebral perfusion and oxygenation. Loss of consciousness may be rapid, but when gradual, various autonomic symptoms (presyncope) can be confused with SPS, and the syncopal episode confused with a complex partial or tonic-clonic seizure. Characteristically, there is lightheadedness, visual blurring or "graying out," muscle weakness, tinnitus, gastrointestinal symptoms (e.g., nausea), diaphoresis, and pallor (69).

Confusion with epilepsy arises because both syncope and partial seizures may begin with similar autonomic symptoms and lead to loss of consciousness and even convulsive movements (70). Syncope differs from partial epilepsy in that it is often related to posture, does not arise out of sleep, and has a longer aura. Syncope is less often associated with urinary incontinence, convulsions, or postictal symptoms such as confusion or focal neurological deficits.

CONCLUSION

The evaluation of paroxysmal subjective symptoms is difficult. Such symptoms may represent SPS when they reliably precede other partial-onset seizure types. Problems arise when symptoms occur in isolation or are inconsistent with the presumed location of the epileptic focus. This chapter provides an overview on these imitators. An open mind remains the best diagnostic tool for these complaints.

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11 Dizziness or Vestibular Problems Resembling Seizures

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Prior to the work of Ménière in the 1860s, when it was made clear that vertigo was most often of otic origin, the symptom, loosely defined, was commonly considered to be a manifestation of a paroxysmal cerebral disorder. In an excellent historical overview of the linkage between vertigo and epilepsy, Bladin (1) documents the medical, social, and legal problems arising from a nosographic conjunction in the nineteenth century into a poorly defined clinical entity, "epileptic vertigo." Although the term was in general use from its introduction by Esquirol in 1838, to the early twentieth century, there was considerable disagreement among prominent clinicians about the condition it defined. A lack of clarity and a drift in its meaning also was evident in the writings of the more prolific authors of the period, such as Hughlings Jackson (2) and Gowers (3). However, it should be noted that there was as much vagary in the use of the terms "dizziness," giddiness," and "vertigo" to describe the subjective symptoms as there was in designating clinical entities with such terms as "epileptic (or epileptoid) vertigo," "petit mal," or "slight paroxysm of epilepsy."

Many authors used the term "giddiness" interchangeably with "vertigo," whereas others reserved its use for mild, nonspecific symptoms of spatial disorientation or confusion. Clear examples of the former are not confined to the literature on epilepsy or otic disorders. For example, Duchenne (4) wrote "Giddiness is usually the first symptom of cerebellar disease … staggering [is caused] by giddiness and therefore I have called it *vertiginous staggering* [titubation vertigineuse]." The use of this term can be found in the English literature of the 1940s, for example: "[In] thrombosis of this branch (posterior inferior cerebellar artery) … the patient is taken with intense giddiness and, if standing, tends to fall to one side" (5). Interestingly, the section in which this quotation appears is referenced in the index under "vertigo."

Use of "giddiness" to connote a mild or uncertain vertiginous experience or other vague symptom can be found with increasing frequency beginning at the end of the nineteenth century—for example, Gowers, although he observes that "the original meaning of 'giddy' was mirthful (a sense still extant) and that of 'dizzy' was foolish or dull" (3). As for the term epileptic vertigo, it continues to appear in the literature, along with such others as epileptic dizziness, epileptic nystagmus and epileptic tinnitus, despite its problematic history and the widespread acceptance of more contemporary seizure classifications. It must be emphasized that the replacement of the term in no way minimizes the clinically significant link between vertigo and epilepsy.

From the extensive and expanding literature on cortical stimulation, it is clear that numerous sites exist from which contralateral turning of the eyes, head, and trunk can be elicited (6,7). Cortical substrates for the production of vertigo that may be associated with intrinsic epileptic excitability have also been known for more than half a century. For example, Fulton (8), citing the work of Foerster (9) and Penfield and Boldrey (10), noted that stimulation in the conscious human brain of Brodman area 22, particularly in its posterior region, generates the sensation of vertigo. Penfield and Jasper (7) reported inducing a seizure, which they classified as vertiginous, by occipital lobe stimulation.

In this chapter, we address the problem of distinguishing vertigo of cortical origin—that is, as a symptom of simple or complex partial epilepsy—from the paroxysmal syndromes arising in disorders of the vestibular system. The goal in each case is to make such distinctions on the basis of positive clinical information and avoid exclusionary diagnoses whenever possible. Since the clinical patterns resulting from lesions in the vestibular pathways are defined by locus, it is helpful to begin with a detailed review of the peripheral and central mechanisms underlying normal and pathologic vestibular function.

ANATOMY AND PHYSIOLOGY OF THE VESTIBULAR SYSTEM

The vestibular system is responsible for sensing motion and for generating the compensatory movement required to maintain the stability of the body, head, and eyes in space. The components of this system include the vestibular labyrinth, the vestibular portion of the VIIIth nerve, the vestibular nuclei, and their brainstem and cortical connections. The majority of what the vestibular system does is at a brainstem level and functions below the level of conscious perception. As the primary example, the vestibulo-ocular reflex (VOR) acts as a stabilizing system for the visual system. Sensing both linear and angular movements, the VOR stabilizes gaze by moving the eyes so that they counter head and body movement. This fixes the image on the retina and ensures adequate acuity (Figure 11.1).

It is critical to understand that all of the semicircular canals operate as opposed pairs. Each horizontal canal is oriented so that movement causing excitation on one side leads to inhibition on the other side. Since the primary afferent neurons have a tonic firing rate, excitation and inhibition are expressed as increases or decreases in firing rate in each nerve. The vertically oriented canals are also paired, with each anterior canal opposing the contralateral posterior canal. The otolith organs sense linear acceleration, which occurs with linear motion or with changes in orientation with respect to gravity (Figure 11.1d–e). These organs are also paired, with each side excited by ipsilateral head tilt and inhibited by contralateral head tilt.

This push-pull arrangement is preserved in the central portion of the vestibular system. Although a detailed description of vestibular neuroanatomy is beyond the scope of this chapter, a brief discussion of the connections of the horizontal semicircular canals is instructional. Much of the VOR operates through a three-neuron arc (12) which—like a muscle stretch reflex—is subject to descending control but operates without conscious awareness. In the case of angular acceleration about a vertical axis, the cupula of the horizontal semicircular canal is deflected, causing a change in hair cell ionic currents (13; Figure 11.1 a–b.). The resultant receptor potential causes a change in the firing rate of afferent fibers in the vestibular nerve, which synaptically excite neurons in the ipsilateral medial vestibular nucleus (Figure 11.2). These neurons project directly to the contralateral abducens nucleus, leading to the contraction of the lateral rectus motoneurons. The medial vestibular nucleus neurons also send projections across the midline to the medial longitudinal fasciculus, ensuring conjugate movements of the two eyes. Because the connections are excitatory, increased firing from a canal afferent leads to contralateral movement of the eyes (Figure 11.1c). In the event of a unilateral vestibular lesion, the tonic activity from the intact side drives the eyes to the side of the lesion, generating a constant speed, slow-phase movement. When the eyes are deviated substantially across the midline a saccadic eye movement—or fast phase—resets the eyes to a position near the midline. This results in the linear nystagmus characteristic of vestibular disorders.

Vestibular Cortex

Although the VOR is largely mediated at a subcortical level, the conscious experience of vestibular stimulation—either as natural motion or as vertigo—indicates a cortical representation of the vestibular system. A number of cortical areas have been labeled "vestibular cortex," derived from the anatomical areas in a variety of species. Guldin et al. (15) undertook to define cortical areas in the squirrel monkey physiologically by determining which had vestibularly driven neurons. They located vestibular inputs to areas 3a, parietoinsular vestibular cortex (PIVC), area 7, and the "visual posterior sylvian area." Vestibular units were rare in areas 3a and 7. The visual posterior sylvian area responded best to optokinetic input (i.e., full-field visual stimulation), whereas PIVC responded best to vestibular input. Dense interconnections exist between

FIGURE 11.1

The peripheral vestibular apparatus. (a–c) Representation of semicircular canal with stereocilia and kinocilia of hair cells on crista embedded in cupula. (a) Position of hair cells and cupula with head stationary. (b) During head acceleration in the clockwise direction, the inertia of the endolymph causes the cupula and hair cell cilia to deflect in the counterclockwise direction. (c) For head rotation to the right about the yaw or long body axis, this produces a compensatory eye movement to the left over the angular vestibulo-ocular reflex (aVOR). (d) Representation of utricular macula with head upright, showing hair cells, otolithic membrane and otoconia. (e) Head tilt to the left causes movement of the otoconia in the direction of gravitational force (g), deflecting the sterocilia and kinocilia of the hair cells. The eyes counter-roll against the head tilt, which tends to maintain the relative position of the retina in space. (f) Linear translation of the head to the right (arrow over head) causes similar deflection of the otoconia and hair cells to the left. For sudden, high-frequency head movements, the linear vestibulo-ocular reflex (IVOR) produces a compensatory eye movement to the left. [Reprinted from (11)]

3a and PIVC. Bottini et al. (16) studied humans by position emission tomography (PET) cerebral perfusion patterns in response to cold caloric stimulation. They demonstrated activation in the contralateral temporoparietal junction, posterior insula, putamen, anterior cingulate cortex, and primary sensory cortex (S1). In another human study, Bucher et al. (17) reported that galvanic stimulation at the mastoid level was associated with bilateral activation in the middle part of the insula, the posterior part of the insula, and the transverse temporal gyrus. Control stimulation (for pain) given in the C4–5 regions similarly resulted in the activation of the middle part of the insula. From the comparison of primate physiology and human PET data, it

FIGURE 11.2

The horizontal vestibulo-ocular reflex. With excitatory stimulation of the cupula of the horizontal semicircular canal, impulses are generated in the vestibular portion of the eighth nerve (VIII). Projections to the medial vestibular nucleus (MVN) in the dorsal pons make excitatory synapses on neurons that project to the contralateral abducens nucleus (VI). Excitatory projections onto motor neurons cause stimulation of the lateral rectus muscle (LR). Excitatory projections onto interneurons give rise to impulses that travel up the opposite medial longitudinal fasciculus to the oculomotor nucleus (III). Excitatory projections onto motor neurons cause stimulation of the medial rectus (MR). The net result of stimulation of the cupula is conjugate deviation of the eyes in a direction opposite that of the head turn. (Reprinted from [14])

would appear that the temporoparietal junction and the posterior insula are the most justifiable candidates for a vestibular cortex in the human. This also corresponds to the region of the posterior insula that Brandt et al. (18) identified as giving rise to disruptions in perception of the spatial vertical following stroke.

The Physiology of Vertigo

Under normal conditions of motion, the vestibular input reaches consciousness only minimally. By this we mean that awareness of motion usually can be taken for granted as a confluence of visual, tactile, auditory, and vestibular inputs that all indicate the same direction and speed of motion. Specific conscious awareness of the vestibular input usually arises from a situation in which there is sensory mismatch; on a windowless elevator, or within the cabin of a ship, for instance. Prolonged sensory mismatch of this sort often gives rise to motion sickness.

When the sensation of motion is illusory, we label the symptom vertigo. In such cases, a pathologic asymmetry arises in the vestibular system, causing nystagmus and a sensation of motion. This can be caused by a lesion in the labyrinth, the vestibular nerve, or the central vestibular system. In the case of the horizontal semicircular canal and its afferents, the mechanism for the nystagmus can be understood from Figure 11.2. Because vertigo is a vestibular sensation, unaccompanied by visual motion (or corroborating tactile or auditory signals), the sensory mismatch is generally pronounced, causing nausea and vomiting. Lesions of the vestibular nuclei, such as occur in a posterior inferior cerebellar artery (PICA) stroke syndrome, also give rise to vertigo. Interestingly, supratentorial strokes give rise to nonspecific dizziness, but not to vertigo (19,20). In contrast, as mentioned earlier, electrical stimulation of the posterior portion of the superior temporal gyrus gives rise to a sensation of rotation (7).

THE CLINICAL HISTORY

Definition of Terms

For the diseases considered in this chapter, patients typically present complaining of "dizziness." Unfortunately this term, much as is the case with giddiness, covers a broad range of neurologic and non-neurologic symptoms and serves for most patients as a general purpose term for sensory disorientation or imbalance. Similar common but relatively useless terms include "woozy," "spacey," and "drunk." It is useful to further categorize symptoms into *vertigo, intolerance of visual motion, lightheadedness, imbalance,* or a *rising sensation.* The vernacular is quite variable regarding the meaning of these terms; it is very important, therefore, to provide definitions for each of them.

Vertigo is the illusory sensation of motion. A true history of vertigo is of great value in identifying vestibular pathology, whether it is localized to the peripheral end organ, the vestibular nerve, or the central vestibular system. It should be determined whether there is a positional component to the vertigo; that is, whether the vertigo is brought on or made worse with changes in head position with regard to gravity or with regard to the neck.

A closely related symptom is that of oscillopsia. Oscillopsia is an illusory sensation of visual motion, frequently swinging or oscillating. This may occur when there is vestibular nystagmus or when there is failure of the VOR to stabilize the eyes during head motion. In the former case, patients often report that the "vertical hold" has failed, making an analogy to television. In the latter, patient liken the experience to viewing the world through a shaky, hand-held video camera.

Many patients with vestibular loss also complain of intolerance of visual motion. Typically, complaints include an inability to walk down a supermarket aisle

without feeling disoriented or nauseated. Similar complaints include intolerance of crowds (e.g., in malls or in train stations) and of large-screen movie theaters. The complaint is heard most often from patients with vertigo following head trauma, but may be reported by those with various types of peripheral vestibular disease. The symptom may result from an excessive reliance on visual cues to motion following loss of vestibular function.

Lightheadedness should be distinguished from vertigo or visual disorientation. This term should be reserved for the symptoms that precede syncope. Most patients are familiar with the sensation, either from having fainted at some point in the past or from getting up quickly after a prolonged period lying down. Lightheadedness is presumably due to cerebral hypoxia and may be cardiac or vasovagal in origin. The workup of syncope or lightheadedness need not include vestibular investigation unless there is a reasonable suspicion of vasovagal syncope triggered by vertigo. Such cases are exceptionally rare.

It is important to remember that anxiety may lead to symptoms similar to lightheadedness, possibly from hyperventilation. Visual disorientation is also reported in anxious states. Hypertension is associated with vague symptoms of lightheadedness or nonspecific dizziness, but not with vertigo. More often, hypertensive patients experience lightheadedness when their blood pressure drops, presumably related to antihypertensive medication.

Imbalance, is the inability to maintain the center of gravity, and its presence need not be associated with vertigo, visual disorientation, lightheadedness, or any other symptom. It is important to ask patients about feeling unsteady, about stumbling, and about falling. The causes of imbalance may be sensory or motor.

A rising sensation in the epigastric region without a clear sensation of whole body motion is common in epilepsy (occurring in 37% of hippocampal sclerosis cases and 15% of lesional cases). A rising sensation should be distinguished from vertigo, which is much less common with seizures and is more often seen with extratemporal lesions (21).

Symptoms may change character over time. It is not unusual for chronic vestibular disorders to give rise to vertigo initially and less well-defined symptoms of disorientation over time. A complete description of the patient's first attack is often the best indicator of their pathology. Although many patients become less able to describe their symptoms as time passes, the early episodes tend to remain clear in recollection. As an example, patients with long-standing benign paroxysmal positional vertigo may describe their symptoms as an "uncomfortable" feeling when supine, but will clearly recall the first several episodes as vertigo. Appropriate maneuvers will trigger both nystagmus and the uncomfortable feeling, thus confirming that the patient's experience of the typical vestibular episode has changed.

Precipitating Factors

For most patients, vestibular symptoms are episodic and not continuous. The factors that precipitate symptoms may provide important clues as to the etiology of the attacks. Vertigo brought on by bending or by lying supine and turning to one side is typical of benign paroxysmal positional vertigo (BPPV), a peripheral vestibular syndrome caused by otoconia or other debris in the semicircular canal. Lightheadedness brought on by getting up quickly from a lying or sitting position is typical of orthostatic hypotension. However, patients with BPPV may also have brief vertigo and nystagmus on sitting up quickly. Patients with vestibular loss may report fleeting vertigo or imbalance associated with rapid turning. This may be related to the imbalance between the two peripheral end organs.

Cerebrospinal fluid pressure changes are transmitted to the vestibular system through the cochlear aqueduct, therefore perilymph fistulas may be exacerbated by increases in intracranial pressure. Pressure from the intracranial space is transmitted to the membranous labyrinth, and perilymph is forced into the middle ear cavity through the fistula. As a result, anything that constitutes a Valsalva maneuver may trigger an episode of vertigo. This includes lifting heavy objects and straining at a bowel movement. Coughing or sneezing may also precipitate symptoms. Loud noises or sounds of a particular frequency may give rise to Tullio's phenomenon—vertigo elicited by noise. All of these are related to the transmission of pressure into the labyrinth, resulting in a stimulation of the vestibular system. This is interpreted by the patient as vertigo, oscillopsia, or both.

Hyperventilation may precipitate vertigo in a variety of vestibular conditions, both central and peripheral (22). Minor et al. (23), for example, reported nystagmus with vestibular schwannoma. Walker and Zee (24) have demonstrated that hyperventilation can also increase the downbeat nystagmus seen in cerebellar disorders. Patients develop vertigo after 1 to 2 minutes of hyperventilation, and nystagmus can be seen. Hyperventilation can, of course, also precipitate seizures and hyperventilation syndrome. The presence of nystagmus is the best clue to the vestibular origin of the symptoms. The distinction between hyperventilation syndrome and epilepsy is covered extensively in Chapter 18 of this volume.

Emotional factors are also important to recognize in anxiety or panic disorders. Panic attacks may be recognized by the associated anxiety and hyperventilation. Agoraphobia may present as dizziness triggered by

TABLE 11.1
Duration of Symptoms for Common Causes of Vertigo

FLEETING	SECONDS	MINUTES	HOURS	DAYS
Vestibular hypofunction	BPPV	TIA	Stroke	Vestibular neuritis
	BPV of children	Migraine	Migraine	Stroke
	Seizure	Ménière's	Ménière's	Psychogenic
	Perilymph fistula		Acoustic neuroma	Multiple sclerosis

leaving the home or entering open areas. Vertigo often induces anxiety, thus making distinct diagnoses difficult.

Duration of Symptoms

The duration of vertiginous attacks can be one of the most helpful features in making the diagnosis (Table 11.1). At issue here is the duration of individual episodes and not the time since the first attack. Since many patients develop a baseline level of imbalance or discomfort onto which the attacks of vertigo are superimposed, it is important to question them about the duration of the spinning or whirling, as distinct from the duration of associated symptoms.

Fleeting vertigo is most likely related to a fixed vestibular lesion, such as that which follows vetibular neuritis or the late stages of Ménière's disease. When a loss of vestibular function occurs on one side, head movements may elicit a mismatch of signals between the two ears, or a visual vestibular mismatch, resulting in vertigo. It is important to understand that this is not the major symptom of either of these conditions, but rather a late sequela.

Symptoms lasting from 4 to 90 seconds are typical of BPPV (25). Most attacks last 30 to 60 seconds, but may be aborted in some cases by reassuming an upright position. As Morrell (26) points out, the benign paroxysmal vertigo of children is fairly common. Attacks last seconds to minutes, occur only several times per year, and generally resolve by age 7 years. The children have a normal EEG, abnormal vestibular function, and report no loss of consciousness. Vertigo in epilepsy typically lasts seconds to a minute (27–29) and is often associated with lateralized sensory or motor phenomena or by alteration of consciousness. Isolated vertigo as a manifestation of a seizure is extremely rare. An equally rare alternative is persistent perilymph fistula. In these cases, Valsalva maneuver may result in a small leakage of perilymph into the middle ear cavity. This causes vertigo and sometimes hearing loss or tinnitus. The brief duration of the vertigo probably has to do with the amount of time it takes the vestibular hair cells to adapt to constant deflection (30). Equilibration of perilymph may take considerably longer.

Attacks lasting 2 to 20 minutes are less common. This duration is consistent with a transient ischemic attack (TIA) affecting the posterior circulation. The vascular differential is discussed in detail in chapter 17 of this volume, but will be touched on briefly here. Characteristically, posterior circulation TIAs are accompanied by diplopia, visual field defects, ataxia, hemisensory loss, or hemiparesis. These related symptoms should make the diagnosis clear in most cases. Whether isolated vertigo may represent a TIA is controversial. Clearly this can occur, but in most cases, associated neurologic symptoms appear within days if there are subsequent attacks (31). Baloh (32) disagrees, and believes that isolated vertigo on a vascular basis is under-reported, although confirmation of the mechanism of the attack is lacking in most cases. In support of this, Norrving et al. (33) studied twenty-four patients age 50 to 74 years, with risk factors for cerebrovascular disease (diabetes, hypertension, potential embolic sources, or cigarette smoking) presenting to the emergency room with less than 24 hours of isolated vertigo. Six of these patients (25%) had caudal cerebellar infarcts on imaging studies performed 14 to 44 days after the onset of symptoms. On the basis of the literature and clinical experience, it is recommended that vertigo with associated neurologic brainstem symptoms be evaluated as TIA. In the elderly, vertigo without sudden hearing loss should raise the suspicion of TIA.

The major attacks of Ménière's disease last 20 minutes to 24 hours (34,35). Although it is not possible to make the diagnosis of Ménière's disease without associated hearing loss or tinnitus, early cases of Ménière's—in retrospect—may present with purely vestibular symptoms. Therefore, the duration of the attack may be the most useful clue regarding etiology. Acoustic neuromas may present with attacks of vertigo, most likely due to microvascular infarction of the nerve. These attacks may also last for hours. However, it is worth noting that vertigo is relatively unusual with acoustic neuroma, and most patients present with isolated progressive hearing loss.

Attacks of vertigo lasting more than 24 hours are strongly suggestive of vestibular neuritis. Nausea and vomiting generally persist throughout the first day. Vertigo lasts 2 to 3 days. For a few days beyond this period, patients may still report mild vertigo with their eyes closed. Many patients report fleeting vertigo associated with head movements for months afterwards.

Vertigo lasting more than 3 days is often seen in acute CNS disease, although symptoms may resolve in a shorter period. Vertiginous episodes associated with multiple sclerosis, for instance, may last days, but are accompanied by other neurologic signs and do not often result in vomiting. The same is generally true of posterior fossa infarcts, although anterior inferior cerebellar artery (AICA) territory strokes do not always have signs on examination beyond nystagmus and asymmetries of smooth pursuit (33). A continuous sensation of vertigo lasting longer than 1 or 2 weeks without daily variation is probably a psychogenic phenomenon.

Vestibular Symptoms in Epilepsy

Before embarking on an investigation of vertigo in epilepsy, it is important to clarify the terminology used to describe auras, either as simple partial seizures or as the remembered portion of a seizure before consciousness is lost. Erkwoh (36) raises the important distinction between the vestibular aura of vertigo and psychopathologic terms such as the sensation of getting lighter, detaching from the earth, and floating or plunging into a precipice. Both true vertigo and these other phenomena may be reported by epileptics and those with psychiatric disease (Table 11.2).

In his study of 1,563 patients diagnosed with epilepsy over a 15-year period Erkwoh (36) found 325 patients who reported auras and 46 (14.2%) who had nonspecific dizziness, staggering, or a sensation of walking on waves. Of the forty-six patients, twelve had psychomotor seizures exclusively, fifteen mixed complex-partial and generalized, and ten had only generalized seizures. None of the patients had isolated vertigo as the manifestation of seizure. As noted above, Fried et al. (21) found an epigastric rising sensation to be a common aura, but vertigo or dizziness to be less so, occurring in 14% to 17% of confirmed epilepsy patients. Table 11.3 lists features that may suggest seizures as the cause of reported vertigo.

THE NEUROTOLOGIC EXAMINATION—KEY ELEMENTS

The preceding makes it clear that "dizziness" is a nonspecific complaint. Whether the complaint is of subjective dizziness or of imbalance, the complete examination must assess all the systems involved in maintaining balance. The maintenance of the center of gravity requires the successful interplay of the motor systems—pyramidal, extrapyramidal, and cerebellar—guided by information from the visual, vestibular, and somatosensory systems. Failure of any one of these systems, motor or sensory, results in a loss of balance under particular circumstances. The examination of the patient, therefore, must include a "standard" neurologic examination and an expanded vestibular examination that concentrates on eye movements. We cover here only the portion of the examination specific to the vestibular system.

The portions of the examination most unique to the patient with vestibular complaints can be broken into two basic parts based on the two types of problems described earlier: we look for evidence of a vestibular imbalance and for evidence of decreased function. The neurologist's greatest diagnostic contribution is careful examination for pathologic nystagmus. In a study by Kroenke et al. (37), the most useful diagnostic procedure—more so than testing or imaging results—was an examination for nystagmus. Primary position nystagmus is virtually pathognomonic of such a vestibular imbalance. Surprisingly, even large-amplitude nystagmus can be overlooked by a casual observer. There are several things that one can do at the bedside to increase the chances of picking up such a nystagmus.

As nystagmus can either be enhanced or dampened by convergence, it is important to have the patient look first at an object in the distance and then at a near target

TABLE 11.2
Rare But Striking Imitators of Epilepsy

- Tumarkin's otolithic crisis describes falls in patients with "burned out" Ménière's disease. Patients fall without warning, lose voluntary control of balance, but *remain conscious.*
- Tullio's phenomenon describes the brief vertigo or oscillopsia *induced by sound* in some patients with perilymph fistulas.

TABLE 11.3
Features Suggesting Seizures as the Cause of Vertigo

- Personal or family history of epilepsy
- Focal signs on examination
- Complex auditory hallucinations
- Visual illusions or hallucinations

such as the examiner's finger held a few inches from the patient's nose. Despite a clear-cut vestibular imbalance and careful observation, some patients appear not to have any primary position nystagmus. This is almost always due to visual fixation by the patient. There seems to be an inherent assumption by the CNS that the world is stable; therefore, it uses visual information to stabilize a world that, based on vestibular input, seems to be moving. There are several ways to decrease fixation and bring out the underlying primary position nystagmus. The most efficient method in our opinion is performed using the hand-held ophthalmoscope. The patient is asked, while sitting in the dark, to fixate on a distant target. The examiner looks at the fundus for any slow phases that are indicative of a primary position nystagmus. While looking at the disc, one can then occlude the opposite eye with the other hand. Thus, the patient can no longer see out of one eye while you are blinding the other, very effectively eliminating fixation. This gives a highly magnified view, thus making all but the smallest amplitude nystagmus readily visible.

Nystagmus *typically* consists of slow and fast phases; the more important of the two is the slow phase, as its shape and direction reflect the vestibular organ driving it. The direction of the nystagmus is important in localizing the source of pathology. Nystagmus due to a peripheral vestibular is almost exclusively mixed in direction—oblique or mixed horizontal and torsional. Purely horizontal nystagmus is more likely to be due to a gaze paresis. Purely vertical nystagmus is due to brainstem or cerebellar disease. Purely torsional nystagmus strongly suggests a lesion affecting the central vestibular pathways. Another type of nystagmus that is fairly easy to discern on physical examination is pendular nystagmus. In this condition, the eyes oscillate back and forth *with no fast phase*. This type of nystagmus, if not congenital, is characteristic of *severe cerebellar disease* and is most frequently seen in multiple sclerosis.

Thus far, the discussion of nystagmus has centered on its appearance in primary position. The variation of nystagmus with gaze is extremely important. The horizontal component of nystagmus caused by vestibular disease does not change direction with gaze. The oblique angle may shift somewhat, but a shift from essentially rightward nystagmus to essentially leftward nystagmus with gaze indicates a lesion located elsewhere in the CNS. Central nystagmus often changes direction with gaze. Gaze-paretic nystagmus, by definition, has a slow phase that is always directed toward primary position. Put another way, it is right beating on right gaze and left beating on left gaze. Unlike vestibular nystagmus, gaze-paretic nystagmus can also be evoked with vertical gaze, more commonly seen on upgaze than downgaze. Congenital nystagmus may also have a gaze position in which is no nystagmus is present—known as the null position. The null position may not be in primary position. Congenital nystagmus also changes direction on either side of the null position.

Two other direction-changing patterns bear mention at this point. Nystagmus that changes direction over time, with no dependence on gaze, is known as periodic alternating nystagmus (PAN) and is due to lesions of the cerebellar nodulus. During the examination, the nystagmus may appear, at times to be beating to the right and at other times to be beating towards the left, independent of gaze. Therefore, repeated observations of the eyes are warranted. PAN typically changes direction every 90 seconds, and the velocity changes gradually during this cycle.

Detecting a decrease in function on either one or both sides of the vestibular system is most often relegated to the laboratory. However, several simple bedside tests of the VOR may provide accurate qualitative data. One such test is called "mini-calorics." It is commonly, but incorrectly, thought that calorics on an awake patient results in severe nausea and vomiting. Whereas 20 to 100 cc of ice water, as is used in an ICU setting with a comatose patient, will have a marked effect on a normal patient, "mini-calorics," using less than 1.0 cc of cold water, can be done with relatively few adverse side effects. The presence of a response on one side and none on the other confirms a peripheral problem. Some physicians quantify the response to mini-calorics by timing the latency or duration of nystagmus from each ear. We have not found this to be worth the additional effort.

Head-shaking nystagmus has been shown to be a very sensitive indicator of vestibular asymmetry (38). However, it provides little information regarding the central or peripheral location of the lesion (39). The test can be done either with or without Frenzel goggles. The patient is asked to close the eyes while the examiner holds the head firmly, hands positioned over each ear. The head is then rapidly rotated back and forth at a rate of approximately 2 to 3 rotations per second and this is continued for 10 to 15 seconds. Immediately on stopping, the patient is asked to stare straight ahead while the examiner looks for any slow drift indicative of nystagmus.

A subjective assessment of the VOR can be made by having the patient read from a near card while the head is still and then again while moving the head back and forth at about 1 to 3 times per second. If the VOR is normal, the eyes move opposite to the direction of head movement to remain fixated in space and on the target. Visual acuity will not change. If the VOR is decreased, then the eye will move with the head and no longer be fixated on the target. Thus, the vision will be degraded. A careful observer may even

be able to tell you in which direction the card looks more blurred, thus implying a greater deficit VOR in that direction.

A more objective assessment of the VOR can be obtained by using an ophthalmoscope. The physician fixates on the patient's optic disc while the patient fixates on a distant target. The physician then gently moves the head from side to side, continuously watching the fundus for movement of the disc. A decrease in VOR will be seen as nystagmus, as the patient must continually refixate the target. Observing the fundus will enable seeing movements of the eye as small as 0.5 degrees.

A simpler and more practical VOR assessment can be done in a few seconds. The examiner holds the patient's head firmly on each side and instructs her to keep her eyes fixed on the examiner's nose. When it is clear that the patient is paying attention, the head is moved approximately 60% of the total range of motion to one side. The head is turned abruptly to the midline as rapidly as possible. If the VOR is normal, the eyes will not move from the examiner's nose. If the VOR is defective, the eyes will have moved with the head and therefore have to saccade back to the fixation point (40). Normally, the VOR will be able to keep up with even the fastest movement.

Nystagmus may also be elicited or altered by changes in body position. When the head is tilted with respect to gravity, the otolith organs receive constant stimulation. The influence of gravity in the presence of a central or peripheral vestibular lesion results in nystagmus, typically mixed in direction.

The Dix-Hallpike test is a positioning maneuver intended to stimulate the vertical semicircular canals (25). With the head turned 45 degrees to one side, moving the patient from a sitting to a supine position results in rotation in the plane of a vertical canal pair. In the normal patient, no nystagmus occurs following this maneuver. In benign paroxysmal positional vertigo (BPPV), otoconia not firmly attached to the maculae fall into the posterior canal, thus eliciting vertigo and nystagmus. The nystagmus is a mix of upbeating and torsional movements, with the upper pole of the eye beating toward the dependent ear. Although we believe that the Dix-Hallpike maneuver is best performed with Frenzel glasses, it has been demonstrated that torsional nystagmus is not well suppressed by visual fixation.

In BPPV, the Dix-Hallpike maneuver results in nystagmus after a latency of several seconds. The duration of the nystagmus is characteristically 15 to 30 seconds. Central nervous system lesions may result in nystagmus with little or no latency. This nystagmus may not habituate and lasts as long as the patient's head is hanging back. As the direction of this nystagmus is not necessarily torsional, the effect of fixation is unpredictable. For this reason, we continue to recommend the use of Frenzel glasses. When faced with positioning nystagmus that does not habituate, be sure there is a change in the nystagmus pattern seen in the upright or purely supine positions, if any.

FEATURES SUGGESTING OTOLOGIC CAUSES OF VERTIGO

Hearing Loss

Otologic complaints, such as hearing loss, tinnitus, or fullness provide important clues to the location of a lesion. Unilateral hearing loss accompanies peripheral, not central, disease because auditory pathways become bilateral after the first synapse in the cochlear nucleus. Central lesions at the root entry zone of the auditory nerve are the principal exception, and these are rare (41). Therefore, the presence of hearing loss is a fairly reliable indicator of peripheral disease. See Table 11.4.

The sudden onset of vertigo and hearing loss suggests a lesion of the labyrinth itself. This can be viral, although for unclear reasons viral disease generally results in vertigo or hearing loss but not both. The etiology of sudden vertigo and hearing loss may also be vascular, as noted earlier. The internal auditory (labyrinthine) artery arises from the anterior inferior cerebellar artery (AICA). An infarct in the territory of the internal auditory artery is difficult to distinguish from a viral infection of the cochlea and vestibular labyrinth, in that both may present as vertigo and sudden deafness. However, a more proximal AICA territory infarct would result in cerebellar symptoms as well as vestibular and auditory dysfunction. The sudden onset of sensorineural hearing loss in this syndrome helps to distinguish it from a lateral medullary infarct.

Particular patterns of hearing loss also may suggest a specific disease process. In an acute vestibular syndrome with vertigo lasting more than 24 hours, unilateral hearing loss indicates either labyrinthine infarction or labyrinthitis. In either case, the hearing loss is usually profound, but incomplete loss may be seen with labyrinthitis. In a chronic or progressive dysequilibrium syndrome, unilateral hearing loss may indicate the presence of a vestibular schwannoma. Impaired speech

TABLE 11.4
Features Suggesting Otologic Causes of Vertigo

Hearing loss
Temporally linked tinnitus
Tullio's phenomenon

recognition is characteristic of an eighth-nerve lesion (42,43). Episodic vertigo and hearing loss lasting less than 24 hours is typical of Ménière's disease. The chronic interictal hearing loss in this condition is classically in the low frequencies. However, the hearing loss may be flat across frequencies, downward sloping, or upward sloping (44). It is important to understand that asymmetric hearing loss is common, affecting about 8% of the general population and a large proportion of the elderly. Asymmetric hearing loss is present in 26% of dizzy patients (45) and does not necessarily indicate the site of vestibular pathology.

Hearing loss is common in postconcussive dizziness (46). However, the loss generally resolves. Similarly, post-traumatic perilymph fistulas are accompanied by severe hearing loss that typically resolves with bed rest (47–49). Masses within the inner ear, such as cholesteatoma, of course, disrupt hearing as well as inner ear function. In contrast, the diagnosis of vestibular neuritis excludes hearing loss by definition. BPPV, while it may rarely accompany Ménière's disease or tumors of the cerebellopontine angle, does not by itself involve hearing loss. As a general rule, it is safe to say that hearing loss related temporally to vestibular symptoms, indicates peripheral disease. The remainder of the history and the physical examination are required to rule out additional central disease. Normal hearing, in contrast, does not rule out peripheral disease.

Temporally Linked Tinnitus

Tinnitus may be seen with central as well as peripheral lesions, but at least one pattern can be helpful. In Ménière's disease, the acute episodes of hearing loss are accompanied by a roaring tinnitus that improves as the hearing recovers. Aural fullness is also a seen in acute episodes of Ménière's disease, although this symptom, too, is non–specific.

Tullio's Phenomenon

Sound-induced vestibular symptoms include vertigo, oscillopsia, imbalance, and nystagmus. As mentioned earlier, these symptoms, comprising the Tullio phenomenon are seen in the setting of a perilymph fistula or superior canal dehiscence (50), as previously noted. The otoliths lie directly adjacent to the stapes footplate.Ï

TESTING OF VALUE IN VERTIGO

Tests relevant to the dizzy patient include audiometry, electronystagmography (ENG)—specifically for caloric testing—rotary chair testing, brainstem auditory evoked responses (BAER), posturography, and magnetic resonance imaging (MRI) of the posterior fossa. As noted in the section on the otologic causes of vertigo, audiometry has value because it identifies concurrent disease in the labyrinth or the eighth nerve.

Electronystagmography

ENG testing is useful in documenting the presence of vestibular hypofunction. This test compares the velocity of nystagmus produced by caloric irrigation of each ear. In a normal ear, slow-phase velocity of nystagmus is proportional to the temperature of the stimulus and relies on the integrity of the horizontal semicircular canal. We denote each peak response by the temperature (C or W) and by the ear (AS or AD), thus, CAD, CAS, WAD, and WAS refer to the four peak velocities measured. A *sensitivity difference* can be calculated using the following formula:

$$\frac{(\text{CAD} + \text{WAD}) - (\text{CAS} + \text{WAS})}{\text{CAD} + \text{WAD} + \text{CAS} + \text{WAS}}$$

Therefore, the sensitivity difference is mostly a measure of peripheral vestibular function. However, the specificity of a sensitivity difference is disappointing. For instance, Allum et al. (51) found a mean sensitivity difference of 29% in patients with documented brainstem disease compared to a mean of 45% in patients with peripheral vestibular loss. These can be compared to a mean of 2% for normals, with a standard deviation of 16%. The measure, therefore, is a useful discriminator for vestibular disease, but does not, by itself, indicate peripheral disease. Asymmetries of 25 to 30% or more are generally taken to be the threshold for calling a study abnormal.

Fitzgerald and Hallpike (52) also developed the *directional difference* using the following formula:

$$\frac{(\text{CAD} + \text{WAS}) - (\text{CAS} + \text{WAD})}{\text{CAD} + \text{WAD} + \text{CAS} + \text{WAS}}$$

This calculation represents the asymmetry between vestibular responses with leftward slow-phases and those with rightward slow phases. Both central and peripheral vestibular disorders may be associated with directional asymmetries. Whereas directional differences of 30% or more (in most laboratories) indicate a vestibular abnormality, there is no localizing value to this asymmetry (53).

Pitfalls in the interpretation of caloric testing include difficulties with irrigation, the presence of middle ear effusion, and asymmetries of bony structure or density. Middle ear effusion increases the thermal conductance to the inner ear, thus resulting in artificially elevated responses. Asymmetries in the temporal bone

may also affect thermal conductance in unpredictable ways. Another shortcoming of caloric testing is that if both sides of the vestibular system are malfunctioning (whether central or peripheral), there may be no directional or sensitivity difference. The diagnosis of a bilateral vestibular deficit is made if the total response (CAD + WAD + CAS + WAS) is less than 32 deg/sec. A bilateral weakness does not distinguish between central and peripheral dysfunction.

Rotary Chair Testing

Whereas the caloric test simulates a rotational vestibular response, rotation of the patient about a vertical axis produces a physiologic vestibulo-ocular response. Rotational testing avoids those pitfalls of caloric testing having to do with thermal conduction. More significantly, because the velocity of rotation can be carefully controlled, VOR gain (eye velocity/head velocity) can be calculated. These studies are often quite sensitive for the presence of vestibular disease and provide specificity for peripheral vestibular abnormalities. The VOR also provides a more reliable indicator of bilateral vestibular disease than caloric testing. Unfortunately, rotary chair testing is not available in most centers and therefore rarely presents itself as a practical diagnostic tool.

Brainstem Auditory Evoked Responses

Brainstem auditory evoked responses (BAER) can be useful in identifying a vestibular nerve lesion or a brainstem lesion. It is less sensitive than magnetic resonance imaging (MRI) testing for the presence of a small vestibular schwannoma. Estimates of sensitivity range from 89% (54) to 96% (55), compared to a nearly 100% sensitivity for MRI. BAER should probably be reserved for those patients with progressive unilateral hearing loss when MRI is not available. It should also be noted that substantial hearing loss precludes the collection of useful data from a BAER. Brainstem lesions may be detected by BAER. However, these lesions should also be picked up by neurologic examination. In the presence of a neurologic deficit, we recommend MRI imaging and would forego BAER testing.

Posturography

As noted earlier, the vestibular system is one of three sensory systems that provide input for control of posture. The Romberg test addresses the importance of vision (and therefore the sufficiency of vestibular and somatosensory function) qualitatively in the maintenance of posture. Dynamic posturography provides a quantitative assessment of sway using moving force plates that approximate the center of gravity from measures of the center of force beneath each foot. The orientation of the moving force platforms can be linked to the subject's center of gravity. Thus, as the subject sways forward, the front of the platforms tilt downward. This sway-referencing has the effect of eliminating somatosensory feedback from the ankle joints. Comparison of the amount of sway in each of several conditions (using eye closure, sway referencing of the platform, and sway referencing of the visual surround) provides measures of the relative efficacy of each sensory system. Despite the limitations of posturography in diagnostic specificity, the test provides useful measures of postural strategy that may be diagnostically and therapeutically relevant. Another useful measure of sway is a qualitative description of the amount of the relative amounts of lateral versus anterior-posterior sway. In normal subjects, there should be relatively little lateral sway. Excessive lateral sway is generally correlated with deliberate or psychogenic imbalance.

Magnetic Resonance Imaging

The role of imaging studies in diagnosing the dizzy patient is small, but critical. When abnormalities are detected on neurologic examination, imaging helps confirm the localization of the lesion and aids in a pathologic diagnosis. If the neurologic examination is normal, imaging is usually not indicated. One exception, as noted earlier, is the older patient with vascular risk factors presenting acutely with vertigo. These patients have a 1-in-4 chance of having a posterior fossa stroke and their examination may reveal only asymmetric smooth pursuit (33). Computed tomography (CT) imaging is generally insensitive for cerebellar lesions; therefore, MR imaging is far more valuable. The third reason for imaging the dizzy patient is to rule out vestibular schwannoma. We have analyzed epidemiologic data to demonstrate that the probability of a patient with vertigo having a vestibular schwannoma is less than 1-in-9,000 (45). For patients with dizziness and asymmetric hearing loss, the probability increases only to 1-in-600. Conversely, progressive asymmetric hearing loss is far more suggestive of a cerebellopontine angle mass and may warrant imaging. CT is insensitive to small masses in this area. Magnetic resonance imaging with gadolinium enhanced T1-weighted spin-echo images is capable of detecting intracanalicular schwannomas as small as 2 mm (56). Since smaller tumors are unlikely to be treated surgically, the significance of tiny masses not seen on MR imaging is debatable. MR is therefore considered the "gold standard" for CPA masses.

In summary, if on examination abnormalities are detected that suggest CNS disease or invasive otologic

disease, imaging should be performed. In cases of acute vertigo, if the patient is at high risk for cerebrovascular disease, by virtue of age and additional risk factors, imaging should probably be pursued. CT scanning will be far less helpful than MR imaging of the posterior fossa and its vasculature. If the patient does not fall into one of these categories; that is, the patient is dizzy but has no abnormalities on careful examination, we recommend a hearing evaluation with pure tone and speech audiometry. If a progression of asymmetric hearing loss is not documented, we do not believe imaging is warranted. Progressive hearing loss with abnormal speech reception thresholds and speech discrimination loss probably warrants MRI of the internal auditory canals, although there are those who still argue for BAER as a screening tool. CT scanning lacks the sensitivity of MRI for investigation of the posterior fossa, and we do not recommend it for the dizzy patient unless MRI is unavailable.

VERTIGINOUS SEIZURES

As we have seen, literature accumulated over much of the last century clearly established that vertigo can occur as a manifestation of epilepsy. However, it is only in more recent years that requisite correlative studies have been done to determine the true incidence of vertigo in epileptic seizures, to describe more completely its diagnostic features, and to identify more reliably the associated cortical foci.

In a systematic study of dizziness (incuding vertigo), Hughes and Drachman (57) found that thirty-four of forty-eight or 71% of randomly selected patients with confirmed seizure disorders experienced some type of dizziness, compared to 31% in an age- and gender-matched control group. However, in only four of the forty-eight seizure patients was the dizziness characterized as vertigo; thus, the overall incidence of vertigo in this group was 8.3 percent. Two-thirds of the epilepsy patients in their study reported the dizziness to occur immediately prior to their seizures, but 71% experienced it at times unassociated with the seizure. No mention was made of what clinical features of a seizure apart from dizziness were present in these patients, but it is not at all clear that any had vertigo as an isolated symptom. In another arm of this study, the authors found no significant differences in the incidence of slow wave or sharp wave EEG abnormalities between a group of ninety-seven patients complaining of dizziness and another matched control group. Of interest was the finding of a correlation between a subgroup of the patients whose dizziness was characterized as syncopal and bitemporal sharp waves, although the EEG abnormalities and the clinical symptoms were not coincident in this study.

Palmini and Gloor (58) queried 123 patients with identified foci (most were surgical cases) regarding their symptoms; vertigo was experienced as an aura by three. One had a frontal focus and two parieto-occipital. Of fifty-six seizure patients prospectively evaluated, four had vertigo as an aura. Of these four, one had a frontal focus, one temporal, and two parieto-occipital.

Kogeorgos et al. (28) described thirty patients referred for a primary symptom of dizziness but in whom epilepsy was the ultimate diagnosis. In all patients, the dizziness was brief, lasting no more than a few seconds. True vertigo was reported by only fourteen patients, and these noted no postural triggers. The frequency of vertigo attacks ranged from one a week to many times daily and had been present for 6 months to 42 years. By the time of their evaluation, seven patients with vertigo had also experienced generalized convulsions. In these seven, dizziness occurred both with and without seizures. Twenty-eight of thirty EEGs showed temporal sharp waves: fifteen left, seven right, and six bilateral. The remaining two had atypical generalized spike and wave abnormalities.

In a rare example of a seizure disorder presenting as isolated vertigo, Kluge et al. (27) reported a 5-year-old boy who experienced episodes of severe rotation lasting 10 to 20 seconds. These occurred 5 to 7 times daily and often awakened him from sleep. Three months after onset, an EEG showed intermittent slow waves frontocentrally on the left. Another month later, vertigo was occasionally followed by clonic movements of the right arm. These movements, but not the vertigo, could be suppressed by carbemazepine. On neurologic examination, coordination of the right hand and hopping on the right foot were slightly impaired. VEEG confirmed vertigo accompanied by left frontocentral electrical seizures. There was no ictal or interictal nystagmus. A fibrillary cystic astrocytoma was resected, and the episodes resolved.

NYSTAGMUS IN EPILEPSY

Nystagmus with or without vertigo may be seen during seizures. The occurance of nystagmus in a conscious patient without vertigo suggests a nonvestibular origin. Investigators have pointed out that gaze-paretic nystagmus has slow-phases with exponential decay; that is, the eye slows down as it approaches the midline, and that vestibular nystagmus has linear slow-phases. The shape of the waveform should therefore correlate with the focus and the vestibular or nonvestibular origin.

Beun et al. (59) described five cases of epilepsy in which nystagmus was not accompanied by vertigo, although two described oscillopsia. All had other features to suggest epilepsy. In each, the nystagmus lasted from 20

to 90 seconds. The EEG foci in four of these patients were parietal or posterotemporal. In the last, no specific focus could be identified but generalized spike–wave activity at 4/sec was seen. This lasted for tens of seconds to several minutes. In those with an identified focus, the fast phase of the nystagmus was contralateral to the focus. In a typical case, a patient experienced episodic oscillopsia with nystagmus lasting up to 30 seconds and recurring during a 30 to 45 minute period. This was accompanied by right parietal spiking. Unfortunately, nystagmus waveforms were not described.

Kaplan and Tusa (60) reported eight patients with nystagmus during seizures. In one case, the spiking was frontocentral and occipital; in another, the spiking was occipital. In all the others, the spiking was parietotemporo-occipital. In all cases, the nystagmus beat contralateral to the side of the focus with an exponential decay of the slow-phase. The authors proposed that epileptic nystagmus requires a lesion that produces a gaze deviation together with diffuse dysfunction or a decreased level of consciousness. This produces a loss of gaze-holding ability (or leaky integrator), which results in a pattern resembling gaze-paretic nystagmus having exponentially decreasing slow-phases. Thurston et al. (61) reported a similar case with gaze-evoked epileptic nystagmus. This patient had head and eye deviation and an exponentially decreasing slow phase. Ictal nystagmus lasted 90 seconds and none was seen interictally. A right temporo-occipital focus was identified.

In contrast, Furman et al. (62) reported a 52-year-old woman with a history of generalized epilepsy who had episodic vertigo associated with blurred vision and gait instability lasting approximately 1 minute. These occurred five to eight times daily. The interictal neurologic examination was normal. Linear nystagmus was recorded during one episode while seated. About 5 seconds of decay can be seen at the end of the recording. Based on rapid buildup and decay, the authors felt this was more of a pursuit (direct pathway) mechanism than a velocity storage (indirect pathway) mechanism. They viewed this, then, not as a vestibular cortex seizure, but a pursuit cortex seizure. However, our view of the nystagmus record is that a decay period of 5 to 7 seconds is entirely consistent with human vestibular after-nystagmus and that the linear slow-phases suggest a vestibular origin. On reviewing their EEG records, we also felt that the earliest spiking originated from mid- and posterior temporal derivations, consistent with a source within vestibular cortex.

VESTIBULOGENIC SEIZURES

A distinct condition is that of vestibulogenic epilepsy in which there is pathology within the vestibular system that triggers seizures (63). Weintraub and Smith (29) reported eight patients in whom vertigo was felt to be an epileptic manifestation of vertebrobasilar insufficiency. All patients in the study had other neurologic signs or symptoms that were either static or unassociated with episodic vertigo. The clinical descriptions in this paper were not always complete, but at least two patients appeared to have seizures triggered by acute manifestations of vestibular pathology. Unfortunately, it was not clear whether the focal epileptiform features reported in the EEGs were temporally correlated with the vestibulogenic symptoms.

Cantor (64) reported a case of temporal lobe seizures provoked by unilateral caloric stimulation. The patient was 44 years old and had had two episodes of staring with automatisms. He presented with episodes of tinnitus, tremulousness, and dizziness. Caloric stimulation of the right ear resulted in right temporal theta and spikes. The patient experienced tinnitus and generalized clonic movements. Bilateral temporal spiking could also be seen.

Ahmed's case of "epilepsia tornado" (65) involved a 43-year-old man who reported 2-3 episodes a week of prolonged vertigo followed by headache, beginning 8 months after a head injury without loss of consciousness. There was no loss of consciousness in an attack, but each time the patient "was unable to recall events accurately" for minutes afterwards. EEGs were said to show left temporal theta, and weak evidence for interictal irritative activity was presented. Although caloric stimulation did not induce an attack, the spontaneous episodes followed a period of vertigo, and hence, if they were indeed seizures (and not migraines), would be classified as vestibulogenic.

FEATURES SUGGESTING SEIZURE AS THE CAUSE OF VERTIGO

History of Epilepsy

The previous section describes the typical attack of vertigo (or oscillopsia) seen in epilepsy: the vertigo lasts no more than 90 seconds and has no positional triggers. Other features are very helpful in leading the clinician to consider epilepsy (Figure 11.3). The first is a personal or a family history of epilepsy. Many, perhaps most, the cases reported in the literature were known to have epilepsy at the time their vertigo was linked with seizure in the clinician's mind. In those rarer cases where no diagnosis of epilepsy already exists, alteration of consciousness is the most important clue. Dix (66) stated it simply when he asserted that attacks of vertigo due to peripheral disease are not associated with loss of consciousness. This is unmistakably true, but there are times when the clinician may be confused by patients reporting

FIGURE 11.3

Flowchart for the neurologic workup of a patient with recurrent vertigo lasting seconds to minutes. A history of alteration of consciousness or a history of epilepsy warrants intensive EEG monitoring. Central abnormalities on neurologic examination or on vestibular testing warrant MR imaging of the brain. A positive Hallpike maneuver or peripheral findings on vestibular testing positively identifies peripheral vestibular disease.

extreme disorientation with severe vertigo, such as in Ménière's disease. A careful history is usually sufficient to rule out an actual alteration of consciousness.

Another feature of Ménière's disease may be mistaken for seizure in its late stages. Tumarkin (67) described the development of sudden falls in patients who had largely "burned out" their vertigo attacks after years of Ménière's disease. He noted that often these patients have the feeling they are being thrown or pushed to the ground.

This phenomenon is felt to be related to residual otolith dysfunction in endolymphatic hydrops; hence the term *Tumarkin's otolithic crisis*. In a recent study by Ishiyama et al. (68), seven patients with drop attacks

were described: patients fell without warning and remained conscious but lost voluntary control of balance. These patients underwent ablative vestibular surgery, and the drop attacks were eliminated.

The proximity of otolith organs to the oval window, clearly a factor in the development of the Tullio phenomenon also provides the basis for a clinical electrophysiologic test of vestibular function. The test, involving a vestibular evoked myogenic potential (VEMP), utilizes a short latency averaged response in the sternocleidomastoid muscle (SCM) evoked by brief, intense ipsilaterateral acoustic stimuli—usually clicks or tone pips. Defects in the vestibulocollic reflex pathway, from saccular receptors to the SCM, are reflected in alterations or absence of the ipsilateral VEMP (69–71).

Focal Signs on Examination

If focal neurologic signs are found on examination of a patient with episodic vertigo, it is clear that a complete clinical workup is required to determine the anatomy and etiology of the disorder. However, it is no more likely that the vertigo will prove to be driven by irritative activity in the vestibular cortex than it would be in the absence of focal signs, since none have been reported in "pure" cases of vertigo, dizziness, ocular deviation, or nystagmus in epilepsy.

Complex Auditory Hallucinations

As noted above, tinnitus does not definitively distinguish the peripheral causes of vertigo. However, in seizures, complex auditory hallucinations associated with vertigo strongly suggest that the vertigo is related to a temporal lobe focus (63). The hallucinations, almost always localized to a perceptual half-space, may range from a simple buzz to complex experiences involving environmental sounds, such as a knocking automobile engine or a flushing toilet, fragments of recognized music, or perceived utterances from phonemes to word sequences. Bartolomei et al. (72) described a patient, 5 months after a bout of status epilepticus, who developed episodes of dizziness, coupled with the hallucinated sound of an airplane propeller and followed by a generalized seizure.

Visual Illusions or Hallucinations

Visual illusions or formed visual hallucinations in conjunction with vertigo may also suggest a temporal lobe focus, although other etiologic and anatomic possibilities exist for this connection. Persistent visual and auditory percepts (palinopsia and palinacousis), some with related vertigo, have been considered as manifestation of seizures (73,74). In addition to supportive clinical features already discussed, Jacobs et al. (75), reported the occurrence of irritative features in the EEGs of patients during palinacoustic episodes. However, the electrophysiologic data presented in the paper are too limited to add much to the clinical presumption of a connection between these illusory auditory and visual phenomena and seizures.

BPPV is a Key Differential Diagnosis

The abrupt onset of vertigo in BPPV may lead wrongly to a diagnosis of epileptic seizures, particularly in children. In a series of 850 children attending an epilepsy clinic for seizure disorders, Gibbs and Appleton (76) found that eighty-one were incorrectly diagnosed; four of these were found on review to have BPPV. Morrell (26) notes that the condition occurs in neurologically intact children between the ages of 1 and 5 years, too young for many of them to give an accurate description of their symptoms. As is the case with adults, the author observes that in BPPV, the child retains consciousness, displays abnormal vestibular function, and has a normal EEG. Brandt and Dieterich (77), in their analysis of vestibular falls, suggest that a differential feature of a cortically driven vertigo is the direction of body displacement in attack, which unlike the clinical rule in peripheral vestibular disorders, is in the same direction as the nystagmus. Although this finding is of some theoretic interest, it is not useful in the management of cases in which the disorder underlying the symptom of transient, paroxysmal vertigo is not known. In sum, one should not consider a diagnosis of epilepsy in these vertiginous patients who maintain consciouness, have postural triggers, a history of epilepsy or drug use, and a normal neurologic examination. A casual EEG recorded between episodes, even with standard forms of ictal activation, such as sleep deprivation, is not helpful in either ruling out or establishing an epileptic source of the vertiginous syndrome. If there is a reasonable clinical suspicion of seizure, video-EEG monitoring should be done to document the occurrence of epileptiform features in the EEG *during* an episode.

Vascular Etiologies Must Be Considered

A number of vascular syndromes that include symptoms of vertigo and other vestibular abnormalities may imitate seizures. Distinguishing features are discussed in detail in Chapter 17 of this volume.

CONCLUSION

In surveys of the final diagnosis of patients presenting with vertigo, vestibular disease accounts for 95% of cases and seizure represents well under 1% (36,75,76). Conversely, in the series by Kogeorgos et al. (28) the

TABLE 11.5
Diagnostic Value of Testing in Vertigo

TEST	FINDING	SIGNIFICANCE
Audiometry	Asymmetric sensorineural hearing loss	Documents a peripheral lesion
	Asymmetric loss of speech discrimination	Suggests a lesion of the VIIIth nerve
Oculography	Ocular motor abnormality	Documents a central lesion
ENG (calorics)	Sensitivity difference	Suggests a peripheral lesion
Rotary chair test	Unilateral loss of VOR gain and time constant	Documents a peripheral lesion
	Bilateral loss of VOR gain and time constant	Documents a bilateral peripheral lesion
	Increased VOR gain	Documents a cerebellar lesion
Platform posturography	Abnormal sensory organization test	Documents a sensory abnormality

patients presenting with vertigo represented less than 1% of all new cases of epilepsy. Even considering known seizure patients, according to Palmini and Gloor (58), the frequency of auras in patients with partial seizures is about 80% and only about 5% of those patients experience vertigo as an aura. Other investigators report only about 50% of patients having an aura. Suffice it to say that epilepsy should be considered as the underlying cause of vertigo only under exceptional circumstances. The key exceptional circumstance is an alteration of consciousness.

Many patients with known seizures who experience vertigo with seizure and also without seizure have been reported. In such cases, the clinician may have questions about the episodes of vertigo without seizure. From our perspective, this comes down to the distinction between vertigo in epilepsy and vestibulogenic epilepsy. The approach to such patients should be both a vestibular workup and epilepsy monitoring. If there is a documented vestibulopathy as well as indication that the vertigo triggers seizures, then treatment of the underlying vestibulopathy should assist in the reduction of seizure frequency.

The cases of isolated vertigo as a manifestation of seizure are sufficiently rare to be individually reportable (27). The features of vertigo associated with seizure are frequent attacks (many times daily), brief duration (30 to 90 seconds), and the absence of positional triggers. For patients presenting with these features, our recommendation is to rule out vascular causes in the acute setting. In the subacute or chronic setting, we recommend vestibular testing. Should neither of these investigations lead to a diagnosis, video-EEG monitoring is recommended. Table 11.5 lists the diagnostic value of various tests in diagnosing the cause of vertigo.

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12 Movement Disorders That Imitate Epilepsy

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The word "seizure" evokes images of involuntary movement. Therefore, it is not surprising that during the early part of the twentieth century, medicine generally ascribed all episodic or paroxysmal movements to some form of seizure (1). Since that time our understanding has evolved to permit the differentiation of an array of movement disorders that at times mimic epileptic phenomena (Table 12.1). Beyond classification, reaching an accurate diagnosis has important implications for clinical management, prognosis, and patient counseling on issues ranging from driving laws to career and family planning.

This chapter takes a practical approach to the differentiation of frequently confused epileptic and movement disorders. A series of case vignettes is used as a point of reference to guide our review of common clinical dilemmas.

Case Study #1. Mr. J is a 41-year-old man with a history of hypertension and a history of generalized tonic-clonic seizures from childhood. He developed acute weakness and numbness of the left side of the body including face, arm, thorax, and leg, this resolved over 1 week. One week later he developed involuntary movements of his left arm, characterized by episodic flexor posturing lasting 5 to 30 seconds. There was no alteration of mental status. His exam was otherwise normal. Magnetic resonance imaging (MRI) revealed a subacute right thalamic infarction.

The case history is an example of a patient presentation that poses the question of epilepsy versus movement disorder. First, as in all neurologic disorders, a good patient history is essential. The clinician should

TABLE 12.1
Movement Disorders and Related Conditions That Imitate Epilepsy

Chorea	Tardive dyskinesia and dystonia
Ballismus	Tics and Tourette's syndrome
Athetosis	Stereotypies
Dystonia	Meige syndrome
Cramps and spasms	Blepharospasm
Isaac's syndrome	Hemifacial spasm
Stiff-person syndrome	Tremor
Myoclonus	
Paroxysmal ataxia	
Paroxysmal dyskinesia	

inquire about both the patient's history of epilepsy or movement disorder and the family history, since genetics may play a role in both disorders. The medical history includes attention to medications (especially new additions or changes in dosage) and past medical conditions. For example, in this case presentation of stroke, the location and type of stroke is important since cortical lesions are more likely to give rise to seizure, whereas movement disorders are more frequently seen following subcortical or basal ganglia lesions (2,3).

Both the history and the phenomenology of the abnormal movements are useful. The timeframe of the movement disorder, including the patient's age at onset and the timing of events in the medical history, such as comorbid conditions, surgical procedures, medications, or in this case, a stroke, should be considered. The time of day of episodes may be important since some forms of epilepsy are associated with sleep while some forms of movement disorders improve with rest or are precipitated by movement. Triggers to the movements including stress, medications, hunger, fatigue, or activity may also help differentiate between movement disorder and epilepsy. Of course, direct observation of an episode is very important although it is not always feasible. Therefore, one must inquire specifically about which body parts move, and in what manner. For example, movements that vary may be more characteristic of a movement disorder than epilepsy (e.g., chorea), whereas more stereotyped movement that is episodic (e.g., tic) may be either movement disorder or epilepsy. Understanding the speed and rhythmicity of the movements can also aid in differentiation. Whereas seizures usually involve fast, rhythmic movements, movement disorders can be fast or slow, some with regular rhythm (tremor) and others more erratic (dystonia, myoclonus, ballismus). Although there are exceptions, the presence of a premonitory aura or an alteration of mental status during or after the episodes is usually indicative of epilepsy.

POST-STROKE EPILEPSY

The presence of unusual movements following a stroke is a common setting for a clinician confronted with differentiating between epilepsy and a movement disorder. Seizures are a common manifestation after stroke, occuring in one form or another, including both motor and nonmotor manifestations, in approximately 10% of patients (4,5). They are twice as likely in hemorrhagic versus ischemic strokes, and usually occur after lesions involving the cortex (6). One study showed that 3.5% of patients with subcortical strokes experienced at least one seizure (7). Recurrent seizures develop in 2.5 to 4% of patients after stroke, and are more common following large, cortical, or hemorrhagic stroke (5,6).

Simple partial seizures that cause focal abnormal movements, usually involving a limb or part of the face without effecting mental status, may occur after stroke. Seizures are usually episodic, but if the movements are continuous, they are referred to as *epilepsia partialis continua,* which may be refractory to therapy. Partial seizures generally involve rhythmic jerking movements or rhythmic muscle spasms, but they may also involve dystonic posturing. Seizures with motor symptoms involving the stroke-affected side of the body can be challenging to distinguish from a movement disorder. Complex partial seizures can also be confusing if the alteration in mental status is not pronounced. Generalized seizures are less likely to present a dilemma.

Epileptic seizures are included in the differential diagnosis in the first case presentation because of the previous history of a seizure disorder, the temporal association with stroke, and the brief, episodic nature of the attacks.

POST-STROKE MOVEMENT DISORDERS

Movement disorders have been described in association with stroke since the nineteenth century (8). The Lausanne stroke registry study demonstrated that 1% of patients have abnormal hyperkinetic movements following acute stroke. These included hemichorea, hemiballismus, dystonia, myoclonus, and asterixis. Lesions were universally subcortical, with the most common site being the thalamus, as well as the basal ganglia and adjacent white matter (2). Indeed, thirteen of twenty-two patients with thalamic lesions were shown in one study to have developed some form of abnormal movement, most frequently contralateral dystonia. These were specifically seen with damage to the ventral intermediate (Vim) and ventral caudal (Vc) nuclei (9). An earlier study also demonstrated that dystonic movements were associated with thalamic infarcts, whereas chorea and ballismus were more often seen contralateral to lesions of the subthalamic region (3).

The subcortical location of this patient's stroke, the preserved consciousness, and the phenomenology of the movements raise the index of suspicion of a movement disorder in this case. The following sections review commonly observed movement disorders.

CHOREA, ATHETOSIS, AND BALLISMUS

Chorea, athetosis, and ballismus are often considered to lie on a continuum (10,11), and progression from one to the other is frequently observed during the resolution of acquired disorders, thus suggesting a common pathology (12).

The word chorea is derived from the Greek word for dance, and is best described as brief, unpredictable, nonrhythmic, jerking, involuntary movements that appear to flow from one body part to another. Ballismus describes more violent flinging motions of a limb or body part that tend to be more proximal than distal. Athetosis is characterized by more continuous sinuous and writhing movement.

Chorea is classically represented by Huntington's disease and Sydenham's (poststreptococcal) chorea, although there are many causes of chorea. Huntington's disease (HD) is an autosomal dominant disease caused by trinucleotide repeat expansion in the gene for the protein, huntingtin (13). HD is characterized by chorea, psychiatric disturbance, and progressive cognitive dysfunction resulting in dementia. Diagnostic uncertainty may occur early in the course of HD, when symptoms are mild and occasionally unilateral, although the family history, unrelenting progression, and genetic testing generally permit clear differentiation of the disease.

Benign hereditary chorea is a rare disorder of autosomal dominant inheritance localized to chromosome 14q (14). It is characterized by the childhood onset of choreiform movements, primarily of the upper extremities, which progress to a peak intensity in adolescence and are usually unresponsive to therapy. There are no other symptoms, and imaging is normal. Differentiation from epilepsy is aided by the presence of similarly affected family members and the presence of a normal electroencephalogram (EEG) during movements (15).

Sydenham's chorea generally begins during childhood when idiopathic epilepsy is also likely to present. Characterized by a self-limiting course of chorea, carditis, and signs of rheumatic fever, it is preceded by a streptococcal illness, and classically affects preadolescent females. The incidence of this disorder has markedly declined in recent decades due to increased use of antibiotics in the treatment of strep throat (16).

Chorea may be symptomatic of many types of systemic and metabolic disorders, and is often reversible. Metabolic derangements, such as hyperthyroidism (17), hormonal shifts, such as in pregnancy or oral contraceptive use (18), and systemic disorders such as systemic lupus erythematosus, primary antiphospholipid antibody syndrome, and paraneoplastic disorders may all produce reversible chorea (19,20). Chorea may also be a presenting symptom in other less common and protean disorders such as neuroacanthocytosis and Wilson's disease (21).

In the case of all the above disorders, the symptoms are usually bilateral, although only one limb or one side may be affected. In epilepsy, bilateral movements are associated with a change in consciousness, which is less common in choreic disorders.

Stroke is a common secondary cause of chorea and generally results in unilateral symptoms, contralateral to the infarct (11). Infarcts that result in chorea are most frequently located in the basal ganglia, thalamus, and subthalamic nucleus (2,3). The timing and course of the movement disorder is varied. In a retrospective study, 58% of movements resolved within two weeks (2), while some persisted for years. Another study reported that 40% of patients had persistent symptoms until death (3). However, the intensity of symptoms usually improved over time. The most effective therapy is the administration of dopamine blocking agents (12), with a recent emphasis on atypical neuroleptics, given their reduced risk of tardive dyskinesia (22,23). Valproic acid and benzodiazepines, as well as thalamotomy (24), and deep brain stimulation (25) have been tried with varied results.

Ballismus is most commonly observed in the setting of structural lesions of the contralateral basal ganglia and subthalamic nucleus (2,3). Cerebral infarct is the most common cause, but tumors of the same region have also resulted in ballismus (26). Systemic derangements including fever (27) and hyperglycemia (28) have been reported to cause or exacerbate hemiballismus in patients with underlying lesions or a history of less severe movement disorders. Medications including levodopa, phenytoin, and oral contraceptives have also been implicated. Bilateral ballismus has been reported, but is rare (29).

Following cerebral infarct, hemiballismus is often self-limited. For both transient or persistent hemiballismus, therapy with dopamine antagonists such as haloperidol (12) or risperidone (22) can be useful. Other medications that may ameliorate ballismus include benodizepines, tetrabenazine, and reserpine. Therapy with valproic acid has also been reported to be effective (30,31).

Athetosis is most often described in association with chorea, as choreoathetosis. It may also occur in isolation, when patients solely exhibit slow, sinuous, writhing motions. It is most frequently reported in patients with cerebral palsy (32), ascribed to perinatal insults resulting in lesions of the basal ganglia and thalamus (33,34). As with chorea, athetosis may be observed in a number of conditions, including structural lesions, demyelinating disease (35), central nervous system (CNS) infections (36), and drug-induced disorders (37–39). The diagnostic approach and management are similar to that for chorea and ballismus.

DYSTONIA

Like chorea, dystonia may mimic epilepsy, particularly when involuntary movements are episodic or paroxysmal rather than continuous. Dystonia may occur as a primary disorder or may be secondary to numerous

other conditions. Dystonia is characterized by sustained, often twisting postures of a specific body part. It is produced by involuntary muscle contraction resulting in sustained posturing or facial grimacing that can be focal, segmental, or generalized in distribution. Dystonia is caused by abnormal basal ganglia function and has been associated with derangements in brainstem and spinal cord inhibitory interneuronal circuits, as well as changes in thalamic control of cortical motor planning and execution (40). It is characterized by the cocontraction of agonist and antagonist muscles and the impaired integration of sensory inputs (41). Indeed, sensory modulation of dystonia is clinically apparent in the phenomenon of sensory tricks known as *geste antagoniste*. For example, patients with cervical dystonia may obtain transient symptomatic relief from tricks such as lightly touching their own face.

Dystonia can be placed into five categories: primary dystonia, dystonia plus, secondary dystonia, heredodegenerative dystonia, and psychogenic dystonia (42). Primary dystonias, without other neurologic abnormality or clear neuropathology, include both genetic and sporadic/idiopathic forms. Sporadic forms, which are the most common, typically present in adulthood with focal symptoms, such as torticollis, blepharospasm, or task-specific dystonias, such as writer's cramp (43). No clear gene defects have been reported. However, a strong association between a specific allele in the D5 dopamine receptor gene and sporadic cervical dystonia was recently reported (44). This has led to speculation that a genetic predisposition and a secondary environmental insult may be required to develop the disorder.

Genetic forms of primary dystonia are diverse, presenting focally, segmentally, or as generalized symptoms, with severity ranging from mild to severely disabling. The most severe generalized form, previously called dystonia musculorum deformans or idiopathic torsion dystonia, now termed DYT1 dystonia, is the best understood. Onset is in childhood or adolescence, usually presenting with a dystonia of the legs that commonly spreads to affect all body regions (45). The gene defect, a CAG deletion in the TOR1A gene on chromosome 9 (46) [which encodes Torsin A, an ATP binding protein expressed in dopamine neurons in the substantia nigra (47)], is transmitted in an autosomal dominant fashion with about 30% penetrance (48,49). It is especially common among Ashkenazi Jews, accounting for 90% of early-onset limb dystonia in that population (46). The same gene defect accounts for 40 to 60% of early-onset limb dystonia in non-Jewish populations (50). This defect is not found in cases of adult onset focal dystonias (46).

Adult onset focal dystonias have been described in several families, and studies report that between 2 and 15% of patients with focal dystonia have affected relatives (51). One gene defect in several European families localized to chromosome 18p (DYT7) results in the onset of cervical dystonia and spasmodic dysphonia around age 40 (52,53). Two loci have been linked to adult onset dystonia presenting primarily with craniocervical and limb dystonias. The first in two German families was associated with chromosome 8 (DYT6) (54), and the second, in an Italian family, was linked to chromosome 1 (DYT13) (55).

Dystonia-plus syndromes include Dopa-responsive dystonia and myoclonus-dystonia. Dopa-responsive dystonia (Segawa's disease) is dominantly inherited and characterized by the childhood onset of dystonia and parkinsonian features that fluctuate through the day and are exquisitely and persistently responsive to low doses of levodopa (56). Defects in the GCHI gene for the enzyme GTP cyclohydrolase, required for the biosynthesis of tetrahydrobiopterin, are implicated (57,58). Myoclonus-dystonia is a dominantly inherited disorder marked by the childhood onset of the combination of dystonia and myoclonic jerks that are sensitive to alcohol. Two gene loci have been found, one on chromosome 7q21-31 (59,60) and one in a family with a missense mutation in the D2 dopamine receptor (61).

Dystonia can also be a significant feature of heredodegenerative diseases such as Huntington's disease, Wilson's disease, and Machado-Joseph disease, as well as Parkinson's disease, progressive supranuclear palsy, and several mitochondrial disorders. In Parkinson's disease, dystonia may be observed during the "on" or "off" periods, both related to anti-parkinsonian therapy, or as a symptom of the underlying disorder. For a more complete list of secondary causes of dystonia, see Table 12.2.

Treatment of dystonia is primarily symptomatic. The management of focal dystonia has been significantly enhanced by the use of botulinum toxin therapy (62,63). Cervical dystonia and blepharospasm respond particularly well to botulinum toxin injection. Both abnormal postures and pain may be relieved by injection. Generalized dystonia is more difficult to treat. Partial symptomatic relief can be achieved with the use of anticholinergic drugs (64) and tetrabenazine (65), with lesser response from benzodiazepines and baclofen. Individual patients may respond to antiepileptic drugs or levodopa (66).

MUSCLE CRAMPS AND SPASMS

Cramps are the result of the involuntary, painful shortening of a muscle that can often be relieved by stretch or massage. Electromyography (EMG) performed during a muscle cramp reveals normal, but high-frequency action

TABLE 12.2
Secondary Causes of Dystonia

Heredodegenerative
- Huntington's disease
- Neuroacanthocytosis
- Wilson's disease
- Hallervorden-Spatz
- Ataxia-telangiectasia
- Machado-Joseph disease
- Dentatorubrapallidoluysian atrophy
- Gangliosidoses
- Lipofuscinoses
- Niemann-Pick
- Rett syndrome
- Metachromatic leukodystrophy
- Amino and organic acidurias
- Lesch-Nyhan syndrome
- Mitochondrial disorders
- Parkinson's disease
- Corticobasal degeneration
- Multisystem atrophy
- Progressive supranuclear palsy

Chemical/toxic
- Copper
- Manganese
- Cyanide
- Methanol
- Cocaine
- Amphetamine
- Carbon monoxide

Medications
- Neuroleptics
- Antihistamines
- MAO inhibitors
- Levodop disease
- Dopamine agonists
- Ergotamine
- SSRIs
- Buspirone
- Anesthetics
- Carbamazepine
- Disulfiram

Vascular
- Infarction
- Hemorrhage
- Vascular malformation
- Arteritis
- Anoxia
- Trauma
- Tumor
- Pachygyria
- Infection
- Lupus/antiphospholipid antibody syndrome
- Creutzfeld-Jacob disease
- Demyelination
- Syringomyelia
- Kernicterus
- Hydrocephalus

potentials. Cramps are often seen in the setting of dehydration, dialysis, and electrolyte imbalances, and usually do not represent neurologic pathology.

Although cramps and spasms can complicate many neurologic disorders, they comprise the major symptoms in Isaac's and stiff-person syndromes. Stiff-person syndrome, first described by Moersch and Woltman in 1956 (67), is characterized by progressive muscle stiffness with superimposed painful cramps. Startle-induced spasms are common and may result in confusion with stimulus-induced seizures. However, the presence of pain and the sustained spasms with muscle rigidity between spasms are not characteristic of epilepsy. Stiff-person syndrome is frequently associated with antibodies to glutamic acid decarboxylase and is often coincident with other autoimmune disorders (68,69).

Patients may experience symptoms in all body parts, although the axial musculature is primarily affected, often leading to exaggerated lordosis. Onset is often asymmetric, thus making differentiation from other disorders, including focal dystonia and epilepsy, difficult in the early stages. EMG studies of patients with stiff-person syndrome demonstrate normal motor action potentials, but voluntary relaxation is not possible, thereby causing significant pain and disability. Therapy with benzodiazepines, especially diazepam is beneficial (70), and intrathecal baclofen has provided relief in a subset of patients (71). There are reports of more effective and long-lasting improvement with IVIg or plasmapheresis (72,73).

Isaac's syndrome (neuromyotonia) is believed to be an autoimmune channelopathy, related to antibodies to potassium channels (74). Patients with Isaac's syndrome experience cramps and myokymia and can be seen to have muscle twitches that may appear similar to fasciculations. Myokymic discharges on EMG appear as continuous muscle fiber activity with fasciculations and doublets (75). Clinically, these present as a slow

undulation of the involved muscle and overlying skin. Steroid therapy and plasmapheresis have been effective in controlling symptoms (76,77). Myokymia may also be seen in the setting of multiple sclerosis or mass lesions compressing the brainstem (78).

Approach to Patient #1

The clinical challenge posed by Mr. J's presentation is related to the transient nature of his symptoms and the complicated history of both acute stroke and a childhood seizure disorder. The physical exam was not helpful since there were no deficits between episodes. Diagnostic investigations excluded the possibility of metabolic aberration or infection. MRI revealed only the recent thalamic stroke. A routine EEG was normal. Several antiepileptic drugs were empirically introduced without a change in the frequency or severity of the episodes. To identify the cause of the involuntary movements, video-EEG monitoring was performed. Several episodes were observed over 24 hours with no alteration of the EEG. A normal EEG may be seen during simple partial seizures; however, the absence of any EEG abnormality suggested that these episodes might be nonepileptic in nature. The episodes were each less than 30 seconds and characterized by sinuous movements and flexor posturing of the left arm. A functional disorder was unlikely due to the proximity of the onset of the movement disorder with a contralateral thalamic infarct, as well as the absence of discernible secondary gain or psychopathology. Mr. J was diagnosed with post-stroke choreoathetosis. Both phenytoin and carbamazepine were titrated down without an increase in event frequency and clonazepam was introduced. He was discharged from the hospital and at follow-up 3 weeks later, the frequency and severity of episodes had improved.

Case Study #2. C.S. is a 15-year-old obese female with a history of hyperthyroidism, referred to the movement disorder center with a chief complaint of involuntary "jerks." These began around 12 years of age, prior to her diagnosis of Grave's disease, and recently increased in frequency and severity. Treatment of hyperthyroidism did not result in improvement of the movement disorder. Four episodes occurred during the office visit. The movements were characterized by sudden, rapid, and forceful head and trunk rotation to the right and right arm abduction lasting several seconds with no alteration of consciousness. These episodes caused considerable alarm among family members. Episodes were reported to occur up to 20 times a day, with no identifiable triggers. Her neurologic examination was otherwise normal. There was a history of psychological stress related problems at home, in school, and with socialization.

Both epilepsy and movement disorders may commonly present in childhood and adolescence. This patient's movements are rapid and stereotyped, and could be explained by partial epilepsy, epileptic or nonepileptic myoclonus, or paroxysmal dyskinesia. The history of stress and behavior problems raises the possibilities of problems adjusting to illness or alternatively, psychogenic symptoms.

Attention to the family history, birth history, and developmental history are especially important in disorders presenting in childhood, because perinatal insults may result in either epilepsy or movement disorder later in life. As mentioned in the previous case, a thorough medication and medical history are essential, particularly in regard to the timing of onset of the movements in relation to other historical events. For example, in this patient, the diagnosis of Grave's disease followed the onset of movements, therefore medications started for that condition are unlikely to be the cause of the movement disorder. However, the thyroid disorder itself may either be a causative or contributory factor.

Hyperthyroidism is associated most commonly with enhanced physiologic tremor, which can be seen in the majority of patients. Chorea is occasionally seen in hyperthyroid patients (79) and has also been reported in one case of euthyroid Hashimoto's encephalopathy (80). Movement disorders are less often seen in patients with hypothyroidism, although ataxia has been described (81).

MYOCLONUS

Myoclonus is a particularly protean movement disorder; there are many potential etiologies and pathophysiologies. In fact, myoclonus may be either epileptic or nonepileptic. Friedreich first described myoclonus in 1881, coining the term *paramyoclonus multiplex* (82) for very quick, shocklike muscle jerks. Myoclonus is usually described as a rapid, involuntary muscle contraction, originating from the brain or spinal cord, that causes a jerking movement. It can also be caused by a brief pause of tonic muscle activity; it is then referred to as negative myoclonus. Myoclonus in its many forms can involve isolated muscle groups or may include whole segments or the entire body. Symptoms can involve various parts at different times or always be limited to a specific region. Myoclonus can be idiopathic or symptomatic; focal, segmental, or generalized; epileptic

TABLE 12.3
Classification of Myoclonus

Physiologic
- Hiccoughs
- Hypnic jerks

Essential
- Inherited myoclonus dystonia

Symptomatic
- Degenerative
  - Huntington's disease
  - Alzheimer's disease
  - Corticobasal degeneration
  - Friedreich's ataxia
  - Ataxia-telangiectasia
  - Wilson's disease
  - Parkinson's disease
  - Progressive supranuclear palsy
  - Hallervorden-Spatz
- Storage diseases
  - Gaucher's disease
  - Tay-Sachs disease
  - Gm2 gangliosidoses
  - Krabbe's disease
  - Aminoacidurias
- Infectious/prion
  - Creutzfeld-Jakob disease
  - SSPE
  - Meningitis
  - Syphilis
  - Whipple's disease
  - Herpes simplex encephalitis
- Vascular
  - Stroke
  - Ischemic
  - Hemorrhagic
  - Postanoxic (Lance-Adams syndrome)
- Metabolic
  - Uremia
  - Hepatic encephalopathy
  - Hypoglycemia
  - Hyperglycemia
  - Hypokalemia
  - Hyponatremia
- Medication
  - Antidepressnats
  - Antibiotics
  - L-DOPA
  - Phenytoin
  - Cocaine
  - Amphetamines
- Toxic
  - Bismuth
  - Methyl bromide
  - Heavy metals
- Tumor
- Trauma
- Miscellaneous
  - Celiac disease
  - Demyelination
  - Drug withdrawal (alcohol, sedatives)
  - Decompression illness

Epileptic
- Nonprogressive
  - Juvenile myoclonic epilepsy
  - Familial adult myoclonic epilepsy
  - Autosomal dominant cortical Myoclonus and epilepsy
  - Photosensitive myoclonus
  - Epilepsia partialis continua
- Progressive
  - Unverricht-Lundborg disease
  - Lafora disease
  - MERRF
  - Neuronal ceroid lipofuscinoses
  - Sialidoses
  - Dentatorubralpallidoluysian atrophy
  - Olivopontocerebellar degeneration

or nonepileptic. Although myoclonus is sometimes clearly nonepileptic, and at other times is clearly a form of epilepsy, gray areas also exist where myoclonus appears to lie between both movement disorder and epilepsy.

The classification of myoclonus is complex. Diverse classification schemes employing anatomic, physiologic, and etiologic factors have been proposed (83). Anatomic and physiologic classifications are useful in furthering our understanding of pathology; however, for the purposes of diagnosis and treatment, an etiologic approach is more useful. Weiner and Lang (84) presented a scheme based partially on the classification proposed by Fahn, Marsden, and VanWoert (85), that divides myoclonus into four categories: *physiologic* (common muscle jerks such as hiccoughs and hypnic jerks); *essential* (idiopathic myoclonus without other neuropathology); *symptomatic* (due to an underlying abnormality); and *epileptic* (myoclonus as part of an epileptic syndrome). (See Table 12.3).

Essential Myoclonus

Essential myoclonus, hereditary essential myoclonus, and myoclonic dystonia are a group of disorders characterized by onset in the first two decades of life and having autosomal dominant inheritance. These syndromes are differentiated by the extent to which dystonia is present, as well as the response of symptoms to alcohol. Despite these distinctions, some believe that the differences between them are no larger than the heterogeneity between affected members of the same pedigree. This had led some to suggest a common designation of inherited myoclonus-dystonia (86).

The course of these syndromes is usually described as benign, although the movements can be quite disabling to some patients. The incidence is believed to be about 1 per 100,000 persons (87), although this may be an underestimate. Patients experience myoclonic jerks, often of the arms and axial muscles. Dystonia, often torticollis or writer's cramp, commonly occurs and may be the predominant symptom. Symptoms may be responsive to alcohol (86,88,89). Affected individuals generally have an otherwise normal neurologic exam, and labs and imaging studies are usually normal. Mutations of the D2 dopamine receptor gene on chromosome 11q23 have been described in one large family with the disorder (90), and mutations of the SCGE gene on chromosome 7q21 have also been reported in several families (59,91,92). Treatment of the disorder can be challenging, since whereas alcohol may ameliorate the myoclonus, drugs tend to be less effective. There are a few reports of symptomatic relief of essential myoclonus with deep brain stimulation of the thalamus (93,94).

Symptomatic Myoclonus

Numerous toxic, metabolic, and infectious derangements are associated with myoclonus (Table 12.3). Neurodegenerative disorders, such as Huntington's disease (95), Alzheimer's disease (96), and corticobasal degeneration (97) may also give rise to myoclonus. In children, genetic disorders including Friedreich's ataxia, ataxia-telangiectasia, Wilson's disease, storage diseases such as ceroid-lipofuscinosis, and Tay-Sachs disease should also be considered (98–101). Myoclonus is a well-recognized, frequent, and early prominent symptom in Creutzfeldt-Jakob disease. In most of these disorders, myoclonus is one symptom in a diverse clinical presentation. Although myoclonus may be confused with seizure activity in these settings, the other symptoms associated with the underlying diagnosis may often tip the hand towards myoclonus rather than epilepsy.

Diagnostic confusion between seizure and myoclonus may arise following cerebrovascular insult. Myoclonus may be seen subsequent to subcortical stroke (2,3,9). It is also commonly seen in hypoxic injury, often after cardiac arrest and resuscitation. Although many patients with post-hypoxic myoclonus do not survive, those that do may develop action-induced myoclonus (Lance Adams syndrome) that is often accompanied by grand mal seizures and gait abnormalities (102).

Spinal myoclonus arises from the spinal cord, often secondary to injury from tumor, trauma, infection, ischemia, demyelination, or degeneration. It is characterized by spontaneous, rhythmic contractions of the muscles innervated by an affected spinal cord segment, usually one limb and the adjacent trunk muscles (103,104). The movements may be stimulus sensitive and may persist in sleep. This form of myoclonus has also been seen after spinal anesthesia or contrast administration (105,106). Propriospinal myoclonus, more recently described, is characterized by nonrhythmic axial jerks that spread slowly rostrally and caudally, resulting in flexion or extension of neck, trunk, hips, and knees (107,108). This type of myoclonus is usually idiopathic and may also be stimulus sensitive. Previously believed to be a separate entity, recent reports suggest that propriospinal and spinal myoclonus may overlap (109).

Myoclonic Epilepsy

Myoclonus may be seen in patients with generalized epilepsy, both tonic-clonic and absence. It may also be a central feature of epileptic syndromes, some of which are described below. Myoclonic epilepsy varies in severity from benign nonprogressive syndromes to progressive forms that are universally fatal. Juvenile myoclonic epilepsy, a nonprogressive form, also known as the morning myoclonus of Janz, is characterized by adolescent onset, myoclonus upon awakening, and early morning generalized tonic-clonic seizures and occasional absence seizures (110). It is common, representing 5 to 10% of all epilepsies, and has been generally described as idiopathic (111). However, recent genetic studies have shown linkage to the EJM-1 locus on chromosome 6p (112–114). This linkage was not seen in other kindreds, suggesting genetic heterogeneity (115,116). Juvenile myoclonic epilepsy is often characterized by photosensitivity, whereas in pure photosensitive epilepsy, myoclonus and generalized seizures occur only with photic stimulation. Valproic acid, lamotrigine, topirimate, and levetiracetam have been advocated as first-line therapy (117).

Familial adult myoclonic epilepsy is similar to the juvenile form, but with onset in adulthood. It has been linked in one Japanese family to chromosome 8q24 (118,119), but the absence of linkage in a Spanish pedigree suggests genetic heterogeneity (120). In addition, a

recent report describes an Italian pedigree with patients exhibiting nonprogressive, adult-onset rhythmic limb myoclonus and rare complex partial and generalized tonic-clonic seizures. Designated autosomal dominant cortical myoclonus and epilepsy, this syndrome is linked to chromosome 2 (121).

The more malignant epileptic syndromes with myoclonus include the progressive myoclonic epilepsies (PME). These disorders have many names and have been alternately categorized by "lumpers" and "splitters," resulting in some confusion in the literature. The first descriptions of this syndrome over a century ago by Unverricht (122) and Lundborg (123) reported several families in Estonia and Sweden with a progressive course of myoclonus and seizures. Between then and now, many names, including Baltic myoclonic epilepsy, Ramsey-Hunt syndrome, and Unverricht-Lundborg disease, have been used. Modern methods of genetic and molecular characterization are beginning to help sort things out. Presently, five major disorders are described: Unverricht-Lundborg disease (ULD), Lafora's disease, neuronal ceroid-lipofuscinosis, myoclonus epilepsy with ragged red fibers (MERRF), and sialidoses (124). There are a number of rarer forms of PME as well. Together, they account for approximately 1% of epilepsies seen at epilepsy centers, although considerable geographic and ethnic variability exists (125). A thorough discussion of all of these syndromes is beyond the scope of this chapter.

PME is characterized by progressive myoclonus, tonic-clonic seizures, ataxia, and dementia. Onset is usually in late childhood or adolescence, but may occur at any age. EEG is abnormal, with diffuse slowing and variable spikes, polyspikes, and spike and wave complexes with marked photosensitivity (126,127). EEG performed concurrently with myoclonic jerks suggests a cortical source consistent with epilepsy, although EEG abnormalties are not seen in all cases (126,127).

Treatment of PME is difficult. The complete control of seizures and myoclonus is rare, and the disease is progressive. Phenytoin should be avoided, since it has been associated with symptomatic deterioration (128,129). These reports were specific to ULD, but most authors recommend avoidance of phenytoin in all PMEs. Valproate and clonazepam (129), as well as piracetam (130), and more recently zonisamide (131) have all been beneficial. There are also anecdotal reports of improvement with vagal nerve stimulation (132).

Classification of Epileptic Myoclonus

Based on electrophysiologic findings, Hallett proposed a classification system that describes epileptic myoclonus in relations to different forms of epilepsy (133). *Cortical reflex myoclonus* is described as a fragment of focal or partial epilepsy. The term "reflex" infers that jerks can be stimulated by auditory, visual, or sensory input. This type of myoclonus is not disease specific, but is seen in diverse disorders including PME, post-hypoxic myoclonus, metabolic encephalopathy, and cortical-basal ganglionic degeneration (134). A cortical localization can be demonstrated by jerk-locked back-averaging of EEG that shows a positive-negative spike 15 to 40 ms before the jerk is seen on EMG. The EMG shows a very brief discharge of 15 to 30 ms (134). Markedly enlarged somatosensory evoked potentials (SEP), also attesting to a cortical source, are characteristic and are seen exclusively in this type of myoclonus (135,136). Giant SEPs are associated with hyperexcitable cortical long-loop reflexes, but their significance is unclear.

Reticular reflex myoclonus is described as a fragment of generalized epilepsy. Patients experience brief generalized myoclonic jerks that affect proximal and flexor muscles more greatly than distal and extensor muscles. Similar to cortical reflex myoclonus, these jerks also increase with action and sensory stimuli (137). They are believed to arise from the brainstem, from activity of the gigantocellular nuclei of the pons and medulla (138). EEG may show some spike activity, but jerk-locked back-averaging of EMG demonstrates that they are not time-locked (139). EMG discharges are longer, ranging up to 100 ms. Not surprisingly, given the subcortical origin, SEPs are normal.

Primary generalized myoclonus is described as a fragment of primary generalized epilepsy. This is characterized by small focal jerks, usually of the fingers. Termed "minipolymyoclonus," this can be difficult to differentiate from chorea. Generalized myoclonus is also seen. EEG shows slow bilateral frontocentral negativity preceding the jerks (140).

Because clinical presentations may be similar, Hallett describes three electrophysiologic criteria for distinguishing between epileptic and nonepileptic myoclonus (133). EMG burst length in epileptic myoclonus is usually less than 50 ms, whereas in nonepileptic myoclonus it ranges from 200 to 300 ms. Muscle activity in epileptic myoclonus is synchronous, whereas jerking may be asynchronous in nonepileptic myoclonus. And nonepileptic myoclonus does not have the EEG correlate that is often found in epileptic myoclonus.

PAROXYSMAL DYSKINESIA

Paroxysmal dyskinesia lies squarely in the borderland between epilepsy and movement disorders. Prior to Mount and Reback's paper in 1940 (141), describing familial paroxysmal choreoathetosis, most authors described these disorders as unique forms of epilepsy

with names like extrapyramidal epilepsy (142), reflex epilepsy (143,144), striatal epilepsy (145), and subcortical epilepsy (146). Although there is still some controversy, a growing consensus believes that paroxysmal dyskinesias are nonepileptic in nature.

The most common and most well described paroxysmal dyskinesia is paroxysmal kinesigenic choreoathetosis (PKC). It is characterized by brief, jerky, choreiform, or dystonic movements lasting seconds to minutes that are provoked by voluntary movement or startle (147). PKC may be inherited or sporadic, with sporadic forms dominating in the United States. In contrast, a Japanese paper reported that 97 of 150 cases were inherited (148). Autosomal dominant forms have been localized to chromosome 16p11-q12 (149), and a second locus has been described at chromosome 16q13 (150).

PKC also may be secondary to other disorders including multiple sclerosis (151), stroke (152), HIV (153), hypoparathyroidism (154), hyperthyroidism (155), and it may be psychogenic (156).

Primary PKC usually begins in childhood, with peak activity during adolescence resulting in up to 100 attacks a day. Some patients describe a sensory prodrome of dizziness, muscle tension, tingling, or numbness, although neurologic examination between attacks is usually normal. MRI (157), EEG, and autopsy results (158,159) are generally unrevealing. Nagamitsu et al. reported a large study with eighty-four of one hundred patients with a normal "interictal" EEG and twenty-nine of thirty-one patients had no EEG changes recorded during an attack (148). Interestingly, SPECT scanning has demonstrated an increased perfusion of the contralateral basal ganglia during attacks (157).

The disease is nonprogressive and treatment with antiepileptic medications, especially carbamazepine (160,161), phenytoin (147), and more recently, oxcarbazepine (162) and lamotrigine (163) is often effective.

In contrast to PKC, in paroxysmal nonkinesigenic choreoathetosis (PNKC), the attacks are not stimulated by movement. However, they may be triggered by stress, sleep deprivation, caffeine, alcohol, or tobacco use. Attacks in PNKC are longer, lasting minutes to hours. Dystonic posturing in PNKC may be uncomfortable, and generally occur less frequently than attacks of PKC, at most a few times a day. Speech may be affected during attacks of PNKC and this may be misinterpreted as a change of mental status, thus resulting in further confusion with epilepsy.

Similarly to PKC, there are genetic forms with autosomal dominant inheritance, in this case localized to chromosome 2q (164). However, most forms of PNKC are sporadic or symptomatic, with a panoply of causes including multiple sclerosis, trauma, stroke, HIV, metabolic derangements, hypoparathyroidism, hyperthyroidism, and psychogenic etiologies (165).

Analogous to PKC, diagnostic investigations in PNKC including CT and MRI, CSF, EEG, autopsy, "non-ictal" PET scans, and "ictal" MR single positron emission computed tomography (SPECT) scans are all without findings (166–169).

The second major difference of PNKC is that the syndrome is quite refractory to therapy. Clonazepam may be partially effective, and acetazolamide, anticholinergics, and haloperidol have been useful in individual cases (168,170). Recently, however, some hope has arisen for the efficacy of alternate-day oxazepam (171) as well as gabapentin (172). Interestingly, both phenytoin and levodopa have been shown to worsen episodes (171).

Paroxysmal exercise-induced dystonia or intermediate paroxysmal nonkinesigenic dystonic choreoathetosis is a disease similar to PKC, with episodes lasting longer and induced by extended exercise. There are reports of both familial and sporadic forms (173–175). Paroxysmal ataxia exists as both familial forms, some with concurrent nystagmus or myokymia (176), and those due to metabolic defects including Hartnup's disease (158), pyruvate decarboxylase deficiency, and maple syrup urine disease (177).

Although the differentiation of these syndromes is often difficult, the diagnostic challenge is further increased by their overlap with epilepsy. Demirkiran et al. found a frequent family history of idiopathic epilepsy in patients with paroxysmal dyskinesias, and Tan et al. reported a series of cases showing 8% of patients to have both epilepsy and PKC (178). However, the clinician is aided by the nature of the movements, absence of loss of consciousness or generalization, and normal imaging and EEG.

PSYCHOGENIC MOVEMENT DISORDERS

Although some neurologic disorders now known to be organic were once ascribed to psychiatric causes, various neurologic presentations including movement disorders and seizure are often diagnosed with a psychogenic etiology. In a large series, 3.3% of patients presenting to a movement disorder clinic were found to have a psychogenic etiology (179). Half of the patients presented with tremor, however, dystonia, myoclonus, and parkinsonism were also seen. In another report, myoclonus was found to be the most common psychogenic movement disorder, accounting for nearly 10% of all patients with myoclonus (180). Interestingly, up to 30% of patients exhibiting psychogenic movements also have a coincident organic movement disorder (181,182).

These patients are often difficult to differentiate from those with organic disease. Several factors

described by Fahn have been found helpful in making the distinction (182). A psychogenic cause maybe diagnosed when the movements disappear when the patient is not being directly observed, or with placebo therapy. Phenomenology that is inconsistent with recognized movement disorders or accompanied by bizarre signs and symptoms is also supportive. Symptoms that fluctuate over time or change with distraction may be also indicative of psychogenicity. Finally, the presence of multiple somatizations, or a history of psychiatric illness may raise the concern of a psychogenic etiology.

Approach to Patient #2

The patient's episodes of sudden jerking movements suggested myoclonus and raised the question of epilepsy versus movement disorder. The family history and history of childhood development were unrevealing. In addition, the neurologic examination was normal, making symptomatic myoclonus or the progressive myoclonic epilepsies less likely. The complexity of the movements were not characteristic of essential myoclonus, but raised a concern of paroxysmal dyskinesia, which often presents in adolesence. Neuroimaging and EEG were normal. Trials of clonazepam and valproate were not beneficial. Videotelemetry was performed, revealing a normal EEG during several episodes. The frequency of the episodes was noted to increase with direct observation, especially when the family was in the room. Further discussion with the patient and family revealed that the young teenager was depressed and withdrawn from her peers, while gaining increasing attention from her family related to her symptoms. A diagnosis of psychogenic paroxysmal dyskinesia was made.

Case Study #3. N.H. is a 52-year-old woman with a past medical history of hypertension and GERD, for which she takes verapamil and metoclopramide. She presented with a chief complaint of 1 month of facial jerking. The movements began with involuntary muscle twitching around the right eye. Over time, the right facial spasms had increased in frequency and severity, resulting in intermittent full closure of the eye and pulling of the mouth to the right. Other than the intermittent facial movements, her neurologic examination was normal.

Abnormal movements of the face are commonly seen in both epilepsy and movement disorders. Tardive dyskinesia, tic, stereotypy, hemifacial spasm, blepharospasm, and Meige syndrome are all associated with facial twitching that may resemble seizure activity.

TABLE 12.4
Medications Associated with Tardive Dyskinesia

Neuroleptic drugs	Antiemetics
Typical antipsychotics	Droperidol
Chlorpromazine	Metoclopramide
Fluphenazine	Prochlorperazine
Haloperidol	Promethazine
Perphenazine	Antidepressants with
Pimozide	dopamine- receptor
Thioridizine	blockade
Thiothixine	Amoxapine
Trifluperazine	
Atypical antipsychotics	
Olanzapine	
Risperidone	

TARDIVE DYSKINESIA

Although primarily seen in patients treated with antipsychotic medication, tardive dyskinesia and tardive dystonia may develop in any patient receiving medication with dopamine blocking activity, including antipsychotics, antiemetics, or antidepressants (Table 12.4). Tardive dyskinesia (TD) is defined as abnormal involuntary movements following 3 months of cumulative exposure to neuroleptics (continuous or discontinuous) with no other identifiable cause for the movement disorder. The movements of tardive dyskinesia are choreiform but generally more stereotyped than typical chorea. Face, mouth, head, and neck are most often involved, followed by hands and arms.

The emergence of chorea in the setting of an evolving neurologic disorder often presents a dilemma: when the patient has been treated with dopamine blocking agents, it can be difficult to decipher. Is the chorea a symptom of the primary neurologic syndrome or a sign of tardive dyskinesia (183)? Chorea may not be distressing to the patient, often causing more distress for the patient's family. There is a wide range of severity—from a mild cosmetic problem to severe cases that may be disabling, or even life threatening (184,185).

Two meta-analyses have demonstrated that the prevalence of tardive dyskinesia with the chronic use of traditional antipsychotic medications is between 17.6 and 20% (186,187). In schizophrenics on neuroleptic medication, the incidence was 5% in the first year, increasing linearly to 19% after 4 years (188). Incidence is higher in women and the elderly. Tardive dyskinesia

may develop with the use of any dopamine receptor antagonist, but the risk is significantly reduced with the use of atypical antipsychotic medications (189,190).

The pathophysiology of tardive dyskinesia is not well understood, and there are several competing theories. Traditionally, TD has been attributed to denervation hypersensitivity with increased numbers and affinity of D2 dopamine receptors in the striatum (191). However, this explanation is incomplete as receptor changes in animal models did not correlate in timing with symptoms and occurred in all animals tested, whereas TD does not occur in all individuals exposed to neuroleptics. A second theory focuses on a reduction in glutamic acid decarboxylase activity in striatal GABA neurons in animals and humans treated with neuroleptics (192). These changes have been correlated with the presence of TD in patients (193). Recent theories suggest that glutamate excitotoxicity results in the disinhibition of thalamic output from pallidal GABAergic neurons projecting to the thalamus (194–196). MRI and SPECT scans, as well as postmortem examination, have shown no specific changes associated with TD (197–199).

The management of TD is challenging, so prevention of the disorder is extremely important. Neuroleptic medication should be used only when clearly indicated, and atypical antipsychotics should be used when feasible. When tardive dyskinesia occurs, the reduction and/or discontinuation of the offending medication is desirable. However, one's ability to discontinue the neuroleptic is limited by the severity of the initial indication as well as the tendency for the dyskinesia to be aggravated by withdrawal of the dopamine-blocking effects of the neuroleptic. Symptoms remit within 3 months after discontinuation of the neuroleptic in approximately one-third of patients (200). Remission is more likely in younger patients and those taken off the medication early. If symptoms persist, or discontinuation of medication is not possible, TD may be ameliorated with the administration of reserpine, tetrabenazine, or benzodiazepines (201–203). Valproate (204), piracetam (205), donepezil (206), baclofen (206), melatonin (207), and vitamin B6 (208) have reportedly been helpful in selected cases.

TARDIVE DYSTONIA

More recently recognized as a distinct disorder, tardive dystonia is also related to the chronic use of dopamine receptor antagonists. The movement disorder is, of course, dystonic, with sustained, contorting muscle contractions causing twisting or posturing (209). Similarly to tardive dyskinesia, these symptoms are less likely to develop with the newer atypical antipsychotics (209). In contrast to tardive dyskinesia, the onset of tardive dystonia tends to be earlier, often within the first 3 months of therapy (210). This is especially true in male patients who are generally younger at onset of symptoms (211). Tardive dystonia often begins focally, at the head and neck, but progression to generalized dystonia is common. Neck extension and truncal arching, at times forceful and disabling, may occur.

Meta-analysis reveals that tardive dystonia develops in 3 to 5% of patients treated with dopamine receptor antagonists (212). Unfortunately, full remission is not common. A longitudinal study demonstrated that only 14% had relief of symptoms after 5 years of follow-up, suggesting that the pathologic alterations may be irreversible (214). Remission is more likely in those with shorter exposure, so neuroleptic medication should be used with due caution and should be discontinued, if possible, when symptoms occur. In focal dystonia, therapy with botulinum toxin injections may be useful (213–215). For more generalized symptoms, pharmacologic therapy may ameliorate, but not abolish the movements. Improvement may be achieved with reserpine, tetrabenazine, and high dose anticholinergics (216). Benzodiozepines and other muscle relaxants may be helpful. In severe cases, the reintroduction of neuroleptic medication, preferably atypical agents, may be necessary. Clozapine may be especially helpful since it is unique in its efficacy in ameliorating dystonia without simultaneously inducing extrapyramidal symptoms. Caution must be observed with this medication, given the risk of agranulocytosis as well as its tendency to lower the seizure threshold. Intrathecal baclofen, thalamotomy, and deep brain thalamic stimulation have also been helpful in selected cases (217–220).

Tardive dystonia must be clearly delineated from acute dystonic reactions that occur in a significant percentage of patients upon institution of therapy with dopamine blocking agents. Acute dystonic reactions can range from simple torticollis to generalized opisthotonos. Symptoms usually resolve after treatment with anticholinergic drugs (221).

TICS

Tics are very common and especially frequent in children, where studies demonstrate that between 4 to 50% of school-aged children have tics (222,223). Tics are involuntary movements or vocalizations that can be transiently suppressed by the individual. One hallmark of tics is the building up of an urge to "tic" that is relieved by its performance. Tics tend to wax and wane in frequency and severity, sometimes moving from one body location to another.

Tics can be divided into three types. Simple motor tics can be clonic (eye blinking), dystonic (blepharospasm

or torticollis), or tonic (isolated muscle tensing). Complex motor tics may include touching, jumping, or obscene gestures. Vocal tics can be simple (throat clearing or grunting) or complex (words or phrases).

Tics have many causes. They are commonly seen in isolation in normal subjects as well as in a diverse range of neurologic disorders, from structural lesions related to trauma or stroke, to genetic or neuropsychiatric disorders (224). Tics are classically associated with Gilles de la Tourette's syndrome (TS). First described in 1825 by Itard (225) and later by Gilles de la Tourette, the diagnosis of TS requires multiple motor and one or more vocal tics, occurring many times a day, nearly every day or intermittently for at least 1 year (226). Onset of TS is insidious, usually beginning around age 5 with simple motor tics (227), and progressing over time to include phonic tics. Patients are able to suppress tics, but experience mounting tension that is relieved by the tic. Some patients feel compelled to repeat tics until they are done "just right."

Tic disorders tend to peak in adolescence and may plateau later in life. Phonic tics are especially likely to resolve in adulthood. Coprolalia, is rare, affecting less than 10% of patients (228), although one study in Japan found up to 50% of patients to be affected (229), thus suggesting some phenotypic heterogeneity.

TS may be familial or sporadic. Family members of TS patients may have only simple tics, suggesting that diverse tic presentations may be different manifestations of the same pathology. This is supported by the concordance of TS in 50 to 70% of monozygotic twins, which rises to 89 to 94% concordance when any form of tic is considered (230). Genetic analysis has not found a specific cause or mode of inheritance, although preliminary linkage has been seen with several genetic loci, including areas on chromosomes 4q, 8p, 19p, 16q, and 7q (231–234). Some association with prenatal care and Apgar scores at birth has also been described, suggesting a possible environmental contribution (235).

Significant comorbidity exists between TS and neuropsychiatric disorders. It has been estimated that 40 to 70% of children with TS have attention deficit hyperactivity disorder and that 30 to 60% have obsessive compulsive disorder (OCD) (236,237).

TS may be part of a group of post-streptococcal syndromes known as PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) (238). This theory is based on the finding in TS patients of B lymphocyte antigen D8/17, a marker for rheumatic fever, as well as antibodies to streptococcal proteins (239,240). Antineuronal antibodies to striatal structures have also been seen (241). The pathophysiology of TS is not understood, but abnormalities in the basal ganglia, frontal-subcortical pathways, and limbic connections are likely to play a role (242–244).

The most effective therapy is the use of dopamine receptor antagonists. These drugs carry the risk of tardive dyskinesia, which is less likely to develop with atypical neuroleptics such as olanzapine and risperidone. Clonazepam, guanfacine, and clonidine may be efficacious, with less risk (245–248).

Tics and tic disorders may be differentiated from epilepsy by the variability of the movements, the urge to perform tics, and the ability to suppress them.

TABLE 12.5
Common Stereotypic Movements

Face, head, and neck	Lip smacking, lip biting, smiling, grimacing, vocalizations, head banging, nodding, head shaking
Arms and hands	Finger tapping, finger waving, hand wringing, fists, eye poking, touching or stroking self or objects, hair pulling, scratching
Legs and feet	Toe tapping, leg swinging
Trunk and whole body	Body rocking, pelvic thrusting, jumping, pacing

STEREOTYPIES

A stereotypy can be described as any repetitive, purposeless action. This includes a broad range of movements from simple activities such as finger tapping or eye blinking, to more complex behaviors such as headbanging or self-mutilation (Table 12.5).

Stereotypies may occur alone or may be secondary to trauma, drugs, or toxic-metabolic insult. They may also be part of a disease process such as Tourette syndrome, tardive dyskinesia, or neuroacanthocytosis. In severe cases, the movements may be functionally disabling.

Like tics, stereotypies may be consciously suppressed and are decreased by distraction. However, in contrast to tics, stereotypies are not preceded by a progressive urge or relief following the activity. Rather, they appear to be self-stimulating behaviors in response to subconscious tension and anxiety (249). Although normal infants and children may exhibit stereotypic behaviors such as head banging or rocking (250,251), stereotypies are more frequent in neglected children. Studies demonstrate that animals kept in a

low-stimulus environment will develop self-stimulating stereotypies (252).

Stereotypies are common with severe mental illness, retardation, and autism. In fact, stereotypic behaviors have been described in 34 to 66% of institutionalized retarded adults (253,254). The incidence of movements was inversely correlated with IQ and directly correlated with length of institutionalization. In the case of Rett syndrome, an autistic disorder affecting female children, stereotypies including hand wringing, rubbing, and clapping, may become so severe as to interfere with functional use of the hands (255). Stereotypies are also seen in about one-quarter of patients with either catatonic schizophrenia or obsessive-compulsive disorder (256,257). Interestingly, a study performed on a random sample of college students showed stereotypies to be much more common in healthy subjects than was previously thought (258). Only a subset of these actions were time-consuming or problematic. There appears to be a large overlap between normal and pathologic stereotyped behaviors, suggesting that the abnormality is best defined primarily by the frequency of the movements and the degree to which they interfere with daily activities. This principle holds true for most movement disorders.

The pathophysiology of stereotypies is not well understood; however, it is clear that dopaminergic pathways are involved. Intrastriatal injections of dopamine or the systemic ingestion of dopaminergic drugs induce stereotypic behaviors in rats (259,260). These movements cease with the administration of neuroleptic medications. Similarly, chronic amphetamine abusers develop a decreased repertoire of normal activities, which are progressively replaced by stereotypies.

The need for treatment of stereotypies should be guided by their frequency and severity and the presence of functional impairment. Underlying disorders such as OCD may respond to treatment and ameliorate stereotypies. Behavioral interventions may be helpful. If medication is necessary, neuroleptic drugs are the most effective. Benzodiazepines, lithium, baclofen, and opiate antagonists have also been beneficial (261,262).

HEMIFACIAL SPASM

Hemifacial spasm (HFS) is characterized by involuntary, irregular, tonic, and clonic movements of muscles innervated by the seventh cranial nerve. HFS is usually unilateral, although 5 of 158 subjects had bilateral involvement in one study (263). The onset of spasm is usually at the orbicularis oculi muscle, later spreading to include the lower facial musculature. The hallmark of HFS is the autonomous firing of CN VII with no ability for voluntary control or suppression. Onset is most commonly in midlife, and complete remission is rare. HFS is presumed to be related to vascular compression of the facial nerve at its root exit zone in the brain stem. Thorough MRI/MRA studies have shown 88 to 93% of affected facial nerves with evidence of neurovascular compression, versus 56% of the contralateral unaffected nerves in the same patients (264). A past history of Bell's palsy or facial nerve injury increases the incidence of HFS, and an association with arterial hypertension has been reported as well (265,266). HFS has also been reported secondary to tumors, pontine lacunar infarcts, and demyelinating disease (267). Although the bulk of cases are sporadic, there are rare reports of familial hemifacial spasm (268–271) with an autosomal dominant inheritance pattern (272,274).

HFS may be reduced or even abolished with microvascular decompression surgery, which may be successful in up to 90% of patients (272,273), although there is the risk of surgical complications. Therapy with botulinum toxin is the mainstay of treatment of HFS due to high efficacy with minimal risk. In several studies, 80 to 95% of patients significantly improved (274,275). Injection must be repeated every few months, with continued benefit from injections over many years. Medications including carbamazepine, phenytoin, and gabapentin have limited usefulness (276).

BLEPHAROSPASM AND MEIGE'S SYNDROME

Blepharospasm is a focal dystonia characterized by the involuntary contractions of the orbicularis oculi muscles, resulting in the bilateral closure of the eyes. This can range from a relatively benign increase in blink frequency to sustained eyelid closure that the patient cannot overcome. This latter form results in functional blindness and disability. Onset is gradual and usually occurs in midlife. Secondary causes, include ophthalmalogic disease (277), infarcts (278), and medications (279) have been described. The origin of primary blepharospasm is not known. However, an increased risk is seen in those with a family history of dystonia (280). Magnetic resonance spectroscopy of patients with primary blepharospasm has revealed evidence of striatal neuronal loss, thus suggesting an underlying pathology of the basal ganglia (281). Therapy is symptomatic, with botulinum toxin injections as the mainstay of treatment.

Meige's syndrome or craniocervical dystonia encompasses the dystonic contractions of blepharospasm in addition to spasms of the lower facial muscles, jaw, and neck. Both blepharospasm and Meige's syndrome result in bilateral facial muscle contractions. As in blepharospasm, most cases have no known cause. However, these symptoms can be seen as

a result of chronic neuroleptic medication, thus representing a form of tardive dystonia (282). More rarely, structural lesions of the basal ganglia and degenerative diseases can lead to secondary Meige's syndrome (283). Once again, botulinum toxin is the most effective therapy.

Approach to Patient #3

The insidious onset of mild unilateral eyelid twitching with gradual progression in severity of spasms to involve the ipsilateral lower face unilaterally is a classic presentation of HFS. Even in the absence of other neurologic signs, one cannot exclude the possibility of a mass in the cerebellopontine angle or a demyelinative plaque as the cause of seventh nerve impairment. An MRI of the brain with contrast was obtained and was negative. The patient was diagnosed with HFS and responded well to botulinum toxin injections.

Other etiologies to be considered in the differential diagnosis of this patient include tardive dyskinesia/dystonia related to chronic metoclopramide administration, seizure, or facial tic. The very rapid muscle spasms of HFS are quite different from the stereotyped choreic movement of tardive dyskinesia, as exemplified by orobuccolingual chewing movements. Sustained involuntary facial grimacing and eyelid closure may occur with tardive dystonia; however, this is generally bilateral and symmetric. Seizure is another cause of unilateral facial twitching; however, the history of insidious onset with gradual ramping up of the severity of spasms over months is less likely to be characteristic of a seizure disorder. The same could be said of facial myoclonus, which could be caused by medication, but would not be expected to evolve over time in such a characteristic maner. Facial twitching associated with seizure is also more rhythmic and episodic, and more likely to be associated with sensory and other neurologic phenomena. Facial tics are less likely to develop in a middle-aged patient and are suppressible, unlike HFS, which is completely autonomous.

Conclusion

These three patient case studies pose examples of the challenges in differentiating movement disorders from epilepsy. Although no simple test or algorithm can clearly make the distinction, there are some key points towards making the correct diagnosis. An adequate history of the frequency and timing of episodes, as well as triggers and associated symptoms may be facilitated by the use of symptom diary. Observation of the movements and video monitoring, when necessary, are irreplaceable in arriving at the correct diagnosis.

Although routine studies, such as CT and MRI, are often normal in both movement disorders and epilepsy, certain findings such as mesial temporal sclerosis or thalamic stroke may help tip the scales towards epilepsy versus movement disorder. Other imaging studies such as PET and SPECT scans are not yet clearly useful, but may prove to be so in the future.

The response to medication may be helpful, such as the amelioration of chorea with introduction of a neuroleptic, although both movement disorders and seizures may respond to similar medications, such as benzodiazepines. In certain situations, such as dopa-responsive dystonia, medication challenge can be diagnostic.

The differentiation of epilepsy and movement disorders is similar to medical assessment and diagnosis in general; it requires a thorough systematic approach, an attention to detail, and often the test of time.

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13 Hyperekplexia and Other Disorders of Startle: Differential Diagnosis with Epilepsy

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It is customary to start a presentation on startle by referring to the normal reflex, a common reaction in animals and humans, preparing the subject to respond by fighting or by escaping as quickly as possible (1). Fatigue or stress predispose to increased startle, and great variation of the extent of this reflex exists in the population, with some individuals aptly described as hyperstartlers. Excessive startle is also a frequent but not an obligatory feature of people with multiple tics or Tourrette syndrome.

The three main disorders manifesting with excessive startle are hyperekplexia, startle epilepsy, and jumping (2). The early distinction between startle epilepsy and startle disease comes from the work of Alajounanine and Henry Gastaut, who used the terms *maladie du sursaut* for the nonepileptic process and *epilepsie sursaut* for persons in whom excessive startle was coupled with epileptic clinical manifestations (3). The differential diagnosis of these disorders is not always easy, and a misdiagnosis of epilepsy is almost always suggested in people with abnormal startle, particularly in those with startle disease.

HYPEREKPLEXIA

Kirstein and Silverskjold published a report on a family with several affected individuals who they considered to have an unusual form of epilepsy, but which in retrospect was startle disease (4). Two major papers were then published by Kok and Bruyn (5) and by Suhren, Bruyn, and Tuynman (6), and the clinical pattern of nonepileptic startle disease or hyperekplexia emerged (7). A key feature is an exaggerated and persistent startle reaction to unexpected auditory, somatosensory, or visual stimuli. The onset of the disease is usually in infancy and even in the perinatal period (8). Attacks of tonic stiffening may interfere with breathing, and affected children have been described as having a stiff baby syndrome (9). Recognition of these attacks and the risk of children of affected parents being affected is important since the infant may die due to tonic stiffening leading to apnea. Regurgitation may also occur.

Associated features are hiatal, inguinal, or umbilical hernias and congenital dislocation of the hips, presumably all related to the rigidity.

Infants are often delayed in walking and develop falling attacks, again caused by brief, generalized, but nonepileptic tonic spasms. These spasms may occur in response to surprise and sensory stimuli as well as due to strong emotions such as stress or fright. The child falls without being able to prevent herself but without loss of consciousness. It is the peculiarity of the stimuli and of the circumstances which often leads to the diagnosis. One of our patients carried a diagnosis of spastic quadriparesis, quite common in this condition, since the

children are often rigid. The child collapsed like a log when he caught a small fish, which fell on to him as he pulled it out of the water. An epileptic etiology was first suspected. Affected sisters presented with drop attacks long considered to be epileptic but which did not respond to considerable antiepileptic medication. On further questioning the mother, the role of startle became apparent, and one of the children stiffened and collapsed when a metal kidney basin was dropped on the stone floor. She hit her head and cried, but there was no impairment of awareness. In older children and rarely in adults, a short period of generalized stiffness may occur following the startle response, during which voluntary movements are impossible, thus resulting in unprotected falls with fractures and more rarely head injury. Here, too, a diagnosis of epilepsy is usually entertained. The risk of overmedication with antiepileptic drugs, when the nature of the process is not recognized, is not negligible.

Excessive startle persists throughout life and is best elicited by gently tapping the tip of the nose or forehead. This response is similar to the McCarthy reflex. It may also be more apparent under stressful conditions. The hypertonia or generalized muscular rigidity gradually diminishes with time, but as the exaggerated response to startle persists, it leads to an unusual and uncertain gait, somewhat broad based and with a tendency to walk along the walls, and touch the wall, in the expectation of any abnormal stimulus. Hyperreflexia is sometimes found, particularly in the lower extremities.

Nocturnal episodes of generalized clonus, most marked in the lower extremities and lasting up to many minutes, sometimes develop. The person remains conscious, but is generally upset by the continuing violent involuntary movements that seem to be triggered by fatigue, loss of sleep, or stress. The attacks are generally well identified by their families, but may lead to misdiagnosis by even the best movement disorder cognoscenti, who are led to consider a diagnosis of conversion reaction (10).

Rarely, there is a degree of stiffness later in childhood or in adults, which may be long-lasting and may involve one or more limbs. This is somewhat reminiscent of the stiffness found in infants and, in the limited experience available, has been associated with recurrences of symptoms related to cessation of medication (11).

Intelligence is usually normal, but in some individuals there may be a degree of mental retardation and epileptogenic EEG abnormalities may be present, although seizures in affected individuals are exceptional (6). This suggests more widespread cerebral involvement. The patients respond dramatically to clonazepam, which abolishes most clinical features except for the head retraction on nose and forehead tapping (7).

Because of intermittent excessive startle in family members of clearly affected individuals, we wondered about the possibility of a minor form of the disorder in addition to the full-blown or major form of startle disease (6,7). Thus, the mother of two affected girls, while going through a difficult divorce, startled excessively and literally rose off the chair when the phone rang, but these features then disappeared as her life settled down. Later studies by Tijssen and colleagues suggested that this minor form merely represents excessive physiologic startle, since these individuals did not have the identified molecular mutation (12).

Startle disease is inherited as an autosomal dominant, with a high penetrance of over 90% and with variable expressivity. Sporadic and autosomal recessive forms have been described, and the familial and sporadic cases appear to have the same clinical phenotype. Sporadic cases may represent either a new mutation in the proband, autosomal recessive inheritance, germline mosaicism, or lack of penetrance in affected relatives (7,13,14).

In the last decade the molecular basis of startle disease has been clarified according to the work of Shiang et al (15). It consists of an abnormality of the inhibitory glycine receptor (GLYR). They found two different missense mutations occurring in the same base pair of exon 6 of the alpha 1 subunit of the inhibitory glycine receptor GLRA1: G1192A and G1192T, resulting in amino acid substitution at codon 271 of arginine > leucine and arginine > glutamine respectively. They found mutations in four of seven families tested. The first mutation was confirmed in a Swiss family reported by Schorderet et al. (16), and in the original German Dutch family described Suhren et al.

The finding of two point mutations at the same position suggested that arginine at position 271 is critical for the function of the inhibitory glycine receptor. The evaluation of the large German Dutch family showed that the mutation was not present in patients with the minor form—that is, in individuals with only an excessive startle reaction to unexpected, particularly auditory, stimuli. This can be due to exaggerated normal startle or to a modifying gene which, together with a mutation in GLRA1, results in this mild form of startle disease (17).

Functional studies of the inhibitory glycine receptor showed that picrotoxin is a competitive antagonist of the alpha 1 subunit of the human GLYR. The two mutations described transform picrotoxin from an allosterically active competitive antagonist to an allosteric potentiator at low concentrations and to an uncompetitive antagonist at higher concentrations. Thus, the allosteric transduction pathways of both agonists and antagonists converge at a common residue prior to the activation

gene of the channels, suggesting that this residue may act as an integration point for information from various extracellular ligand bindings sites (18).

Functional studies have shown that agonist binding in the GLYR initiates the opening of a chloride-selective channel that modulates the neuronal membrane potential. Missense mutations substituting arginine 271 with either leucine or glutamine result in a redistribution of GLYR single-channel conductances to lower conductance levels. The binding of the glycinergic agonists beta alanine and taurine to mutated GLYRs does not initiate chlorine current, but competitively antagonizes currents activated by glycine. Thus, arginine 271 mutations result in an uncoupling of the agonist binding process from the channel activation mechanism of the receptor.

In summary then, an enormous amount of new information has surfaced during the last decade regarding the molecular basis of hyperekplexia. Nine mutations of the GLYRA1 gene have been identified, five dominant and four recessive. One of the recessive mutations is a null mutation, and two others occurred in a compound heterozygote. No mutation of GLYR has been identified in a number of familial cases and in nonallelic genetic heterogeneity. This suggests nonallelic genetic heterogeneity and the possibility of mutations in other GLYR subunits exists. Three mouse models of hyperekplexia have been identified, one with a missense mutation of GLYRA1, one with an insertion mutation at GLYRB, and one null allele at GLYRA1 (19).

These molecular advances should lead to improved genetic counseling, prevention of neonatal deaths and complications, increased knowledge of the mechanisms involved in abnormal startle and, eventually, rational therapy. For now, treatment with clonazepam or valproic acid in low doses brings about adequate though incomplete improvement (7,11,19).

However, some patients have symptomatic hyperekplexia due to central nervous system (CNS) pathology. Patients with static perinatal (20), postanoxic, or post traumatic encephalopathy, sarcoidosis, or paraneoplastic disease etiology have been described. Brainstem lesions (21,22) may also produce this clinical picture, and these various symptomatic startle abnormalities must be distinguished from startle epilepsy, which is not always easy given the paucity of electroencephalographic (EEG) abnormalities in some patients with frontal epilepsy.

STARTLE EPILEPSY

In startle epilepsy, the most effective stimuli may be auditory or tactile, more rarely visual. The coexistence of neurologic abnormalities greatly facilitates the diagnosis. Startle epilepsy may occur in patients with infantile hemiparesis, quadriparesis, diffuse encephalopathy, secondary generalized epilepsy, Down syndrome and, only exceptionally, in patients with normal intelligence and normal neurologic status. The pathophysiology of startle epilepsy has been studied by Chauvel et al (23). They showed that the seizure starts in the muscles first involved in the startle reflex, propagates to the contralateral limb, and then moves to the ipsilateral side. The abnormality is usually frontal or frontoparietal, involving the supplementary motor area and the vicinity of the paracentral lobule (24,25). Aguglia et al. and Gastaut found mesial frontal atrophy in 40% of patients with startle epilepsy, frontal or central spikes in half, evoked frontocentral spikes in one third, and frontal spike foci in all (26).

Startle epilepsy is quite variable in its response to antiepileptic medication. Some patients are easily controlled and remain with only minor, though still abnormal responses to startle. In others, the abnormal response progresses despite optimal antiepileptic medication to falling, with its attendant risks of injury. In the presence of identifiable structural lesions, surgical treatment after appropriate localization studies is quite effective. In others, particularly in the absence of a visible lesion, the potential for surgical treatment is low: occasional patients are condemned to life in a wheelchair. A specific response of startle epilepsy to clonazepam has been suggested by Jimenez Roldan, but this has not been confirmed (27).

JUMPING AND OTHER CULTURE-BOUND SYNDROMES

Excessive startle is also a feature of the culture-bound syndromes known since the late 1800s. The Jumping Frenchmen of Maine were described by Beard, occurring in loggers working in the Moosehead Lakes area of Maine (28). The clinical features are excessive startle, echolalia, echopraxia, and forced obedience. Later studies by Kunkle have stressed the occasional late appearance of symptoms after a nonspecific illness (29). The familial nature is obviously not compatible with a learned process, though good family studies are not available. Drs. Marie Helene and Jean-Marc St.-Hilaire described several jumpers who, in response to startle, adopted a fighting stance and swore (30). They, like Rabinovitch (31), assumed that this was a learned behavior designed to amuse bystanders by startling susceptible individuals, but this is unlikely to explain the genetic features.

In patients with the culture-bound syndromes, forced obedience to such orders as "throw it," "punch," or "hit" may bring about not only embarrassment, but occasionally danger.

An analogous disorder, *myriachit, amurath,* or *icotta* has been described in Siberia, the former by Hammond, then Surgeon General of the United States (32). *Latah* in Malays, *Goosey* and *Raging Cajuns* in the United States, *Jaun* in Burmese, *Bahtsche* in Thailand, *Mali Mali* and *Silok* in the Philippines, and *Lapp Panic* probably represent analogous, if not identical, disorders (33). The studies of Simmons (34) and Carly Tanner (35) were carried out in *Latah* subjects in Malaysia. They stressed the behavioral features and the social utilization of such behaviors. *Imu,* a behavioral disorder in the Ainu of Hokkaido in Northern Japan, likely represents the same process. The early descriptions come from Uchimura, who also filmed affected persons (36). The current perspective among Japanese neurologists on Hokkaido suggests that the process occurred mainly in women and that it is currently dying out. A biological cause of *Imu* is firmly denied.

When one reviews the descriptions of these various disorders, a great similarity of the clinical features, with increased startle, echolalia, echopraxia, and more rarely, forced obedience is inescapable. It is the social superstructure that varies; the clinical features of startle epilepsy and of hyperekplexia, however, are always absent. Most likely, these culture-bound startle disorders represent an unusual form of tics.

The molecular basis remains unknown, similar to the situation in Tourette syndrome, with which these disorders share many clinical features, including the genetic background.

The differential diagnosis of startle disorders is mainly between the three entities described. Occasional cognitive deficit or epileptogenic abnormalities in rare patients with startle disease contribute to the diagnostic difficulty. The rare occurrence of startle epilepsy in individuals without other overt neurologic abnormalities represents another diagnostic dilemma.

However, in most individuals awareness of the diagnostic possibilities should lead to recognition of the underlying process.

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14 Encephalopathy as a Mimic of Seizures

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The terms *delirium, encephalopathy,* and *acute confusional state* are all used to describe a disorder of diffusely disturbed cortical function. Some have reserved the term delirium for acute confusional states that are accompanied by psychomotor hyperactivity, but we avoid this term because of its frequent ambiguous use. The term acute confusional state is suboptimal because *confusion* is a nontechnical term that may result from perturbation of any of a number of cognitive processes. The term *encephalopathy* is clearer and reflects the global disturbance of cognitive function that forms the core component of the clinical syndrome.

Encephalopathy may result from a wide range of pathologic processes and is, therefore, more appropriately regarded as a syndrome (of many possible etiologies) than as a specific disease. The range of disease processes that may cause encephalopathy is broad and beyond the scope of this chapter (see Table 14.1). Many causes are medical illnesses, often including organ failure or other metabolic derangements, as well as infections and medication administration or withdrawal. Seizures and the postictal state are two of the many causes of encephalopathies. In this sense, seizures do not mimic encephalopathy but are rather one of its many causes.

Since encephalopathy is often characterized as an alteration of consciousness or a global disturbance of cognition, this chapter begins with a discussion of the anatomic basis for arousal and cognition. This is followed by a brief discussion of the etiology and pathophysiology of encephalopathy.

To be able to recognize seizures as the specific cause of an encephalopathy it is necessary to know something about the clinical phenomenology of encephalopathy and whether this is in any way determined by etiology. That is to say, are there any distinguishing clinical features that should lead the clinician to suspect seizures (or other etiologies) as the cause of an encephalopathy? We then consider the utility of the electroencephalogram (EEG) in the diagnosis of encephalopathy. Finally, we conclude with a discussion of the similarities and differences between epileptic and other causes of encephalopathy.

THE ANATOMY AND PHYSIOLOGY OF AROUSAL

Normal cognition requires functional cerebral hemispheres and an intact ascending arousal system that is necessary to keep the cortex active. To understand the diversity of pathologic processes that may cause encephalopathy, it is useful to review the functional anatomy of the ascending arousal system and its hemispheric projections. For example, an understanding of

TABLE 14.1
Causes of Delirium

I. Central Nervous System	
Cerebrovascular	Infarction or transient ischemic attack
	Hemorrhage: intracerebral or subarachnoid
	Hypertensive encephalopathy
Trauma	Concussion or contusion
	Subdural or epidural hematomas
Infection	Meningoencephalitis
Neoplastic	Primary or metastatic tumor
	Carcinomatous meningitis
Ictal	Seizures, especially complex partial
	Nonconvulsive status epilepticus
	Postictal states
Sensory or sleep deprivation	
II. Systemic Disease	
A. Infection:	Systemic infection: with fever, septicemia.
	Organ infection; e.g., pneumonia, urinary tract infection
B. Metabolic	
Drug intoxication:	e.g. with anticholinergics, dopamine agonists, steroids, benzodiazepines, barbiturates, other sedatives, anesthetics.
Withdrawal states:	e.g. with alcohol, barbiturates, benzodiazepines
Electrolyte: hyponatremia, hypernatremia, hypercalcemia	
Hypoglycemia/hyperglycemia	
Hypercapnia	
Hepatic insufficiency	
Renal insufficiency	
Hormonal: hypothyroidism/hyperthyroidism, hypercortisolemia	
C. Vascular/hematologic	
Hypotension, hypoperfusion	
Oxygenation problems, congestive heart failure	
Hyperviscosity syndrome	
Hypoxia	
Carbon monoxide poisoning	
D. Paraneoplastic states	

the role of cholinergic projection systems facilitates an understanding of why anticholinergic drugs may cause encephalopathy and confusion (1).

The ascending arousal system comprises cholinergic projections from the rostral pontine tegmentum and monoaminergic and histaminergic projections from the brainstem and basal forebrain (2). The thalamic relay neurons may be conceptualized as the gatekeepers of cortical arousal. These neurons have two distinct physiologic states—a transmission mode and a burst mode (2). In transmission mode, the resting membrane potential of these neurons is near threshold so that afferent synaptic potentials cause these neurons to fire and transmit the incoming sensory information to the cortex. In contrast, when hyperpolarized by GABAergic input from the thalamic reticular nuclei, the thalamic relay neurons enter burst mode, during which incoming synaptic activity generates bursts of synchronized activity that project to the cortex (2).

The cholinergic pedunculopontine tegmental (PPT) and laterodorsal tegmental (LDT) nuclei project to the thalamic relay neurons and the thalamic reticular nuclei, activating the former and inhibiting the latter (2). They thus facilitate the transmission mode of the thalamic relay neurons. Serotonergic and noradrenergic input from the raphe nuclei and locus coeruleus respectively, together with histaminergic and cholinergic projections from the tuberomammilary and basal forebrain

nuclei, activate the hemispheres via diffuse cortical projections (2). Together, these cholinergic and monoaminergic projections compose the ascending arousal system.

Normal wakefulness requires that the cortex be both awake and receptive to incoming stimuli. The monoaminergic, histaminergic, and cholinergic projections from the raphe, locus coeruleus, and basal forebrain arouse the cortex, and the cholinergic input from the PPT and LDT nuclei maintain the thalamic relay neurons in transmission mode so that the cortex can receive and process afferent information. The electroencephalographic accompaniment of this wakeful state is primarily a relatively desynchronized EEG (but with a more regular, alpha-frequency rhythm occipitally when the subject is awake but with eyes closed). Slow-wave sleep, by contrast, is characterized by decreased activity of the ascending arousal system. In sleep, the thalamic relay neurons enter burst mode, the electrographic correlate of which is a relatively synchronized and slower background EEG (2).

PATHOPHYSIOLOGY OF ENCEPHALOPATHY

The pathogenesis of encephalopathy is incompletely understood, and the discussion that follows represents a collection of ideas and concepts that have emerged from recent research. There is probably no single pathophysiology. Rather, many different perturbations of brain function may produce the same clinical syndrome. Potential mechanisms include a deficiency of substrates for oxidative metabolism (e.g., hypoglycemia), impaired synaptic transmission, and gross alterations in the water and electrolyte composition of the internal milieu. These mechanisms may be interrelated. For example, hypoxia and hypoglycemia may affect the synthesis and release of neurotransmitters (3) and thus adversely affect synaptic transmission.

The cholinergic hypothesis proposes that a cholinergic deficit is central to the pathophysiology of encephalopathy. The importance of the pontine tegmental cholinergic projections to the thalamus in maintaining arousal has already been discussed. Intuitively, dysfunction or decreased activity within these nuclei and their projections would result in a decreased level of arousal. Supporting evidence for this hypothesis is derived from the observation that anticholinergic drugs have a propensity to cause an encephalopathy (1) that may be reversed by cholinergic drugs (e.g., physostigmine, an acetylcholinesterase inhibitor) (4). Furthermore, decreased oxidative phosphorylation may impair acetylcholine synthesis, and the resulting cholinergic deficiency may constitute the common denominator in toxic-metabolic encephalopathies [summarized in (5)].

The role of other neurotransmitter systems is less clear. Haloperidol, a potent dopamine antagonist, may reverse an encephalopathy, thus suggesting a role for dopaminergic excess in the pathophysiology. This is the proposed pathophysiology of bupropion-induced encephalopathy (6). It is unclear whether the encephalopathy that can result from dopamine agonists used in the treatment of Parkinson's disease results from the same mechanism.

Encephalopathy can occur as a consequence of excess serotonin and is one of the most prominent symptoms of the serotonin syndrome. In view of the importance of serotonergic projections from the raphe nuclei in maintaining arousal, it is not intuitive that serotonin excess would produce an encephalopathy. However, serotonin pathways are more widespread, and it may be either that other serotonergic systems are relevant or that it is the imbalance between serotonergic and cholinergic brainstem projection systems that results in an encephalopathy.

As the predominant inhibitory neurotransmitter in the brain, gamma-amino-butyric acid (GABA) is intuitively an important factor in the pathophysiology of a syndrome characterized by diffuse cognitive impairment. GABAergic projections from the thalamic reticular neurons to the thalamic relay neurons serve as the gatekeeper to incoming sensory stimuli. Increased GABA activity in this pathway causes the thalamic relay neurons to enter burst mode. Increased serum ammonia—in hepatic encephalopathy, for example—results in the increased synthesis of glutamate and glutamine (3), both of which are precursors for GABA synthesis. GABAergic transmission, therefore, is likely enhanced in hepatic encephalopathy.

For the most part, the pathophysiology of encephalopathy is thought to involve a diffuse disturbance that affects either the ascending arousal system in the brainstem or both cerebral hemispheres. This is true for the toxic-metabolic encephalopathies, those that result from the effects of medication (drug intoxication or withdrawal) and for those that result from nonconvulsive status epilepticus or the postictal state. However, it is important to recognize that focal (unilateral) hemispheric lesions may sometimes provide the substrate for a syndrome that resembles the encephalopathic state. Horenstein and colleagues (7), for example, described nine patients with a fluctuating encephalopathy characterized by disorientation, inattention, agitation, restlessness, and auditory or visual hallucinations; six of these patients had a homonymous hemianopia. Postmortem examination showed infarction of the under surface of the temporal and occipital lobes, involving the lingual and fusiform gyri as well as the calcarine cortex. Mesulam and colleagues (8) described three patients with

acute infarction in the right middle cerebral artery territory whose presentation was dominated by what they described as an acute confusional state, characterized by inattention, agitation, and an inability to maintain a coherent stream of thought or action. However, EEGs were not performed in either of these studies; it cannot be excluded entirely that the encephalopathy followed seizures caused by the acute stroke.

THE CLINICAL FEATURES OF ENCEPHALOPATHY

Clinically, encephalopathy, as a syndrome, must be defined operationally; that is, in terms of the presence of particular signs and symptoms. Unfortunately, there has been relatively little formal study of encephalopathy, and those efforts that have been made have been hindered by the variable criteria used to define the syndrome. The observed clinical manifestations of encephalopathy depend on how the syndrome is defined, and in turn, the operational criteria used to define the syndrome determine the observed symptoms and signs. With this caveat in mind, it is useful to examine those studies that have investigated the phenomenology of encephalopathy.

A useful conceptual approach describes encephalopathy as a disorder of higher cortical function that typically involves a range of cognitive abilities, including attention, orientation, memory, perception, and language. Alterations in mood, psychomotor activity, and the sleep–wake cycle may also be present.

Attention is a complex cognitive task that requires selectivity (the ability to focus on a specific stimulus), concentration (the ability to maintain this focus), and set shifting (the ability to switch the focus from one stimulus to another). Patients with encephalopathy have impaired attention (9), and some researchers have even defined encephalopathy in terms of a global disorder of attention (10–12). Distractibility, or a shifting of sets too quickly, is a common feature of poor maintenance of attention in encephalopathies. Inattention has been reported to occur in 17% to 100% of encephalopathic patients [quoted in (13)].

Orientation to person, place, and time refers to the ability of an individual to identify and locate herself in space and time. Disorientation is common in encephalopathic patients, occurring in 43% (14) to 88% (15) of cases. Disorientation for time represents the mildest form and is typically the first to appear and the last to resolve (16). Disorientation for place and person may occur when the encephalopathy is more severe. It is usual for the patient to mistake an unfamiliar place for a familiar one and thus locate himself in his home rather than in a hospital or identify the doctor or nurse as a friend rather than as a healthcare professional. It is rare for an encephalopathic patient to lose awareness of his own identify.

Reduplicative paramnesia is an interesting variation on this theme, in which there is a distortion rather than a loss of memory, and in which confusion about location (hence *paramnesia of place*) is most common. To clarify, the patient's answer is incorrect, but it is clear that the patient must have some access to the correct information. Geschwind provides the example of a patient in the Beth Israel hospital in Boston who claimed to be in the Beth Israel hospital in Concord, New Hampshire (which does not exist). When questioned about this, the patient insisted that there was another Beth Israel hospital in Concord that was a branch of the hospital in Boston (10).

Memory impairment is common, occurring in 64 to 90% of patients [quoted in (13)], but attentional deficits make it difficult to be certain that a true amnestic disorder is present. Partial or total amnesia for the encephalopathic period is invariable (16). Reference has already been made to the entity of *reduplicative paramnesia*.

Perception refers to the process whereby incoming sensory information is grasped, interpreted, and integrated. It is disturbed in 17% to 55% of patients with encephalopathy [quoted in (13)]. Defective perception facilitates the distortion or misinterpretation of sensory stimuli and results in the generation of false perceptions (i.e., illusions and hallucinations). There are few studies of the phenomenology of hallucinations in encephalopathy. In their retrospective chart review, Webster and colleagues (17) recorded the presence of hallucinations in 32% of patients with encephalopathy, with the relative frequencies of visual, auditory, and tactile hallucinations being 27%, 12%, and 3% respectively. The implication is that the hallucinations are multimodal in a significant number of patients. Similar proportions were observed in the study by Cutting, in which hallucinations were visual in 33%, auditory in 18%, and tactile in 4% of patients (18). Olfactory and gustatory hallucinations were not encountered in either of these studies. Vocal, and particularly commanding and threatening hallucinations, are strongly suggestive of psychiatric illness, particularly schizophrenia. Typically, the hallucinations of encephalopathies and psychosis are quite varied in content, while those of epileptic seizures tend to be repetitive and stereotyped over longer periods.

Delusions, the maintenance of fixed false beliefs, are estimated to occur in 20% to 47% (15,17–19) of patients with encephalopathy, with the majority of these being of the paranoid variety (17,18). Some evidence exists that the delusions of encephalopathy have a par-

ticular character. In the study by Cutting, the self was *not* the principal character or center of the delusion among patients with encephalopathy (18). This was rarely the case among patients with schizophrenia. This distinction appeared to be the most significant discriminator between the delusions of encephalopathy and those of schizophrenia. Moreover, only two (of thirty-five) patients with encephalopathic delusions had Schneiderian first-rank symptoms (specific types of delusions and hallucinations that involve themes of passivity; for example, thought intrusion, thought broadcasting, alien penetration, etc.). It has been suggested that delusions in encephalopathy are also the consequence of impaired perception. Thus, delusions may be part of the confabulation process whereby the patient attempts to "fill in" the gaps in knowledge that result from impaired perception (3).

A formal *thought disorder* was present in 64% of patients in the series by Cutting (18) with illogicality, apathy, slow speech with impoverished output, tangentiality, and circumstantiality being most commonly observed features. (Pressured or distractible speech, incoherence, neologisms, perseveration, echolalia, blocking, and excessive self-reference are other components of thought disorders.)

Language dysfunction in encephalopathy is not infrequent, occurring in 41% to 93% of cases [quoted in (13)]. Chédru and Geschwind formally studied language function in twenty-four patients with an acute confusional state defined in terms of the presence of impaired or fluctuating attention (11). They noted a number of abnormalities, including difficulty with word finding, as demonstrated by an anomia for low frequency words on formal tests of naming, and hesitations, repetitions, circumlocutions, or use of one word for another during spontaneous speech. Paraphasic errors were rare during spontaneous speech but were present with reading and repetition. Writing was almost always abnormal, with impaired construction of the letters, poor spatial organization (i.e., letters and words poorly arranged on the page), and spelling errors (12). Speech was also poorly organized, with a tendency to interrupt a sentence in the middle and introduce a new idea or to modify the meaning of a sentence by adding another sentence beginning with a transition word ("but" or "because"). Cummings and colleagues similarly observed word finding difficulty, circumlocution, and occasional paraphasic errors in their single patient (20).

Alterations in psychomotor activity are more variable, but often present in encephalopathy. Psychomotor activity refers to the verbal and nonverbal behavior of the patient and includes voluntary and involuntary movement, flow of speech, character of nonverbal vocalizations, and motor response reaction times. Psychomotor activity in encephalopathy may be increased or decreased. This distinction has formed the basis for the classification of encephalopathy into hyperactive and hypoactive subtypes. Psychomotor hyperactivity includes hypervigilance, restlessness, fast or loud speech, irritability, combativeness, impatience, swearing, easy startling, euphoria, fast motor responses, and distractibility. Encephalopathy with such hyperactivity is often referred to as delirium. Withdrawal states may include not only hyperactive motor function but also severe autonomic abnormalities, as in alcohol withdrawal leading to delirium tremens.

Psychomotor hypoactivity includes apathy, decreased arousal, lethargy, sparse or slow speech, slowed movements, and prolonged reaction time. Such hypoactive encephalopathies can be so severe that the patient may be lethargic, stuporous, or even comatose. In the study by Liptzin and Levkoff (21) of 125 patients with encephalopathy diagnosed according to DSM-III criteria, 15% were classified as hyperactive, 19% as hypoactive, and 52% as mixed, with the remainder failing to meet their criteria for either.

The psychomotor profile may, at least in part, depend on the etiology of the encephalopathy, with the hyperactive variety more common when the etiology is drug-related (intoxication with CNS stimulants like amphetamines and cocaine or withdrawal of sedating agents such as alcohol, benzodiazepines, or barbiturates) (21). Hypoactive encephalopathies and even stupor or coma may be more common with systemic organ failure or with sedation by GABA-mediated drugs like benzodiazepines or barbiturates.

An inversion of the sleep–wake cycle (a pattern in which the individual sleeps during the day and is awake at night) may be an early feature of encephalopathy. Sleep disturbance and disruption of the normal sleep–wake cycle occur in 25% to 96% of patients with encephalopathy [(9), and quoted in (13)]. Harrell and Othmer examined the relationship between sleep deprivation and encephalopathy following open-heart surgery in twenty-seven patients (22). They found that cognitive impairment preceded sleep loss, thus suggesting that the disruption of the sleep–wake cycle is a symptom of encephalopathy. The daytime somnolence of sleep-deprived patients or patients with inversion of the sleep–wake cycle and encephalopathies contributes to their fluctuating level of arousal, inattention, and global impairment of cognitive function.

A final feature of encephalopathies is *asterixis,* from the Greek *sterigma* meaning "to support," literally meaning the inability to maintain a fixed posture. It refers to the intermittent "lapse of posture" of the outstretched limb that was originally described in patients with liver disease (23). It has since been recognized to

occur in a variety of metabolic disorders (24–26). It is also seen in association with anticonvulsant drug toxicity (27). It is regarded as a common manifestation of a toxic-metabolic encephalopathy even though no data indicate the frequency with which asterixis accompanies encephalopathy. The sensitivity and specificity of asterixis in the diagnosis of encephalopathies is unknown.

Having discussed the individual symptoms of encephalopathy, it is easier to understand what is meant by terms like *confusion* and *disturbed consciousness* that are often used to describe encephalopathic patients. These terms describe the behavioral outcome of decreased arousal, impaired attention, disorientation, distractibility, and circumlocutory and tangential speech.

Finally, the temporal evolution of symptoms is an important feature in the diagnosis of encephalopathy. Often, it is a syndrome of fairly rapid onset (hours to days). Encephalopathies generally do not appear over minutes, a time course more suggestive of epileptic seizures or vascular disease. The subacute onset of encephalopathies is particularly relevant in distinguishing this clinical entity from dementia. Fluctuation and nocturnal exacerbation of symptoms are said to be typical and diagnostically important. The subject may have so-called "lucid intervals," during which attention is improved and the patient has a greater capacity for appropriate interaction with his environment. The duration of these intervals may vary from minutes to hours (16).

ELECTROENCEPHALOGRAPHIC FEATURES OF ENCEPHALOPATHY

A number of different electrographic patterns have been described in patients with encephalopathy (28). Generalized slowing of the background rhythm is by far the most common. The degree of background slowing and the presence of more specific patterns (e.g., alpha coma, see below) depend on the severity of the encephalopathy.

Generalized asynchronous slow waves are waves of less than 8 Hz over both hemispheres such that there is no constant temporal relationship between the waves on each side. Although similar patterns may be observed in normal subjects during drowsiness and sleep, this slowing represents the characteristic finding in encephalopathy (29). When mild, there may simply be a small amount of 4 to 7 Hz (theta) slowing superimposed on an otherwise normal background. This may progress to a preponderance of these slower frequencies in the absence of normal rhythms. With increasing severity, the background rhythm slows further to 1 to 4 Hz (delta), and this may be either disorganized and irregular or form a fairly regular, moderately high-voltage pattern.

Romano and Engel were the first to document clearly the relationship between the clinical encephalopathic state and accompanying EEG changes (30). They studied fifty-three patients with encephalopathy (defined primarily on the basis of an attentional deficit) of varying cause. They examined this cohort both clinically and with EEG on many occasions during their illnesses and following recovery and observed EEG abnormalities in all patients with encephalopathy. In the absence of concomitant focal cerebral lesions, the EEG changes were invariably generalized. There was no correlation between the nature of the EEG changes and the cause of the encephalopathy. However, there was a correlation between the extent of the clinical syndrome and the severity of the EEG changes, and the EEG improved along with clinical improvement.

In 1977, Pro and Wells performed a detailed literature review of studies in which patients were examined with an EEG during the encephalopathy as well as after substantial resolution of the encephalopathic process (29). All the studies they reviewed supported the conclusion of Romano and Engel (30), that the basic EEG pattern slows with encephalopathy and quickens with recovery. They also made the important observation that EEG during encephalopathy may not always become recognizably "abnormal." For example, in patients whose normal background rhythm lies in the fast normal range, there might be significant slowing with encephalopathy and yet the frequency may still fall within the normal range for alpha activity (29). They also noted that it might be difficult to identify a record as clearly abnormal when low-voltage fast activity predominates, and the pathologic change might only become apparent with serial studies (29).

In addition to these changes, a number of particular EEG waveforms and rhythms have been described in encephalopathy of different etiology and severity—usually in the more severe cases. These include generalized fast activity, alpha-coma, triphasic waves, and burst-suppression. For the most part, these EEG patterns are also nonspecific.

Generalized fast activity in a comatose patient should arouse the suspicion of drug intoxication, especially with drugs that are known to increase beta activity such as barbiturates and benzodiazepines. Typically, this is in the 12 to 16 Hz range, somewhat slower than the 16 to 25 Hz activity encountered with the use of these medications in the awake patient (31,32).

Triphasic waves are blunt spike and slow-wave complexes that comprise waveforms with three phases of increasing duration. The second wave of the complex is relatively positive in polarity and usually has the greatest amplitude of the three phases. These often occur in bursts, and there may be an (apparent) ante-

TABLE 14.2
Seizures as a Mimic of Encephalopathy

Clinical Feature of Encephalopathy	Seizure that Resembles Encephalopathic Feature
Confusion (disorientation, inattention, distractibility, amnesia)	Nonconvulsive status epilepticus
Psychosis (perceptual disorder, thought disorder, delusions, hallucinations)	Ictal and postictal psychosis
Language disorder	Ictal aphasia
Asterixis	Epileptic negative myoclonus

rior-posterior lag of 25 to 100 msec on bipolar montages. These waves are usually bisynchronous, but may show shifting asymmetries. The term "triphasic wave" was initially coined by Bickford and Butt in 1955 (33), and these waveforms were initially thought to be specific for hepatic encephalopathy. Subsequent series showed that this is not the case. In 1972, Simsarian and Harner identified triphasic waves in forty-two patients with metabolic encephalopathy, half of which were nonhepatic in origin (34). Similarly, Karnaze and Bickford reported fifty patients with triphasic waves, twenty-eight of which were due to hepatic encephalopathy, ten to uremia, nine to anoxia, one to hypoglycemia, and two to hyperosmolality (35). Triphasic waves are common in encephalopathies but are not specific for hepatic encephalopathy.

Alpha coma refers to an alpha frequency pattern that occurs in patients who are comatose. Typically, the alpha activity is either generalized or frontally predominant and unreactive to alerting stimuli. It is most commonly seen following cardiorespiratory arrest and is associated with a very poor prognosis (36). It may also occur following drug intoxication, in which case the prognosis is more variable and often better (37), or after major pontine lesions (such as hemorrhage), in which case the prognosis is dismal. The alpha rhythm, in this case, is often thought to be similar to the rhythmic beta activity of thalamocortical circuits, but slower due to the medication effect and without the usual intermittent desynchronization that is associated with cortical activity in wakefulness (38).

Burst-suppression is a pattern characterized by generalized periodic bursts of polymorphic and often sharp complexes (lasting at least 1 second) that alternate with periods of relative quiescence. For most disease processes, the EEG demonstrates a lower and lower voltage pattern with worsening of the encephalopathy until it loses all signs of cortical activity (becomes "flat"). The burst suppression pattern is most commonly encountered in patients who are deeply comatose due to drug intoxication or following cardiorespiratory arrest. In the latter circumstance, the prognosis is almost uniformly poor. In a review of 116 published cases, Kuroiwa and Celesia described a 96% mortality rate (39) among patients with suppression bursts as a prominent feature of their EEGs.

SEIZURES AND RELATED DISORDERS THAT PRODUCE AN ENCEPHALOPATHY

With a description of the phenomenology of encephalopathy in place, it is now possible to consider the ways in which seizures may lead to some of the same clinical manifestations (Table 14.2).

Nonconvulsive Status Epilepticus (NCSE)

Nonconvulsive status epilepticus (NCSE) is the group of seizure disorders most likely to mimic the global disturbance of higher cortical function that represents the essential feature of encephalopathy. Focal nonconvulsive seizures, most commonly those from the temporal lobe, may also cause the delusions, hallucinations, and frank psychosis that may mimic the perceptual disturbances encountered in encephalopathy. Seizures arising from the left temporal and frontal lobes and surrounding areas may produce aphasia. Epileptic negative myoclonus may resemble asterixis. Details of different seizure disorders, and how they mimic the various manifestations of encephalopathy, are discussed below.

Clinical Features

Nonconvulsive status epilepticus (NCSE) includes prolonged seizures characterized by confusion, speech or language impairment, automatisms, and amnesia. Unfortunately, no uniformly accepted classification exists for the different varieties of NCSE. One approach is to base classification on the electrographic pathophysiology of the syndrome. In this scheme, NCSE can

be divided into generalized status, in which the seizure appears generalized (also referred to as *spike-wave stupor*), and complex partial status, in which the ictal activity remains focal, at least initially (also referred to as *psychomotor status*). Generalized NCSE includes absence (or *petit mal*) status, in which there is thought to be a primary generalized seizure disorder. This approach can also accommodate simple partial forms of NCSE, such as aphasic status epilepticus, in which the dominant (if not the only) manifestation of ictal activity is an aphasia. Simple partial status of frontal lobe origin can be characterized by prolonged affective and/or cognitive symptoms. One difficulty with this approach is that it may not be possible to differentiate these different types of SE at the time of clinical presentation.

It may be more appropriate to conceptualize NCSE as focal (simple partial or complex partial) or generalized, with the latter being either primary (i.e., absence status) or secondarily generalized. In the EEG study by Granner and Lee, for example, some forms of generalized NCSE appeared to be focal in onset (40). Some EEGs had clearly focal ('F') and some clearly generalized ('G') patterns. However, many EEGs demonstrated bilateral, widely distributed epileptiform discharges, but with a focal predominance ('GF' group). Importantly, some of the GF patients showed focal discharges either following the administration of intravenous diazepam for status or during an interictal EEG. Also, one patient with two episodes of status had a generalized ictal pattern on one occasion and a focal pattern on the other. Thus, some cases assigned to the GF group may have harbored an underlying focus from which epileptiform discharges generalized secondarily. Furthermore, other investigators have suggested that status with bisynchronous generalized epileptiform discharges (that would usually be labeled as absence status) may result from the transformation of focal frontopolar ictal discharges (39). In these circumstances, the interictal EEG may be helpful in revealing either focal or generalized interictal discharges.

This classification provides a useful conceptual framework, but it also suggests that it may not be absolutely necessary to distinguish absence from complex partial status, at least immediately in the clinical setting. The distinction may not have a clear therapeutic or prognostic implication at that time. The distinction can be very important, however, in the longer range treatment and prevention of future episodes of NCSE

For simple partial NCSE, the clinical manifestations will be determined by the anatomic location of the ictal electrical discharges. Aphasia (42–47), for example, may result from seizures arising from language areas (48). One must be sure that there is an actual aphasia in order to make this diagnosis, as focal seizures from many brain areas can cause a sudden speech arrest, without a true aphasia. Temporal lobe seizures may manifest as psychosis (49).

By definition, consciousness is impaired in both complex partial and absence status. This may vary from mild inattentiveness to complete unresponsiveness with minimal (if any) response to painful stimuli (50,51). Automatisms may be *stereotyped* (repetitive movements identical in form, that follow a regular sequence, including chewing, blinking, and swallowing) or *reactive* (coordinated complex and apparently purposeful movements, including walking around, drinking a glass of water, lighting a cigarette, etc.) (52). Even the "reactive" automatisms of epileptic seizures tend to recur in a similar fashion; that is, with a stereotyped pattern in a larger sense.

Absence status was described well by Andermann and Robb in a series of thirty-eight patients (53). The essential feature was a prolonged confusional state that varied from a subjective feeling that only the affected individual could recognize, to a deep sleeplike state from which it was difficult to arouse the patient. A fluctuation in the level of arousal and in the ability to perform tasks may be observed in some patients. Motor performance is often clumsy, and there is usually little or no spontaneous speech. Hiccups, quivering of the lips, expressionless appearance, or panicky expression may be seen. The eyelids may be half closed, and there is a tendency to keep food in the mouth without chewing. Complex *(reactive)* automatisms were rare, but rhythmic blinking *(stereotyped)* automatisms or small amplitude myoclonic facial or upper limb jerking were often present. The duration varied from 30 minutes to 2 hours and commonly terminated with a generalized seizure. Similar clinical manifestations have been described by others (54,55).

In their series of eight patients with complex partial status epilepticus (CPSE), Ballenger and colleagues (56) recognized two types of patients—those with EEG evidence of continuous complex partial seizures and those with recurrent complex partial seizures. Arousal was impaired in all patients and varied from mild confusion (with preserved ability to carry out requests) to complete unresponsiveness. The level of responsiveness fluctuated in most of the patients (with either type of CPSE), being improved, but not normal, during the "interictal" phase. Automatisms of some sort were common. These were most commonly *stereotyped* among patients with recurrent complex partial seizures and more often *reactive* in those with continuous complex partial seizures. The duration varied from 1.5 to 24 hours and tended to be shorter with continuous seizures. Protracted CPSE may occasionally last as long as 3 months (57). The range of

TABLE 14.3
The EEG of Encephalopathy and Nonconvulsive Status Epilepticus

ENCEPHALOPATHY	NONCONVULSIVE STATUS EPILEPTICUS
Generalized asynchronous slow (< 8 Hz) waves that vary from intermittent 5–7 Hz slowing with normal background rhythm to a very slow (2–3 Hz) background rhythm	3–3$^1/_2$ Hz spike and slow wave in absence
	In other NCSE: atypical spike and slow wave, polyspike and slow wave, rhythmic delta with intermittent spikes
Triphasic waves	
Alpha coma or burst-suppression (when encephalopathy progresses to coma)	

clinical manifestations of all types of NCSE is detailed exquisitely by Kaplan (58).

Treiman and Delgado-Escueta emphasized the importance of fluctuations in the clinical behavior of some patients with complex partial status (59). This may permit a clinical differentiation of this syndrome from other causes of "twilight states." They described eleven patients with CPSE who fluctuated between two separate behavioral phases—one characterized by partial responsiveness and speech as well as semipurposeful complex *(reactive)* automatisms, and another with total unresponsiveness characterized by staring, speech arrest, and stereotyped automatisms. They noted that, with an increasing duration of status, the patient may appear to enter a continuous twilight or fugue state, but that careful observation should still permit the detection of the two clinical and electrographic phases. In some cases, fluctuation may represent the starting and stopping of seizures in NCSE. The seizures may be continuous in other patients. Both types of cases are compatible with a diagnosis of SE. Fluctuating levels of consciousness in CPSE have also been described by others (52,60,61).

Some patients with CPSE fail to demonstrate this cyclical behavior and instead have a prolonged confusional state. Markand and colleagues described a 20-year-old woman with recurrent periods of confusion lasting as long as 2 days (62). She would not respond to questions during these periods but could be taken to the bathroom by an attendant. Automatisms were present during these periods. To further confuse matters, some authors have suggested that fluctuations may also be seen in absence status. In the hospital-based series of thirty-two patients with NCSE described by Tomson and colleagues (63), which included fourteen patients with CPSE and eighteen with absence status, cycling was noted in four patients in each group. Thus, cycling or fluctuation is insufficiently sensitive to permit the reliable differentiation of complex partial from absence status.

The presence or absence of an earlier history of seizures does not seem to be helpful in distinguishing *absence* from *complex partial* status. In a hospital-based series of thirty-eight patients, the presentation with NCSE (of both types) was the first manifestation of epilepsy in approximately 30% of patients (63). Similarly, the lack of a history of seizures in absence status (54,55) and complex partial status (41) has been documented in other series.

Electroencephalographic Features

A broad range of EEG changes has been reported in NCSE (Table 14.3). The essential difference between absence and complex partial status is the generalized or focal location of the ictal activity.

In perhaps the most comprehensive series of EEGs in NCSE, Granner and Lee reported the ictal and interictal EEG findings in eighty-five separate episodes of NCSE (40). The EEG records were analyzed in terms of morphology, frequency, distribution, and persistence. Morphologies included "typical spike and wave" (3–3.5 Hz rhythmic spike and slow-wave complexes), "atypical spike and wave," "multiple spike and wave" (repetitive complexes of two or more spikes followed by a slow-wave), or "rhythmic delta with intermittent spikes." They concluded that the ictal discharges of NCSE are heterogeneous, with instances of each morphology occurring in both focal and generalized categories. The discharge frequency was ≤ 3Hz in 96% of cases, and there was substantial overlap in the discharge frequency distribution in the different groups. A continuous ictal EEG pattern was slightly more common than an intermittent pattern (frequent ictal discharges with frequent pauses lasting more than a few seconds). No significant differences were apparent between these patterns in the different groups, but the intermittent pattern was more common in those with focal ictal

discharges. This observation may be relevant to the claim that clinical cycling of behavior is more common in complex partial status.

Ictal, Interictal and Postictal Psychosis

A complex relationship exists between epilepsy and psychosis (defective reality testing). For the sake of clarity, it is helpful to make a distinction between *ictal, postictal,* and *interictal* psychosis. Interictal psychosis refers to the psychosis that may occur in patients with epilepsy in whom the symptoms are not temporally related to the seizures. This concept should be distinguished from *ictal* psychosis, in which psychotic symptoms are the direct manifestation of seizures, and from *postictal* psychosis, in which psychotic symptoms follow seizures.

Interictal psychosis has been the subject of many studies. Most investigators report symptoms reminiscent of schizophrenia (64–66). Perez and Trimble, for example, examined twenty-three patients with active psychosis and unequivocal underlying epilepsy and compared the results with those from ten patients with schizophrenia (67). A diagnosis of schizophrenic psychosis was made in approximately half the patients with epilepsy, a classification based on the presence of Schneiderian first-rank symptoms. Affective psychosis was the second major diagnostic category.

Postictal psychosis is not uncommon, but there are relatively few detailed reports of its clinical phenomenology (68–70). Psychosis may develop following either primary generalized (68,70) or complex partial seizures (69). In the majority of patients, a clear history is present of either a prolonged seizure or an increased seizure frequency prior to the onset of psychosis. Full recovery from the seizures and postictal confusion were observed in most patients, with psychosis developing after a lucid interval lasting anywhere from a few hours (70) to 1 month (69). Logsdail and Toone reported confusion in most patients (although details of what is meant by this are not provided; 68). Paranoid delusions (that are typically poorly systematized) are common (68,70), as are affective disorders (68,69). Hallucinations are common and are usually visual, less often auditory, and rarely tactile or olfactory (68,70). Multimodal hallucinations occur in a significant minority of patients. In the end, postictal psychosis is a heterogeneous disorder with features that may resemble a paranoid delusional syndrome, a schizophrenia-like illness, or an affective disorder.

The term *ictal* psychosis describes the occurrence of psychotic symptoms in association with epileptiform activity on EEG; it is an example of NCSE. There are limited descriptions of this phenomenon. Tucker and colleagues described twenty patients with temporal lobe epilepsy who were admitted to a psychiatric service because of a behavioral disturbances (49). The range of symptoms included intense episodic affective symptoms, either panic-like attacks or depressive mood swings (70%), paranoid ideation (30%), Schneiderian first-rank symptoms (25%), and hallucinations (auditory in 50%, visual in 40%, olfactory in 30%, and tactile in 10%). Critical features included the episodic nature of the symptoms and the consistency of symptoms in each patient over time.

Postictal Encephalopathy

A brief period of postictal confusion is typical following generalized convulsive seizures. Occasionally, however, this state may be prolonged, and under such circumstances, it is necessary to consider the possibility of ongoing nonconvulsive seizures (71). Several series show that NCSE can be demonstrated in 5% to 26% of comatose patients in intensive care units when EEGs are used more extensively in such patients (72–74).

Occasionally, the period of postictal confusion may last much longer, even in the absence of ongoing seizures. Biton and colleagues, for example, described eleven patients who developed a prolonged period of postictal confusion, lasting from 4 to 10 days (75), which they referred to as a prolonged postictal encephalopathy (PPIE). In each case, the PPIE followed a cluster of generalized tonic-clonic, absence, or complex partial seizures. Extensive investigations found no underlying toxic-metabolic cause or ongoing seizure activity, with the only persistent abnormality being an encephalopathic EEG. There are similar reports of PPIE following electroconvulsive therapy (76).

Epileptic Negative Myoclonus

In considering seizures as a mimic of the clinical manifestations of encephalopathy, the question arises whether asterixis is ever ictal. Epileptic negative myoclonus (ENM) is a rare disorder characterized by a transient interruption of tonic muscle activity that is accompanied by a time-locked spike or slow-wave over the contralateral sensorimotor cortex (77). Although asterixis and epileptic negative myoclonus (ENM) are both characterized clinically by a transient loss of tonic muscle activity, the clinical appearance of the two is often quite different. In the study by Guerrini and colleagues, the abnormal movements of ENM were limited to one arm in two patients, to the legs in one other, and were multifocal in the remaining two (78). In their review, Obeso and colleagues concurred that ENM typically manifests itself as a loss of tonic activity in the postural muscles (neck, trunk, or proximal leg muscles;

TABLE 14.4
Differentiation of Seizures and Nonconvulsive Status from (Nonepileptic) Encephalopathies

SEIZURES AND NCSE	ENCEPHALOPATHIES
1. History of seizures (but de novo occur) Nocturnal spells Risks for seizures (head injury, stroke, CNS infection, family history of seizure)	History of metabolic disturbances, diabetes, renal failure, liver disease, anesthesia, post-operative setting
2. Reduced or discontinued anticonvulsants	History of medication, drug use, abuse; recent exposure to anticholinergics, dopamine agonists, steroids, benzodiazepines, barbiturates, other sedatives, anticonvulsants
3. Focal examination, CNS lesions	Laboratory evidence of metabolic derangement, organ failure
4. Sudden onset: seconds (may be missed)	Subacute onset: hours, days
5. Jerking, twitching, rhythmic nystagmus; rhythmic myoclonus or other motor activity	Asterixis (symmetric) Irregular, multifocal myoclonus
6. Repetitive, stereotyped automatisms, may include catatonia	Few, if any, nonstereotyped automatisms
7. Sterotyped hallucinations	Multimodal, nonstereotyped hallucinations
8. May include aphasia (infrequent)	Other altered or reduced speech
9. EEG with epileptiform abnormalities	Profound slowing on EEG; Caution: triphasic waves may appear sharp
10. May improve with intravenous benzodiazepines	Usually worsens with sedative medication
11. Clinical deficit may have discrete onset/end; may fluctuate	Deficit may fluctuate somewhat, but often steady and quite prolonged, at least by common impression
12. Often remain awake or sluggish, especially without convulsions	May progress to stupor, coma

79). The asterixis of encephalopathy is invariably bilateral and involves the arms. While it may also be present in the legs, it is rarely (if ever) confined to the legs.

SIMILARITIES AND DIFFERENCES BETWEEN ENCEPHALOPATHY AND NCSE

It should be apparent from the preceding descriptions that there is extensive overlap between the clinical features of encephalopathy and those of NCSE (see Table 14.4.). Disorientation is common in both encephalopathy (14,15) and NCSE (41,52,54,55,61,63). Attention is impaired in most patients with encephalopathy (10) and in NCSE (41,54,61,62). Memory impairment (54,61) and confabulation (80) are common in NCSE. Perceptual disturbances in the form of delusions and hallucinations are characteristic of certain encephalopathic states, such as drug and alcohol intoxication and withdrawal, and of complex partial seizures with a temporal lobe origin (80).

There is a general impression (without a large volume of published data) that the time course of the illness can help in distinguishing encephalopathy (unrelated to seizures) from seizures or NCSE. NCSE, and particularly CPSE, may fluctuate more widely. Although encephalopathies may fluctuate somewhat, they often appear to be more prolonged—related to the illness that causes them. Clinical phenomena such as hallucinations and motor abnormalities may be more paroxysmal in seizures or NCSE.

A detailed analysis of the phenomenology of ictal and postictal psychosis, as well as the psychosis that accompanies encephalopathy, indicates that it is difficult to distinguish these disorders from each other. To a greater or lesser extent, each can also be characterized by prominent affective and sometimes schizophrenia-like symptoms, as well as paranoid delusions (17,18,49, 67–70). Even though hallucinations are most often auditory in encephalopathy and in ictal psychosis, and more frequently visual in postictal psychosis and in drug withdrawal states, the relative frequencies of different modality hallucinations does not permit a reliable distinction between these disorders. Strongly stereotyped and repetitive hallucinations suggest seizures more than encephalopathy.

The speech and language disturbances of both encephalopathy and NCSE are well described. Ictal speech disturbances are common and include speech arrest or mutism, dysarthria, and abnormal vocalization

(groans, moans, etc.; 81). Mutism or marked reduction in spontaneous speech may also occur with encephalopathy (52,55,60,80). Although impaired word finding, anomia for low frequency words, hesitations, and circumlocutions are common with encephalopathy, aphasia is rarely, if ever, present (11). The literature on ictal aphasia comprises a collection of case reports (42–47). Virtually every type of aphasia has been described as a manifestation of NCSE. Seizures do not seem to produce any single type of aphasia. Finally, only in a minority of cases is there other evidence of seizure activity (e.g., clonic limb movements, olfactory hallucinations, impaired consciousness following the aphasia) to indicate the epileptic nature of the aphasia. Nevertheless, the difficulty is in distinguishing ictal aphasia from other causes of aphasia—not from encephalopathy.

As noted before, the psychomotor changes in encephalopathy include both the hyperactive and hypoactive ends of the spectrum. A similar range of change has been described in patients with NCSE. Patients with NCSE are described as having decreased spontaneous activity (54,61), slow responses (55,63), and perseveration (41). Some are described as somnolent (54) or lethargic (80). Conversely, other reports of NCSE describe patients as mildly hypomanic (41), agitated (54,80), disinhibited, and with increased verbal fluency (41). It is difficult, therefore, to distinguish encephalopathy from seizures on the basis of the psychomotor changes alone.

Some patients with NCSE have subtle motor signs like facial or limb myoclonus, eyelid twitching, or forced head or eye deviation that suggest underlying seizure activity. Such motor manifestations were observed in eighteen of thirty-two patients in one series (63) and seven of twenty-three patients in another (80). The subtle motor activity of seizures may often appear more rhythmic, while the asterixis and multifocal myoclonus of encephalopathy (e.g., in chronic renal failure) are more asynchronous, but we are not aware of any formal studies that demonstrate this distinction clearly.

Automatisms are a feature of NCSE but have not been described in patients with encephalopathy of other causes. The precise frequency with which automatisms occur in patients with NCSE is unknown, but they may be more common in CPSE than in absence status. Automatisms were reported in four of eleven cases of adult onset absence status (55), five of ten cases of CPSE in one series (41), and seven of eight in another (56). In the latter report, the authors summarized seventeen previously published cases of CPSE and recorded the presence of automatisms in nine patients. In general, therefore, the presence of automatisms should suggest NCSE strongly as the cause of encephalopathy, particularly when they are repetitive and stereotyped. However, their absence does not exclude seizures.

A number of reports have described the response of patients with NCSE to the intravenous administration of an anticonvulsant, usually a benzodiazepine. An improvement would not be expected in patients with encephalopathy of a nonepileptic nature, in whom sedating drugs would be expected to aggravate the encephalopathic state. Correspondingly, triphasic waves may represent an epileptic sign in a minority of cases, or may be the sign of a nonepileptic encephalopathy. One study showed that intravenous benzodiazepines could blunt or abolish such triphasic waves caused by a metabolic encephalopathy and that this did not imply an epileptic origin (82).

In a series of thirty-two patients with NCSE, Tomson and colleagues reported an immediate and lasting clinical and electrographic response to intravenous benzodiazepine (5–10 mg of diazepam or 1 mg of clonazepam) in ten patients and a temporary response in a further eighteen (recurrence of status in the latter group occurred over a period of hours; [63]). In an EEG-based study, Granner and Lee reported a response rate of 90% in patients with generalized status—100% in the group with generalized status with focal features, but only 60% in the group with focal status (40). Such impressive results are not described uniformly. Thomas and colleagues reported failure to respond or early relapse in eight of ten patients with CPSE of frontal origin (41), but these were particularly refractory cases. Also, the response to medication, even with clear NCSE, is often delayed for hours or even days, thus limiting this response as a useful diagnostic criterion for NCSE (76,80). In conclusion, a clinical response (even if transient) to intravenous benzodiazepines can help to distinguish encephalopathy due to seizures from NCSE due to other causes. Seizures are particularly suggested if the response is rapid. The absence of a response, however, is not helpful.

It may be extremely difficult to determine clinically whether NCSE is the cause of an encephalopathy. This difficulty, and the importance of EEG in these circumstances (Table 14.3), are illustrated by the report of Towne and colleagues, who sought to determine the frequency with which NCSE was the cause of coma in intensive care unit patients (74). Among 236 patients with coma and no clinical evidence of seizure activity, electrographic NCSE was identified in nineteen cases (8%). In a similar study of hospitalized patients with altered consciousness, Privitera and colleagues found EEG evidence of NCSE in 37% (83).

Finally, in many patients both nonepileptic encephalopathies and NCSE may coexist, with both

being caused by some underlying disease. Certain toxic-metabolic conditions and drug-withdrawal states may cause both encephalopathy and seizures. Medications themselves, such as lithium, baclofen, ifosfamide, and even anticonvulsants may cause both encephalopathies and seizures or NCSE. The process causing the encephalopathy may trigger or decrease the threshold for a seizure. The possibility of the co-occurrence of these two disorders should not be neglected. For example, uremic encephalopathies and the cerebral effects of many medications may lead to both altered mental status and NCSE (51), making it very difficult to determine how much of the altered mental status is due to the epileptic versus the metabolic component. In most such cases, aiming treatment at the underlying disease is crucial, but most of these patients need anticonvulsants as well.

These studies illustrate the great importance of EEG monitoring in the evaluation of patients with encephalopathy of unclear cause, even in the absence of subtle motor manifestations that would suggest underlying seizure activity.

CONCLUSION

Encephalopathy is a common cause of morbidity and mortality in hospitalized patients, especially the elderly. Its causes are protean and include systemic toxic-metabolic disturbances, drug intoxication and withdrawal, and focal brain lesions, as well as seizures and the postictal state. Because the successful treatment of encephalopathy depends on recognition of its cause, it is important to consider seizures that would require anticonvulsant therapy. It can be extremely difficult clinically to distinguish an ictal encephalopathy (i.e., due to seizures) from an encephalopathy due to other disease processes because of the extensive overlap in their clinical phenomenology. The presence of automatisms or subtle motor manifestations (especially if repetitve and stereotyped), as well as clinical improvement in response to the administration of intravenous benzodiazepines, should raise a strong suspicion of underlying seizure activity. The specificity of these symptoms for an ictal encephalopathy is high, but the sensitivity is relatively low. Their absence, therefore, should not deter one from considering NCSE as the cause of an encephalopathy. The EEG is an invaluable tool in the diagnosis of seizures as the cause of encephalopathy because the electrographic findings of NCSE almost invariably differ from those that accompany encephalopathy of other causes. Finally, an absolute distinction between seizures and other causes of encephalopathy may occasionally not be possible, and ictal and nonictal encephalopathies may coexist.

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15 Neuroendocrine, Metabolic and Toxic Imitators of Epilepsy

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Many types of paroxysmal events may mimic seizures during the course of medical illnesses. The appropriate treatment depends on the correct diagnosis, requiring a vast knowledge of non-neurologic conditions. A careful history, including review of previous medications, as well as physical examination remains the foundation from which the etiologic diagnosis is eventually established. It is preferred, if the means are available, to observe the event rather than simply obtain a history of the event by an observer. The physician should consider the event a symptom of central nervous system (CNS) dysfunction that may be primary or secondary. The events may include phenomena that are not mutually exclusive to seizures. For example, patients with hepatic encephalopathy may have seizures and asterixis. More severe hepatic encephalopathy may be associated with coma and decerebrate posturing.

Phenomena mimicking seizures include chorea, dystonic posturing, ballismus, hemiballismus, and intermittent tremor. Exaggerated reflex movements, spasms, and certain respiratory movement also may mimic seizures. For example, snorting and exaggerated respiratory phases also may mimic seizure phenomenology. Catathrenia is a parasomnia that occurs during the expiratory phase of respiration. REM behavior disorder, periodic limb movements of sleep (PLMS), and other sleep disorders might be confused with seizures. The posturing seen with cerebral insults, transient neurologic deficits associated with migraine, and drug-induced movement disorders are some disorders that may be seen in acutely ill patients. These include the central anticholinergic syndrome (CAS) and the SSRI-induced serotonin syndrome. Hypoglycemia seen with insulin overdose is frequently mistaken as an epileptic seizure by observers who view the transient alteration in consciousness associated with tachycardia, and profuse sweating.

Metabolic Conditions

Encephalopathies may be associated with electrolyte disturbances, hypocalcemia, hypercalcemia, hypoglycemia, hypothyroidism, thyrotoxic storm, the adverse effects of drugs, organ failure, and many other conditions. Paramyoclonus multiplex is a term coined by Friedreich to describe a form of myoclonus of unknown etiology (1). The contractions are seen to start in the muscles of the upper arms and shoulders and spread to other parts of the upper body. Myoclonus refers to the shocklike contractions of a group of muscles, irregular in rhythm and amplitude, and usually asynchronous and asymmetrical in distribution. If these contractions occur singly or in a single group of

muscles, the condition is referred to as myoclonus simplex. If the contractions occur in a widespread distribution, the condition is referred to as myoclonus multiplex or polymyoclonus. It is observed frequently in patients with acquired metabolic disorders. Prototypic disorders are uremic and anoxic encephalopathies. An occasional seizure may complicate a toxic or metabolic encephalopathy.

Hepatic Encephalopathy

The causes of hepatic pathology may be classified by viral, toxic, metabolic, autoimmune, ischemic, neoplastic, and miscellaneous etiologies (*e.g.,* alcohol, acetaminophen, and valproate are toxins well-known to the neurology community). Biliary sclerosis is an autoimmune cause. Common causes of hepatic encephalopathy include alcoholic hepatitis, infectious hepatitis, and toxic hepatitis.

Wilson disease, acquired hepatocerebral degeneration, Reye syndrome, and fulminant hepatic failure, among other disorders, may lead to hepatic encephalopathy. Manifestations progress through four stages. Stage I is incipient encephalopathy. In stage II, mental status deteriorates and asterixis develops. In stage III, focal or generalized seizures may occur. Stage IV is marked by coma and decerebrate posturing. The incidence of seizures varies widely and may occur in up to 33% (2). Hypoglycemia, complicating liver failure, may be responsible for some seizures. Hyperammonemia is associated with seizures and may contribute to the encephalopathy of primary hyperammonemic disorders; treatments that reduce ammonia also ameliorate the encephalopathy (3).

Uremia

As in all metabolic encephalopathies, a change in mental status is the hallmark of uremic encephalopathy. An unusual feature of uremic encephalopathy is the simultaneous neural depression (obtundation) and neural excitation (twitching, myoclonus, generalized seizures). Epileptic seizures occur in one-fourth of uremic patients (4). The reasons for this may be quite varied.

The incidence of seizures in a series of almost 800 bone marrow transplant (BMT) patients treated with cyclosporin was 5.5% (5). Seizures occur in more than 10% of BMT recipients according to Patchell et al. (6). These patients were not treated with antiepileptic drugs (AEDs), and the seizures did not recur. Seizures are usually generalized and mostly associated with metabolic derangements. These seizures are sometimes associated with the drugs used to "condition" the bone marrow: busulfan is associated with generalized seizures (7).

Hyponatremia

Because convulsive disturbances are usually secondary processes, the effective management of associated seizures requires an identification and treatment of the primary disorder in conjunction with a correction of the fluid and/or electrolyte disturbance. Hyponatremia is defined as a serum sodium level of less than 115 mEq/L. Hyponatremia is one of the most frequent metabolic abnormalities, occurring in 2.5% of hospitalized patients (8). Neurologic symptoms including seizures are seen more frequently in acute hyponatremia (9–11), with mortality rates estimated to exceed more than 50% when convulsive activity is present (12). Urgent but not immediate correction to levels greater than 120 mEq/L is essential. However, the degree of rapidity with which hyponatremia is corrected is controversial. Rapid correction of hyponatremia is associated with central pontine myelinolysis (CPM), manifested clinically by pseudobulbar palsy and spastic quadriparesis (13). Originally described in patients with alcoholism and malnutrition, it was later observed in dehydrated patients undergoing rehydration (14). Norenberg et al. (15) noted that in each of twelve patients with CPM there had been a recent rapid rise in serum sodium. Pathologic features of CPM include symmetric, noninflammatory demyelination in the basis pontis, with relative neuronal and axonal sparing. In animal models of CPM, a rapid correction of sustained vasopressin-induced hyponatremia with hypertonic saline is followed by demyelination (16,17). Hyponatremia corrected at rates greater than 12 mEq/L/day may be exceedingly aggressive (15).

Hyponatremia is sometimes seen as an iatrogenic effect of prescribed drugs (18) and as complications of the abuse of illicit substances such as Ecstasy or methylene dioxymethamphetamine (MDMA) (19,20). Hyperthermia and hyponatremia are the most significant acute adverse effects of MDMA (21) (see below). Some combinations of drug use may also lead to hyponatremia. For instance, hyponatremia and water intoxication complicated with coma may result as a combined effect of nonsteriodal anti-inflammatory drugs (NSAIDs) and desmopressin (22). Desmopressin used in the treatment of primary nocturnal enuresis and central diabetes insipidus may be used with NSAIDs. Physicians should be aware of this serious and potentially fatal side-effect and avoid the combination of these two drugs. There are other potentially dangerous combinations as well.

Serum sodium is most commonly reduced as a result of either sodium depletion, water intoxication, or both (12), thus resulting in hypo-osmolar hyponatremia. Hyponatremia with normal osmolality is rare, but may be seen in patients with hyperlipidemia or hyperproteinemia. Hyperosmolar hyponatremia occurs

in hyperosmolar states such as hyperglycemia, and is discussed later in this chapter. Hypo-osmolar hyponatremia may be associated with normal extracellular fluid volume, hypovolemia, or hypervolemia (23). Hypo-osmolar hyponatremia with hypovolemia may be seen from renal disorders (diuretic use, Addison's disease) or extrarenal loss (vomiting, diarrhea, or third-spacing). The syndrome of inappropriate ADH (SIADH), hypothyroidism, and certain drugs (including carbamazepine and psychotropic agents) may cause hypo-osmolar hyponatremia with normal volume. Hypo-osmolar hyponatremia associated with hypervolemia, frequently noted in patients clinical edema, occurs in cardiac failure, nephrotic syndrome, and acute or chronic renal failure. The therapeutic implications of these conditions are great since the appropriate therapy for normovolemic or hypervolemic hyperosmolar hyponatremia is water restriction. Hypovolemic hyponatremia is managed by replacement of water and sodium (23).

Hypocalcemia

Tetany is the most frequent neuromuscular symptom in patients with hypocalcemia (24) and can be mistaken for seizure activity. It is the clinical manifestation of spontaneous, irregular, repetitive action potentials originating in peripheral nerves. Latent tetany may be unmasked by hyperventilation or regional ischemia (Trousseau test). Seizures due to severe hypocalcemia (<6 mg/dl) are relatively infrequent, but may occur in up to 25% of patients. Hypocalcemia also occurs with vitamin D deficiency and renal tubular acidosis. Although rare, nutritional rickets still occurs in the United States, and occasionally presents with hypocalcemic seizures (25). Carpopedal spasm, tetany, and cramping, may all occur with hypocalcemia or borderline hypocalcemia with hyperventilation. During hypercalcemia the EEG may be diffusely slow.

Hypomagnesemia

Hypomagnesemia is associated with seizures usually only when serum levels are less than 0.8 mEq/L. Since secondary hypocalcemia may be produced by a decrease in or end-organ resistance to circulating parathyroid hormone magnesium levels should be measured in the refractory hypocalcemic patient who does not respond to appropriate calcium supplementation. Treatment requires the administration of intramuscular 50% magnesium sulfate every 6 hours. Because the precipitation of respiratory muscle paralysis may be induced by transient hypermagnesemia (26), intravenous calcium gluconate should be administered concurrently.

Hypoglycemia

Hypoglycemia commonly provokes seizures, and the most frequent etiology of the hypoglycemic seizure is related to insulin or oral hypoglycemic agents. Another common cause is the use of drugs that interact with oral hypoglycemic agents (27). Occasionally, the etiology may not be obvious. Islet cell dysmaturation syndrome, associated with infantile hyperinsulinemic hypoglycemia, is characterized by islet cell hyperplasia, pancreatic adenomatosis, and nesidioblastosis has been reported (28). Rarely, inborn errors will be responsible for recurrent hypoglycemia.

Neuroendocrine Tumors and Paroxysmal Symptoms

Many patients with malignant metastasizing tumors present clinical symptoms related to hormone hyperproduction. Tumor-associated hypoglycemia from metastatic colorectal adenocarcinoma has been reported in adults (29). The so-called "insulinoma syndrome" depends on the excessive production of insulin and proinsulin, resulting in hypoglycemia. (30). Several types of syndromes associated with gastroenteropancreatic endocrine tumors are caused by the overproduction of a specific hormone. These include the so-called carcinoid syndrome, characterized by flushing, diarrhea, wheezing, and right heart disease. Carcinoid syndrome is predominantly associated with the serotonin- and tachykinins-producing carcinoids of the midgut. The well-known Zollinger-Ellison syndrome is gastrin-mediated. The glucagonoma syndrome is characterized by necrolytic migratory erythema, diabetes, and diarrhea. The biochemical diagnosis of endocrine digestive tumors is based on general and specific markers. The best general markers are chromogranin A and pancreatic polypeptide. Specific markers for endocrine tumors include insulin, gastrin, glucagon, vasointestinal polypeptide, and the primary catabolic product of serotonin, 5-hydroxyndoleacetic acid (5-HIAA).

Pheochromocytoma almost always causes prominent symptoms and physical findings. Paroxysmal events are associated with spells of sudden severe headache, palpitations and diaphoresis, and pallor. These spells may last minutes to an hour. Blood pressure is almost always markedly elevated during the spell.

A pheochromocytoma-induced hypertensive crisis may trigger a hypertensive encephalopathy characterized by altered mental status, focal neurologic signs and symptoms, or seizures. Other neurologic complications include stroke due to cerebral infarction or an embolic event secondary to a mural thrombus from a dilated cardiomyopathy. Intracerebral hemorrhage also may occur

because of uncontrolled hypertension. Other symptoms include tremor, nausea, anxiety, sense of impending doom, epigastric pain, flank pain, constipation or diarrhea, and weight loss.

Thyrotoxicosis may be associated with nervousness, diaphoresis, heat intolerance, palpitations, tremor, and fatigue. Hashimoto's thyroiditis may be associated with thyrotoxicosis intitially and then with hypothyroidism. This condition differs from Hashimoto's encephalopathy, which is discussed later.

Porphyria

The disorders of heme biosynthesis are classified into two general groups, erythropoietic and hepatic. Seizures and other neurologic manifestations occur only in the hepatic group, which comprises acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria (31). Acute intermittent porphyria is characterized by neurovisceral and neuropsychiatric manifestations. The major manifestations of the hepatic porphyrias are neurologic, including neuropathic abdominal pain, neuropathy, and mental disturbances. Seizures may occur. Seizures are more common during acute attacks. The risk of seizure during an acute attack is 5% to 15%. Acute attacks are often precipitated by iatrogenically introduced offending agents. The onset of seizures may occur up to 28 days after exposure to the offending agent. Although most seizures are generalized, focal seizures may also occur. The mechanism of the epileptogenesis is not well understood. Cortical deficits and psychiatric symptoms may also develop. These include encephalopathy, aphasia, apraxia, cortical blindness, anxiety, agitation, confusion, depression, hallucinations, anxiety, paranoia, and violent behavior.

The diagnosis of porphyria should be considered in any patient in which seizures worsen following the administration of standard antiepileptic drugs. A cornerstone of treatment is the provision of carbohydrates as a major portion of daily caloric in take to lower porphyrin excretion. Drugs that are porphyrogenic should be avoided, including phenytoin, barbiturates, carbamazepine, succinimides, and oxazolidinediones. Gabapentin has been used to control complex partial and secondarily generalized seizures in patients with porphyria (32,33).

GASTROINTESTINAL DISEASE AND SEIZURES

In patients with established celiac disease, epilepsy, with an incidence of 1% to 6%, is the most frequent neurologic complication, often associated with bilateral occipital calcifications (34). In nontropical sprue or celiac disease, neurologic complications occur in approximately 8% to 10% of adults with celiac disease (35). These include epilepsy (associated particularly with occipital calcifications and folate deficiency), cerebellar ataxia, peripheral neuropathy, myositis, neuromyotonia, myasthenic syndrome, myelopathy, and dementia accompanied by brain atrophy in adults. In celiac disease, small bowel damage by gluten may lead to chronic malabsorption. Today, celiac disease is diagnosed earlier and severe malabsorption is rare. Possible mechanisms for CNS injury include potential deficiencies of calcium, magnesium, and vitamins; genetic factors (36); and isolated CNS vasculitis (37). Malabsorption may be occult, and seizures may be the predominant feature. Restricted dietary gluten may produce rapid improvement.

Neurologic symptoms are found in symptomatic and asymptomatic celiac disease. In a general neurology clinic outpatient, Hadjivassiliou et al. found positive antigliadin antibodies as a marker of gluten sensitivity in a high proportion (57%) of patients with undiagnosed neurologic diseases, especially patients with ataxia and peripheral neuropathy (38). The frequency of proven celiac disease in this group was 16%. It was suggested that gluten sensitivity should be considered as a state of heightened immunologic T- and B-lymphocyte–based responsiveness to ingested gluten proteins in genetically predisposed individuals. The brain seems to be particularly vulnerable.

Hadjivassiliou et al. suggested that focal white-matter lesions in the brain may represent an extraintestinal manifestation of celiac disease (38). These lesions may be ischemic in origin as a result of a vasculitis or caused by inflammatory demyelination. Inflammatory bowel disease (ulcerative colitis and Crohn's disease) is associated with a low incidence of focal or generalized seizures. Not surprisingly, generalized seizures frequently are associated with infection or dehydration. In approximately half of patients with focal seizures, a vascular basis is suspected (39).

Whipple's disease is a multisystem granulomatous disease caused by *Tropheryma whippellii* (40). About 10% of patients have neurologic involvement including dementia, ataxia, or oculomotor abnormalities. As many as 25% of patients with CNS involvement have seizures (41). Early treatment is crucial, as untreated patients with CNS involvement usually die within 12 months (42). Some patients have developed cerebral manifestations after successful antibiotic treatment of gastrointestinal symptoms (43). Although several drugs that cross the blood–brain barrier have been recommended for treatment, such as chloramphenicol and penicillin (44), a high incidence of CNS relapse led Keinath et al. (45) to recommend penicillin 1.2m U, and streptomycin

TABLE 15.1
Toxic Encephalopathies

	Clinical Findings	
Syndrome Type	**CNS Effects**	**Peripheral Effects**
Central Anticholinergic Syndrome	Hallucinations, confusion, sedation, seizures, mydriasis, hyperthermia	Decreased gut motility, dry skin and oral mucosa, tachycardia, urinary retention
Sympathomimetics Cocaine, amphetamines	Agitation, seizures	Diaphoresis, hypertension, hyperthermia, tachycardia, cardiac dysrhythmias
Serotonin Syndrome	Confusion, agitation, myoclonus, hypomania, dysarthria, orobuccal dyskinesias, tremor, rigidity with cog-wheeling, hyperreflexia, incoordination	Dysautonomia, hyperthermia, diaphoresis, diarrhea, mydriasis, tachycardia
Neuroleptic Malignant Hyperthermia	Marked rigidity, consciousness disturbance	Hyperthermia, dysautonomia, rhabdomyolysis

1.0 g/day for 10 to 14 days, followed by trimethoprim-sulfamethoxazole twice a day for 1 year. However, treatment of the underlying disease may not lead to prevention of seizures requiring AED treatment (46). Because malabsorption is a significant problem, the use of a suspension or elixir of the appropriate AED therapy is recommended. The most effective drugs are trimethoprim-sulfamethoxazole and third-generation cephalosporins (47,48).

TOXIC OR DRUG-RELATED CONDITIONS

Several types of syndromes produce characteristic clinical scenarios that include seizures or paroxysmal activity that resemble seizures. These are summarized in the Table 15.1.

Antidepressants

At nontoxic doses, the selective serotonin reuptake inhibitors (SSRIs) (49), venlafexine (50), and possibly the tricyclic antidepressants are associated with an emergence of periodic limb movements of sleep in some patients. SSRIs are also associated with excessive slow eye movements during non-REM sleep (49). These drugs may have an associated seizure risk of approximately 0.2% (51). The SSRIs may have an antiepileptic effect at therapeutic doses (52). However, when combined with other serotonergic agents or MAO inhibitors, the serotonin syndrome may occur. The serotonin syndrome consists of delirium, tremors, and occasionally seizures (53). Triphasic waves may be seen in the EEG (54). Other symptoms include agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, and fever. Linezolid, a new synthetic antimicrobial, is an important weapon against methicillin-resistant *Staphylococcus aureus* (MRSA). There are reports of serotonin syndrome developing after concomitant use of linezolid and the selective serotonin reuptake inhibitor paroxitene, citalopram (55), and mirtazapine (56). St. John's Wort, used in combination with the SSRIs has precipitated the serotonin syndrome (57).

Antipsychotics

Antipsychotic drugs have long been known to precipitate seizures (58,59). Both phenothiazines and haloperidol have been implicated, but the potential is greater with phenothiazines, and seizures occur more frequently with increasing dosage (60). Clozapine is an atypical antipsychotic drug (dibenzodiazepine class) for the treatment of patients with intractable schizophrenia. It may also be useful for tremor and psychosis in Parkinson's disease (61,62). Like other antipsychotic agents, the incidence of seizures increases with increasing dosage (63). If seizures occur, a dosage decrease should be considered. If a reduction of dosage is not practical, it is reasonable to add an AED such as phenytoin or valproate. However, carbamazepine should be avoided since antipsychotic drugs may induce agranulocytosis.

Miscellaneous Drugs

Some encephalopathic patients with a supratherapeutic concentration of baclofen or lithium develop epileptiform abnormalities on the EEG. Although the patients may not have seizures, their clinical conditions of confusion may mimic nonconvulsive status, thus tempting the naïve clinician to a diagnosis of partial seizure. Lithium is a drug that may precipitate seizures (64). Patients with a history of spike and wave discharges on EEG have been reported to have exacerbations of their EEG abnormalities associated with cognitive or neuropsychiatric events when taking tiagabine. Accompanying symptoms include dizziness, asthenia, somnolence, nervousness, tremor, impaired concentration, speech or language problems, and confusion. Rare cases of nonconvulsive status epilepticus have been reported. Phencyclidine is associated with a distinctive EEG pattern showing generalized sinusoidal 6.0 cps theta activity interrupted approximately every 4 seconds by generalized slow wave discharges.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a potentially lethal antipsychotic drug (APD)-induced thermoregulatory disturbance. Neuroleptic malignant syndrome is a rare yet potentially fatal adverse reaction generally associated with typical neuroleptics (65). It has also been associated with olanzapine (66). It has been reported to occur with all drugs that affect the central dopaminergic system (including dopamine agonists and levodopa; see below). Dopaminergic transmission in the lateral hypothalamic area is essential for heat dissipation (67). The classic triad involves the autonomic nervous system (fever in 100%), the extrapyramidal system (rigidity), and cognitive changes. Mental status changes occur in 75% of patients. These changes may start as drowsiness and progress to stupor and coma. Other symptoms may include seizures, pyramidal tract findings, ocular flutter, and cardiac arrhythmias. Two characteristic laboratory findings are high creatine kinase (CK) and leukocytosis. Interestingly, many of the patients are iron deficient. The cerebrospinal fluid (CSF) is usually normal. The EEG can show diffuse slowing. Tachypnea, diaphoresis, and labile blood pressure may also occur. The fever does not usually exceed 41°C. It may peak before the motor systems become prominent. Rigidity and tremor are the most frequent extrapyramidal findings. Neuroleptic malignant syndrome (NMS) is a particularly dangerous complication in patients with Parkinson's disease (PD) (68).

An elevation in body temperature is the most frequent symptom of levodopa withdrawal malignant syndrome (69). The body temperature can be as high as 40 °C, but in rare cases, the body temperature remains normal. Altered consciousness is the third most common symptom of levodopa withdrawal malignant syndrome (69). The level of consciousness may range from drowsiness to coma. Coma in patients with PD is usually associated with serious complications such as severe pneumonia, disseminated intravascular coagulation (DIC), rhabdomyolysis, and/or acute renal failure. A marked increase in serum CK is the laboratory hallmark of malignant syndrome. It can be as high as above 10,000 IU/L. This marked increase in serum CK is usually due to massive rhabdomyolysis, as revealed by positive serum and urine myoglobin. Massive rhabdomyolysis may lead to acute renal failure due to plugging of the renal tubules. Rhabdomyolysis is believed to be caused by increased calcium release from the sarcoplasmic reticulum (67). The molecular mechanisms for this increased calcium release are unknown.

The increase in CK may be only mild in some patients with levodopa withdrawal malignant syndrome. Such mild increase may be due to focal subclinical rhabdomyolysis or to an increase in the permeability of the muscle membrane.

Cocaine

Cocaine, a biologic compound, is one of the most abused recreational drugs in this country. Common neurologic complications include tremors and generalized seizures (70). Daras et al. described seven patients with cocaine-induced movements, including choreoathetosis and parkinsonian tremor. These patients were seen in 2 years at a municipal hospital, during which 701 visits were attributed to complications of cocaine. Dopaminergic changes were hypothesized to have caused the abnormal movements (71). Cocaine can, of course, also provoke seizures, exacerbate a pre-existing seizure disorder, or cause an ischemic or hemorrhagic stroke that leads to seizures (72). Seizures can occur immediately after drug administration, without other signs of toxicity.

Convulsions and death may occur within minutes of overdose. The majority of seizures are single and generalized, induced by intravenous or "crack" cocaine, and may or may not be associated with any lasting neurologic deficits. Most focal or repetitive events are associated with an acute intracerebral complication or the concurrent use of other drugs (73).

MDMA

The ring-substituted amphetamine derivative 3,4-methylenedioxymethamphetamine (MDMA) or Ecstasy is another widely used recreational drug. It stimulates the

release and inhibits the reuptake of serotonin (5-HT) and, to a lesser extent, other neurotransmitters such as dopamine. It is widely available in several states as a "club drug" and is distributed at "raves." In the hot and crowded conditions of raves or dances, mild versions of the serotonin syndrome often develop, in which hyperthermia, mental confusion, and hyperkinesia predominate (74). The hyperkinesia is typified by continuous sucking facial movements; users frequently "suck down" large volumes of fluids to avoid dehydration and in the vain hope to avoid hyperthermia. They may wear pacifiers as necklaces. The sucking movements may appear as oral automatisms to the uninformed observer.

Gamma Hydroxybutyric Acid (GHB)

Gamma-hydroxybutyric acid (GHB) or sodium oxybate is a drug that has recently been introduced for restricted use in patients with narcolepsy who experience episodes of cataplexy, a condition characterized by weak or paralyzed muscles. However, it is also a popular drug among recreational drug users. GHB is a naturally occurring substance in the human brain. It was initially synthesized during the 1960s. Later it was sold over the counter to body-builders as a growth-hormone stimulator to increase muscle mass and fat catabolism; one of its street names is Growth Hormone Booster. Its abuse potential may stem from its ability to induce a euphoric state without a hangover effect. The additional effects of increased sensuality and disinhibition further explain its popularity. Other street names include Liquid Ecstasy, Liquid X, and Easy Lay. It has also been implicated as a drug involved in date rapes.

Its abuse can lead to a severely depressed level of consciousness. With acute overdose patients have had delirium and transient respiratory depression (75). Also, a state of aggressive behavior was observed when the patient was stimulated during periods of frank apnea. Overdoses can be fatal. Physicians who work in emergency departments and acute care settings are often faced with the evaluation and management of patients who "took something at a party" and present with altered mental status; the ingestion of GHB should be considered in such cases (76).

GHB is believed to bind to GABA B and GHB-specific receptors. It blocks dopamine release at the synapse and produces an increase in intracellular dopamine. This is followed by a time-dependent leakage of dopamine from the neuron. It reportedly lengthens slow wave sleep. Its toxicity is dose-dependent and can result in nausea, vomiting, hypotonia, bradycardia, hypothermia, random clonic movements, coma, respiratory depression, and apnea. Combining it with other depressants or psychoactive compounds may exacerbate its effects. Other subjective effects reportedly include euphoria, hallucinations, relaxation, and disinhibition. Deaths involving solely GHB appear to be rare and have involved the recreational abuse of its euphoric effects. Its abuse frequently involves the use of other substances such as alcohol or MDMA (77).

Central Anticholinergic Syndrome

Many drugs used in anesthesia and the intensive care unit may cause seizures. Although the elucidation of each drug is outside the scope of this chapter, we review the central anticholinergic syndrome (78), a common disorder associated with blockade of the central cholinergic neurotransmission. Acetylcholine modulates many interactions among most other central transmitters. The clinical picture of central cholinergic blockade is identical to the central symptoms of atropine intoxication, including seizures, agitation, hallucinations, disorientation, stupor, coma, and respiratory depression. Such disturbances may be induced by opiates, ketamine, etomidate, propofol, nitrous oxide, and halogenated inhalation anesthetics as well as by H2-blocking agents such as cimetidine. Although there is an individual predisposition for central anticholinergic syndrome, it is unpredictable from laboratory findings or other signs. The postanesthetic syndrome can be prevented by the administration of physostigmine during anesthesia.

Drug-induced Movements Resembling Seizures

Chorea has been associated with the use of phenytoin, lamotrigine, and phenytoin–lamotrigine combinations. Beach et al. have speculated that this may reflect a synergistic effect on central dopaminergic pathways (79). Patients with severe myoclonic epilepsy in infancy may be particularly vulnerable to phenytoin-induced choreoathetosis (80). Chorea has also been associated with the use of valproate. Because valproic acid–associated chorea seems to be dose related, avoiding excessive fluctuations of serum levels by the use of divalproex sodium sprinkles may be effective (81).

VASCULITIC ENCEPHALOPATHIES

Vasculitic encephalopathies can have particularly difficult presentations. Hashimoto's encephalopathy is a vasculitis that is associated with generalized or partial seizures. It is also associated with a fluctuating mental status that may wax and wane spontaneously over days. The condition also is associated with abnormal interictal EEGs (82). Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy

or CADASIL is a migrainous condition characterized by stroke and eventually dementia. *CADASIL coma* is reportedly an underdiagnosed acute encephalopathy (83). A reversible acute encephalopathy lasting 1 to 2 weeks and presenting with fever, acute confusion, coma, and seizures followed by full recovery is the characteristic course.

Patients frequently had a history of migraine with aura and were misdiagnosed as having viral encephalitis. CADASIL should be considered in acute unexplained encephalopathies.

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16 Parasomnias, Sleep Disorders, and Narcolepsy—Sleep-Time Imitators of Epilepsy

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Although all humans sleep, this normal but altered state of consciousness remains a mysterious and poorly understood phenomenon. Some aspects of sleep, such as normal dreaming, are well known to everyone. However, even variations of normal sleep can be confusing and concerning to patients and physicians. Abnormal sleep, including dyssomnias (ineffective or inefficient sleep, such as insomnia) and parasomnias (behavioral changes associated with sleep phenomena, such as cataplexy) can be severely disruptive and interfere with a patient's ability to work, drive, or even simply watch television.

Many disorders of sleep share with seizures the properties of paroxysmal onset and/or altered consciousness. It is therefore not surprising that they can be mistaken for seizures, and that seizures can occasionally be mistakenly diagnosed as sleep disorders. This chapter briefly reviews normal sleep physiology and the effects of sleep on seizures and on epileptiform activity in the EEG. The majority of the discussion concerns various aspects of normal and abnormal sleep that can be confused with epilepsy. Finally, differential diagnoses and approach to the patient are discussed.

NORMAL SLEEP PHYSIOLOGY

An understanding of the disorders of sleep begins with a review of the fundamentals of sleep physiology. Sleep is not a simple lack of awareness, but a complex series of distinct sleep phases, each of which has the potential for alterations that can be normal phenomenon, can represent a sleep disorder, or could be confused with epilepsy.

Sleep is divided into two general classes: REM sleep and non-REM sleep. These were defined in the original monograph by Rechstaffen and Kales (1) that remains the standard for classifying sleep. Although deviations from this system have been proposed, the criteria set forth in this monograph remain the primary means of describing normal sleep states. Each stage is defined by a combination of electrophysiologic parameters including electroencephalogram (EEG), respiration, eye movements, and electromyogram (EMG).

In an awake adult, the EEG consists of low-voltage fast activity with little or no frequencies slower than 8 Hz. The record is frequently interrupted by eye movement artifact and EMG. If the patient relaxes with eyes closed, a stereotyped "posterior dominant rhythm" in the alpha (8.5–13 Hz) range appears over the posterior head regions. This can be interrupted by concentration or by opening the eyes. Clinically, the patient is fully aware of the environment, and muscle tone is high.

Non-REM sleep is divided into four stages [Figure 16.1;(2)]. Stage 1 is defined by the onset of a low-voltage, intermixed pattern of frequencies on EEG and the interruption of the posterior dominant rhythm. Vertex sharp waves may be present, as may positive occipital sharp transients of sleep (POSTS). Bursts of high-amplitude,

diffuse, rhythmic delta activity can occur, particularly in children and adolescents (hypnogogic hypersynchrony). Eye movements can be present, but these are slow and rolling compared with the sharp, predominantly vertical movements occurring with wakeful blinking. There is slight relaxation in musculature. Physiologically, this stage is "drowsiness." Patients may have some continued awareness of their surroundings and can be aroused easily.

In stage 2, the low voltage intermixed pattern continues; however, sleep spindles (bursts of 14–16 Hz vertex activity lasting at least 0.5 seconds) and/or K complexes (high-amplitude biphasic discharges at the vertex) must be present. Arousal is slightly more difficult than from stage 1. In stage 3, between 20% and 50% of the record must be occupied by high-voltage delta activity. In stage 4, this increases to over 50%. Throughout these non-REM sleep stages there is a further, progressive decrease in muscle tone. Stages 3 and 4 (also called slow wave sleep) are the most difficult to arouse from, and can be associated with transient confusion on awakening.

REM sleep is a physiologic return to a low-voltage intermixed pattern. It differs from stage 1 by a profound reduction in muscle tone, rapid eye movements, and sawtooth waves on EEG (Figure 16.2). In this state, the most vivid dreams occur.

In normal patients, nocturnal sleep consists of a fairly stereotyped pattern of cycling through the various sleep stages (Figure 16.3). Patients descend through stages 1, 2, 3, and 4, followed by REM in a cycle lasting about 90 minutes. The cycle then repeats over the night, with progressively less time spent in slow wave sleep and more in REM sleep. In a normal young adult, stage 1 is less than 10% of the recording, stage 2 about 50%, and slow wave and REM about 20% each. Sleep efficiency (the time spent asleep divided by the time awake) should be well over 90%.

Sleep is a complex physiologic condition, in which various brainstem and higher pathways become more or less active in various stages. Sleep is also only one of a number of circadian rhythms that humans (and all mammals) have; others include temperature and hormonal secretion (the most important of which are melatonin, growth hormone, and cortisol). Abundant evidence suggests that sleep is important: it is conserved throughout the animal kingdom, and animals and humans will go to great lengths to achieve sleep. Dolphins, which live in the water but must continuously surface to breath, have evolved so that each cerebral hemisphere sleeps independently, with the other available to control this behavior for continued respiration. Sleep deprivation results in a rebound phenomenon, where most of the lost "essential sleep" (slow wave and REM) will be recovered during subsequent sleep. Yet, our understanding of the function of sleep is elusive. The most popular theories have to do with consolidation of memory (3–5). However, investigations have given variable results possibly because there are many types of memory (procedural, declarative, verbal, nonverbal), and these may be involved in different ways. This is an active area of research and could yield insight into the purpose of sleep, the complexities of sleep physiology, and the basis for sleep disorders.

INTERACTIONS BETWEEN SLEEP AND EPILEPSY

This chapter addresses various sleep disorders and their resemblance to epileptic seizures. However, a complex interrelationship exists between sleep and true epileptic seizures on many levels. This includes the expression of interictal epileptiform discharges, syndromes of sleep-associated seizures, effects of sleep on seizure occurrence, and the effects of seizures and anticonvulsant medications on sleep structure.

Sleep and sleep deprivation are known to increase interictal epileptiform discharges (6,7). For focal discharges, the greatest frequency is in slow wave sleep (8). All types of epileptiform discharges decrease dramatically during REM sleep.

Sleep is also associated with a number of normal patterns that can sometimes be confused with interictal epileptiform activity. Vertex sharp waves occur almost exclusively during the lighter stages of sleep. Their characteristic broad morphology, central distribution, and negative polarity make them easily recognized in most cases. In some patients, particularly young children, these can be unusually sharp or occur in runs; thus they are more easily confused with epileptic sharp waves. However, in all cases, there is no disturbance of background rhythms.

Small sharp spikes (also known as benign epileptiform transients of sleep, or BETS), also typically occur in light sleep. These are of low amplitude, diphasic, and temporally maximal with a low amplitude slow wave following. They have a broad distribution and sometimes a transverse dipole. They may best be seen with long interelectrode distances, particularly when referenced to the contralateral ear. Small sharp spikes are probably a normal phenomenon of no clinical importance (except when mistakenly confused with epileptic spikes).

Positive occipital sharp transients of sleep (POSTS) occur maximally in the occipital regions. Their positive polarity makes them easily distinguished from negative epileptiform sharp waves, except when seen in a bipolar montage, where polarity can be ambiguous. Like BETS and vertex sharp waves, they mostly occur during light sleep.

Sleep influences the expression of most types of epilepsy, but in a few syndromes the effects are marked.

FIGURE 16-1

EEG in non-REM sleep. The recordings are from a 19-year-old woman and show a single channel (C3–A2). The arrow shows a K-complex; the underlined areas are sleep spindles. From Carskadon and Dement 1994, p. 16.

In the syndromes of awakening grand mal epilepsy and juvenile myoclonic epilepsy, seizures are largely or completely confined to immediately following nocturnal sleep or daytime naps. In other syndromes, such as benign Rolandic epilepsy, most seizures occur during sleep (9). Frontal lobe partial seizures tend to occur more frequently during sleep (57% of all seizures) than do temporal lobe seizures (43% of all seizures), but temporal lobe seizures secondarily generalize more often when arising from sleep (31%) than do frontal lobe seizures (10%, 10).

Epileptic seizures also have profound effects on sleep. Nocturnal seizures may cause only a brief arousal, but are followed by sleep that is less efficient, with significant decreases in REM and possibly slow wave sleep. Even wake-time seizures can cause decreases in REM the following night (11). Patients with epilepsy commonly report daytime drowsiness (12), and nocturnal seizures, recognized or unrecognized, can be a cause of drowsiness, along with medication effects and coexisting sleep disorders.

SPECIFIC SLEEP PHENOMENA AND SLEEP DISORDERS CONFUSED WITH SEIZURES

A large number of normal and abnormal sleep phenomena can, frequently or infrequently, be confused with seizures. Like epileptic seizures, these are rarely

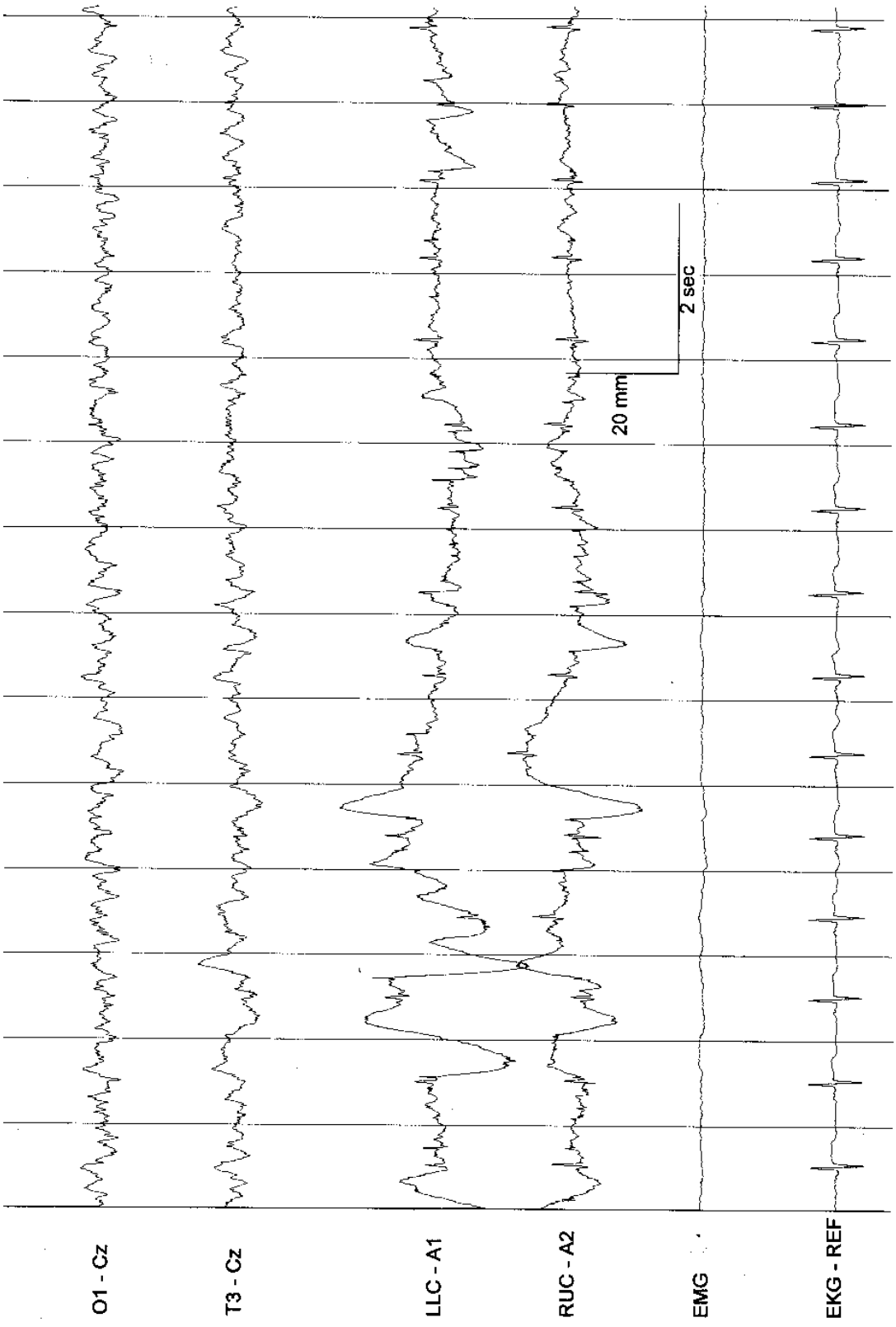

FIGURE 16.2

Normal REM sleep in a 37-year-old woman. While the EEG channels are similar to stage 1 in Figure 16.1, there are rapid eye movements and decreased EMG.

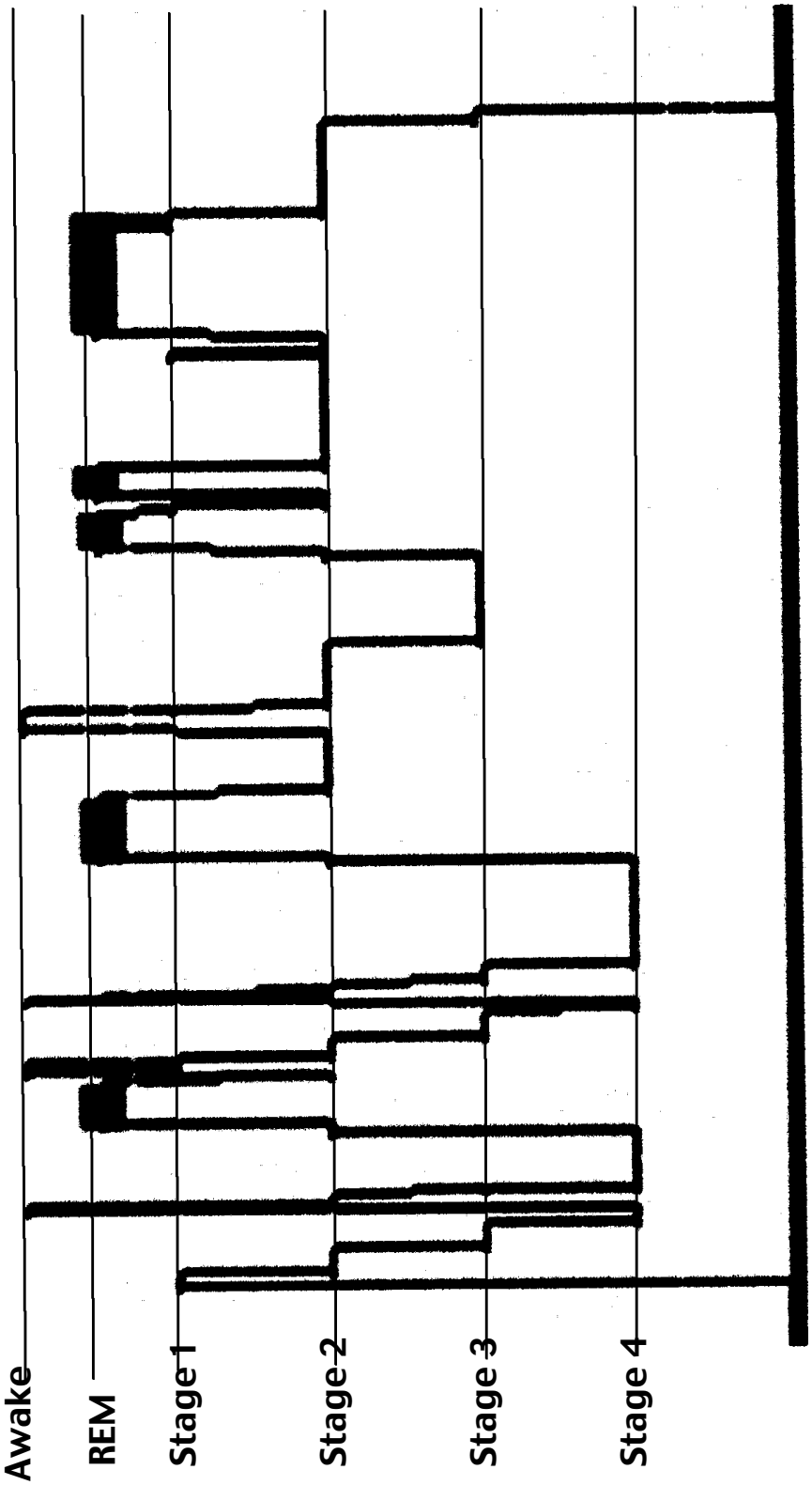

FIGURE 16.3

Normal sleep structure in a 42-year-old woman.

TABLE 16.1
Characteristics of Specific NREM Sleep Disorders and Seizures

	Seizure	Sleep drunkenness	Sleep terrors	Somnambulism	Somniloquy	Sleep Enuresis	PLMS
Incontinence	+	–	–	–	–	+	–
Tongue biting	+	–	–	–	–	–	–
Confusion	+	+	+	+	+	–	–
Tonic-clonic movements	+	–	–	–	–	–	–
Drooling	+	–	–	–	–	–	–
Amnesia	+	+	–	+	+	–	–
Occur awake	+	–	–	–	–	–	–

PLMS: periodic limb movements of sleep.

TABLE 16.2
Characteristics of Specific REM Sleep Disorders and Seizures

	Seizure	Nightmares	Cataplexy	Sleep paralysis	Hypnic hallucinations	REM behavior disorder
Incontinence	+	–	–	–	–	–
Tongue biting	+	–	–	–	–	–
Confusion	+	–	–	–	–	–
Tonic-clonic movements	+	–	–	–	–	–
Drooling	+	–	–	–	–	–
Amnesia	+	–	–	–	–	–
Occur awake	+	–	+	+	+	–

observed by the evaluating physician, and diagnosis is often based on history. Also as with epileptic seizures, this history can be quite unreliable. These phenomena almost always occur at night, so that the beginning of even dramatic episodes is unwitnessed, and patients frequently have little or no recall of the events.

The general classes of events to be discussed are normal sleep phenomena, insomnias (including sleep apnea), and parasomias. The latter are divided into those more commonly associated with non-REM and REM sleep (Tables 16.1 and 16.2). Conditions posing the greatest diagnostic challenges are listed in Table 16.3.

Normal Sleep Phenomena

Most aspects of normal sleep are easily distinguished from epilepsy. "Sleep starts" occur in nearly all people at one time or another, and consist of a sudden extension of one or more limbs; this is synchronous, may involve the trunk, and occurs while falling asleep. This is occasionally associated with a brief dream image, such as that of falling. Sleep starts can be exacerbated by sleep deprivation or by excessive use of stimulant medications, including caffeine. Only rarely would these be confused with seizures, perhaps when they are unusually violent or frequent.

"Sleep drunkenness" consists of prolonged confusion when awakening, usually from the deeper non-REM stages of sleep. Complex behaviors may be undertaken without conscious awareness (13). Patients (typically children) may arise from bed, stumble while walking, have slurred or incomprehensible speech, and have no memory of the event. The occurrence of sleep drunkenness is increased by factors that deepen sleep (such as sleep deprivation and hypnotic medication) or disturb sleep (as in sleep apnea; 14). Potential confusion with seizures occurs because the awakening may be unwitnessed, and the subsequent, transient confu-

TABLE 16.3
Sleep Disorders Most Commonly Confused with Epilepsy

WAKEFULNESS	NON-REM SLEEP	REM SLEEP
Sleep attacks	Sleep terrors	Hypnogogic hallucinations
Cataplexy	Somnambulism	Sleep paralysis
	Sleep enuresis	REM behavior disorder
	Somniloquy	Nightmares
	Periodic limb movements/ restless legs syndrome	

sion is consistent with a complex partial seizure or postictal state.

Insomnia and Idiopathic Daytime Somnolence

Insomnia and daytime sleepiness are extremely common phenomena. According to a survey by the National Sleep Foundation in 2001, 7% of Americans have drowsiness sufficient to interfere with normal activities on a daily basis, and another 14% experience this at least several times a week (15). Drowsiness can have serious health consequences as well; 1% of respondents in this same poll reported having automobile accidents because of falling asleep while driving. Sleep disorders are often not reported to physicians and typically are not a part of a routine evaluation.

The symptoms of sleepiness are not often confused with epilepsy. They are, however, so pervasive that some unusual presentations can be confused with seizures. Rare patients report that they have lost a period of time, or suddenly find themselves in bed or on a sofa not knowing how they have gotten there. If the events are unwitnessed, it may be impossible to distinguish an epileptic seizure from a sleep attack, except through video-EEG monitoring (see below).

Sleep Apnea

Obstructive sleep apnea is arguably the most important sleep disorder in terms of morbidity and mortality. Prevalence varies widely, depending on sampling technique and definition, but is probably at least 3% (16). It is characterized by repetitive episodes of complete or partial airway obstruction and is accompanied by symptoms of either excessive daytime sleepiness or insomnia.

Upper airway obstruction in sleep apnea usually occurs between the epiglottis and the soft palate. As muscle tone decreases during non-REM and particularly REM sleep, the potential for obstruction increases. Obesity of the upper body can also contribute to the disease. The most common complaints are excessive daytime sleepiness and frequent awakenings, but there can also be associated bruxism (grinding of teeth), dry mouth on awakening, morning headaches, erectile dysfunction, memory deficits, and snoring. Treatment options include continuous positive airway pressure (CPAP), oral appliances for repositioning of the airway, surgery (uvulopalatopharyngoplasty), and conservative treatments (sleep positioning, weight loss; 17).

The usual symptoms of sleep apnea are not easily confused with epilepsy. However, severe hypersomnolence can result in sleep attacks with apparent sudden loss of consciousness; the individual typically presents the appearance of normal sleep. In some individuals, sleep apnea can provoke epileptic seizures or be the primary reason for the intractability of epilepsy (18,19). In these cases, seizures are probably triggered by hypoxia during apneic episodes, possibly associated with cardiac dysrhythmias. The disorder is particularly important as it is frequently overlooked, and appropriate treatment can result in a resolution of seizures.

Disorders Predominantly Associated with Non-REM Sleep

Sleep Terrors

Sleep terrors are much more common in children than adults, and are also referred to as pavor nocturnus (or, in adults, as incubus attacks). They usually resolve by adolescence; in adults they can be a manifestation of psychopathology such as severe emotional stress (20) or be triggered by medication (sedative-hypnotics, stimulants, neuroleptics), alcohol, or sleep deprivation. Typically, the patient suddenly sits up and screams. He will be inconsolable, and may be very confused. A parent or onlooker who hears the cry and finds the patient confused may then give a history compatable with a nocturnal seizure. The patient is usually amnestic for the episode, adding to its potential confusion with seizures.

Sleep terrors usually occur during the deeper, non-REM stages of sleep and therefore are more common in the early part of the night. An EEG, if recorded, may therefore show polymorphic or rhythmic delta activity consistent with delta sleep or arousal. Episodes can be precipitated by agents that increase deeper sleep and by sleep deprivation. Treatment is usually not required; however, if this becomes necessary tricyclic antidepressants and benzodiazepines have been used (21). Behavioral treatments including psychotherapy, relaxation techniques, or hypnosis may be more appropriate.

Sleep terrors can usually be distinguished from seizures by their exclusive occurrence in sleep combined with the characteristic dream imagery, predominant fear, and rapid recovery. Abnormal movements, prolonged confusion, drooling, and tongue biting are suspicious for seizure. When doubt exists, 24-hour ambulatory EEG or video-EEG monitoring should confirm the diagnosis.

Somnambulism, Somniloquy, and Sleep Enuresis

Sleep walking (somnambulism), somniloquy (sleep talking), and sleep enuresis (bedwetting) are also very common in childhood and rare in adults. Somnambulism consists of leaving the bed and performing complex activities, such as walking, without memory for the event. It begins during slow wave sleep, and is of various duration and complexity. Sometimes the patient can be agitated during the episode. The prevalence in children is between 1% and 17%, with the peak incidence at age 12. In adults, the prevalence is lower but somnambulism remains relatively common (up to 2.5%; 22,23).

Somniloquy can occur in NREM or REM sleep. It is very common (particularly in children), benign, and should be easily distinguished from nocturnal seizures. Unlike seizures, speech during somniloquy is random (although may be slurred and nonsensical); ictal speech tends to be stereotyped in a given individual. With somniloquy there should be no abnormal movements, drooling, tongue biting, or incontinence. No treatment is required.

Sleep enuresis can occur in NREM or REM sleep, although the former is probably more common. The cause remains unknown, although genetic, behavioral, and psychologic factors have been suggested (24). Possible treatments include behavioral conditioning with a bell and pad device, or the use of tricyclic antidepressants (probably effective through their anticholinergic action). Urologic consultation is usually not indicated. As these episodes are typically unwitnessed, atypical characteristics suggestive of seizure, including nocturnal injury, tongue or lip biting, or morning muscle soreness, warrant neurologic evaluation and probably video-EEG monitoring to rule out unrecognized seizures.

Periodic Limb Movements and Restless Legs Syndrome

Periodic limb movements and restless legs syndrome are both relatively common conditions. The incidence of restless legs syndrome is between 2.5% and 15% (25,26). Periodic limb movements occur in about 5% of young adults. However, the prevalence may be as high as 44% in patients over age 64 (27–30). They often occur together and have many characteristics in common, thus are discussed together.

Periodic limb movements consist of repetitive cycles of rhythmic movement, usually occurring in one or both legs but sometimes involving the arms. Patients are unaware of the movements but may report frequent awakenings. The history from a bed partner may be of jerking movements in sleep, therefore potentially resulting in a confusion with epilepsy. On closer questioning, however, the movements are not clonic, are typically limited to a single limb, and occur many times during the night at regular intervals. Most commonly, they occur in clusters every 5 to 90 seconds, with each movement lasting 0.5 to 5 seconds (31).

Restless legs syndrome is usually characterized by an itching or burning sensation in the legs that occurs when the patient is relaxed, particularly when trying to go to sleep. This is followed by movement of the legs with relief of the sensation. The movement can be suppressed voluntarily. However, typically, the urge to move becomes overwhelming. Many patients need to actually walk to stop the sensation. As opposed to periodic limb movements, restless legs syndrome becomes manifest during wakefulness or drowsiness as opposed to sleep. However, the result is that the patient is unable to sleep, and it results in daytime drowsiness. Similar to periodic limb movements, a description of irresistible shaking of the legs could be confused with epilepsy; a major difference is that restless legs syndrome can be suppressed voluntarily whereas an epileptic seizure cannot be suppressed.

Uremia is an important cause of restless legs syndrome, and prevalence may be as high as 40% (32). Other important associated conditions include iron deficiency anemia, pregnancy, peripheral neuropathy, and drugs (neuroleptics, caffeine).

The treatment of both conditions begins with a search for underlying cause. Either condition can be asymptomatic, but if associated drowsiness requires pharmacologic treatment, dopaminergic agents (carbidopa/levodopa, bromocriptine), benzodiazepines (clonazepam), opioids (codeine), and anticonvulsants (gabapentin, carbamazepine) have all been used.

Sleep Starts

Most people have experienced sudden jerking movements upon falling asleep. This phenomenon, known as benign hypnic myoclonus or sleep starts, is easily recognized as such under most circumstances. Rarely, hypnic myoclonus can be unusually violent, very frequent, or repetitive. This could be confused with myoclonic seizures or even tonic-clonic seizures if not directly observed. The key in most circumstances is that the phenomena are restricted to sleep, always or virtually always in the transition between sleep and wakefulness, and not associated with other phenomenon.

TABLE 16.4
Drug Effects on Sleep and Sleep Disorders

	Effects on Sleep		Effects on Sleep Disorders	
Drug	**Positive**	**Negative**	**Improves**	**Worsens**
Alcohol	↓ sleep latency	↓ SWS, ↑ arousals		Arousal disorders
Antidepressants (tricyclic, SSRI)		↓ REM-sleep		Arousal disorders
Antihistamines	↓ sleep latency			Arousal disorders
Neuroleptics				Arousal disorders
Sedative/hypnotics (benzodiazepines, barbiturates)	↓ sleep latency	↓ SWS, REM-sleep		Arousal disorders, OSA
Stimulants (amphetamines)		↑sleep latency	Daytime somnolence	Arousal disorders

OSA: obstructive sleep apnea.

Hypnic jerks actually have a broader phenomenology and can consist of any sensory symptom, including flashes of light or brief formed images, loud noises, pain, or a floating sensation. These other types are rarer but should be considered whenever a paroxysmal phenomenon occurs in the sleep–wake transition.

Dreaming

Dream imagery also occurs during non-REM sleep, although compared to the complex plots in REM sleep, it is typically simple, such as a single frightening image. This is rarely a difficult diagnosis, with the possible exception of an associated confusional arousal.

Bruxism

Bruxism (teeth grinding) can occur during any sleep stage but predominantly during non-REM sleep. It typically occurs as an isolated phenomenon, and the absence of other motor phenomena, vocalization, or confusional arousal makes its distinction from epileptic seizures easy.

Many of the these phenomena can be induced by illness, sleep deprivation, emotional stress, alcohol, or other drugs. Medications that can induce disorders of arousal include neuroleptics, sedative/hypnotics, stimulants, and antihistamines (24,33,34); medications that cause sleep disturbance are summarized in Table 16.4. Treatment is usually not necessary, and reassurance of the benign nature of the condition should suffice. An avoidance of sleep deprivation or possibly offending medications should also be advised. In cases where the disorder results in a potential for injury or excessive daytime sleepiness, tricyclic antidepressants or benzodiazepines may be used.

Disorders Predominantly Associated with REM Sleep

Nightmares

Nightmares consist of frightening dreams that often awaken the patient from sleep and can be accompanied by agitation. Unlike NREM phenomena like sleep terrors, there is usually no limb thrashing or ambulation. A history usually identifies these as benign events. However, if specific dream imagery is not recalled, a history of sudden fear followed by confusion might be mistaken for nocturnal seizures.

Narcolepsy and Isolated Hypnic Hallucinations, Sleep Paralysis, and Cataplexy

Narcolepsy is a complex disorder in which various sleep phenomena associated with REM sleep invade normal wakefulness. It is defined as a clinical tetrad that includes excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, and sleep paralysis. Only 10% to 15% of patients experience all symptoms (35). All have excessive daytime somnolence, and associated cataplexy occurs in about 70%, hypnagogic hallucinations in 30%, and sleep paralysis in 25%. The individual symptoms can all be confused with epilepsy, including somnolence, which can result in sleep attacks. All can also occur as isolated symptoms, without a diagnosis of narcolepsy.

Narcolepsy is a relatively unusual disorder. Incidence is about 0.05% in Caucasians but may be higher in other populations (36). There is a positive family history of hypersomnolence in up to 50% of cases, with cataplexy also common in families (37). Onset typically occurs in adolescence or young adulthood; onset after 55 years of age is very uncommon (35,38).

Excessive daytime sleepiness is required for the diagnosis of narcolepsy; however, this symptom is unlikely to be mistaken for epilepsy. Patients report an irresistible sleepiness culminating in a "sleep attack", where sleep onset can occur while talking, driving, or walking. Some patients may experience periods of extreme drowsiness but continue activities, during which time they may not recall what has occurred. They may drive to unplanned places or be able to perform complex tasks, then suddenly wake and be unaware of what has occurred. The combination of these experiences with sleepiness should verify narcolepsy, although these episodes could also be misinterpreted as confusional states and be mistaken for epilepsy.

Cataplexy is generally more disturbing to the patient and can be mistaken for epilepsy. These episodes consist of a sudden loss of muscle tone (most commonly in the face or knees) with preserved consciousness. This can result in falling and paralysis, but more often is limited to buckling of the knees or slurring of speech. Because of the slow onset, injury is very uncommon. Brief twitching of facial or limb muscles can occur and, when rhythmic, add to the potential confusion with epilepsy. Cataplectic attacks classically occur in the setting of strong emotion, most commonly laughter (39) but also anger, fear, surprise, or excitement (36). The association with external emotion can aid in the distinction from epileptic seizures. Although seizures are widely believed to be increased by stress, association with positive emotion is not typical.

Sleep paralysis consists of the inability to move or speak with onset during the process of falling asleep (or, less commonly, upon awakening). It typically lasts less than 10 minutes although can persist for up to 30 minutes. The episode may be quite frightening to the patient. It can sometimes resolve when someone touches the patient. Hypnagogic (or hypnopompic) hallucinations also occur while falling asleep (or waking up). The content can be simple (a brief image of a face) or complex (an entire scene occurring in the room). These hallucinations are usually visual although auditory, somatosensory, vestibular, and olfactory hallucinations also can occur. The sensation is incorporated into the waking background, and the patient is fully aware during the episode.

The diagnosis of narcolepsy is primarily based on a history of these symptoms, with cataplexy and excessive daytime sleepiness the most common. Confirmatory tests include polysomnography, multiple sleep latency test (MSLT), and human leukocyte antigen (HLA) typing. Polysomnography shows decreased sleep latency (less than 10 minutes) and decreased REM latency (less than 20 minutes). MSLT can show a mean sleep latency of less than 5 minutes, with two or more sleep-onset REM periods considered highly suggestive of narcolepsy. Sleep onset REM can also occur with severe REM sleep deprivation due to any cause (including sleep apnea). HLA subtypes are highly sensitive for narcolepsy in whites, but are a poor marker in African Americans. Up to 35% of the general population carry the same subtypes (35).

Cataplexy, hypnagogic hallucinations, and sleep paralysis can occur in the absence of narcolepsy and, in these cases, are more likely to be mistaken for epilepsy. Episodes of cataplexy are reported in up to 29% of young adults (40,41). Sleep paralysis is quite common, occurring in up to 60% of normal subjects (36,42), although the prevalence of repetitive episodes is probably about 5% (43). Hypnagogic and hypnopompic hallucinations occur in up to 19% of normal subjects (44); these are also unlikely to be repetitive when benign. Sleep deprivation may increase the likelihood of these phenomena. When occurring in normal subjects, reassurance is typically all that is required, although recurrent cataplexy may require treatment (as described below).

The treatment of narcolepsy is both behavioral and pharmacologic. Patient education can be of enormous benefit by assuring the benign nature of the symptoms and avoiding potentially dangerous situations (driving or operating heavy machinery while drowsy). Scheduled daytime naps can greatly reduce the disruption caused by sleep attacks. Drug treatment depends on the prominent symptomatology. Daytime sleepiness is treated with amphetamines, particularly methylphenidate, or with modafinil. Cataplexy usually responds to tricyclic antidepressant drugs, most commonly imipramine, protryptyline, and clomipramine. Selective serotonin reuptake inhibitors (SSRIs; fluoxetine, paroxetine) and sodium oxybate have also been used. Treatment of hallucinations or sleep paralysis, when necessary, can also be with tricyclic antidepressant drugs.

REM Behavior Disorder

REM behavior disorder was described relatively recently (45,46). It is characterized by agitated, sometimes violent movements occurring during REM sleep. Kicking, punching, jumping, and running from the bed are commonly seen. Injury is also common, and can occur to either the patient or the bed partner. Patients typically report that a dream sequence occurs during the episode. Most patients are male, and the majority are over age 60

years (47,48). About half of patients have known neurologic disorders, most commonly Parkinson's disease, dementia, or multisystem atrophy (47,48). There may also be an association with post-traumatic stress disorder (49). Physiologically, the disorder consists of an absence of normal atonia and increased phasic and tonic EMG activity during REM sleep; these can be documented on routine polysomnography with chin and axial EMG.

The pathophysiology of REM behavior disorder almost certainly involves a dysfunction in the pontine tegmentum, an area known to be responsible for atonia during REM sleep (50). Most patients do not have structural lesions of the pons, but the disorder is thought to arise from an imbalance of neuronal regulation in this area, which is responsible for regulating REM and non-REM sleep.

The history of bizarre, semipurposeful behavior with confusion may be impossible to distinguish from seizures or postictal behavior. Unlike most partial seizures, REM behavior disorder will be restricted to sleep and usually occur in the early morning when REM is most prevalent. The memory of a dream sequence, if present, is helpful in distinguishing the two. If in question, diagnosis is readily made with video-EEG monitoring, ideally with simultaneous examination of polysomnographic parameters. Treatment with benzodiazepines (typically clonazepam) is usually successful (49).

DIAGNOSTIC AND TREATMENT STRATEGIES

As with nearly all cases involving epilepsy, a careful history is by far the most important part of making a diagnosis. Both seizures and parasomnias can be paroxysmal, and in many cases have similar clinical semiology (see Tables 16.1 and 16.2). Those which are most commonly confused with epilepsy are cataplexy, sleep attacks (especially related to narcolepsy), night terrors, and REM behavior disorder. Episodes that occur only during sleep should raise the suspicion of a sleep disorder, although cataplexy and sleep attacks occur with the patient awake. Additionally, many patients with sleep disorders have excessive daytime somnolence, and daytime attacks can occur during naps. Conversely, in many epilepsy syndromes attacks occur predominantly or exclusively during sleep (such as benign Rolandic and nocturnal frontal lobe epilepsies). Excessive daytime somnolence is suggestive of an underlying sleep disorder, particularly narcolepsy but also restless legs syndrome, sleep apnea, and periodic limb movements. This can be helpful in diagnosis; however, frequent nocturnal seizures also disrupt sleep and result in similar symptoms.

A description obtained from the patient is obviously essential, as both epilepsy and parasomnias can have important subjective symptoms that could not be observed by an onlooker. An aura of paroxysmal fear is suggestive of epilepsy, but a sudden fall with preserved consciousness after an external frightening event or anger is more consistent with cataplexy. Awareness of events during the attack can be present in simple partial seizures, but some degree of awareness is seen in parasomnias, especially REM behavior disorder, hypnagogic hallucinations, and catalepsy. Onlookers or bed partners can also be important sources of diagnostic information, and should be interviewed whenever possible. A patient may think he or she simply lost consciousness, whereas an onlooker can recognize prolonged drowsiness beforehand, suggestive of a sleep attack, or drooling and oral automatisms consistent with a partial seizure.

Ambulatory versus Inpatient EEG Monitoring

In cases where diagnosis remains uncertain, a routine EEG is often the test of first choice. Clearly epileptiform activity (spikes or spike–wave discharges) is highly suggestive of epilepsy, although about 1% to 2% of normal individuals will have epileptiform abnormalities on EEG (51). However, a normal EEG does not rule out the presence of epileptic seizures and is seen in up to 50% of patients on the first study (52). If the diagnosis remains in question, continuous EEG monitoring can be helpful. A prolonged EEG is useful because there is an increased likelihood of capturing abnormal interictal discharges, which (if epileptic) increase the likelihood that the episode in question is a seizure. Prolonged EEG can also record the actual event, potentially showing sleep phenomena or epileptic discharges.

Ambulatory EEG has improved markedly in recent years, allowing sixteen-channel recordings and (in some cases) electronic montage changes during interpretation. No technologist monitors the EEG during these studies, as is the case with inpatient recordings. Therefore, a nonfunctional electrode can remain undetected and make the entire study uninterpretable. The timing of the event depends on the reliability of the patient or caregiver. Video monitoring is usually not available, raising the possibility that artifact can interfere with the episode of interest and even be misleading. Simultaneous independent video can help, but if it is not time synchronized it still may be difficult to definitively determine artifact from physiologic changes.

Inpatient video-EEG remains the gold standard for the diagnosis of paroxysmal disorders. Patients are observed and tested by trained personnel during recordings, and the recording is generally of the highest quality. The chief disadvantage, compared to ambulatory recordings, is expense; therefore, ambulatory recordings may be useful as a screening tool with inpatient recordings only when the question remains ambiguous.

TABLE 16.5
AED Effects on Sleep and Sleep Disorders

	Effects on Sleep		Effects on Sleep Disorders	
Drug	**Positive**	**Negative**	**Improves**	**Worsens**
Barbiturates	↓sleep latency	↓SWS,REM		OSA
Benzodiazepines	↓sleep latency	↓SWS,REM	Sleep terrors	OSA
Carbamazepine			RLS	
Felbamate				Insomnia
Gabapentin	↑SWS, ↓arousals		RLS, PLMS	
Levetiracetam				
Lamotrigine				
Oxcarbazepine				
Phenytoin	↓sleep latency	↓REM		
Tiagabine	↑SWS			
Topiramate				
Valproic acid				
Zonisamide				

REM = Rapid eye movement
SWS = Slow wave sleep

Polysomnography and Video-EEG Polysomnography

When the primary suspicion is of a sleep disorder, polysomnography is the most helpful initial test. This allows a more complete assessment of sleep structure in general and of the stage of sleep from which the abnormality arises. When there is suspicion of periodic limb movements or restless legs syndrome, EMG disc electrodes can be placed on the legs to help in diagnosis. In cases where an epileptiform EEG has been obtained previously or where there remains a suspicion of epilepsy or concurrent epilepsy, most polysomnography equipment allows for monitoring of a full complement of EEG electrodes when necessary.

In a few highly specialized centers, it is possible to perform polysomnography and video-EEG simultaneously. This is most helpful when sleep disorders and epilepsy coexist in the same patient, thereby allowing for more efficient evaluation and insight into any interrelationship between the two. However, in most areas video-EEG and polysomnography must be performed as separate studies.

Treatment of Patients with Sleep Disorders and Epilepsy

In cases where epilepsy and sleep disorders coexist, the most important aspect of treatment is awareness of the conditions. If seizures become more frequent or more severe in a patient with known sleep apnea, for example, careful questioning and re-evaluation of the sleep apnea may be necessary to determine whether sleep apnea is contributing to the deterioration. New sleep disorders can occur and exacerbate epilepsy. Comedication is also a particularly important issue in epilepsy patients who have sleep disorders. The use of benzodiazepines for sleep is more problematic because of the risk of withdrawal seizures if treatment is interrupted or abruptly stopped. Stimulant medications, such as methylphenidate, can worsen seizures, and modafinil is a better choice when this type of medication is necessary. For all patients, anticonvulsants must be chosen carefully. Medications that decrease sleep latency (such as phenobarbital, phenytoin, or benzodiazepines) can be dosed primarily or exclusively at bedtime to induce sleep. In patients with poor sleep consolidation, medications such as gabapentin may actually improve sleep, also with higher doses given at bedtime. In patients with poor sleep, medications that can be alerting (lamotrigine, felbamate) should be dosed earlier in the day. In some cases, anticonvulsant medications can impair sleep regardless of administration time. Although studies vary, phenytoin, valproate, and barbiturates can increase nocturnal awakenings (9,53), and a change in medication should be considered when this becomes problematic. A summary of the effects of AEDs on sleep and sleep disorders is contained in Table 16.5.

In any sleep disorder that includes significant daytime somnolence (particularly obstructive sleep apnea

and narcolepsy), driving must be discussed with the patient. In cases where somnolence is severe, driving may need to be forbidden until effective treatment is instituted. In others, patients must be carefully counseled regarding the risks of driving while sleepy, and drowsiness must be minimized through treatment (medication, scheduled naps, etc).

CONCLUSION

Sleep disorders are a common phenomenon, and many share the paroxysmal quality of epileptic seizures. An awareness of these conditions is therefore crucial for the neurologist seeing patients with spells. In patients with an initial presentation of paroxysmal events, sleep disorders must be ruled out, particularly when events are restricted to sleep. In patients with known epilepsy, nonepileptic sleep disorders frequently coexist and have the potential to worsen seizures—in addition to the morbidity conferred by the sleep disorder itself. Finally, both sleep disorders and epilepsy are common phenomena, such that both may be present in the same patient. In these cases, diagnosis and treatment of both diseases is usually required before either can be completely controlled. Certain agents for treating epilepsy can worsen sleep, and sleep agents can exacerbate epilepsy, thus requiring particularly careful choices in patients with both conditions.

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17 Cerebrovascular Imitators of Epilepsy

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Seizures are nearly always manifested as acute attacks of altered neurologic function. The attacks are usually brief, lasting seconds to a few minutes. As such, any disorder that occurs in attacks or spells must be considered in the differential diagnosis of seizures. The Australians have a wonderfully nonspecific term that they use for attacks—they refer to them as "turns," and "funny turns" if the attacks are in any way unusual.

In this chapter I concentrate on vascular conditions (including migraine) that occur in attacks. The discussion first focuses on the two commonest vascular disorders—migraine and transient ischemia—and then describes less common conditions.

CLINICAL FEATURES USED TO SEPARATE SEIZURES, TRANSIENT ISCHEMIA, AND MIGRAINE

Case Study #1. A 75-year-old man with a history of hypertension, hypercholesterolemia, and a previous myocardial infarct suddenly developed numbness and weakness of his right hand. When he attempted to speak, wrong words came out, according to his wife who was with him at the time. Within a few minutes, his arm and speech returned to normal.

Case Study #2. A 36-year-old man suddenly developed jerking of his right fingers. The jerking quickly spread to his right arm and face, and his head and eyes turned to the right just before he lost consciousness and slumped to the floor. He was a skier and had had a serious head injury 2 years before.

Case Study #3. A 25-year-old woman noted tingling in her right thumb. The tingling gradually spread to her other fingers and then up her arm during a few minutes. As the tingling spread, her fingers began to feel numb. The tingling spread to her face as the feeling in her fingers returned to normal. After the tingling cleared, she noticed that she could not read, and she made errors in speech. About 20 minutes after the onset, her speech and feeling were normal but she began to have a severe left temporal headache.

These three case studies describe typical patients with a transient ischemic attack (TIA) (patient 1), a seizure (patient 2), and a migraine attack (patient 3). All

TABLE 17.1
Features of Seizures versus TIAs versus Migraine Attacks

SEIZURES	TIAS	MIGRAINE
One sensory modality	At times more than one modality but affected simultaneously	Spread from one modality to another
Positive symptoms	Negative symptoms	Positive, then negative symptoms
Rapid spread	All symptoms at onset	Gradual spread over minutes
All symptoms clear together	All symptoms clear together	Symptoms clear in one modality before onset of symptoms in another modality
Headache follows	Headache may precede, accompany, or follow	Headache usually follows
Duration 1–3 min	Duration 1–30 min most common; may last hours	20–30 min most common
May begin early in life	Usually >40 yrs old	Often begins in teens or twenties
Spells occur over years	Usually limited to weeks or months	Spells occur over years
May have had head trauma or neoplasia	Stroke risk factors present	Usually family history of migraine
No sex difference	Slightly male > female	Female > male
Decreased level of consciousness postictally	No decrease in consciousness	No decrease in consciousness

patients are not this typical. A number of features are useful in separating these three disorders. Table 17.1 tabulates the major differential points discussed in more detail below.

Positive Versus Negative Symptoms

Seizures involve the discharge of neurons. This causes so-called "positive" symptoms that indicate activity or overactivity of neural discharge. Migrainous auras also involve discharging nerve cells, with the discharging focus traveling slowly along a neural path. Most investigators characterize this spread as that of *spreading depression,* which is different from the movement of seizure discharges. Migrainous auras also most often begin with positive symptoms. In contrast, ischemia of the brain or retina causes a cessation of neural discharge and so-called "negative" symptoms that indicate a loss of function.

Contrasting the visual symptoms patients describe at the onset of seizures, migraine, and ischemia involving the occipital brain regions serves as a useful example of the positive versus negative aspects of symptoms. Seizures that originate from regions near the visual striate cortex often manifest as visual displays that patients see and may be able to describe. Depending on the location of the seizure focus, these displays may be formed or unformed objects or scenes. Spots, flashing lights, colors, people, objects, moving scenes are all plausible. Migrainous auras also most often begin with positive visual phenomena. Attacks commonly begin with a small formed object or objects. The objects vary greatly; stars, circles, squares, zig-zags, pointed lines, fireflies, lightning bolts, heat waves, pinwheels, rods, and beads are just a few of the names that patients give to the forms (1–3). At times, the forms are linear and contain angles and straight edges. An early migraineur described his aura as consisting of lines that looked like a fortified town with bastions. The resemblance of the edges and lines to forts led to the frequent use of the term "fortifications" and fortification spectra to describe this type of visual experience (1). Often the forms are bright and may be colored, especially red, green, blue, extra-white, or purple. Migraineurs usually describe some type of motion, both in-place, and across the visual field. In-place motion is often described as flickering, shimmering, rotating, oscillating, or like a kaleidoscope (2).

Ischemic lesions involving the visual cortex, as occur in occlusive disease of the posterior cerebral artery, manifest as loss of vision. Patients most often describe a void or darkness or absence of vision to one side.

Similarly, in the somatosensory sphere, seizures arising in the superior parietal lobe cortex usually involve paresthesias or thermal sensations in the contralateral limbs. Migrainous auras may involve paresthesias or dysesthesias that spread from one body part

to another, sometimes moving slowly from one finger to another. TIAs or strokes involving the same regions usually manifest as numbness or loss of feeling.

Seizures emanating from the motor cortex involve jerking and muscle contractions of the contralateral limbs, whereas transient ischemia produces weakness. Migraine almost never causes rhythmic jerking or excess limb movements.

Some seizures seem to present with negative symptoms. In these cases, subtle clinical evidence may exist of increased activity in the form of local twitching, or positive symptoms preceding the negative symptoms and going unappreciated.

Spread or March of Symptoms During Attacks

Seizures may involve a spread of discharge that causes relatively rapid movement and the progression of positive symptoms, usually referred to as Jacksonian seizures. The spread is very quick, usually occurring within seconds. A key feature of the visual symptoms during migrainous auras is this build-up and spread of the visual forms. The individual forms often become brighter, or larger, or more objects may appear with time. The visual objects also often gradually move across the visual field, usually during a period of minutes. Loss of vision—a *scotoma*—often follows in the wake of the positive visual symptoms. In migrainous auras, symptoms also often move from one modality to another, usually after clearing in the first modality. For example, an attack might begin with sparkling in the right visual field, with the scintillating visual objects moving to the right, followed in their wake by darkness. As vision clears, tingling might begin in the right thumb and spread from one finger to the next, gradually moving up the right arm. As the tingling moves, the fingers may begin to feel numb. TIAs rarely spread during a short time. Visual loss is complete at onset, as is numbness or weakness. There may be a stepwise increase in symptoms and signs, but not a gradual systematic movement of abnormalities along a visual field or body region. Symptoms in TIAs almost never shift from one modality to another. All the modalities that will become involved do so at onset.

Time Duration of Individual Attacks

Single seizures are usually brief, lasting seconds to a few minutes at most. The time duration of TIAs is very variable, but the great majority of attacks last less than 1 hour (4–6). Most last only a few minutes. TIAs rarely last only seconds. Migrainous auras usually last about 20 minutes on average, although occasionally they can persist for hours.

Time Span During Which the Attacks Occur

The key point in relation to time span is that migraine and seizures are often chronic repetitive conditions that may reoccur over many years, whereas TIAs rarely continue to occur for more than 6 months. In patients with occlusive vascular disease, with time, collateral circulation develops and active endothelial lesions and plaques heal, thus ceasing to be prominent sources of emboli. If these compensatory mechanisms fail, the patient has a stroke and TIAs usually stop. In any case, TIAs almost never persist for years. TIAs related to an occlusion of small penetrating arteries may present as very frequent stereotyped repetitive attacks over hours or days before a stroke. These repetitive attacks are sometimes referred to as "shotgun attacks" because the timing is suggestive of rapid volleys from a gun.

Age at Onset

Although seizures, migraine, and brain ischemia can all begin at any age, seizures and migraine are much more common in the first decades of life, whereas occlusive vascular disease is more common in the geriatric years. Occlusive vascular disease is most often a condition that develops in later life and is unusual in the young. In contrast migraine most often starts in the second or third decade of life. Seizures can begin at any time but are common in children and young adults.

Genetics

Familial tendencies exist in each of the three conditions. Most migraineurs have a family history of migraine, but many patients do not know whether or not their family members are predisposed to headaches and the type of headaches that they have. Often the physician must ask family members or instruct the patient to ask about headaches. Many patients assume that everyone has headaches. Patients with seizures also often have family members who have had seizures (and most patients are aware of family members who have had seizures). Patients with occlusive vascular disease often have a family history of strokes, heart attacks, hypertension, diabetes, and other risk factors for stroke.

Etiology—Risk Factors and Concurrent Illnesses

Vascular occlusive disease patients who have TIAs and strokes most often have prevalent risk factors for stroke, such as smoking, hypertension, hyperlipidemia, peripheral vascular occlusive disease with limb claudication, coronary artery disease with angina pectoris and/or myocardial infarction, and other types of cardiac

disease that might serve as a source of embolism to the brain. They are also often overweight and lead a sedentary life style. It is unusual to find a patient with TIAs who has no risk factors for atherosclerosis.

Many acute and chronic medical conditions predispose to seizures including primary and metastatic tumors, inflammatory disorders of the brain, and past strokes.

Precipitants of Spells

TIAs are occasionally precipitated by positional changes that reduce cerebral blood flow. Attacks may occur after suddenly standing up, arising from a stooped posture, or an increase in antihypertensive treatment. Some visual spells of monocular blindness are precipitated by exposure to bright light. Migrainous attacks are often precipitated by abrupt changes in activity, altitude, and temperature. Some patients with so-called reflex seizures have attacks only after specific activities or exposures, for example, reading, hearing music, or strobelike light. Of course omitting anticonvulsant drugs is a frequent prelude to seizures. Syncope often follows blood drawing, standing in one place for a long time, drawing blood, removing a cast with a buzz saw, and eating a large meal. Some patients repeatedly faint after urinating or defecating.

Consciousness and Awareness During Attacks

Loss of consciousness is extremely rare in patients with TIAs or migraine but is common with syncope and seizures. During a migraine or a TIA, others can gain the attention of the patient, whereas during many seizures this is not possible.

Nature of the Symptoms and Their Stereotypy

The symptoms during TIAs differ greatly and depend on the blood vessel and arterial territory affected.

Internal Carotid Artery (ICA)

The single most important clue to a carotid artery localization of the occlusive process is an attack of transient monocular loss of vision. The visual loss is most often described as a dimming, darkening, or obscuration. An apparent shade or curtain usually falls from above but may move from the side like a theater curtain. After a brief period of seconds or a few minutes, the curtain lifts or recedes, usually leaving no permanent visual loss. These attacks of transient visual obscurations are caused by decreased blood flow through the ophthalmic artery, the first branch of the ICA. Transient monocular visual loss occurs when the lesion affects the ICA proximal to the ophthalmic artery (in the neck or proximal carotid artery siphon) or involves the ophthalmic artery itself. Diminished flow or pressure in the ophthalmic artery is a clue to the presence of carotid artery disease. Some patients with ICA dissections have frequent brief attacks of transient monocular visual loss. This finding has been called *carotid allegro* (7,8), and when it occurs in a young person along with neck, face, or head pain is virtually diagnostic of an ICA dissection. An ipsilateral Horner syndrome and pulsatile tinnitus are other clues to the presence of ICA dissection.

Patients with ICA occlusive disease also often have attacks of hemispheral ischemia. Episodes of hemispheral ischemia are also usually brief, lasting only a few minutes. Attacks may be quite varied and include different deficits in different limbs during individual attacks, but some spells are stereotyped. In some patients with critical stenosis, the attacks are very frequent and may be precipitated by suddenly standing or by a drop in blood pressure. Frequent, very brief machine-gun-like attacks usually mean low flow due to proximal severe stenosis, whereas emboli usually produce longer, less frequent attacks.

Some patients with severe ICA occlusive disease (usually >90% stenosis or occlusion) have attacks during which the contralateral arm or leg has repetitive shaking movements that can be easily confused with seizures (9,10). These so-called "limb shaking spells" often occur after rapidly standing up or arising from a stooped posture. Usually, when standing or active, the patient develops a tremor with impressive shaking and oscillation of the arm and hand contralateral to the occluded ICA. There is no march, and no flexion–extention progression of the movements. Occasionally, the lower extremity is involved and there are course flapping movements of the leg. The shaking stops when the patient sits or lies down and is due to ischemia rather than a seizure.

Middle Cerebral Artery (MCA)

Intracranial occlusive disease affecting the intracranial ICA and its major branches (the middle, anterior, and anterior choroidal arteries) is much less common than ICA disease in the neck. However Asians, blacks, women, and diabetics often have intracranial occlusive disease without appreciable atherostenosis in the neck. The TIAs that occur in patients with MCA occlusive disease are identical to the hemispheral attacks in patients with ICA disease, except that they are more often stereotyped. Left MCA related attacks are often characterized by some abnormality of speech.

Anterior Cerebral Artery (ACA)

Attacks involving the ACA most often involve numbness and tingling of a lower limb.

Vertebrobasilar Large Arteries

Posterior circulation TIAs include symptoms quite different from those related to anterior circulation occlusive disease. Dizziness, vertigo, sharp facial pain and burning, double vision, ataxia, numbness or weakness involving structures on both sides of the body, and bilateral visual loss are frequent symptoms. The symptoms depend heavily on the location of the vascular occlusive disease. Narrowing of the extracranial vertebral artery (ECVA), almost invariably at or very near its origin from the subclavian artery, is quite common and parallels the frequency of ICA disease (1). Patients with ECVA or subclavian artery occlusive disease often have attacks of dizziness, loss of balance, diplopia, and visual blurring. The attacks are brief and are often repetitive. These attacks are explained by a decrease in blood flow to the medulla and cerebellum.

Patients with occlusive disease of one of the intracranial vertebral arteries (ICVAs) often have attacks containing fragments of the lateral medullary syndrome. Burning in the ipsilateral face, veering or leaning to the side, vertigo, blurring of vision, and gait ataxia are most common. These TIAs are related to decreased blood flow to the lateral medulla. When both ICVAs are narrowed, blood flow to the medulla, pons, and the posterior portions of the cerebral hemispheres is compromised. Some patients with bilateral ICVA disease also have occlusive lesions in their basilar arteries and the ECVAs. Because of a low-flow system, the symptoms are often positionally sensitive, worsening when the patient sits or stands or when blood pressure falls either spontaneously or after treatment. Usually, TIAs continue and are multiple and stereotyped. Attacks may include transient loss or dimming of vision, loss of postural tone, ataxia, memory loss, and bilateral limb weakness.

When the basilar artery (BA) is narrowed or occluded, TIAs most often include motor and oculomotor symptoms—diplopia, bilateral leg weakness, ataxia, and dizziness are most common. Numbness is unusual. Often only one side of the body becomes weak, but the loss of strength can shift sides in different attacks. Some patients with multiple sclerosis have paroxysmal attacks, most often of dysarthria and ataxia, that can be confused with basilar artery TIAs and seizures (11,12).

Posterior cerebral artery (PCA) occlusive disease is less common than disease of the vertebral and basilar arteries. The frequency of intrinsic PCA disease parallels that of disease of the intracranial anterior circulation MCAs and ACAs. TIAs in the distribution of the PCAs usually consists of transient hemianopic visual symptoms, sometimes accompanied by transient hemisensory symptoms on the same side. Loss of vision is most common but sparkling and flashing also occur in a hemianopic field. Sensory symptoms are usually hemisensory and involve paresthesias. Most often the symptoms are either visual or sensory but they can occur concurrently. They rarely if ever move from one modality, visual or sensory, to the other, as occurs in a migrainous aura.

Penetrating Arteries

Penetrating artery disease patients also have TIAs but less often than those patients with large-artery occlusive disease. Arteries that penetrate from the intracranial anterior, middle, and posterior cerebral arteries and the ICVAs and basilar arteries are damaged by hypertension and by microatheromatous disease. These vessels penetrate at right angles from their source arteries and supply the basal ganglia, internal capsule, thalamus, and brainstem. TIAs, when they occur, are invariably stereotyped and most often involve weakness of the limbs on one side of the body or numbness or paresthesias on one hemicorpus (8). The TIAs usually occur over a short period of time (<1–3 days).

Embolism

Embolism is the most common cause of brain ischemia. Emboli arise from the heart, aorta, or proximal extracranial and intracranial arteries. When the emboli arise from an arterial source, the attacks invariably involve either the carotid artery territory on one side or the vertebrobasilar territory. Emboli coming from the heart or aorta can go to any territory, so that symptoms and signs during strokes and TIAs are extremely varied. Attacks caused by embolism are usually longer than those related to the hemodynamic insufficiency related to severe occlusion of feeding arteries.

Migraine

The symptoms during migrainous auras are mostly visual, somatosensory, and vestibular. In most migraineurs, the attacks are similar but the visual display may vary and usually affects different hemianopic fields in different attacks. Similarly, somatosensory attacks can affect different body sides and different body parts. In some patients, aphasia and confusion can follow visual and somatosensory symptoms but aphasia is rarely the only symptom. Although weakness and opthalmoplegia can occur, it usually involves individuals who have had attacks of hemiplegic migraine since youth. Similarly, opthalmoplegic migraine rarely develops after age 20.

Some patients with migraine can have attacks that contain features usually associated with so-called temporal lobe seizures, for example, unusual smells or tastes, déjà vu, or feelings of out of body experience. They may also develop visual illusions, metamorphopsias, and visual agnosias similar to that described in "Alice in Wonderland" syndrome.

Some symptoms and findings during seizures are rarely if ever found during TIAs, for example mouthing and swallowing movements, déjà vu, depersonalization, hearing songs or musical pieces, bad odors or tastes, and the like.

Accompaniments During and After Attacks

Migraineurs often have severe headache after or during attacks. Vomiting after an attack is also very common. Photophobia and phonophobia are also frequent features of migraine attacks. Patients who have migraine with aura usually also have attacks of headache without aura.

Loss of consciousness during an attack is common during seizures but extremely rare during migraine or TIAs. Loss of memory is also unusual after an ordinary migraine or TIA but is a common finding after a seizure. Incontinence and tongue biting are virtually diagnostic of seizures, although some patients with syncope do lose urine during an attack, and syncope can be precipitated by micturition and defecation in some individuals.

Headaches are often present in a frequency unusual for that individual in patients who have large artery disease and TIAs, but headaches rarely accompany or follow a TIA attack. Headaches and reduced alertness are very common after seizures.

Special note should be made of a disorder usually called basilar artery migraine, after Bickerstaff (13). This disorder most often occurs in girls but can develop at any age; the attacks can be confused with prolonged seizures. The first symptoms in the majority of patients are visual. Bilateral visual loss, or bilateral bright scintillations, which at least partially obscure vision are usually noted at onset. Patients with basilar artery migraine develop vestibulocerebellar dysfunction including vertigo, dysarthria, and gait and often limb ataxia. Double vision and oscillopsia are also common symptoms. Paresthesias are also often present, sometimes affecting all limbs and the perioral and facial regions. The symptoms and signs usually last from 2 to 45 minutes and are almost invariably followed by an occipital throbbing headache often accompanied by vomiting.

Examination of patients during a basilar migraine attack can show opthalmoplegia, ataxia, limb incoordination, and dysarthria. Some patients lose consciousness during an attack (14). The EEG is often quite abnormal during or after an attack (15–18).

Brain and Vascular Imaging

Patients with TIAs may have evidence on computed tomography (CT) and/or magnetic resonance imaging (MRI) of brain infarcts and often show important vascular imaging abnormalities (CTA, MRA, and extracranial and transcranial ultrasound). Seizure patients may have congenital abnormalities, tumors, or regions of atrophy.

LESS COMMON MIMICS ATTRIBUTED TO, OR CONFUSED WITH CEREBROVASCULAR DISEASE

Transient Global Amnesia (TGA)

Case Study #4. A 68-year-old man was vacationing in Aruba. On a hot day, he dove into the pool and swam several laps vigorously. When he came out of the water, he approached his wife and asked "Where are we? How did we get here? Who is the lady next to you?" (A woman with whom they had dined the night before). He seemed restless. His facial appearance and limb motions and vocabulary seemed normal to his wife. After she had answered his questions, a moment later he repeated the same queries. When she questioned him, he could not tell her when they came and could not recall any of the events that occurred during the 2 weeks they had been in Aruba and the occasion for the trip (fortieth wedding anniversary).

Transient global amnesia (TGA) is a syndrome of sudden onset that occurs mostly in late life and is characterized by repetitive queries, anterograde memory failure and retrograde memory loss, and an attack-duration of hours (1,8,19,20). The usual attack begins abruptly. The patient seems confused and repetitively asks questions about what they are doing and sometimes where they are. Other TGA patients become uncharacteristically quiet and withdrawn at the onset of an attack. Patients are unable to retain the answer to the repetitive queries and ask them again and again. When questioned during an attack, they may be unaware of events of the past days, weeks, months, and even years. After the attack is over (< 24 hours), the retrograde amnesia gradually shrinks, but the patient never regains memory of events during the attack of TGA. Despite the loss of memory, they may be able to drive, calculate, play a musical instrument, and deliver a lecture. The same precipitants can provoke migraine and TGA: emotional stress especially sudden and unexpected, cerebral

TABLE 17.2
Criteria for TGA [modified from (22)]

1. The onset of the attack should have been witnessed (to exclude head injury or seizure)
2. An accurate account of the individual's behavior and function during the attack should be available
3. The attack should involve only memory (visual migraine-type scotomas are allowed but not visual, sensory, or motor loss of function)
4. The patient should ask repetitive queries during the attack
5. The attack should last less than 24 hours

angiography, sexual intercourse, activities associated with physical effort or exercise, immersion in cold water ("amnesia by the sea"), hot bath or shower, and motor vehicle travel (1,19–21). TGA occurs more often in migraineurs than is expected by chance. Many features of TGA favor the interpretation that at least some attacks are probably due to vasoconstriction and most likely represent dysfunction of the dominant left medial temporal lobe structures (1,19,21). Seizures can be associated with transient amnesia but repetitive queries are not a feature of postictal amnesia. Strokes causing dysmemory involve predominantly the posterior cerebral artery (PCA) territory and, nearly always, the memory loss is accompanied by visual and/or somatosensory symptoms and signs. Repetitive queries are not a part of PCA-territory strokes.

CT and MRI are invariably normal. Positron emission spectroscopy (PET) and Single positron emission computed tomography (SPECT) scanning during an attack may show abnormal blood flow and activity in the medial temporal regions, especially on the left. The EEG may also show some temporal lobe slowing but does not show spikes or seizure discharge. In patients who meet the criteria for TGA [Table 17.2; (22)] I do not believe that either EEG or brain imaging is necessary.

Episodic Vertigo

Case Study #5. A 75-year-old woman noted severe dizziness when she arose from her bed to urinate during the night. There was a sensation that the room was spinning vigorously in a clockwise direction. She held on to the bedpost to keep from falling. The vertiginous feeling was momentary, but during the day she noted some transient spinning each time she turned. She had a feeling of nausea and vomited in the morning. As long as she stayed quite still she did not feel dizzy.

Occasional seizures contain vertiginous elements, and some patients with vertigo may faint, presumably related to a vagal response. For these reasons paroxysmal attacks of vertigo, most often of peripheral origin, is among the differential diagnostic considerations in patients in whom a diagnosis of epilepsy is being considered. Dizziness and vertigo in patients with peripheral vestibulopathies is often triggered by sudden movements and positional changes. Vertigo is also a common component of TIAs in patients with vertebrobasilar occlusive disease. Patients with posterior circulation occlusive vascular disease rarely have isolated attacks of vertigo without other brain stem or cerebellar symptoms (1). A general rule is that isolated attacks of vertigo lasting more than 3 weeks without other symptoms are rarely explained by occlusive vascular disease.

Drop Attacks

Case Study #6. An 80-year-old woman was walking on an unpaved dirt road that contained some stones. All of a sudden, she dropped to the ground because her legs went out from under her. She did not become dizzy or faint before she went down, and she remained alert at all times. For several months before this, her walking was a bit less secure and examination showed bilateral Babinski responses and reduced vibration sense in her feet. Her vitamin B12 blood level was quite low.

Some patients have attacks in which they lose postural tone and suddenly go down to the ground without losing consciousness. These spells have customarily been called "drop attacks." Akinetic seizures can closely resemble drop attacks. For reasons that are unclear, a myth exists that these drop attacks usually are caused by so-called vertebrobasilar insufficiency. In reality, posterior circulation occlusive disease almost never causes isolated drop attacks without other symptoms of brainstem or cerebellar ischemia.

Dropping can occur in relation to many disparate mechanisms. Some patients have an exaggerated flexion response, thus, if they unexpectedly step on a stone or other object, the legs may flex and they drop. Conditions that cause pyramidal tract abnormalities, such as cervical spondylitic myelopathy or subacute combined degeneration due to pernicious anemia, can also cause

unexpected sudden dropping. Some patients with vertigo drop suddenly at the onset of an attack.

Spasms and Movements Related to Subarachnoid Hemorrhage

Case Study #7. A 55-year-old woman suddenly clutched her head, her legs and arms stiffened, and she fell. She then vomited and had difficulty responding to questions or gentle shaking.

When an aneurysm leaks blood under arterial pressure into the cerebrospinal fluid space around the brain, intracranial pressure increases abruptly, causing headache, vomiting, and altered consciousness. Patients may suddenly have their legs buckle or drop to the ground. At times, decerebrate or decorticate posturing and extensor spasms of the limbs ensue. These sudden subarachnoid bleeds can be confused with seizures but the abnormal posturing is most often a reflexion of increased intracranial pressure and not due to seizures. Some patients with subarachnoid hemorrhage develop brain ischemia in the days after the initial bleed. This is due to vasoconstriction.

Adventitious Limb Movements in Patients with Brain Ischemia

Case Study #8. A 67-year-old man with diabetes and hypertension awakened with difficult-to-control movements of his left arm. When he attempted to reach for an object, the arm would seem to move and "dance" without his control, and he could not use his arm and hand for fine movements. Examination showed a slight left hemiparesis and choreoathetoid movements of the left arm.

I have already described so-called "limb shaking TIAs" in patients with severe ICA occlusive disease. These repetitve jerking motions are often misinterpreted as seizures. Patients with ischemic lesions in the basal ganglia can present with choreoathetoid movements, but these usually coexist with some limb weakness and are not often confused with seizures unless the ischemia is transient. Limb movement disorders are also found after posterior circulation infarcts. Choreiform movements are common in patients with lateral thalamic infarcts. Hemiballism, a movement disorder characterized by flinging proximal movements of the upper and lower extremities, usually with an internal rotatory component, has classically been described in patients with small hemorrhages and infarcts involving the subthalamic nucleus. Ballism is not specific for lesions of the subthalamic nucleus and has also been described in lesions of the striatum, in which case choreoathetoid movements are usually also found. In patients with hemiballism, a hemiparesis may precede the abnormal movements or may appear as the movements recede. In some patients with occlusive lesions of the distal basilar artery, clonic athetoid movements, myoclonic jerks, grimacing, and bilateral ballism may appear (1).

Some patients with *Moya Moya* syndrome have episodic abnormal adventitious choreiform motions that can occur in brief attacks. These spells can be precipitated by activity and hyperventilation and represent basal ganglionic ischemia.

Limb Posturing and Movements in Patients with Basilar Artery Occlusion and Pontine and Putaminal Hemorrhages

Case Study #9. A 74-year-old man with past coronary artery surgery and long-standing hypertension noted weakness in his left arm and leg during the morning. Later in the day, he found that both legs and the left arm were weak, and he had difficulty pronouncing words and swallowing. When he arrived at the hospital, his right limbs began to periodically stiffen and extend, and his level of alertness decreased.

Some patients with basilar artery occlusion have shivering, tremulousness, and decerebrate postures as they become quadriplegic (23,24). Occasionally, the abnormal limb movements are clonic and superficially resemble convulsive motions. Ropper described eight patients with basilar artery occlusion who had such convulsivelike limb movements (23). These movements were more severe on the nonplegic side, thus indicating that partial ischemia might be the cause. Usually, in patients with basilar artery occlusion, the medial pontine tegmentum is also involved, so that internuclear opthalmoplegia, horizontal gaze palsy, or their combination ("one and a half" syndrome), vertical nystagmus, and coma are also found depending on whether the tegmentum is involved bilaterally or only unilaterally (1). Two recent patients having basilar artery occlusion with these abnormal jerking move-

ments were misdiagnosed by the emergency room staff as having seizures, and the patients were erroneously treated with anticonvulsants. Similar posturing and movements are also found in patients with pontine hemorrhages (25).

Some patients with putaminal hemorrhages develop abnormal, jerking, tremulous movements of the ipsilateral limbs before developing a contralateral hemiplegia (25). These abnormal movements can be confused with seizures. They are probably caused by an irritation of descending ipsilateral motor fibers arising from the basal ganglia. Patients with thalamic hemorrhages also may have abnormal movements, although these involve the limbs contralateral to the hematomas.

Paroxysmal Dyskinesias and Ataxias

Case Study #10. A 17-year-old boy described spells in which his left limbs would become wildly uncoordinated and he could not walk straight. These spells were usually precipitated by sudden movements and would last only seconds to a minute or so.

Paroxysmal attacks of ataxia and abnormal movements occur in a variety of conditions including multiple sclerosis (11,12), basilar artery and ICVA occlusive disease-related TIAs, Moya Moya syndrome, and basal ganglionic ischemia. A number of conditions often are grouped together as paroxysmal choreoathetosis and dystonias or dyskinesias in which patients develop paroxysmal attacks of abnormal movements. A variety of names have been given to these disorders including paroxysmal kinesigenic dyskinesia, familial paroxysmal choreoathetosis, and periodic dystonia (26). These disorders occur predominantly in children and young adults, and almost never begin during the commonest stroke-prone decades. Some of the disorders are inherited as autosomal dominants but sporadic cases are described. In some families, attacks are precipitated by movement (so-called "kinesigenic" disorders). The repetitive nature of the attacks, precipitants, familial history, and the stereotyped nature of the movements usually allows recognition.

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18 Hyperventilation Syndrome

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Hyperventilation syndrome is frequently unrecognized by both patients and physicians (including neurologists) and can be a clinical imitator of epilepsy (1). According to one consensus definition, "the hyperventilation syndrome is a syndrome characterized by a variety of somatic symptoms induced by physiologically inappropriate hyperventilation and usually reproduced in whole or in part by voluntary hyperventilation" (2). The symptoms and signs of hyperventilation syndrome are protean (Table 18.1). This chapter focuses on the neurologic aspects and reviews the epidemiology, historic aspects, diagnosis, neurologic presentation, case studies, pathophysiology, differential diagnosis, and treatment of hyperventilation syndrome.

EPIDEMIOLOGY

Hyperventilation syndrome occurs in about 6% to 11% of the general patient population (3). Acute hyperventilation with obvious rapid breathing accounts for perhaps 1% of all cases of hyperventilation, whereas chronic hyperventilation accounts for the other 99% (4). In a clinic evaluating patients with dizziness, hyperventilation syndrome accounted for 24% of the cases (5). Most studies have reported hyperventilation syndrome occurring two to seven times more frequently in women than in men, with most patients ranging in age between 15 and 55 years (6). One large study reported that patients with acute hyperventilation syndrome ranged in age from 5 years to 85 years and was particularly prevalent in women in their late teens (7).

In studies of patients with neurologic symptoms of hyperventilation syndrome, the percentage of females ranges from 50% (8) to 67% (9–11) to 87% (12). In a follow-up study of children and adolescents, 40% were still hyperventilating as adults and many suffered from chronic anxiety (13). Although hyperventilation syndrome is common, general neurology textbooks provide minimal information.

HISTORICAL ASPECTS

Irritable Heart

In 1871, Da Costa published a paper, "On Irritable Heart; a Clinical Study of a Form of Functional Cardiac Disorder and its Consequences," describing 300 Union soldiers with a mysterious illness during the American Civil War (14). He felt the condition could be seen in private practice as well. Symptoms included palpitations, chest pain, shortness of breath or oppression on exertion, indigestion, abdominal distension, and diarrhea. Headache, giddiness, disturbed sleep, and dizziness were

TABLE 18.1
Symptoms and Signs of the Hyperventilation Syndrome

General
Fatiguability, exhaustion, weakness, sleep disturbance, nausea, sweating
Cardiovascular
Chest pain, palpitations, tachycardia, Raynaud's phenomenon
Gastrointestinal
Aerophagia, dry mouth, pressure in throat, dysphagia, globus hystericus, epigastric fullness or pain, belching, flatulence
Neurologic
Headache, pressure in the head, fullness in the head, head warmth
Blurred vision, tunnel vision, momentary flashing lights, diplopia
Dizziness, faintness, vertigo, giddiness, unsteadiness
Tinnitus
Numbness, tingling, coldness of face, extremities, trunk
Muscle spasms, muscle stiffness, carpopedal spasm, generalized tetany, tremor
Ataxia, weakness
Syncope and seizures
Psychologic
Impairment of concentration and memory
Feelings of unreality, disorientation, confused or dream like feeling, déjà vu
Hallucinations
Anxiety, apprehension, nervousness, tension, fits of crying, agoraphobia, neuroses, phobia, panic
Respiratory
Shortness of breath, suffocating feeling, smothering spell, unable to get a good breath or breathe deeply enough, frequent sighing, yawning

"…all indicative of disturbed circulation in the cerebrospinal centres (page 25)." He discussed the differential diagnosis including ways of detecting malingerers. He also excluded frequent seminal emissions and masturbation as the cause. The only explanation Da Costa offered was "…that the heart has become irritable, from its over-action and frequent excitement…(p 40)." During World War I, similar symptoms, often associated with fatigue, were described as "soldier's heart" (15) or "neurocirculatory asthenia" (16).

The Borderland of Epilepsy

Sir William Gowers' 1907 book, *The Border-land of Epilepsy. Faints, Vagal Attacks, Vertigo, Migraine, Sleep Symptoms, and Their Treatment* (17), is the pioneering antecedent of this book. Under the descriptive terms of "vagal and vaso-vagal," he described attacks that occurred more frequently in women than in men and were readily influenced by emotion, but not hysterical. The presentation in various cases included epigastric fullness; fullness in the head; difficulty in breathing; yawning; chest pain; palpitations; a sense of impending death; a slowness of mental operations, a difficulty in thinking or in concentrating attention; a sense of unreality; fatigue; coldness, numbness, and tingling of the extremities; tetanoid spasm of the extremities; blurred vision; and occasionally brief syncope.

Forced Ventilation and Tetany

In 1922, Goldman was the first to make the connection between "forced ventilation" and tetany (18). Symptoms preceding tetany in the eleven cases reported included dizziness; numbness and tingling of the hands, feet, and face; shortness of breath; and attacks of nervousness and crying. He observed that two of the cases, "…both hysterical subjects, undoubtedly must represent a fairly large class. Abnormalities of respiration are a well know symptom of hysteria. (p 1195)" Goldman reasoned that the tetany was due to alkalosis.

The Term "Hyperventilation Syndrome"

Kerr, Dalton, and Gliebe first used the term "hyperventilation syndrome" (19,20) in 1937. They described the variety of symptom complexes caused by a physical phenomena, associated with anxiety states, which could often be reproduced in the examining room with the "hyperventilation test." They also reported factors responsible for the anxiety state and how the medical profession dealt with these patients:

> "During the past several years the world, in general, has been undergoing critical social, moral, and economic changes; and, in the present state of upheaval, an ever-increasing number of patients are observed who present a symptom-complex which is intimately associated with the individual's struggle for security, for independence, or for whatever state is presumed to assure the spiritual and material happiness of the individual. This symptom-complex is essentially a representation of the interaction between emotional and physiological factors. … Patients presenting the well-know pattern of symptoms haunt the offices of physicians and specialists in every field of medical practice. They are often shunted from one physician to another, and the sins of commis-

sion inflicted upon them fill many black pages in our book of achievement. (p 961)" (16).

Common and Uncommon Presentations

In 1953, Lewis argued that acute and chronic hyperventilation syndrome occurred relatively frequently and presented the common and atypical presentations, pathophysiology, and therapy that could be published today with minimal updating (21). He reported that paresthesias were occasionally asymmetrical and could even be unilateral. Tavel, in 1964, described patients with hyperventilation syndrome presenting with unilateral paresthesias at times associated with subjective unilateral weakness involving the left side of the face and body more commonly than the right (22). He believed that the paresthesias originated peripherally in the nervous system.

DIAGNOSIS

The acute form of hyperventilation syndrome is easily recognized even by the general public. However, the chronic form is less easily recognized even by physicians because the breathing rate is not reported as or does not appear rapid and because the symptoms may appear atypical. For example, a respiration rate of 18 combined with an increased tidal volume of 750 ml/minute may lead to overbreathing but not be grossly visible. Since the chronic disorder is intermittent, spot arterial pCO_2 or end tidal volume pCO_2 results can be normal.

The diagnosis depends on reproducing some or all of the symptoms using the hyperventilation test and excluding other possible causes by either clinical reasoning or laboratory testing when indicated. Not infrequently, patients will report only one or two symptoms, but on performing the hyperventilation test, will then report other symptoms during their typical episodes that they did not remember to mention. The hyperventilation test can be performed with either an increased ventilation rate of up to 60/minute or simply deep breathing for 3 minutes (23). Based on a study of healthy subjects, a minimum duration of 3 minutes and end-tidal pCO_2 decreasing to at least 1.9 kPa or dropping well over 50% of baseline should elicit symptoms in most people (24). Dizziness, unsteadiness, and blurred vision commonly develop within 20 to 30 seconds, especially with the patient in the standing position; paresthesias start later (23). Chest pain is reported by 50% of patients after 3 minutes of hyperventilation and by all by 20 minutes (25). For clinical purposes, a measurement of end tidal volume pCO_2 is not necessary. In addition, no clear correlation exists between PCO_2 and neurologic signs (26). The hyperventilation test should not be performed in patients with ischemic heart disease, cerebrovascular disease, pulmonary insufficiency, hyperviscosity states, significant anemia, sickle cell disease, and uncontrolled hypertension (27,28).

For some patients with hyperventilation syndrome, symptoms cannot be reliably reproduced during the hyperventilation test or even on consecutive tests. In some cases, the hyperventilation provocation test lacks test-retest reliability (29). For others, antecedent anxiety and stress, not present during the test, may predispose to symptom formation perhaps due to a hyperadrenergic state (6,30). Different patterns of hyperventilation with different respiratory rates, tidal volumes, and durations may induce different symptoms (31). Finally, as a response to a change in body position from supine to standing, patients with hyperventilation syndrome have an accentuated increase in ventilation that can be calculated with noninvasive measurements of pulmonary gas exchange, and which distinguishes them from healthy subjects (32).

There have been challenges to the concept of hyperventilation syndrome and the validity of the provocation test. In a double-blind placebo-controlled study, Hornsveld and colleagues found the hyperventilation provocation test to be invalid (33). Since hyperventilation seemed a negligible factor in the experience of spontaneous symptoms, they even recommended avoiding the term "hyperventilation syndrome." However, the study may be flawed because of the method of patient selection. Patients were referred because of a suspicion of hyperventilation syndrome and not based on reproduction of symptoms on a hyperventilation provocation test. Moreover, the presenting symptoms of subjects were not provided. Since the symptoms of hyperventilation syndrome can indeed be vague and nonspecific, and since symptoms sometimes may occur only with certain types of anxiety or stress, their conclusion may not apply to different population subsets (34). The subjects' symptoms may have been due to chest wall pain or panic attacks.

From my experience with patients with predominantly neurologic complaints, the concept of hyperventilation syndrome is valuable and the hyperventilation provocation test, despite its recognized shortcomings (35), is useful. In the individual case, if the hyperventilation provocation test fails to reproduce the symptoms but clinical suspicion persists, treatment such as breath holding, slow breathing, or breathing into a paper bag can certainly be suggested on a trial basis.

NEUROLOGIC MANIFESTATIONS

The potential neurologic manifestations of hyperventilation are listed in Table 17.1. Patients referred to different

TABLE 18.2
Complaints of Patients with Hyperventilation Syndrome Referred to Outpatient Neurology Clinics

Study	Pincus, 1978[12]	Perkin and Joseph, 1986[9]
n	30	78
NEUROLOGIC (%)		
Giddiness (lightheaded or dizzy)	80	59
Paresthesias	50	36
Loss of consciousness	6	31
Visual disturbance	NR	28
Headache	37	22
Weakness	27	NR
Inability to concentrate	23	NR
Ataxia	NR	18
Tremulousness	NR	10
Tetany	3	NR
Tinnitus	NR	3
OTHER SYMPTOMS	%	%
Dyspnea	23	53
Palpitations	20	42
Chest pain	17	8
Abdominal pain	10	1
Inability to swallow	23	NR
Nausea	NR	19
Vomiting	NR	1

NR = not reported

specialists may have different symptoms of hyperventilation. For example, patients seen by cardiologists may complain primarily of chest pain, palpitations, and shortness of breath.

Symptoms of Patients Referred to Neurologists

Two studies have reported the complaints of patients referred to neurologists and diagnosed with hyperventilation syndrome (Table 18.2). In the study of Pincus, the chief complaints were usually multiple: 86% of the patients had complaints referable to at least two organ systems and 30% referable to three or more organ systems (9). Seventy-seven per cent of the patients with hyperventilation syndrome were considered to have psychosomatic illness, compared with 28% of controls.

Perkin and Joseph provide detailed descriptions of the symptoms (6). Most patients had more than one symptom. Of the 36% with paresthesias, the following percentages of this group reported paresthesias with the following distributions: 89%, upper limbs; 36%, lower limbs; 29%, face; and 18%, trunk. Patients often reported paresthesias with more than one distribution. In 10% of these patients, the paresthesias were unilateral and only involved the left side of the face or upper limb. In patients with loss of consciousness, the duration reported was brief and convulsive movements were not reported. Of the 28% with visual disturbance, the symptoms included blurring of vision, loss of vision, photophobia, and flashing lights.

Paresthesias

Hyperventilation syndrome is the most common cause of distal symmetric paresthesias (36). Physicians generally recognize bilateral paresthesias of the face, upper, or lower extremities as being caused by hyperventilation. However, most neurologists are not aware that hyperventilation can cause unilateral paresthesias even though this was first described 50 years ago.

Three other reports indicate that unilateral paresthesias occur more often on the left side, similar to the one of Perkin and Joseph cited in the previous paragraph. In 1964, Tavel called attention to this presentation with a report on seven patients who all reported left-sided numbness, tingling, or weakness sometimes occurring in isolation without associated dizziness or dyspnea (19). Tavel then described a group of ninety volunteers who were asked to hyperventilate until somatic symptoms developed, usually after 3 to 5 minutes. Predominantly unilateral symptoms occurred in 16%. Of the 16%, the left side was involved in 64%.

Blau, Wiles, and Solomon described twelve patients with episodes of unilateral paresthesias, with the left side involved in eight (5). Five of the patients described various feelings of weakness, clumsiness, or heaviness of an upper or lower extremity or both.

Three of the patients reported the paresthesias occurring in isolation, without other complaints. The symptoms were reproduced by hyperventilation after 3 to 5 minutes. After instruction in breathing exercises, all patients had improved and no other neurologic disturbance had developed after a mean follow-up of greater than 19 months.

O'Sullivan and co-workers described nine patients with episodic unilateral somatosensory symptoms reproduced by the hyperventilation test (8). The left side was involved in seven of the cases. All the patients reported a reproduction of the symptoms with the hyperventilation test performed with measurement of end-tidal pCO_2. Six of the patients had precipitating stressful life events.

I performed a study of symptom production in 145 senior medical students who were asked to hyperventilate for 2 to 3 minutes during a class (1). Table 18.3

TABLE 18.3
The Distribution of Paresthesias Reported by 145 Medical Students after Hyperventilation

	N (%)
Bilateral	122 (84.1%)
Both hands	49
Both hands and feet	13
Perioral	19
Hands, feet, and perioral	2
Feet	6
Hands and perioral	7
Hands and face	12
Hands, feet, and face	3
Arms	2
Face	2
Forehead	2
Shoulders and arms	2
Shoulders	1
Wrists and feet	1
Hands and tunnel vision	1
Unilateral	22 (15.9%)
Right hand	4
Right hand and perioral	1
Both hands, right toes	1
Right abdomen	1
Right forehead	1
Left hand	10
Left hand and diplopia	2
Left foot	3
Of the bilateral, one side more prominent	
Right > left hand	4
Left > right hand	1
Right > left feet	1

From Evans RW. Neurological aspects of hyperventilation syndrome. *Semin Neurology* 1995;15:118. (With permission.)

details the distribution of paresthesias. Similar to the volunteers of Tavel, 16% reported unilateral paresthesias, with the left side involved in 68%. An additional 4% described bilateral symptoms, but more prominent on one side. Unusual distributions included the right side of the forehead, the shoulders, and the right side of the abdomen. When the paresthesias involved either one or both hands, often the fourth and fifth fingers only were involved. Interestingly, this is a similar distribution to paresthesias in the fourth and fifth fingers reported by some patients with migraine aura (37). Blurred vision was commonly reported, with tunnel vision and diplopia also described.

PSYCHOLOGIC SYMPTOMS

As listed in Table 17.1, patients may report a variety of psychologic complaints. Complaints of anxiety, nervousness, unreality, disorientation, or feeling "spacey" are common. Impairment of concentration and memory may be reported as part of episodes or alternatively as symptoms of an underlying anxiety neurosis or depression. A patient's concern about the cause of the various symptoms of hyperventilation may result in feelings of impending death, fear, or panic, which may accentuate the hyperventilation. Patients with hyperventilation syndrome have a mean group profile very similar to patients with pseudoseizures: a neurotic pattern in which patients respond to psychologic stress with somatic symptoms (7). Other complaints such as déjà vu or hallucinations are rare. A case of déjà vu will be described in the next section. Two cases of auditory and visual hallucinations triggered by acute hyperventilation have been reported (38).

CASE REPORTS

The following case reports from my office practice may help to illustrate some of the common and uncommon neurologic presentations of the hyperventilation syndrome to the neurologist.

Case Study #2. Lightheadness, near syncope. This 38-year-old male presented with near syncopal episodes. He had a 10-week history of almost daily episodes lasting about a minute, during which he would have a feeling of lightheadedness usually while sitting at work. He reported no associated rapid breathing, chest pain, palpitations, dyspnea, or paresthesias. Fifteen years previously, he had a brief fainting spell in a crowded room. There was no history of other syncopal events or seizures. There was no history of psychiatric illness. Prior to neurologic referral, he saw an internist and ENT physician. An evaluation including blood work and an electrocardiogram were normal. General physical and neurologic examinations were normal. The patient was asked to hyperventilate and this exactly reproduced his symptoms.

I reassured him that he had a benign cause of his dizziness and briefly explained the pathophysiology. I suggested that if he had additional spells he should try brief breath holding or breathing into a paper bag. The patient was seen again 2 years later. He told me that when he developed the symptoms, there were layoffs at

work and he was concerned about losing his job. He states that he was actually relieved when, shortly after the consultation, he lost his job. The episodes disappeared. Since then, he has occasional brief episodes of dizziness usually occurring during meetings or with pressure, and they are easily controlled with breath holding.

Comment. This is a common scenario in which an acute stressor, in this case fear of losing his job, precipitates multiple episodes of hyperventilation. Unfortunately, when he saw an internist and ENT physician, the possible diagnosis of hyperventilation syndrome was not considered, and the hyperventilation test was not performed. Hyperventilation syndrome is truly a diagnosis begging for recognition (39). I have seen many other similar cases where the patient has an extensive workup including a Holter monitor, echocardiogram, electronystagmogram, and magnetic resonance imaging (MRI) study of the brain—including internal auditory canal views—without hyperventilation being considered. In my experience, the frequency of episodes will greatly decrease or the spells will stop with the simple treatment outlined.

Case Study #2. Fading away spells in an elderly woman. This 71-year-old woman was seen on referral by her internist with a 1-year or more history of similar spells occurring one to two times per month and lasting less than 1 minute. While sitting, she suddenly has a feeling of fainting or fading away, along with shortness of breath but no other symptoms. No testing had been performed to evaluate this complaint. For many years she had a feeling of smothering in crowds. There was a history of migraine headaches within the last 15 years, polymyalgia rheumatica for over a year improved with treatment, and hypertension. No history of diabetes, ischemic heart disease, or cerebrovascular disease. General physical and neurologic examinations were normal. The hyperventilation test exactly reproduced her symptoms. After being reassured, the pathophysiology was explained and brief breath holding or breathing into a paper bag was suggested as a treatment if she had additional spells.

When contacted $1^1/_2$ years later, she reported one to two mild spells shortly after the initial office visit, aborted with breathing into a paper bag, but no subsequent episodes.

Comment. When older patients have episodes of feeling faint, woozy, dizzy, presyncopal, vertiginous, physicians are appropriately concerned about the possibility of cardiac dysrhythmias, postural hypotension, vestibular dysfunction, or vertebrobasilar insufficiency as the cause. The multiple symptoms of hyperventilation syndrome can mimic angina and transient ischemic attacks. However, hyperventilation syndrome can occur in even the elderly and should be part of the differential diagnosis.

Case Study #3. Episodes of confusion and déjà vu. This 28-year-old male was seen with a 5-year history of stereotypical spells lasting about 45 seconds and occurring about once every 2 to 3 days for the prior 3 months. The patient complained of a strange feeling, a feeling of confusion and déjà vu sometimes associated with coldness and numbness of the left side of the body. During the episodes, he was able to talk and cary out whatever activity he was doing. After the episodes, he felt fine without confusion or headache. One month previously, he had a bad spell in which he developed the prodrome and then had brief loss of consciousness during which he was akinetic but had no tongue biting, incontinence, or postictal confusion. There was no history of head trauma or meningoencephalitis. Family history was negative for seizures. General and neurologic examinations were normal.

A MRI study of the brain was normal. An electroencephalogram (EEG) revealed rare generalized phantom sharp and slow wave activity but no focal or epileptiform abnormalities. A repeat study was also normal. The hyperventilation portion of both studies produced only minimal generalized slowing, during which time the patient reported feeling dizzy and confused.

An initial diagnosis of partial seizures was made, and he was started on carbamazepine. On follow-up 1 month later, he reported stereotypical episodes about every 4 days, despite a therapeutic carbamazepine level. The hyperventilation test produced a feeling of dizziness and confusion but not déjà vu or the cold feeling on the left side. A 4-hour EEG monitoring study showed no epileptiform activity. A repeat hyperventilation provocation test resulted in complaints of only dizziness and tinnitus.

The patient was advised that his spells might be due to hyperventilation syndrome even though the hyperventilation test did not exactly reproduce the symptoms. I suggested trying brief breath holding or breathing into a paper bag if additional episodes occurred. If the episodes were thus controlled or decreased in frequency, he was to taper off the carba-

mazepine. When called 21 months later, he told me that he had only one additional spell, a month after the last office visit, aborted by breath holding. No further episodes occurred. He had tapered off carbamazepine 20 months previously.

Comment. This case illustrates the borderland between hyperventilation syndrome and partial seizures in which the complaints can overlap: déjà vu, a strange feeling, a feeling of confusion, left-sided paresthesias, and syncope. The association of strange feelings and syncope makes the differentiation of hyperventilation syndrome from epilepsy quite difficult (40).

Patients may complain of a variety of unusual psychologic feelings associated with hyperventilation, some of which are listed in Table 18.1. As another example, another patient presented with a 7-year history of recurring brief episodes of feeling "out of control," associated with tingling over the face and arms and reproduced with hyperventilation. With a history of three generalized tonic-clonic seizures 10 years ago, another neurologist had previously diagnosed these spells as being due to partial seizures. Even patients with documented seizure disorders can have "funny spells" from hyperventilation.

The distinction from seizures can be additionally blurred since hyperventilation is an activation procedure for absence and partial seizures (25). Reproducing the symptoms with the hyperventilation test without EEG recording is not diagnostic. Altematively, as in this case, the patient can have the hyperventilation syndrome even when the symptoms are not reproduced. This case is also an example of the production of different symptoms with the hyperventilation test performed at different times.

The EEG may not necessarily make the definitive diagnosis. On an initial study, only about 50% of patients with known epilepsy show epileptiform abnormalities (41). A scalp EEG can be normal during a partial seizure (42). More commonly, an artifact or nonepileptiform variant may be misread as epileptiform, and the hyperventilator can be misdiagnosed as having a seizure disorder (43). The presence of true epileptiform abnormalities alone does not make a diagnosis of epilepsy, since epileptiform abnormalities can be present in persons who never develop a seizure disorder.

Case Study #4. Unilateral paresthesias with dizziness, chest tightness, and dyspnea. This 47-year-old woman was seen with a few week history of daily episodes of lightheadness, nervousness, and a weak feeling with numbness of the left arm, left leg, and perioral area associated with chest tightness and trouble getting a good breath. These episodes lasted minutes at a time. She denied any recent stressors or depression. She saw her internist and had some blood tests and a treadmill test performed, with normal findings. Past medical history was unremarkable. General physical and neurologic examinations were normal. The hyperventilation test resulted in numbing and tingling periorally and in the left upper and lower extremity associated with chest tightness. After a discussion of the suspected hyperventilation syndrome, she was unconvinced by my explanation and protested that she did not breathe rapidly during episodes. The patient wanted to have an MRI study to rule out other causes. The study, which included an angiographic sequence of the carotid bifurcations and circle of Willis, was entirely normal. On telephone follow-up a few months later, she reported no additional episodes.

Comment. The differential diagnosis of this presentation includes angina, structural cerebral pathology such as arteriovenous malformation or neoplasm, partial seizures, and multiple sclerosis. Testing may be appropriate depending on the clinical context. In many cases, if the symptoms can be exactly reproduced with the hyperventilation test, and the neurologic history and examination are otherwise normal, treatment can be tried without obtaining tests while the patient is being observed. In other cases, such as this, the patient may not be convinced by an explanation and desires to have testing done. The precipitant of the hyperventilation syndrome in this case was not certain. The patient had no psychiatric history, did not appear particularly anxious or histrionic, and denied any acute psychologic stressors or depression. For many patients, hyperventilation syndrome may be a "bad habit" of exaggerated thoracic breathing, with episodes triggered by any physical or emotional disturbance that induces increased ventilation thus producing symptoms causing anxiety about the symptoms and sympathetic arousal resulting in increasing ventilation and increased symptoms. (23).

Case Study #5. Unilateral paresthesias in a patient with bipolar disease. This 34-year-old woman presented in 1990 with a 1-month history of stereotypic episodes occurring multiple times daily, each lasting 2 minutes or less. She described a sensation of lightheadedness associated with numbness of the left upper lip, left side of the head, and a feeling that the left arm was asleep. Her speech could be slightly slurred. Her mother, who had observed the patient during some of the spells, stated that there was no associated staring or alteration of consciousness.

There was a history of bipolar disease with multiple psychiatric admissions. During the month before presentation, she reported increased depression. She was taking lithium, fluoxetine, thiothixene, and benztropine. There was also a history of tension-type headaches and perimenstrual migraine without aura. General physical and neurologic examinations were normal. After 2 minutes of hyperventilation, the patient reported lightheadedness, tingling over the left side of the face, a hot feeling of the left arm, and slurred speech, thus reproducing her episodes. I was not certain the speech was slurred.

A magnetic resonance imaging study of the brain with angiographic sequences was normal, including the circle of Willis. She then underwent a cerebral blood flow study. Prior to hyperventilation, an ECG and EEG were normal. The end tidal volume pCO_2 during the resting state was 23 mmHg, which is low. A cerebral blood flow study was then performed by inhalation of xenon-133 in a room-air mix, for 1 minute. Cerebral blood flow values were symmetric and in the low normal range for her age. The patient was then asked to hyperventilate for 1 minute, resulting in a reduction of the end tidal volume pCO_2 to 19 mmHg. During hyperventilation, gray matter flow values decreased maximally in the right parietal region, lower than in the left hemisphere.

The patient was advised to try brief breath-holding or breathing into a paper bag to stop the spells. One month later, she was having zero to four spells per week, aborted by brief breath-holding. Five months later, she reported that her last spell had occurred about 5 months previously.

Comment. The psychiatric differential diagnosis of "funny spells" includes agoraphobia, panic attacks, depression, somatization, generalized anxiety, posttraumatic stress, and psychotic disorders. The symptoms of panic attacks greatly overlap with hyperventilation syndrome, and the differential diagnosis is quite similar (44). The pathophysiology of panic attacks is controversial; (45) hyperventilation syndrome has been suggested as one cause (46–49). Panic disorder patients may have an increased sensitivity to the vasoconstrictive effects on basilar artery blood flow caused by hyperventilation-induced hypocapnia (50), and patients may also have hypersensitive CO_2 chemoceptors (51). Patients diagnosed with panic attacks who report brief episodic unilateral paresthesias or weakness may have their neurologic symptoms reproduced with the hyperventilation test (52). The cerebral blood flow study results in this case are discussed in the next section.

PATHOPHYSIOLOGY

Acute hyperventilation produces a reduction in arterial pCO_2, resulting in alkalosis. Respiratory alkalosis produces the Bohr effect, a "left shift" of the oxygen dissociation curve with increased binding of oxygen to hemoglobin and reduced oxygen delivery to the tissues. The alkalosis also causes a reduction in plasma Ca^{+2} concentration. Hypophosphatemia may occur, perhaps due to intracellular shifts of phosphorus caused by altered glucose metabolism (53). In chronic hyperventilation, bicarbonate and potassium levels may be decreased due to increased renal excretion (54). Finally, stress can trigger a hyperadrenergic state, which may trigger hyperventilation due to beta-adrenergic stimulation (27).

Diminished Cerebral Blood Flow

Central and peripheral mechanisms have been postulated for the production of neurologic symptoms during hyperventilation (55). Voluntary hyperventilation can reduce cerebral blood flow by 30% to 40% (56,57). Symptoms and signs such as headache, visual disturbance, dizziness, tinnitus, ataxia, syncope, and various psychologic symptoms may be produced by diminished cerebral perfusion.

Electroencephalographic Slowing

The precise cause of generalized slowing on EEG studies during hyperventilation is not certain. The slowing is most common and pronounced in children and teenagers, diminishes in young adults, and is rare in old persons (58). A brainstem-mediated response to hypocarbia has been proposed (59). EEG slowing very quickly disappears with the cessation of hyperventilation, even when both the cerebral oxygenation and end-tidal concentration of carbon dioxide are still at low levels (60). The response may be due to metabolic rather than purely hemodynamic factors (61). Hypoglycemia can accentuate the generalized slowing or buildup.

Other Mechanisms

Other mechanisms have been postulated to explain the manifestations of hyperventilation. Muscle spasms and tetany may be due to respiratory alkalosis and hypocalcemia in muscles. A recent study finding no relationship between the rate of fall of pCO_2 and the onset of dizzi-

ness and paresthesias suggests that symptoms may be due to hypophosphatemia (62). Hypophosphatemia can result in symptoms such as tiredness, dizziness, poor concentration, disorientation, and paresthesias. A hyperadrenergic state may result in tremor, tachycardia, anxiety, and sweating. Hypokalemia can cause muscle weakness and lethargy.

The Production of Paresthesias

The cause of bilateral and unilateral paresthesias is not certain; evidence exists for both a central and peripheral mechanism. A reduction in the concentration of extracellular Ca^{+2} may increase peripheral nerve axonal excitability, thus resulting in the spontaneous bursting activity of cutaneous axons that may be perceived as paresthesias (63). Lateralization of symptoms might be explained by anatomic differences in the peripheral nerves and their nutrient vessels (5).

Alternatively, symmetrically decreased cerebral perfusion could account for bilateral paresthesias and asymmetrically reduced perfusion for unilateral paresthesias. O'Sullivan and colleagues reported nonspecific asymmetric slowing on EEG studies in the hemisphere opposite to the side of unilateral paresthesias in hyperventilators and normal bilateral somatosensory evoked potentials (8). Although anatomic differences in the cerebral vasculature might explain the unilateral paresthesias, the normal magnetic resonance angiographic (MRA) findings reported in case studies 4 and 5 argue against this. Additionally, case 5 (1) is the first report ever revealing asymmetrically decreased cerebral blood flow: decreased right parietal area flow with left sided symptoms.

Finally, why do unilateral paresthesias occur more often on the left side of the face and body? The question is intriguing, but the answer is not known. One hypothesis is that psychosomatic symptoms are associated with right hemisphere psychic processes. During stress and emotional arousal, the right hemisphere is activated more than the left (64). Symptoms of conversion or hyperventilation are more likely to occur on the left side of the face and body (8,65). However, this type of explanation does not explain the increased frequency of left-sided paresthesias in normal subjects who are asked to hyperventilate, such as the medical students in Table 18.3.

DIFFERENTIAL DIAGNOSIS

Organic and Physiologic Causes

Hyperventilation syndrome has organic, physiologic, emotional, and habitual causes. Less than 5% of hyperventilators have a solely organic cause, 60% have a psychogenic (emotional and habitual) basis, and the remainder have varying combinations (66). A variety of organic disorders can result in hyperventilation, including salicylism, caffeinism, and other drug effects; cirrhosis and hepatic coma; acute pain such as with a myocardial infarction; splenic flexure syndrome; cholecystitis; fever and sepsis; dissecting aortic aneurysm; respiratory dyskinesia; pulmonary embolism; pneumothorax; interstitial lung disease; asthma; and heat and altitude acclimatization (24).

Neurologic Causes

Neurologic disorders that may cause hyperventilation include Rett's syndrome, Joubert's syndrome, Reye's syndrome, pyruvate dehydrogenase deficiency, biotin-dependent multiple carboxylase deficiency, malignant hyperthermia, brainstem tumor, primary cerebral lymphoma, encephalitis, brainstem strokes, thalamic hemorrhage, syringobulbia, and neurogenic pulmonary edema due to intracranial hypertension (45). Severe hyperventilation can occur in the absence of psychiatric, respiratory, neurologic, or other organic abnormalities (67). However, asthma and pulmonary embolus should be excluded.

Misdiagnoses

In patients diagnosed with hyperventilation syndrome by neurologists, the misdiagnoses of referring physicians have included epilepsy, migraine, multiple sclerosis, arteriovenous malformation, cerebrovascular disease, vertebrobasilar insufficiency, brachial neuritis, angina, malingering, vasovagal attacks, functional, hypoglycemia, and cerebral tumor (5,6). The distinction between angina and hyperventilation syndrome can be difficult because hyperventilation can produce electrocardiogram changes including T-wave inversions, ST-segment depression, and ST-segment elevation in patients without coronary artery disease (68). Some patients with angina may hyperventilate in response to their pain and anxiety.

Panic attacks and disorder, endocrine disorders, cardiovascular disorders such as mitral valve prolapse, unusual seizure types and auras, pseudoseizures, migraine auras, and parasomnias are part of the differential diagnoses of hyperventilation syndrome.

Diagnostic confusion can occur because the symptoms of disorders such as panic attacks and mitral valve prolapse could be due to hyperventilation (69). Hyperventilation might also contribute to some of the manifestations of migraine, such as syncope.

TABLE 18.4
An Explanation of Hyperventilation: A Patient Handout*

Hyperventilation (overbreathing) is the commonest cause of dizziness. It can be overcome by recognizing the cause, and obeying a few simple rules

What are the symptoms?

A person may have one or any number of the following symptoms:
- Light-headedness, dizziness, faintness, "giddiness"
- Tightness or pain in the chest
- Shortness of breath or difficulty getting a good breath
- Dry mouth
- Heart beating faster
- Blurring of vision
- Sweating
- Trembling of hands and legs
- Weakness ("jelly legs")
- Pins and needles in hands, feet, and around mouth
- Headache
- Anxiety, fear, or panic
- Sensation of being unable to breathe
- Spasms of hands and feet
- A feeling of having a heart attack, passing out, losing control or of being about to die

When you overbreathe you may swallow air, causing:
- Distension of the stomach
- Burping
- Passing gas

What do you mean by overbreathing?
- Deep sighing breaths
- Yawning often
- Rapid, shallow breathing
- Deep breathing

There are two types of hyperventilation: acute, which affects 1% and chronic, which affects 99%
- Acute hyperventilation is obvious where someone is breathing way too fast.
- Chronic hyperventilation is not obvious: you can breathe a little too fast and a little too deeply and cause hyperventilation but neither you nor your doctor can tell just by looking at you during a spell.

When is this most likely to happen?
When you are tense, bored, or depressed in crowds, at a party, or out shopping.

(Table continues)

Tonic Spasms of Multiple Sclerosis

The tonic spasms (paroxysmal dystonia) of multiple sclerosis can be somewhat similar to the muscle spasms, tetany, and paresthesias of hyperventilation syndrome. The episodes consist of brief, recurrent, often painful abnormal posturing of one or more extremities without alteration of consciousness, loss of sphincter control, or clonic movements. This posturing lasts for 10 seconds to 3 minutes and recurs as often as thirty times daily. In some patients, brief sensory disturbances may be described in the involved extremity before or during the attack. The demyelinating lesion responsible for tonic spasm may be in the corticospinal tract at the level of the internal capsule or pons (70–72). Treatment with carbamazepine (59) or gabapentin (73) may be helpful. Since the episodes can be the initial presentation of multiple sclerosis (74) and can be triggered by hyperventilation (75), diagnostic confusion might result.

TREATMENT

A variety of treatments have been proposed, including patient reassurance and education; instructions to hold the breath, breathe more slowly, or breathe into a paper bag; breathing exercises and diaphragmatic retraining; biofeedback; hypnosis; psychologic and psychiatric treatment; and medications such as beta blockers, ben-

TABLE 18.4 *(continued)*

How does this cause symptoms?

Normally nature takes care of the rate and depth of breathing. The carbon dioxide in your blood makes you breathe enough to eliminate it and get sufficient oxygen. If you override nature and breathe too much you wash out too much carbon dioxide. This reduces the blood flow to your brain and makes you feel dizzy. It also reduces the available calcium in the blood, which can cause "pins and needles," numbness, tingling, and make the hands and feet spasm.

Adrenalin increases in the bloodstream causing a feeling of anxiety, sweating and trembling, and makes the heart beat faster.

Contraction of muscles causes pain and tightness in the chest and headache.

How can you stop it?

Look for the first signs of sighing or yawning.

Do not:

- Open the windows
- Run outside
- Take deep breaths

Instead:

- Sit down
- Hold your breath and count to 10
- Breathe out slowly and say "relax" to yourself then breathe in and out slowly every six seconds (10 breaths per minute)
- If you wish, you may instead breathe into a lunch bag placed over your nose and mouth for a minute
- As soon as possible, forget about your breathing and let nature do it for you

General principles

- Take it easy. It is not a disaster if you forget someone's name, burn the dinner, or don't have time to mow the lawn.
- Talk more slowly. Walk more slowly. You have plenty of time.
- Think positively. You can handle a problem as well as the next person. Everyone else has their problems, too.
- Spread out your workload through the day. Give yourself enough time for each task.
- Remain calm.
- Don't bottle up your feelings—discuss any worries or thing that make you angry or upset.
- Eat regular meals and don't hurry them.
- Limit caffeine in soft drinks, coffee, or tea.
- Learn to relax your muscles—no frowning or jaw-clenching.
- Exercise regularly.
- Take time out for social activities and holidays.

You can control your attacks completely by following these rules.

* From Lance (79). Modified and used with permission.

zodiazepines, and antidepressants (45). A study of nonpharmacologic treatments found efficacy for educational sessions, breathing techniques and retraining, and progressive relation with the greatest improvement occurring in the group given an explanation and eight sessions of breathing retraining (76). There is a lack of well controlled treatment trials of most of these approaches (77).

In my experience, the results in the case study section are typical: most patients respond to reassurance, education, and instructions to hold the breath, breathe more slowly, or breathe into a paper bag (78). Providing the patient with written materials, such as those used by Lance, may be worthwhile (Table 18.4; 79). If significant symptoms of stress, anxiety, or depression are present, appropriate medication use and psychologic or psychiatric referral may be helpful.

PROGNOSIS

In a follow-up study of children and adolescents, 40% were still hyperventilating as adults, and many suffered from chronic anxiety (80). One-half of patients with acute hyperventilation recover without treatment. Symptoms may persist for more than 3 years in 10% of those with chronic hyperventilation (81). With proper management, perhaps 70% to 90% of adults become symptom-free (82).

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19 Psychiatric Aspects of Nonepileptic Seizures: Psychogenic NES

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Although the true prevalence of nonepileptic seizures (NES) is yet unknown, it is estimated that this disorder occurs in approximately 20% of patients admitted to an epilepsy inpatient unit and in about 5% of patients seen as outpatients. This spectrum of disorders is common and easily confused with epileptic seizures. This chapter summarizes the current issues surrounding terminology, classification, diagnostic approach, and subsequent treatment of the psychogenic nonepileptic group of patients (1).

TERMINOLOGY

Terminology and classification of the group of disorders subsumed under the overall rubric of NES is really quite confusing and has been so for many years. Similarly, the epidemiology of NES has not been adequately studied, and at best, we only have crude estimates of the actual frequency of occurrence of this spectrum of disorders.

Although significant controversy continues by and large, the classification of NES has been established and agreed upon as summarized by Gates (1), NES compromise two distinct sets of disorders. One is due to the physiologic spectrum of dysfunction and is discussed elsewhere in this volume; the other is psychogenic and is discussed at length in this chapter. The descriptive terms used to explain nonepileptic events are not uniformly utilized. For example, many archaic terms continue to be used, including "hysterical pseudoseizure" and "pseudoseizure." "Hysterical seizure" is still used, although it is quite an anachronistic term, especially in the old psychiatric literature referring to conversion disorder, which is only one of many disorders associated with NES under the subcategory of psychogenic NES. Consequently, using the term "hysterical seizure" interchangeably with NES is inaccurate and is much like calling all complex seizures arise in the temporal lobe, knowing full well that complex partial seizures can have many sites of origin. In addition, the term *hysteria* is quite a pejorative term, often replete with negative overtones. Lay people often interpret hysteria as "out of control or beyond reason," thereby starting off the diagnostic clarification in a most uncomfortable position. Similarly, the term *pseudoseizure* is also replete with pejorative overtones, especially in American usage. In fact, many consider the term equivalent to the highly negative term *pseudointellectual.* Consequently, though the term was adopted from the comparatively neutral terminology of "pseudo-cyst," a very nonpejorative medical term, its lay connotation is so colored with overtones that it is rendered impractical for use in communication with patients who have this spectrum of disorders. Therefore, the term *nonepileptic seizure,* though

not an ideal term, is the least offensive term preferred by most American clinicians in the field (2).

In a survey performed by the American Epilepsy Society, NES also was the preferred term used by most clinicians (2). The international agreement in terminology has been more of an elusive issue. For example, the British authors Betts and Duffy (3) have suggested the term "nonepileptic attack disorder" to refer to psychogenic NES. This becomes quite problematic when consideration is given to the significant number of these patients who have experienced sexual assault at the hand of trusted family members or familiar friends of the family. Therefore, using the word "attack" would appear to be quite inadvisable. Figure 19.1 shows recommendations for classifications that are consistent with the current DSM IV classification scheme for nonepileptic seizures that are of psychogenic origin, consistent with the physiological sub-category (4). For psychogenic nonepileptic seizures, as has been discussed to some extent in other chapters in this volume, the specturm of nonepileptic seizures of psychogenic origin is broad. Anxiety disorders are a significant source of misdiagnosis and include panic disorder, with or without agoraphobia, post-traumatic stress disorder, and acute stress disorder (1).

Factitious disorders, which includes Munchausen's and Munchausen's-by-proxy can often be a source of significant confusion (5). The somatoform disorders, in which epilepsy is often just one of the symptoms, can also be quite confounding. The conversion disorders constitute the majority of nonepileptic psychogenic seizures in patients, most commonly due to some significant psychologic or sexual abuse. Dissociative disorders, especially dissociative fugue, depersonalization, and other dissociative disorders also constitute a significant spectrum, as can frank malingering for the purpose of clear secondary gain. It is very important to distinguish factitious disorders from malingering, as malingerers are often sorted out before referral to the epilepsy unit, whereas the factitious patients are not consciously mimicking their symptomatology. It is very difficult, but particularly important, to communicate this to the nursing staff during the diagnostic phase, so that a pejorative insensitivity is not communicated to the patient, thus potentially alienating the patient and precipitating a premature discharge. An addiction analogy has been presented for

FIGURE 19.1

General diagnostic categories that may be observed in patients with nonepileptic events. See the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (Washington, DC: American Psychiatric Association, 1994), for the meaning of numbers in parentheses.

comparison with NES. NES patients provide an interesting correlate for understanding coping mechanisms, difficulties in dealing with unbearable emotions, and a perspective on therapeutic intervention (6).

Here at Minnesota Epilepsy Group, a group that is somewhat unique has been dubbed with identification as "the reinforced behavior pattern." These are cognitively challenged individuals who have unconsciously learned that epilepsy behavior can result in significant control of their environment. By having a "seizure," considerable attention is paid to them and they gain an unconscious control of their environment. There is no specific DSM category for this disorder, so we designate it as a reinforced behavior pattern (1).

EPIDEMIOLOGY

The actual incidence of NES is actually higher than most people realize. As well, there is a significant coincidence of both epilepsy and NES. In most epilepsy centers that accept referrals for alleged intractable epilepsy (7), approximately 20% of patients end up with a diagnosis of NES, with approximately 30% of these patients having both epilepsy and nonepileptic events (1,8).

What is the economic impact of this disorder? No appropriate studies have been performed. When the costs are considered for emergency room visits, ambulance expenses, the direct costs of evaluations, blood tests, medications, inappropriate treatment, complications for patients of nonepileptic status being overly aggressively treated with respiratory suppressants, office visits, time missed at work for the patient and/or caregivers—the actual costs must be staggering. For those involved in the care of these patients, the cost is enormous as caregiver, family, and society (9).

DIAGNOSIS AND TREATMENT

Certainly, the most usual experience for a patient with psychogenic NES is to present to the epileptologist with a history of events essentially indistinguishable from their epileptic counterparts. Often they have had "seizures" for many years, have been seen by many physicians, and have been prescribed multiple medications. Nonetheless, one of the more common historical elements leading to the initial suspicion that NES may exist is multiple seizure types that are ill defined and poorly described by the patient, and having a paradoxical response to increasing antiepileptic drugs. That is to say, medications are increased in dose and number, but the "seizures" actually get worse. Obviously, some patients who have medically refractory epilepsy can have such a history. However, most medically refractory epilepsy patients have a well-defined seizure type or variant of a seizure type. Nonepileptic seizure patients have multiple seizure types that are ill-defined, coupled with multiple medication failures. This should be a potential red flag (10).

In addition, there is often *la belle indifference*—a paradoxical lack of concern about the seizures. This is to be contrasted with behavior during the ictal event itself, during which may be excessive emotional response. Again, these are historical features that may be of significance.

Repeated hospitalizations or frequent emergency room visits should be another potential warning sign that a patient's seizures may be psychogenic or nonepileptic in origin. Similarly, a history of remarkable lack of injury despite repeated falls should also trigger the suggestion of NES. Tongue biting, when it does occur in nonepileptic psychogenic epileptic patients, generally involves the tip of the tongue, whereas, in tonic-clonic seizures it is the side of the tongue that is often significantly lacerated. Incontinence can be seen with NES though it is rare, especially in cultures that are reverent of self-control, such as northern European, Japanese, or Taiwanese (10).

Associated psychiatric disorders are not uncommon in patients with psychogenic NES, particularly depression and occasionally psychosis. Personality disorders are quite common. This actually is of little distinguishing utility because many patients with epilepsy can have co-existent diagnoses of psychiatric disorders as well. Nonetheless, for the psychogenic patient, the treatment of the underlying psychiatric disorder can often facilitate the resolution of the psychogenic seizure (10).

Finally, the history of sexual abuse, especially in childhood, is very common, particularly for adult female patients with conversion disorder NES. In American culture, by and large, a 2:3:1 female to male ratio still exists for NES, with over half the patients having this history of conversion with a significant history of sexual abuse. The problem becomes somewhat difficult when the remarkable frequency of sexual abuse is reported in our society. Finkelhor et al. (11) state that approximately 26% of women and 16% of men in the general population, when questioned in a large national survey, reported a history of some form of sexual abuse.

Interestingly, in the pediatric population, the history of sexual abuse is not particularly common. Other stressors are contributors: family conflict, parental psychopathology, alcohol or chemical abuse or dependence, marital discord, school difficulties, peer relationship problems, and below average IQ are seen as the more common predictors in a disproportionate number of female patients with psychogenic NES. However, as presented by Bowman (12), in adults including twenty-five

men and thirty-five women, childhood sexual abuse contributed to psychogenic NES in half the patients and childhood in one-third.

Remote psychological and physical trauma apparently sets the stage for NES when the emotions they engender are not dealt with. Those emotions are "like old volcanos," as summarized by Bowman, "the simmering emotions lay partially dormant until painful life context and immediate percipients jolt them to life (12)." Personally, I have seen the latency of sexual abuse last as long as 60 years before declaring clinical significance.

In men, as again summarized by Bowman (12), there is a pattern of anger suppression followed by a series of adulthood frustrations. In 35% of the men who were reviewed (eight of twenty-three; only two of thirty-five women), suppressed anger was a commonality. This pattern was usually accompanied by a family history of the dysfunctional handling of anger, personal denial of feeling or expressing anger, or distorted beliefs about anger (12).

VIDEO-EEG MONITORING

The gold standard, as well as the goal, for the diagnosis of NES is to record multiple characteristic events on video-EEG (VEEG) and to document any apparent impairment of awareness in the absence of epileptiform EEG changes. As summarized by Rowan (10), there are cases of epileptic seizures, especially partial simple seizures, that do not generate sufficient EEG changes to confirm the diagnosis on a surface EEG. However, in my experience, the strategy of recording multiple events, looking for a stereotypic pattern consistent with the established semeiology of partial seizures (especially unusual frontal lobe seizures), has rarely failed to clarify which events are epileptic and which are not. However, when VEEG is used in the context of a multidisciplinary team approach to the patient, involving nursing, neuropsychology, psychology, and psychiatry as needed, a definitive diagnosis will transpire.

Some clinical signs are often suggestive when they are observed on VEEG, or when history is obtained of the events, such as gradual onset and gradual cessation. Nonepileptic seizures tend to have a slower, more gradual beginning, becoming increasingly vigorous as the seizure progresses, usually in a nonphysiologic pattern. For example, generalized motor activity may precede loss of consciousness or progressive involvement of body parts in a motor seizure and may not follow the classic jacksonian march that is consistent with the cortical homunculus. Nonetheless, unusual epileptic events, particularly those of frontal origin, can be quite bizarre in appearance. Again, the key is the remarkable stereotypic nature of multiple epileptic events that have been recorded (10).

In a classic paper from 1985 (13), out-of-phase motor activity, particularly out-of-phase arm and leg movements, high-amplitude forward pelvic thrusting, and lack of vocalization at the start of the event (as opposed to the transformation from the tonic to the clonic phase), was described as being suggestive features for distinguishing epileptic from nonepileptic seizures. As subsequent authors have demonstrated (14–16), a differentiation based on these features is not free from errors but can be highly effective in the clinical determination of epileptic and nonepileptic events. The ability of the examiner to modify the pattern of motor activity is also suggestive of NES. Such a modification is difficult, if not impossible, to achieve in events of epileptic origin.

Suggestions of provocation methods to induce NES and thereby expedite the diagnostic process have been a hot topic in recent years (17). Intravenous saline is the most commonly used technique. Schachter et al. (2) surveyed members of the American Epilepsy Society about their use of provocation techniques. Overall, 40% of the 426 respondents used provocation techniques, yet 23% of that group perceived ethical dilemmas in so doing (2). At the Minnesota Epilepsy Group, we do not employ provocation techniques. We consider them potentially misleading, unethical, and a hindrance to the therapeutic transition for our patients, especially those with conversion disorder, many of whom are young women whose faith in a trusted family or authority figure has been violated by sexual or physical abuse. It appears cognitively dissonant and counterproductive to begin a potential long-term therapeutic relationship of insight therapy or other treatment with an inherently deceptive practice. We endeavor to obtain a sufficient recording of events in a reasonable period of time without utilizing provocation techniques (9). Establishing trust in the therapeutic relationship is critical. While recording events, it is of particular value to the patient for the team to suspend judgmental behavior and be supportive as possible.

NEUROPSYCHOLOGICAL TESTING

Neuropsychological assessment of NES has been attempted by many investigators over the years. The findings from the literature summarized by Dodrill and Holm (18) show that, like people with epilepsy, people with NES often fall into the lower quartile of the normal intellectual range. Consequently, differences in IQ are not particularly useful in differentiating epileptic from nonepileptic patients. However, in the area of adjustment, the Minnesota Multiphasic Personality Inventory (MMPI) has been the most commonly used measure and, though the test is not perfect, it does have a correct clas-

sification rate of 70% or better with careful definition of subjects groups. In particular, it shows the classic conversion "V" pattern; that is, elevations in scale 1 (hypochondriasis) and scale 3 (hysteria), with a slightly elevated, or normal, depression scale 2. This obviously is not a foolproof diagnostic tool, but it is helpful (19).

Comprehensive neuropsychological test batteries fail to reveal a characteristic pattern for NES, although, as with the epilepsy population, evidence of a pattern on neuropsychological testing consistent with post brain injury is not uncommon. As suggested by Dodrill (18), application of gender-specific rules to MMPI profiles could be explored, as well as considering the combination of personality variables.

TREATMENT OF NONEPILEPTIC SEIZURES

The treatment of physiologic NES is obviously determined by the underlying condition. As far as psychogenic NES are concerned, despite our long lasting awareness of the existence of "hystero-epilepsy" (a term coined by Charcot in the second half of the 1880s), we have not had a clear NES treatment strategy that has been subject to appropriate prospective evaluation (20). Charcot used ovarian compression. Gowers prescribed iron tonic to correct the presumed underlying anemia and stated that "water when poured on the head of the patient is often effectual, especially if the mouth is opened, however, a second gallon is often more effectual as the first may result in redoubled violence of the seizure (16).

Nonetheless, based on over 20 years of experience, there is a general consensus among epileptologists that nonepileptic seizures of psychogenic origin are a treatable condition. A multidisciplinary team approach appears to be most effective.

Diagnostic clarification by appropriate VEEG recording, interviews with the psychologist and the social worker, and neuropsychological testing with continued dialogue between the team members, can often result in appropriate treatment strategies.

As emphasized by Bowman (12):

- Assessing for depression is critical. If major depression is present, treatment with antidepressants must be undertaken for at least 6 months. Psychotherapy of some form is often helpful, especially when it is targeted at incomplete bereavement, and depression is related to ongoing conflict or stress.
- The possible presence of some form of panic disorder should be assessed. If a panic disorder coexists with depression, initial low doses of selective serotonin reuptake inhibitors (SSRIs) can be helpful. Benzodiazepines should be used carefully, but can be beneficial as supplements to SSRIs. Cognitive therapy to reduce and prevent panic attacks is essential to prevent relapse when anti-panic medications are withdrawn.
- It is important to assess any history of trauma, both in adulthood and in childhood, which can result in directed psychotherapy for verbal processing of the trauma and cognitive restructuring to reduce the impact.
- The possibility of a dissociative disorder, including amnesia, fugue, depersonalization, derealization, and identity alterations, should be evaluated. Again, these are usually related to a history of psychologic trauma. In these patients, hypnosis may be helpful in assisting the person to assess the effect of the trauma.
- Other life events or conflicts that may be causing NES should be explored.
- An effort should be made to identify complicated bereavements, family or marital conflict, or unexpressed anger and frustration (especially in males). Appropriate cognitive therapy should be implemented to address these issues.

Finally, if the cause for NES is not clear, hypnosis may be helpful in teaching the patient how to control the expression of seizures, as summarized by Barry (22).

In the inpatient environment, a supportive, nonjudgmental attitude must be maintained. It is very easy for medical personnel trained to deal with life and death situations to be intentionally or unintentionally pejorative about NES expression. This is counterproductive and does not assist the patient in effecting an appropriate response. The Minnesota Epilepsy Group team approach includes an epileptologist, a clinical neuropsychologist, and a social worker, dedicated nursing staff, EEG technologists, and a consulting psychiatrist. This team performs a very thorough psychologic assessment and examines the relative strengths and weaknesses of the patient and the environmental support system. Treatment guidelines are based on this evaluation. A great deal of attention is paid to the presentation of the diagnosis of NES to the patient and the family, to facilitate and set the stage for continued psychotherapy. This facilitates the patient's understanding of the nature of her condition and of its psychologic causes, and sets the stage for a successful transition of treatment to the outpatient environment. As performed by the Minnesota Epilepsy Group in a 27-month follow-up of twenty-nine adult patients with highly intractable nonepileptic seizures, eleven patients were seizure free and twenty-three experienced at least a 75% decrease in seizure frequency and decreased severity (20). In other studies,

25% to 87% of patients appropriately diagnosed with NES ceased having events (23–30).

Patients tend to do better when they present with a shorter duration of NES especially less than 6 months. Vigorous application of VEEG diagnosis and a multidisciplinary approach should facilitate a better outcome than in previous years, when this technology was less available. Nonetheless, outcome studies are still quite limited. A few small case series suggest that children and adolescents have a better prognosis than adults. Clearly more work is needed to understand the efficacy of different therapeutic approaches and the best way of designing individual treatment plans.

CONCLUSION

The medical world has made significant progress in understanding and treating NES in the last 25 years, but many challenges are still to be faced and much work remains to be done. The economic impact of NES must be investigated, since it will likely justify a more aggressive and comprehensive program of research. We must agree on terminology and, as this chapter suggests, we are getting closer to that consensus. An integrated, multidisciplinary approach to diagnosis and treatment must be reinforced. Population-based epidemiologic studies are needed to direct research to study subgroups of NES for the prevention, treatment, and refinement of the diagnostic evaluation and prognosis. Controlled outcome studies must be standardized and conducted at multiple epilepsy referral centers. Finally, the practice of humility on the part of physician and treatment team is invaluable in treating patients diagnosed with NES.

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20 Coexisting Epilepsy and Nonepileptic Seizures

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Nonepileptic seizures (NES), or what are also called psychogenic, pseudo-, or hysterical seizures are a common problem. They account for approximately 20% of all intractable seizure disorders referred to comprehensive epilepsy centers and present with an annual incidence of about 4% that of true epileptic seizures (1–4). Patients with NES pose difficult diagnostic and therapeutic issues and often suffer from inappropriate, ineffective, and costly treatment, sometimes for many years (5,6). Chapter 19 of this volume deals with the general aspects of the diagnosis and management of NES. This chapter focuses on two especially difficult problems in patients with NES: i) coexisting NES and epileptic seizures and ii) true epileptic seizures misdiagnosed as NES seizures.

Epileptic and nonepileptic seizures are not mutually exclusive phenomena and may coexist in the same patient. How commonly NES and epileptic seizures coexist is not established, with reports varying from a high of more than 50% to a low of about 2% (1). Such widely different estimates of incidence differences relate in part to the populations studied and the criteria used to define coexisting epilepsy in patients with NES (1). Management of such patients with coexisting NES and epilepsy is particularly challenging.

Another challenge is posed by epileptic seizures with characteristics that lead to their misdiagnosis as NES. Although recent advances in video-EEG monitoring have greatly improved our ability to correctly distinguish NES from epilepsy, these monitoring techniques have their limitations (1,7), and it is now recognized that sometimes patients with true epilepsy are misdiagnosed as having NES. A demonstration of epileptiform EEG activity during a clinical seizure is considered to be the most reliable indicator of a true epileptic seizure, but some rare types of partial epileptic seizures, particularly frontal lobe seizures, may manifest with no or minimal EEG changes during clinical events that can also be very bizarre (1). Therefore, sometimes patients with unusual forms of true epilepsy, such frontal lobe epilepsy, can be misdiagnosed as having NES (1). The correct diagnosis and classification of patients with NES is essential for effective treatment.

HISTORY

Historically, what we now term nonepileptic or psychogenic seizures starts in antiquity with "hysteria." First described by the ancient Egyptians, hysteria was regarded as a disorder of women related to a dysfunc-

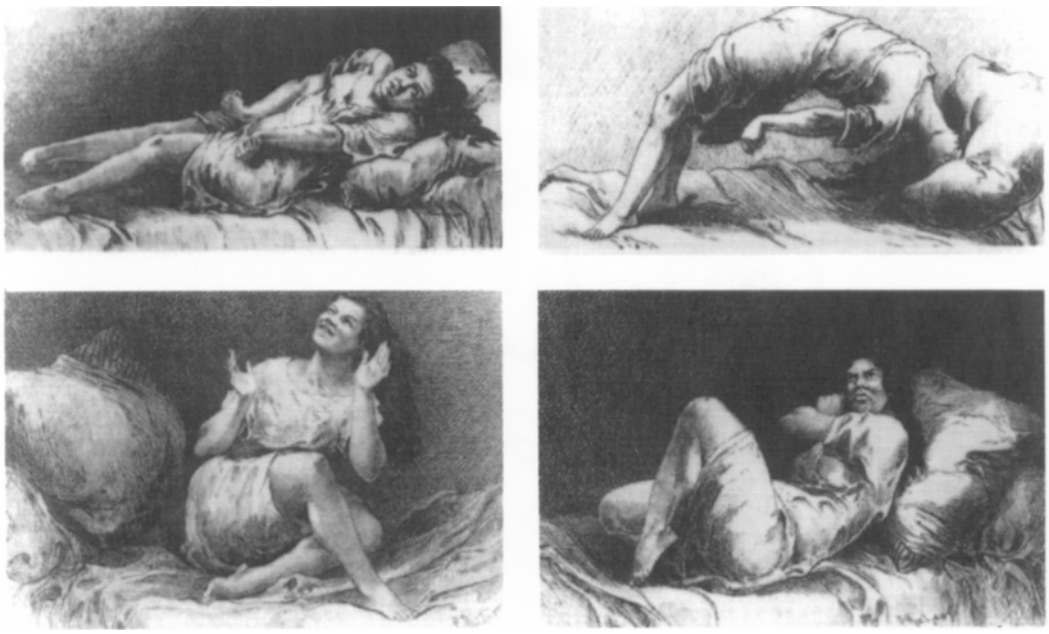

FIGURE 20.1

Drawing of the typical phases of a "hysteroepileptic" attack as defined by Charcot. The phases included from top left and clockwise 1. Epileptoid phase (predominantly tonic spasms) 2. Acrobatic phase (exotic postures such as arching [arc en cercle] or rhythmic body rocking). 3. (bottom left and right) Delirium with emotionally expressive postures such as happiness, ecstacy or fright (From: Etudes Cliniques sur la Grande Hysterie ou 1′ Hysteroepilepsie. by P Richer, 1885.)

tion of the uterus or womb (8,9). Hysteria was regarded as a just physical cause for seizures or epilepsy, with hysterical and other seizures not clearly distinguished. The ancient Greeks adopted Egyptian theories of hysteria; the word *hysteria* derives from the Greek word for uterus (8,9). Both the ancient Romans and Greeks regarded hysteria as a physical disease that could cause seizures. During the Dark or Middle Ages both epilepsy and hysteria were attributed to mystical or supernatural causes, such as possession by demons, with little emphasis on distinguishing them. Even with the Renaissance and the return of classical Greek and Roman perspectives, hysteria and epilepsy were still not clearly distinguished and often viewed to coexist.

In the late 1800s, one of the founders of neurology, Jean Martin Charcot, established hysterical seizures as an important clinical entity with his detailed, elegant descriptions of patients. Charcot formulated clinical methods for distinguishing hysterical seizures from other forms of epilepsy. Still, he presumed that hysteria and epilepsy often coexisted, and he termed seizures due to hysteria as "hysteroepilepsy" or "epileptiform" hysteria (Figure 20.1) (10,11). Charcot postulated that hysterical seizures were some type of organic disorder of the brain, and emphasized their relation to a disturbance of the female reproductive system (10,11). (Figure 20.2)

One of Charcot's most celebrated students, the neurologist Sigmund Freud, observed Charcot's demonstrations, but drew different conclusions. He theorized that hysteria and hysterical seizures were not organic disorders of the brain, as Charcot proposed, but were rather emotional disorders of the unconscious mind due to repressed energies or drives. Freud postulated that hysteria represented a conversion of repressed sexuality, sexual drive or energy into an emotional disorder (9,12). Based largely on the theories of Freud and Charcot, individuals with hysteria were distinguished from those with epilepsy, with hysterical seizures related to psychologic dysfunction, whereas true epileptic seizures were associated with physical or organic brain disorders. At this time, hysterical seizures and epileptic seizures were generally considered not to coexist (9,12).

With the introduction of EEG recording in the 1930s, it became possible to characterize epilepsy as an electrical disorder of the brain with associated electroencephalographic (EEG) changes, and distinguish it

FIGURE 20.2

Lithograph of the Brouillet painting A Clinical Lesson at the Salpêtrière (1887). This shows Charcot using suggestion to induce hysterical collapse in a woman. This is the type of presentation that Freud undoubtedly observed.

from hysterical seizures, which did not have such abnormalities. In addition, in the first half of the twentieth century, the nature of hysteria as seen and diagnosed by physicians changed. The dramatic, theatrical convulsions described by Charcot and his contemporaries appeared less commonly, whereas disorders such as chronic pain seemed to increase (13,14).

However, by the 1960s, several reports confirmed that hysterical seizures were actually still prevelant. New terms were used to describe these disorders including "pseudoseizures," because the term hysteria was thought to be somewhat derogatory, antifeminist, and antiquated (15,16). In the 1970s and thereafter, with the increasing availability of video-EEG monitoring and growth of hospital inpatient epilepsy monitoring units, it was discovered that hysterical, pseudo-, or what were also termed psychogenic seizures, and what we here refer to as NES, were actually still common and that epileptic and nonepileptic seizures coexisted in many patients (1,16).

More recently, mainly in the past 10 years, it has been recognized that some rare patients with seizures initially diagnosed as NES, because of features such as their bizarre manifestations or lack of associated ictal EEG changes, actually have unusual forms of true epileptic seizures, such as frontal lobe epilepsy, or related physiologic rather than psychologic causes for their episodes. Such individuals have been said to have "pseudo pseudoepileptic" seizures, a rather descriptive term. These seizures can be very difficult to diagnose properly unless one appreciates how they present and manifest and remains vigilant for them (1).

Our modern day concept of hysteria has also evolved. Today, hysteria is considered within the broad framework of psychologic disorders known as *somatoform* or *conversion disorders,* but we recognize that its causes are multifactorial and involve psychologic, environmental, and biologic influences (1,14,15). It is further established that it can coexist with physical disorders such as epilepsy.

DEFINITIONS

The term "epilepsy" should be restricted to well-defined disorders of the brain caused by abnormal electrical cerebral discharges, whereas events that resemble

TABLE 20.1
Classification of Nonepileptic Seizures or Events

I. Physiologic nonepileptic seizures or events
(Age dependent: e.g., night terrors or breath-holding spells in children, other syncopes, complicated migraine, and transient ischemic attacks [TIA] in adults)
- **A. Pure**
- **B. Mixed** (with psychological exaggeration or embellishment)

II. Psychogenic nonepileptic seizures
- **A. Somatoform disorders**
  - **1. Somatization disorders**
  - **2. Conversion disorder or reactions**
- **B. Dissociative disorders**
- **C. Factitious disorder** (e.g., Munchausen's syndrome)
- **D. Malingering**

epilepsy but are due to other causes are best termed "nonepileptic seizures" or alternatively "nonepileptic events," with the word "seizure" being used in a more general sense. Historically, many other terms have been used to describe these phenomena including: hysterical seizures, hysteroepilepsy, pseudoseizures, and psychogenic seizures (1). The phrase "nonepileptic seizure" best describes all conditions, both physiologic and psychologic, that are mistaken for epilepsy but which are not due to epilepsy (Table 20.1).

Physiologic NESs are physical disorders that are confused for epilepsy. The specific causes vary depending on age (Table 20.2). If these episodes are uncomplicated by psychologic or emotional features, they can be called "pure" physiologic nonepileptic events. However, sometimes patients' physiologic events are psychologically exaggerated, embellished, or misinterpreted, and may be thought of as "mixed" physiological nonepileptic events (Table 20.1). Physiologic events are responsible for only a small proportion of all patients with nonepileptic seizures (1).

The majority of patients with NES have psychogenic seizures (Table 20.3). In general, any patient with a psychologic disorder that is mistaken for epilepsy can be said to have psychogenic seizures. It is useful to classify psychogenic seizure patients into four major categories (Table 20.1) i) somatoform disorders, ii) dissociative disorders, iii) factitious disorders, and

TABLE 20.2
Clinical Characteristics of Epileptic versus Nonepileptic Seizures

	EPILEPTIC	NONEPILEPTIC
Age at onset	All ages; children and adolescents more common	All ages; 15 to 35 years most common
Sex	Male and female about equal	Female more common; 3 to 1 ratio
Previous Psychiatric History	Occasionally present	Commonly noted
Motor	In generalized convulsions; bilateral movements are usually synchronous	Flailing, thrashing and asynchronous movements more common, side-to-side head movements, pelvic thrusting
Vocalization	Cry at onset; screaming more common	Weeping, crying
Incontinence	Frequent	Occasional
Duration of seizure	Usually less than 2 to 3 minutes	Often prolonged, more than 2 to 3 minutes
Injury	Frequent tongue biting	Uncommon
Amnesia	Common, unconscious during seizure	Variable, sometimes conscious during seizure
Suggestion provokes seizure	No	Often

TABLE 20.3
EEG Characteristics of Epileptic versus Nonepileptic Seizures

	EPILEPTIC	NONEPILEPTIC
Interictal EEG	Spikes and sharp waves common	Normal or nonspecific abnormalities, such as mild slow activity
Preictal EEG	Spikes, sharp waves, or rhythmic ictal activity	Movement artifact
Ictal EEG	Spikes, sharp waves, or rhythmic ictal activity	Movement artifact
Postictal EEG	Slow activity	Normal EEG, preserved alpha

iv) malingering. Somatoform disorders account for the great majority of patients and can be further subclassified (Table 20.1; 1,17). Dissociative disorders are increasingly recognized as a significant psychopathology in some patients with NES (18–20).

EPIDEMIOLOGY

Nonepileptic seizures occur in age groups from childhood (21,22) to the elderly, but most present between the ages of 15 to 35 years (1,7). Very young children and infants are more likely to have physiologic nonepileptic events that may be mistaken for seizures rather than psychogenic seizures. These types of events include gastroesophageal reflux, night terrors, breath holding spells, and pallid infantile syncope (1,21,22).

Patients with nonepileptic psychogenic seizures are reported to account for 5% to 20% of patents with intractable epilepsy seen as outpatients, and 10% to 40% of patients admitted for epilepsy monitoring (1,2,5,7). The only population-based study estimates the incidence of NES to be 1.4 per 100,000 population and 3.4 per 100,000 people in the age group of 15 to 24 years (4).

Nonepileptic seizures occur with greater frequency in women. The exact incidence varies, but women generally account for about 70% to 80% of all individuals with NES (1,2,5). Sociologic and cultural factors influence the occurrence and nature of somatoform disorders.

Coexisting Epilepsy and Nonepileptic Seizures

The true concurrence rate of epilepsy and NES has not been definitively established despite numerous studies and centers reporting their own experiences (Table 20.4). Epilepsy occurs much more commonly than NES, and the incidence of epilepsy in patients with proven NES may not be the same as the incidence of NES in patients with confirmed epilepsy.

The majority of studies have described coexisting epilepsy in patients with confirmed NES (Table 20.4). The largest of these studies reported epilepsy in 12.7% of 110 patients with documented NES (23). However, the variation between studies is noteworthy, with coexisting epilepsy occurring in anywhere from 9.4% to 56% of patients with NES (24–27,29,30,86–89). This large range of rates may largely reflect differences in the criteria used to establish a diagnosis of epilepsy. For example, some studies relied on finding interictal epileptiform activity as sufficient evidence of epilepsy, whereas others restricted diagnostic criteria to capturing true epileptic seizures during video-EEG monitoring. Still other studies depend solely on the patients' histories. Depending on the criteria used to define the presence of coexisting epilepsy, dramatically different rates of concurrence seem to result. For instance, Gates, et al. (24), found that of twenty-five patients with documented NES, fourteen (56%) had evidence of coexisting epilepsy based on either epileptic seizures captured on video-EEG or clinical history, with or without documented interictal epileptiform abnormalities. However, if stringent criteria were used in this study to establish the diagnosis of epilepsy (i.e., only video-EEG documented seizures), then only five (20%) of the patients with NES would have been determined to have coexisting epilepsy. Similarly, Gulick et al. (25) showed that ten (37%) of twenty-seven patients with NES had coexisting epilepsy based on either ictal video-EEG or interictal epileptiform evidence of epilepsy. Had only ictal recordings been accepted as evidence of coexisting epilepsy, then only two (7.4%) of the twenty-seven patients would have met the criteria. Relying on interictal epileptiform abnormalities alone to diagnose epilepsy could theoretically lead to overdiagnosis of

TABLE 20.4

Reference	Age Range	# Patients	# CoE or CoNES (%)		Criteria for epilepsy
Studies reporting coexisting epilepsy in patients with documented NES:					
Gates (24)	16–60y	25 with NES	14	**(56.0)** with CoE	Video EEG or history +/– ii EEG
			5	**(20.0)**	Video EEG only
Sackellares (26)	15–55y	37with NES	18	**(48.6)** with CoE	Video EEG
Gulick/King (25) 1	8–49y	27with NES	10	**(37.0)** with CoE	Video EEG or ii EEG
			2	**(7.4)**	Video EEG only
Krumholz (30)	9–59y	41 with NES	15	**(36.6)** with CoE	History/expert opinion +/– ii EEG
Ramsay (86)		34 with NES	6	**(17.6)** with CoE	Video EEG, ii EEG, or "sufficient documentation"
Luther (29)	9–55y	30 with NES	5	**(16.7)** with CoE	No comment
Lempert (87)	15–78y	50 with NES	7	**(14.0)** with CoE	"Possible/Doubtful ES" (not defined)
Meierkord (2)		110 with NES	14	**(12.7)** with CoE	"Clear clinical evidence" +/– iiEEG
Cohen (88)	10–60y	51 with NES	6	**(11.8)** with CoE	History +/– "clearly abnl" EEG
Lesser (89)		50 with NES	5	**(10.0)** with CoE	Ictal or ii EEG
Benbadis (27)	19–72y	32 with NES	3	**(9.4)** with CoE	ii EEG
Studies reporting coexisting NES in patients with epilepsy:					
Ramani (90)	17–54y	46 with epilepsy "known"	9	**(19.6)** with CoNES	Documented epileptic seizures + abnormal EEG in past
King (91)	16–54y	40 with epilepsy suspected	4	**(10.0)** with CoNES	Ictal or ii EEG
Henry (92)		145 with epilepsy suspected	12	**(8.3)** with CoNES ii EEG	
Gates (24)	16–60y	25 with epilepsy documented	1	**(4.0)** with CoNES Video EEG	
Walsh (28)	6m–74y	184 with epilepsy suspected	4	**(2.2)** with CoNES ii EEG	

NES = nonepileptic seizure(s)
# CoE or NES = number of patients with coexisting epilepsy or coexisting nonepileptic seizure(s)
Video EEG = Video EEG documented epileptic seizure(s)
iiEEG = interictal epileptiform EEG discharges

epilepsy since interictal epileptiform discharges are not necessarily specific for epilepsy. Conversely, restricting the diagnostic criteria to only those patients who had epileptic seizures documented by video-EEG can lead to underdiagnosis due to the limited sensitivity of video-EEG monitoring.

Other factors may influence these estimates of coexisting epileptic and NES. For example, one study relying on the strict criteria of video-EEG documented epileptic seizures as evidence for epilepsy reported a surprisingly high incidence of coexisting epilepsy in up to 48.6% of patients with NES (26), whereas studies with more liberal criteria reported rates of coexisting epilepsy as low as 9.4% (27). Factors accounting for such discrepancies may include differences in patient populations and referral sources for these studies. The true rate of coexisting epilepsy in patients with NES cannot be determined but likely lies somewhere between the extremes reported, with the majority of studies showing concurrence rates of approximately 10% to 18% (Table 20.4). This estimate suggests that only a modest proportion of patients with NES, rather than the majority, have coexisting epilepsy.

Looking at this issue differently by considering how often patients with proven epilepsy have NES, NES has been reported to coexist in 2.2% to 19.6% of patients with true epilepsy (Table 20.4) (24, 28, 90–92). Again, a reason for the variability in results between studies may be that they are not population-based and are, therefore, subject to bias by differences in patient selection and referral sources. Studies may also differ in the definition and interpretation of criteria used to establish the diagnosis of epilepsy (1,28). One large study of video-EEG monitoring of 622 patients with suspected seizures done on an outpatient basis demonstrated interictal EEG abnormalities in 184 patients. Of these 184 with presumed true epilepsy based on the presence of interictal EEG abnormalities four, (2.2%) had coexisting NES documented by video-EEG monitoring during these recordings (28).

The coexistence of epilepsy and NES in a given patient may take one of two forms, sequential and simultaneous. The differences are important in regard to management. In particular, some patients with epilepsy in childhood may develop NES in later life, at a time when their epileptic seizures may no longer be an active problem or are controlled with medications. This would be considered sequential. In contrast, patients with active NES and epileptic seizures occurring concurrently can be said to have simultaneous epileptic and NES. Many studies do not explicitly distinguish between the simultaneous and sequential coexistence of epilepsy and NES. Studies documenting both NES and epileptic seizures with video-EEG monitoring provide the most convincing evidence of the simultaneous coexistence of the two disorders (22,24,25). Even so, capturing both NES and epileptic seizures on video-EEG during the same hospitalization does not necessarily mean that both epilepsy and NES are substantially active problems for a patient. For example, in a patient with intractable NES, the patient's epilepsy may actually be well controlled, but artificially precipitated by drug withdrawal and activation procedures during a hospitalization for epilepsy monitoring.

Most frequently, when epilepsy and NES present in the same patient, they occur sequentially rather than simultaneously, often beginning with the former. Luther, et al. (29) found in their patients with coexisting epilepsy and NES, that NESs were invariably the most current active seizure type and that NESs typically exceeded the frequency of previous epileptic seizures. Similarly, in a study of forty-one patients with NES, fifteen (36.6%) had coexisting epilepsy based on history; however, epileptic seizures were only a remote issue in the majority of patients when they presented with NES (30). The sequential presentation of NES following the resolution of epileptic seizures suggests that in some patients NES may be a learned behavior or perhaps result from a subconscious psychologic or social dependence on being disabled by epilepsy.

The emergence of NES in patients after epilepsy surgery is another interesting phenomenon, which could be another example of a learned behavior. Several authors have documented new-onset NES in patients undergoing evaluation for recurrent seizures following resective epilepsy surgery (31–33). In addition, a study of patients who underwent intracranial neurosurgery for indications other than epilepsy surgery (i.e., tumor or vascular malformation resection or subdural hematoma evacuation) similarly identified a small number of patients who developed NES de novo after surgery (34). Interestingly, the majority of these neurosurgical patients (twelve of seventeen) had a current diagnosis or history of coexisting epileptic seizures. A seizure-free period following surgery was characteristic of many of the patients who later developed NES, although the interval varied widely from within the first few months after surgery (33) up to almost 4 years (32). It was further observed that patients in whom NES emerged following resective epilepsy surgery tended to be female, with right hemisphere dysfunction, and have onset of epilepsy after adolescence (33). Notably, these patients did not differ in preoperative psychiatric diagnoses from those who did not develop NES after epilepsy surgery. Whether patients develop NES due to structural brain damage, a psychosocial dependence on prior epileptic seizures, or a surgically induced state of

"psychiatric instability" (33) predisposing to NES is a matter of debate.

PROVOKING FACTORS

Environmental factors may contribute to the risk for developing NES, particularly psychogenic seizures. Sexual abuse is one such important factor. Historically, this issue is important because hysteria has, since Freud's early observations, been related to repressed sexual drives and associated with sexual abuse in women (1). Recent studies emphasize that a history of sexual or physical abuse may be quite frequent in patients with psychogenic seizures (1,35), and may cause dissociative reactions that could be mistaken for seizures (18,19). One such series reports a history of sexual abuse in nearly 25% of patients with NES; and a history of either sexual abuse, physical abuse, or both in 32% (35). Other series describe an even higher incidence of abuse (18,19). This issue should be explored and integrated into treatment as necessary. Unfortunately, sexual and physical abuse are relatively common in our society and also occur among patients with true epilepsy. In one series, a control population of patients with epileptic seizures reported a nearly 9% rate of sexual or physical abuse (35).

Head trauma has recently been recognized as another provoking factor for NES. For example two recent studies report that 20% to 30% of psychogenic seizure patients attribute their seizures to head trauma, often rather mild head trauma (5,36). It may be that various types of environmental trauma or stress are potential provoking factors for conversion reactions and psychogenic seizures in susceptible individuals.

DIAGNOSIS

Clinical observation has long been the basis for distinguishing nonepileptic from epileptic seizures. However, over the past 35 years, clinical observation has been greatly aided mainly by video-EEG monitoring, but also by other means such as serum prolactin levels neuropsychologic assessments, and outpatient ambulatory EEG monitoring.

A complicating factor in diagnosis is that nonepileptic and epileptic seizures both may occur in a given patient. Approximately 10% to 40% of patients identified as having nonepileptic or psychogenic seizures have been reported to also have true epileptic seizures (1,3). There are several possible explanations for this. Some patients with epilepsy may learn that seizures get attention and fill certain psychologic needs. Alternatively, they may have concomitant neurologic problems, personality disorders, cognitive deficits, or impaired coping mechanisms that predispose them to psychogenic symptoms. In such patients with combined seizure disorders, the epileptic seizures are often controlled or of mainly historical relevance at the time a patient presents with psychogenic seizures (1).

Clinical Observations

No pathognomonic clinical signs allow one to distinguish nonepileptic or psychogenic seizures from epileptic seizures. Nonepileptic seizures are varied and may present with generalized convulsive manifestations, signs of altered consciousness or loss of consciousness, and focal motor or sensory symptoms (25,37–40).

Yet, some clinical observations can be useful (Table 20.2). In particular, psychogenic seizures often last considerably longer than epileptic seizures, which typically persist less than 3 minutes, excluding the postictal state. Also, the nature of the convulsive activity in patients with psychogenic seizures differs from that seen in generalized convulsive epilepsy. With psychogenic seizures, the movements are more often purposeful or semipurposeful, asymmetric or asynchronous, such as thrashing or writhing motions, rather than the tonic-clonic activity of epileptic seizures (38–40). However, it is more difficult to distinguish the movements of psychogenic seizures from the automatisms of complex partial epileptic seizures, particularly frontal lobe seizures (1).

Other clinical differences are notable between psychogenic and epileptic seizures. For example, consciousness and responsiveness may be surprisingly retained during psychogenic seizures. Crying and weeping are more common for psychogenic seizures (41–42). Although incontinence and self-injury are frequently reported by patients with NES (43), they are rarely actually witnessed. In addition, unlike epileptic seizures, psychogenic seizures characteristically do not respond well to antiepileptic drug treatment (1,3,5,7).

Psychogenic seizures are also more likely to be provoked by emotional stimuli and suggestion (1). In fact, provocative procedures may be useful for reproducing events during EEG recording. Provoking or suggesting seizures can be done in several ways, such as injecting saline or placing a tuning fork on the body or head (44–47). They are all accompanied by strong suggestion by the physician that this procedure is likely to bring on a typical seizure. EEG recording and usually videorecording are undertaken simultaneously to enable a confirmation of the nonepileptic nature of the induced event. However, provoking psychogenic seizures raises some ethical controversies. Misleading a patient when provoking a seizure can be harmful to the patient–physician relationship and should be avoided. Nonetheless, provocative testing can be done with honesty, and benefit to the patient (48).

Hypnosis has also been used to induce or provoke psychogenic seizures. In some respects, hypnosis can be considered a special form of suggestion (49).

Video-EEG Monitoring

A diagnosis of nonepileptic or psychogenic seizures is most firm when a characteristic seizure is recorded during simultaneous EEG and video monitoring and demonstrates no evidence of epileptic activity. Patients with generalized convulsive epileptic seizures invariably demonstrate significant EEG changes during ictal EEG recordings. Individuals with complex partial seizures, who may have small or deep seizure foci, still show significant ictal EEG abnormalities in perhaps 85% to 95% of such seizures (1). Even patients with simple partial seizures—seizures that do not impair consciousness—have EEG abnormalities noted in about 60% of those seizures, and if one records multiple seizures, nearly 80% demonstrate some EEG abnormality (50). The ictal EEG recording is particularly important because occasionally interictal or routine EEGs may be misleading. For example, between seizures, some patients with epilepsy may have normal EEGs and some patients with psychogenic seizures may have minor EEG abnormalities (Table 20.3; 1,5,7).

There are several ways to capture a clinical seizure during EEG monitoring. Outpatient monitoring is particularly useful for patients who have daily events or seizures that can be provoked by suggestion. Patients with less frequent events may require extended inpatient video-EEG monitoring. Simultaneous video-EEG recording offers the advantage of permitting careful observation and review of the clinical manifestations of seizures. This can be especially useful when assessing patients with psychogenic seizures because video-EEG recordings are particularly helpful in distinguishing epileptic discharges from movement and muscle artifact.

Epileptic seizures commonly arise during sleep. However, patients with psychogenic seizures are usually awake at the time a seizure starts. This can be difficult to evaluate by history or behavior, because patients with psychogenic seizures may report seizures arising from sleep, or may appear to be sleeping when seizures begin. However, video-EEG monitoring can be useful in showing that the patient with psychogenic seizures is usually not actually asleep when an event begins (51,52).

Prolactin Levels

The serum prolactin level is a test used in patients with suspected psychogenic seizures (53,54). Prolactin levels rise approximately 5- to 10-fold after tonic-clonic seizures, and somewhat less so but still significantly (typically at least 2- to 3-fold) after complex partial seizures (55). This prolactin increase is maximal in the initial 20 minutes to 1 hour after a seizure (53–55). However, although prolactin measures may be useful in distinguishing nonepileptic from epileptic seizures, some false positives and false negatives occur (55,56). Prolactin elevations have been reported after syncope (57). Simple partial seizures, or mild complex partial seizures, particularly those with little motor activity, may not significantly raise prolactin levels. Also, after convulsive status epilepticus or repeated seizures prolactin levels may not be elevated (56,58) (see also Chapter 5).

Neuropsychological Testing

Another important consideration in evaluating patients with suspected psychogenic seizures is their neuropsychologic function. Such an assessment requires a referral to mental health professionals experienced in psychological and psychiatric assessment, psychometric assessment, and psychotherapeutic intervention in patients with neurologic disorders (59,60).

However, mental health professionals should not be expected to determine whether an individual is having psychogenic rather than epileptic seizures, because these professionals generally lack the necessary neurologic training or experience. Moreover, neuropsychologic testing cannot in itself either diagnose or exclude the possibility that a seizure disorder is nonepileptic because of the considerable overlap between epileptic and nonepileptic test results (59,60). The distinction between psychogenic and epileptic seizures is best made by neurologists, particularly those with special expertise in epilepsy, and is based on the consideration of both clinical and neuropsychologic data. Neuropsychologic evaluations aid this assessment by i) determining the potential or likelihood of significant contributing psychopathology or cognitive difficulties, ii) defining the nature of the associated psychologic or psychosocial issues, and iii) determining how a patient might benefit from various psychologically based interventions (1).

EPILEPTIC SEIZURES MIMICKING NONEPILEPTIC SEIZURES

Some events initially diagnosed as nonepileptic actually prove to be epileptic. Such events can be called "pseudo-pseudo" or "epileptic-nonepileptic" seizures (1). Frontal lobe seizures in particular may not be associated with significant EEG changes (even ictally) and therefore may be misdiagnosed as NES. Clinical presentation and proper diagnosis of these types of events warrant emphasis.

Frontal lobe seizures may have unusual, complex clinical manifestations with varying degrees of preserved consciousness so that ictal behavior appears purposeful, and therefore, nonepileptic. Perhaps the most widely recognized of the frontal lobe seizures are those arising from the supplementary motor area (SMA). These seizures are characterized by abrupt tonic posturing, sometimes with contraversive head turning, as in a fencing posture, followed by clonic activity in one or more extremities (61). Unless they secondarily generalize, SMA seizures typically do not impair consciousness and cause little postictal confusion. These seizures may, therefore, be mistaken for psychogenic spells, especially when bilateral limb activity is witnessed without associated loss of consciousness. If awareness is impaired during complex partial seizures, patients may remain in partial contact, sometimes reacting to external stimuli while engaged in automatic activity. Ictal EEG recordings are often normal or obscured by muscle artifact, thus, compounding the diagnostic difficulty (61,62).

Case Study #1. HM is a 38-year-old mildly mentally retarded male who experienced 15 years of nightly episodes occurring from sleep. He had a history of a few convulsive epileptic seizures in childhood, but was reported to be seizure-free and off medications through childhood. However, as an adult in his twenties, he developed strange nocturnal episodes while he was hospitalized in a psychiatric facility for behavioral management problems. These events were diagnosed to be seizures but proved resistant to antiepileptic drug therapy.

These episodes occurred almost every night and sometimes several times a night. He would appear to arouse from sleep, look around in a confused manner and then begin to scream loudly and uncontrollably, turning about in a violent and aggressive manner. These events were very dramatic, and because of his parents' concern that he would hurt himself, he slept with his mattress on the floor. His parents, who slept in an adjoining room, were deeply disturbed by these events, but he had no recall of them. All diagnostic studies, including numerous EEGs and magnetic resonance imaging (MRI), were unrevealing.

The patient was admitted to our epilepsy monitoring unit and numerous typical episodes were recorded. These were very stereotyped and similar each night. However, there were no EEG abnormalities noted with any of the events in terms of preictal, ictal, or postictal changes, but all arose from physiologic sleep. The patient was diagnosed to have night terrors (a physiologic nonepileptic disorder), taken off of his antiepileptic medications, and treated with psychologic supportive care and benzodiazepines at bedtime. However, his episodes persisted.

In view of the stereotyped nature of the events, the clinical presentation from sleep, and his vocalizations and motor manifestations, the possibility of frontal lobe epilepsy was pursued. He was admitted for bilateral intracranial frontal and temporal strip electrodes and discovered to have a regional onset of his seizures from his left frontal lobe. Following additional investigations, he had a left frontal lobectomy and has remained seizure-free following surgery.

As in this patient, frontal lobe seizures tend to occur in clusters, out of sleep, and not uncommonly present with atypical or bizarre semeiology. Notable manifestations of mesial frontal lobe seizures that may easily be confused with hysterical behavior include shouting, laughing, cursing, clapping, snapping, genital manipulation, pelvic thrusting, pedaling, running, kicking, and thrashing (63,64). Not all these behaviors are specific for frontal lobe seizures. For example, bicycling leg movements have also been reported in seizures originating from the temporal lobe (64).

A comparison of clinical characteristics between frontal lobe partial seizures and psychogenic seizures found certain features to be helpful in differentiating the two. Patients with frontal lobe seizures were more likely than patients with psychogenic seizures to have a younger age at onset, shorter ictal duration (*i.e.,* less than 1 minute), stereotyped seizure patterns, nocturnal ictal predominance, and abnormal MRI and EEG findings. In addition, turning to a prone position during a seizure and continuous vocalization, such as a monotonous moan, highly correlated with frontal lobe seizures. Interestingly, a positive psychiatric history, pelvic thrusting, side-to-side head movements, body rocking, and a short postictal state were *not* seen more frequently in patients with psychogenic seizures (65).

Some disorders manifesting with seizure-like attacks are not clearly epileptic but still likely physiologic rather than psychogenic in origin. *Paroxysmal kinesiogenic choreoathetosis or dyskinesia (PKC or PKD)* is a relatively rare neurologic condition that has defied easy categorization as either a movement disorder or a form of epilepsy (see also Chapter 12). One of a group of hyperkinetic movement disorders known as paroxysmal dyskinesias, PKC is defined by attacks of usually unilateral dystonia, chorea, athetosis, or ballism

precipitated by sudden movement. In contrast to paroxysmal exercise-induced dystonia (PED), in which attacks may last for a few hours, PKC events are typically short-lived, lasting seconds to minutes, and may vary in frequency from once a week to over forty per day (66). Some of these disorders are precipitated by movement and are therefore kinesiogenic, while others are unrelated to movement, or nonkinesiogenic (63).

Case Study #2. MF is a 43-year-old male physician with a history since adolescence of peculiar brief episodes of left arm and leg stiffening and posturing. These were evaluated previously with EEGs and brain imaging studies including MRIs without a cause found. He was suspected to have a psychologic or stress-related disorder or epilepsy.

The episodes were precipitated by stress and visual–spacial influences. For example, he might have great difficulty walking in narrow corridors or around tight corners. He did not get relief with medication, including antiepileptic agents, and the symptoms fluctuated over the years. Most recently he had again been prescribed antiepileptic medications. However, the possibility that this was some type of paroxysmal dyskinesia had also been considered.

One day he experienced a typical episode that caused him to fall and strike his head, thus precipitating an severe acute epidural hematoma. Following surgery and a stormy clinical course, he survived and was further evaluated in our epilepsy monitoring unit. Several of these spells were captured and associated with alterations in his consciousness, but not with impressive changes in his EEG. An ictal single positron emission computed tomography (SPECT) scan did not show a clear abnormality. He was suspected to have frontal lobe epilepsy or a form of paroxysmal dyskinesia (or PKC), and he was treated with carbamazepine and benzodiazapines in high doses. His episodes are now improved, but he continues to experience some exacerbations.

Whether PKC and related disorders represent a movement disorder or epilepsy has been intensely debated. Proponents of an extrapyramidal etiology note that the involuntary movements in PKC are characteristic of basal ganglia disease. A nonepileptic etiology is further suggested by the invariable preservation of consciousness and general lack of EEG changes during attacks. Conversely, the paroxysmal, nonprogressive nature of the disorder and the remarkable sensitivity of PKC to treatment with carbamazepine (67) argue for an epileptic origin. It has been reasoned, moreover, that EEG changes are not easily detected during attacks because PKC seizures may be arising subcortically from the thalamus or basal ganglia or from difficult-to-detect foci in the frontal lobes (68). Intracranial monitoring has provided some evidence for this premise. Depth and subdural electrode recording in a patient thought to have PKC demonstrated ictal discharges originating from the supplementary sensory-motor cortex and the caudate nucleus during clinical attacks (69).

Further insight into the association between PKC and epilepsy has been gained from studying families and sporadic cases in which there is co-occurrence of PKC and epilepsy. Some of these patients have been found to have PKC attacks that were immediately followed by a clouding of consciousness and generalized convulsion. Interestingly, interictal epileptic discharges arising most often from the centromidtemporal and frontal regions were also observed in these patients (70). Ion channel gene disorders have been proposed as the potential pathophysiologic link between PKC and epilepsy (71).

Hypnogenic (nocturnal) paroxysmal dystonia is another paroxysmal dyskinesia that has been more firmly established as an epileptic disorder but may be clinically mistaken for NES. It is characterized by brief attacks occurring out of sleep, often beginning with a cry or moan, with eyes open and staring. Hyperkinetic activity such as thrashing or involuntary dystonic hyperextension is typical of attacks, and the majority of patients report that they remain aware despite an inability to control their actions or to respond (72). Events are typically clustered and may recur multiple times in one night (72).

An epileptic origin for this condition was long suspected based on the observation of sporadic daytime seizures in some patients and the ready response of most patients to treatment with carbamazepine, even at low doses (73). Hypnogenic paroxysmal dystonia was eventually redefined as a frontal lobe epilepsy when video-EEG data demonstrated ictal epileptiform activity over the frontal regions and seizure semiology consistent with frontal lobe seizures (72,73). Segregation analysis of families affected with this disorder revealed an autosomal dominant mode of inheritance, making it the first partial epilepsy syndrome to follow single gene inheritance (71). The term *autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)* was subsequently adopted. An underlying molecular defect affecting the neuronal nicotinic acetylcholine receptor has since been found in two families with ADNFLE (74).

The dramatic clinical manifestations of seizures in ADNFLE, together with commonly unremarkable EEGs and an overall unfamiliarity with the disorder, have led to repeated misdiagnosis of patients as having sleep disorders or psychiatric disorders, such as hysteria or hyperactivity. The most common sleep disorders to be diagnosed in error are the benign nocturnal parasomnias, which include night terrors (pavor nocturnus), nightmares, and somnambulism. Night terrors can often be clinically differentiated from nocturnal frontal lobe seizures by their longer duration, associated amnesia, and lack of attack clustering (70,72) (see also Chapter 16).

Seizures arising outside the frontal regions may also mimic NES. *Parietal lobe seizures* may present as pain or intense fear, symptoms readily attributed to nonepileptic causes by clinicians unfamiliar with this ictal manifestation. Most seizures confined to the parietal lobe are clinically silent, and localization of epileptogenic foci within the breadth of the parietal lobes in nonlesional patients is notoriously difficult. Nevertheless, a careful study of patients with lesional parietal lobe epilepsy, including those who have undergone intracranial monitoring, has enabled parietal lobe seizures to be better characterized clinically. Parietal seizures may present as paresthesias or as motor activity such as focal clonic jerking, head and eye deviation, and limb posturing. The most notable clinical features are the sensory symptoms, including feelings of numbness and tingling, pins and needles, crawling, itching, and pain. Though not expressly confined to the parietal lobes, *ictal pain* has been well described in seizures of parietal origin. This pain may manifest as lateralized burning dysesthesias or as excruciatingly severe, cramping abdominal pain. Unilateral head pain has also been reported and can mimic migraine headaches (75). The relative rarity of pain as an ictal phenomenon may lead physicians to pursue extensive diagnostic testing, looking for nonepileptic physiologic etiologies such as appendicitis in patients with parietal seizures.

Parietal lobe seizures have also been associated with paroxysms of irrational terror and palpitations (76), imitating psychogenic panic attacks. In fact, patients with recurrent parietal seizures can meet the DSM-IV diagnostic criteria for panic disorder if their attacks begin without warning, evolve within less than 10 minutes, and are associated with a constellation of symptoms including palpitations, nausea, paresthesias, hot flashes, or chills (17). These seizures can be difficult to distinguish from panic attacks, particularly when there is little ictal correlate on surface EEG (see also chapters 2 and 21). Seizures originating from the posterior parietal lobe have been termed "psychoparetic." These seizures may start with a psychic aura, such as déjà vu or fear, but are then followed by impairment of consciousness and motor arrest, potentially mimicking an emotionally precipitated vasovagal fainting spell (77).

Occipital lobe seizures may be confused with physiologic NES, such as migraine headaches or transient ischemic attacks, as well as nonphysiologic NES, including psychogenic amaurosis (see also chapter 2). Visual hallucinations and amaurosis are the most common occipital lobe seizure manifestations. Hallucinations are typically unformed and elementary such as flashing colored or white lights, straight or jagged lines, or other shapes (78). In contrast to these "positive" visual phenomena, occipital lobe seizures may also feature "negative" visual symptoms, otherwise known as ictal amaurosis. Vision may fade, "black-out," or "white-out" (79) either unilaterally or over the entire visual field. Motor manifestations are also noted in occipital lobe seizures, namely eye deviation with or without head deviation and rapid blinking. In addition, ictal and postictal headache, as well as vomiting and impairment of consciousness, can be associated with occipital lobe seizures (80).

The visual phenomena associated with occipital lobe seizures, particularly in the setting of a peri-ictal headache, lend to ready confusion with migraine headaches. Migraines, like occipital seizures, can present at onset with a visual aura of flashing lights or fortification spectra and can result in a temporary loss of vision over a portion of the visual field. However, the duration of attacks may help distinguish seizure from migraine, with seizures typically evolving over seconds and migraines over minutes (80).

Other diagnoses that require differentiation from occipital epilepsy include syncope and posterior circulation transient ischemic attacks (see also chapter 17). The former may be suspect given the presence of precipitating factors, associated autonomic symptoms, or rapid recovery with recumbency. The latter should be considered in the setting of pre-existing vasculopathic risk factors and in the presence of superimposed brainstem or cerebellar dysfunction (78,80).

Patients with episodic visual loss from occipital lobe seizures have not infrequently been thought to have psychogenic amaurosis (81). Hysterical visual field loss may commonly present as bilateral total or near-total blindness, tunnel vision with concentric loss of peripheral vision, a spiral field on perimetry testing, or a monocular hemianopia (81). EEG abnormalities over the occipital regions, including the disruption or slowing of the alpha rhythm and interictal epileptiform discharges, are present in the majority of patients with occipital epilepsy (76; see also Chapter 1) and should help distinguish these patients from those with psychogenic visual disturbance.

TREATMENT

The correct diagnosis is essential for patients with NES because early diagnosis is associated with better outcome (1,7,22). Yet, even after a diagnosis of NES is established, physicians must follow such patients. In fact, many psychogenic seizure patients benefit from education and support that can be readily provided by the neurologist or primary care physician (1). However, if the neuropsychologic assessment suggests a clinical profile that requires a professional mental health intervention, then an appropriate referral should be made.

The management of patients with psychogenic seizures is similar to that for patients with other types of so-called "abnormal illness behavior" (1). The first consideration should be the manner in which the diagnosis of psychogenic seizures is presented to the patient and family. It is important to be honest with the patient and to demonstrate a positive approach to the diagnosis (82). The physician should emphasize as favorable the good news that the patient does not have epilepsy, and should also stress that the disorder, although serious and "real," does not require treatment with antiepileptic medications and that, once stress or emotional issues are resolved, the patient has the potential to gain better control of these events (1,82).

Nevertheless, not all patients readily accept the diagnosis or this type of approach. Some may seek other opinions, and this should not be discouraged. An adversarial relationship with the patient should be avoided. In fact, the patient should be encouraged to return as desired, and records should be made available to avoid duplication of services.

After the diagnosis of psychogenic seizures is presented, supportive measures should be initiated. Regular follow-up visits for the patient are useful even if a mental health professional is involved (1,83). This allows the patient to get medical attention without demonstrating illness behavior. Moreover, it also offers support to the involved mental health professional. Patient education and support are stressed at these visits. Since family issues are often important contributing factors, family members should be involved.

For patients with coexisting epileptic and nonepileptic seizures, proper treatment depends on defining the nature of the seizures that are causing problems. In many patients with coexisting epileptic and nonepileptic seizures, the events are really sequential rather than truly actively coexisting or simultaneous. Thus, a patient may have a history of epileptic seizures, often in the distant past or in the case of some adults in childhood, and may be on antiepileptic medications for these; then the patient develops different types of events that usually prove to be psychogenic NES. In such cases, the active problem is really not epilepsy, because the patient's epileptic seizures are well-controlled. Therefore, attention and treatment should be directed to the NES, and the patient and family reassured that the epileptic seizures are controlled. An example of such a patient with NES presenting sequentially after control of her true epilepsy following successful surgery for epilepsy is presented in the case.

Case Study #3. R.E. was a 31-year-old woman with intractable complex partial seizures arising from a left temporal seizure focus. She also had a history of depression and anxiety, which she related to her epilepsy. She was monitored in our epilepsy monitoring unit prior to epilepsy surgery and had well-documented epileptic seizures arising from her left temporal lobe. Following surgery, she became seizure-free and remained so for 2 years on carbamazepine.

Then she began to have different events. These consisted of shaking of her arms and legs while she appeared semiconscious. These were initially suspected to be recurrent epileptic seizures, and her carbamazepine was increased and then topiramate was added. However, her events continued to increase in frequency and severity, occurring many times a week. She was admitted for epilepsy monitoring, and the events proved to be nonepileptic, psychogenic seizures. Her antiepileptic medications were reduced, and she was given psychiatric supportive care.

Gradually, the NES resolved, and she has remained seizure-free, except for one or two apparent nonepileptic episodes each year, particularly during periods of emotional stress. She and her family are aware that these are not epileptic seizures, and she functions reasonably well despite them. There is no evidence that her epileptic seizures recurred, but we maintain her on some antiepileptic therapy to prevent a recurrence of her epileptic seizures.

In other such patients, both epileptic and nonepileptic seizures present simultaneously, thus making management even more complex. In such patients, we have found it particularly helpful to focus on the semiology of seizure manifestations as recorded by video-EEG monitoring to distinguish NES from epileptic events. We then direct our treatment of the patient according to the semiology manifesting at that time. For example, the NES of the patient described above consisted of shaking while alert and responsive and were very different from her true epileptic seizures, which we

had previously observed and recorded. Those were classical complex partial seizures with impaired consciousness and automatisms often secondarily generalized with convulsions. By focusing on the clinical characteristics of her seizures, we could determine what type of seizure was likely to be causing her symptoms at a given point in time and could focus our treatment accordingly. We also have found it useful show the such epileptic or nonepileptic seizures to family members to help them understand how to respond best to a patient's symptoms when epileptic and nonepileptic seizures coexist as active problems.

PROGNOSIS

The outcomes of patients with psychogenic seizures vary. Outcome studies show that about half of all patients with psychogenic seizures function reasonably well after diagnosis. However, many have poor functional outcomes, and only about 30% completely stop having psychogenic seizures (1,7,30,84). When the diagnosis of psychogenic seizures is based on reliable criteria such a video-EEG monitoring, misdiagnosis is unlikely, but as noted above for frontal lobe seizures, it can occur. Instead, the usual cause for a poor outcome is related to a patient's chronic psychologic and social problems (1,7,30). Outcomes in patients with coexisting epilepsy and NES have not been extensively investigated, but Meierkord et al. (2) found that patients with epilepsy were less likely to gain complete resolution of their NES than those with NES alone.

It is noteworthy that children with psychogenic seizures appear to have a much better prognosis than adults (21,22). Children may have psychogenic seizures more related to transient stress and coping disorders, whereas adults are more likely to have psychogenic seizures within the context of more chronic psychologic maladjustment, such as personality disorders (22). Another factor accounting for the better outcomes in children is that they are usually diagnosed earlier (21,22).

Patients with stress and coping disorders respond relatively well to supportive educational or behavioral therapeutic approaches. In contrast, patients with somatoform disorders and factitious disorders more often have associated chronic personality problems and, correspondingly, a poorer prognosis (1,84). In addition, recent evidence suggests that patients with nonepileptic psychogenic seizures may benefit from structured treatment programs (85) and continued support by epilepsy specialists or centers (84). As knowledge about the nature of psychogenic seizures and their associated psychopathology is gained, better treatment strategies can be developed that will improve the care and prognosis of these difficult and challenging patients.

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21 Panic Attacks and Panic Disorders: The Great Imitators

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"I thought my head was going to explode! And my hands were shaking so bad I couldn't hold a glass of water. Of course, I couldn't drink anyway since I felt like I was choking. Then my fingers and lips went numb, and I felt weak all over. I was sure I was going to faint. Now I worry all the time about when it is going to happen again" (1).

Faced with a patient exhibiting these symptoms, a neurologist may suspect epilepsy, a cardiologist myocardial infarction, and an endocrinologist pheochromocytoma. In fact, these are all symptoms of a panic attack.

The overlap of symptoms between panic disorder (PD) and other disorders is so great that a patient with PD may seek help from as many as ten physicians before being diagnosed appropriately (2). This is of particular concern because of the significant morbidity of this disorder, which affects approximately 2% of the population worldwide (3). Panic disorder patients experience numerous physical symptoms and have the highest rate of outpatient general medical use among the anxiety disorders (2,4). Furthermore, PD patients have an increased risk of developing several physical disorders, including hypertension, peptic ulcer disease, migraine, mitral valve prolapse, irritable bowel syndrome, and asthma (5).

In addition to their physical complaints, patients with PD suffer from psychosocial impairment. Panic disorder is associated with significant work, family, and social impairment (6). As many as 88% of patients with PD also suffer from depression, and 27% of PD patients have problems with substance abuse (3). The suicide attempt rate in PD is 15%, independent of comorbid depression (3). Quality of life is negatively impacted by the presence of PD, as demonstrated by a study in which 33% of PD patients reported their physical and emotional health as fair to poor, compared to 23% of participants with no psychiatric illness (7). In fact, the quality of life of PD patients may actually be lower than that of patients with other anxiety disorders, because patients with panic experience both mental and physical impairments (8).

Thus, it is extremely important to derive an accurate diagnosis and provide appropriate treatment as early as possible in the course of PD. This chapter provides definitions of panic attacks, panic disorder, and agoraphobia, and discusses the possible etiologies of panic symptoms. A differential diagnosis and guidelines for the diagnosis of PD are presented, with particular emphasis on the similarities and distinctions between panic attacks and seizures. Finally, recommendations for treatment are included.

TABLE 21.1
Symptoms in Panic Attacks
(At least four must be present to diagnose an attack)

1. Palpitations, pounding heart, or accelerated heart rate
2. Sweating
3. Trembling or shaking
4. Sensations of shortness of breath or smothering
5. Feeling of choking
6. Chest pain or discomfort
7. Nausea or abdominal distress
8. Feeling dizzy, unsteady, lightheaded, or faint
9. Derealization (feelings of unreality) or depersonalization (being detached from oneself)
10. Fear of losing control or going crazy
11. Fear of dying
12. Parasthesias
13. Chills or hot flushes

PANIC ATTACKS

Panic attacks are sudden, discrete attacks of unexpected and overwhelming fear that can include physical, cognitive, and behavioral symptoms. Physical symptoms include cardiac and pulmonary symptoms, and gastrointestinal discomfort and neurologic symptoms such as headache and dizziness. Typical cognitive symptoms are catastrophic thinking and the belief that one is about to die, lose control, or go insane. One likely feels a need to flee the current situation, and may eventually avoid anxiety-provoking situations. Panic attacks generally last between 5 and 30 minutes, but can be much longer. To diagnosis an episode as a panic attack, a minimum of four of the thirteen symptoms listed in Table 21.1 must be present (9).

Nocturnal Panic

Panic attacks can occur both during waking and during sleep; attacks that occur during sleep are termed nocturnal panic attacks. The symptoms of daytime and nocturnal attacks are essentially the same, and both may occur often in patients with PD, although daytime attacks are generally more prevalent. It is possible for a patient to experience only nocturnal panic attacks; however, this is not common.

Situational Triggers

Some panic attacks occur in response to a trigger, or a particular situation or stimulus. These attacks are more likely to occur in the presence of the trigger but will not necessarily occur every time. Often, anticipatory anxiety and subsequent avoidance of the particular situation occurs. Common triggers include driving or riding in vehicles and being in large crowds, perhaps because such situations involve loss of control or being trapped.

Situational panic attacks do occur in PD, but may occur in any number of other disorders as well, including social anxiety disorder and post-traumatic stress disorder. The distinguishing feature of PD, required for a diagnosis, is the presence of unexpected or spontaneous panic attacks.

PANIC DISORDER

A diagnosis of PD requires the presence of unexpected panic attacks followed by persistent concern over having another attack, worry about the implications of the attacks, and/or significant changes in behavior as a result of the attacks. The panic attacks cannot be due to the direct physiologic effects of a substance or a general medical condition, and cannot be better accounted for by another mental disorder. The onset of PD is typically during the adolescent years or in young adulthood; onset after age 45 is rare. Twice as many women as men have panic disorder (10).

AGORAPHOBIA

Agoraphobia is a distinct disorder that occurs in approximately one-third of PD patients. Agoraphobia is defined as anxiety over experiencing a panic attack in a situation in which it would be difficult to escape or get help. This anxiety leads to an avoidance of situations in which escape is thought difficult, in many cases rendering the patient housebound. Agoraphobia is a separate disorder from PD and can occur either alone or in conjunction with PD. Agoraphobia is also common in other anxiety disorders. Panic disorder with agoraphobia is more disabling than either PD alone or agoraphobia alone (11). These patients are also more likely to have comorbid disorders and to have higher neuroticism scores (11).

ETIOLOGIES

Theories attempting to explain the origin of panic attacks, PD, and agoraphobia are abundant and include psychologic, biologic, and psychodynamic explanations. Unfortunately, data regarding the etiology of PD are sparse, although the body of evidence has grown over the last several years. It is likely that PD and panic attacks can result from multiple causes, both psychologic and biologic, and can be similarly treated by methods both psychologic and biologic.

Psychologic Theories

Behavior Theory

The behavioral theory of panic attacks centers around the concept of conditioned learning. According to this theory, patients associate certain cues with panic attacks, whereas avoidance of those cues is associated with the relief of not having a panic attack. Cues, or triggers, can be external, such as riding in a car or standing in line, or they can be internal, such as tachycardia or dizziness. As one example, the experience of a panic attack while driving can create an association between driving and panic, such that anticipatory anxiety may develop in future driving situations, which could lead to a full panic attack. The patient may therefore begin to avoid driving situations out of fear of having panic attacks. Behavior theory therefore provides a reasonable explanation for situational panic attacks and agoraphobia and is further supported by the documented effectiveness of behavior therapy as treatment for PD (12,13). However, it fails to explain spontaneous panic attacks or the fact that not all people who experience a panic attack develop further anxiety or avoidant behavior.

Cognitive Theory

In the cognitive model of PD, panic attacks result from cognitive distortions. This theory suggests that initial physical symptoms are misinterpreted as dangerous or life-threatening, thus leading to catastrophic thinking that stimulates increased physical sensations, increased apprehension and anxiety, and consequently the development of panic attacks. For instance, a person may experience mild tachycardia and begin to worry that it is a sign of a serious medical disorder. These thoughts of potential illness and death cause anxiety, the associated physical symptoms, and ultimately lead to a full panic attack. As with behavior therapy, cognitive therapy is successful and in fact is often combined with behavior therapy (13).

Psychodynamic Theory

In the psychodynamic theory, panic attacks transpire because the psychologic defenses are not able to suppress anxiety that arises from unconscious fantasies, particularly those from childhood that involve parental disapproval or separation from parents (14).

Biologic Theories

Noradrenergic Dysregulation

One biologic theory of PD is that there is an overactivity of the norepinephrine system that eventually leads to down-regulation of postsynaptic adrenergic receptors. Several studies utilizing pharmacologic agents have linked the noradrenergic system to panic attacks. Yohimbine is an alpha-2 adrenergic presynaptic antagonist that increases the amount of norepinephrine available. Yohimbine has been shown to induce more anxiety and symptoms of panic attacks in PD patients than in controls (15–17). In addition, patients who experienced panic symptoms also had increased serum levels of the noradrenergic metabolite 3-methoxy-4-hydroxyphenylglycol, or MHPG (18).

Abnormal noradrenergic activity in PD patients has also occurred in response to clonidine, an alpha-2 adrenergic agonist. Several studies have shown that growth-hormone response to clonidine is blunted in PD patients (18), an effect that has also been seen in other anxiety disorders (19–21), and that suggests overactivity of the noradrenergic system. The mechanism behind the blunted growth hormone response is not clear and may be abnormal sensitivity of presynaptic adrenergic receptors or postsynaptic adrenergic receptors.

Data from patients experiencing spontaneous panic attacks as opposed to those induced by pharmacologic agents offer less support for the role of norepinephrine in PD. Panic disorder patients do not have elevated MHPG levels during spontaneous panic attacks (22,23), nor do they seem to have increased activity of the sympathetic nervous system (SNS) at rest (24). However, in a study assessing SNS activity in PD patients, three patients who experienced spontaneous panic attacks did have increases in epinephrine and norepinephrine concentrations, suggesting that SNS activity is a result of panic rather than a stimulating factor (24).

Serotonergic Dysregulation

The strongest evidence linking the serotonergic system to PD is the success of serotonergic antidepressants in treating the disorder (25). Currently the serotonin selective reuptake inhibitors (SSRIs) are first-line treatment for PD and other anxiety disorders. In recent years, evidence has emerged linking serotonergic dysfunction to anxiety in general (26–28), with some data suggesting a specific role in PD (29,30).

It may be that serotonin has an indirect role in PD via its effects on other neurotransmitter systems. Serotonin and norepinephrine have a reciprocal relationship, so that serotonergic projections from the raphe nucleus to locus coeruleus inhibit norepinephrine release, whereas noradrenergic projections from the locus coeruleus to the raphe nucleus stimulate serotonin release (31). In one study, clinical global improvement

correlated with decreases in MHPG in PD patients treated with fluoxetine, an SSRI (29). Furthermore, untreated PD patients had increased volatility of plasma MHPG during clonidine challenge; this volatility was attenuated following treatment with fluoxetine (29). Conversely, other data does not support serotonergic control of noradrenergic function as relevant to PD (32). In a study by Goddard et al., PD patients successfully treated with fluvoxamine had neither decreases in baseline plasma MHPG nor reduced MHPG response to yohimbine (32).

Serotonin also inhibits glutamatergic input to the amygdala (33), which is central to the fear response. Efferents from the amygdala stimulate several brainstem areas associated with behavioral and autonomic symptoms of anxiety and panic; thus, failure of the serotonergic system to block excitatory input to the amygdala may account for symptoms of PD.

GABAergic Dysregulation

Several lines of evidence link the neurotransmitter gamma aminobutyric acid (GABA) to PD. GABA is the primary inhibitory neurotransmitter in the brain, and GABA neurons are abundant in the areas of the brain most associated with anxiety and fear (31), including the amygdala. In animal studies, reductions in GABA are associated with increased anxiety-like behaviors (34,35). Moreover, there is recent evidence that patients with PD have reduced GABA levels in the occipital cortex (36).

Pharmacologic treatment of PD with benzodiazepines also suggests a role of GABA in the disorder. Benzodiazepines, which bind to the GABA-A receptor complex and increase GABA output, are anxiolytic and effective in PD (25). Other GABAergic agents are beginning to be used to treat panic disorder as well, including the anticonvulsants valproate and tiagabine (37–39).

Consistent with the successful use of GABAergic agents to treat PD, there is evidence for abnormal GABA-A benzodiazepine receptor functioning in PD patients. Nutt and Lawson postulated that PD patients have an altered set-point for benzodiazepine receptors (40). In other words, full agonists act as partial agonists and antagonists act as partial inverse agonists (Figure 21.1). Studies with the benzodiazepine receptor antagonist flumazenil support this theory, as flumazenil has no effect on normal controls but is anxiogenic in PD patients (41). Also, PD patients are less sensitive to benzodiazepines (42) and have reduced benzodiazepine receptor binding compared to normal controls (43–45). Reduced benzodiazepine receptor binding in PD patients has been observed in multiple studies and in various brain regions (44–47), although some studies show no differences between PD patients and controls (48,49).

The likely role of GABA in PD is of particular interest because of the similarities between panic attacks and seizures, which also appear to be modulated by the GABA system (50) and which are often treated with GABAergic agents (51,52). The relationship between PD and seizures is discussed in further detail later in the chapter.

Other Neurochemical Systems

Other neurochemicals have been linked to anxiety and panic. Caffeine, an adenosine antagonist, can induce panic attacks in PD patients (53,55). The neuropeptide cholecystokinin (CCK) has been shown to be panicogenic in humans (56). Other neuropeptides may be implicated in anxiety as well, including substance P (57,58). Corticotrophin releasing factor (CRF) may have a role in anxiety (59). Mice bred without the CRF-1 receptor exhibit less anxiety-like behavior than wild-type mice (60), and CRF antagonists are currently in development as anxiolytics. Glutamate also likely has an important role in anxiety and panic. Glutamate is the primary excitatory neurotransmitter in the brain, and like GABA, has many neurons in the areas of the brain associated with fear and anxiety (31). Preliminary evidence suggests that glutamate activity may be important in PD (61,62).

Carbon Dioxide Hypersensitivity

The theory of carbon dioxide hypersensitivity is derived from the finding that PD patients experience more panic attacks than controls during carbon dioxide challenge and during lactate challenge (18). In addition, patients show less sensitivity to carbon dioxide after receiving pharmacologic antipanic treatment than before treatment (63). Panic disorder patients also often have chronic metabolic alkalosis with acute respiratory alkalosis during panic attacks (18). Based on all these findings, PD patients have been theorized to be chronic hyperventilators. Chronic hyperventilation serves to keep carbon dioxide levels low and may thus keep PD patients from panicking.

False Suffocation Alarm Theory

Consistent with the ideas of chronic hyperventilation and carbon dioxide hypersensitivity is Klein's false suffocation alarm theory (64). According to this theory, a suffocation alarm system is normally activated when one is smothering. However, in PD patients, this alarm

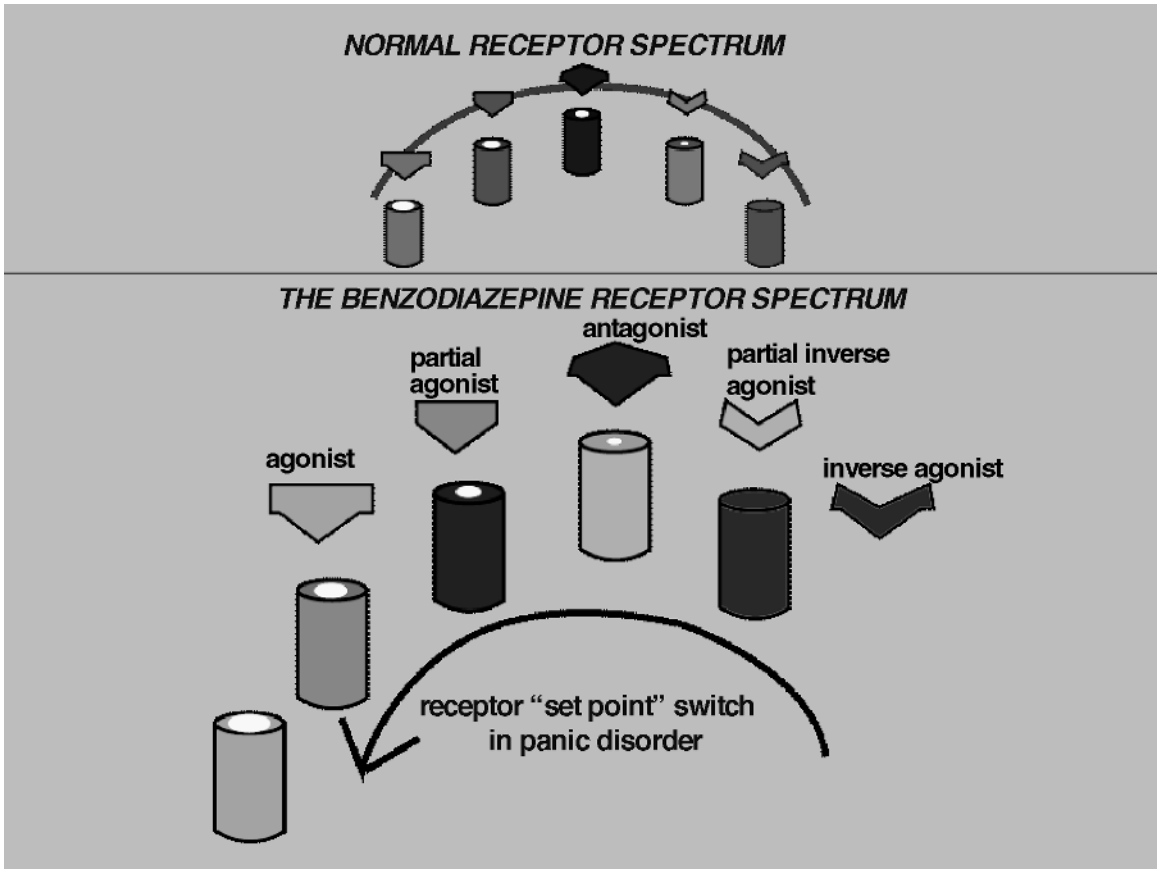

FIGURE 21.1

Receptor set point theory (40). Used with permission from Stahl, Essential Psychopharmacology, Cambridge University Press, 2000.

is triggered inappropriately, resulting in symptoms of panic attacks. The existence of a suffocation alarm system is supported by a disorder known as Ondine's curse, or congenital hypoventilation syndrome, in which patients stop breathing during sleep and yet are not stimulated to breathe by rising carbon dioxide levels (65). Such patients resume breathing when wakened. Under the false suffocation alarm theory, spontaneous panic and chronic anxiety are mediated by different mechanisms. This is supported by studies that implicate the hypothalamic-pituitary-adrenal (HPA) axis in anticipatory anxiety but not in spontaneous panic (66).

Neuroanatomic Findings

Although the locus coeruleus has long been implicated in fear, anxiety, and panic, recent neuroanatomic findings and theories in panic disorder center around the amygdala. The amygdala has efferent and afferent connections to cortical, subcortical, and brainstem structures that are involved in all aspects of the fear response (67,68). The amygdala sends stimulatory projections to the periaqueductal grey matter, which controls motor responses of fear such as freezing (69); to the parabrachial nucleus, which controls respiration (70); to the locus coeruleus, which controls heart rate and blood pressure (31); and to the hypothalamus, which controls the release of steroid hormones (71). Input from the sensory thalamus, prefrontal cortex, and hippocampus to the amygdala can lead to stimulation of the efferent pathways and consequently the autonomic and behavioral symptoms of anxiety and panic (67,68). That the amygdala receives inputs from both the sensory thalamus and cortical regions is important because it illustrates the brain's ability not only to elicit an immediate fear response to stimuli (via the sensory thalamus), but also to incorporate cognitive

TABLE 21.2
All Panic/Anxiety is Not Panic Disorder*

	Spontaneous panic attacks	Situational panic attacks	Anticipatory anxiety	Symptoms of Autonomic arousal	Phobic avoidance
Panic disorder	+++	+/–	+++	+++	+
Agoraphobia	+/–	+/–	+++	++	+++
Social phobia	–	++	++	++	+++
Specific phobia	+–	+++	++	++	+++
PTSD	+/–	+	+/–	+++	+
GAD	+/–	+/–	+/–	+	+/–

*+ – +++: must be present for diagnosis; present in varying degrees; –: not usually present; +/–: frequently present but not needed for diagnosis; PTSD: posttraumatic stress disorder; GAD: generalized anxiety disorder.

evaluation into the response (via the prefrontal cortex and hippocampus) (67,72).

Support for the involvement of the amygdala in panic comes from studies of both animals and humans (73). In animals, the amygdala is active during conditioned fear responses; furthermore, the behaviors and autonomic activity that occur during conditioned fear responses resemble the symptoms of panic attacks (67,74). In humans, electrical stimulation of the amygdala produces autonomic activity and feelings of anxiety (73). Stimulation of the amygdala in humans can also cause cardiovascular effects, gastric effects, and respiratory effects (73), all of which can occur during panic attacks.

The hippocampus may be particularly important to anticipatory anxiety and phobic avoidance in PD, rather than to actual panic attacks (67,75). Animal studies have linked the hippocampus to avoidance behavior (75). This may also account for why both pharmacologic and psychosocial treatments are so effective in treating PD. Gorman et al. (67) hypothesized that pharmacologic agents treat PD by desensitizing the fear network via efferent projections from amygdala to brainstem centers, whereas psychosocial therapy's effectiveness at reducing contextual fear is due to effects on memory (i.e., the hippocampus).

Genetics

The rate of PD in families of patients with PD is 15% to 20%, with a 30% to 40% concordance rate for monozygotic twins (14,76). The risk of PD is 10% for first-degree relatives, compared to 2.1% for other relatives (76). Of all the anxiety disorders, PD has the most evidence for a genetic link.

DIFFERENTIAL DIAGNOSIS

Psychiatric Differential

As mentioned earlier, the distinguishing feature of PD is not the presence of panic attacks in general, but rather the occurrence of spontaneous or unexpected panic attacks. In fact, panic attacks can occur in any of the five major anxiety disorders, as well as in some medical disorders. Thus, the presence of panic attacks alone cannot be used for a diagnosis of PD (Table 21.2). However, although all the anxiety disorders share symptoms, including panic attacks, there are distinct differences between the disorders that allow for appropriate diagnosis.

The symptoms of social anxiety disorder (SAD) include anticipatory anxiety, phobic avoidance, and in some cases, panic attacks. These symptoms are also seen in PD, and although they may manifest in slightly different ways (77,78), it can be difficult to distinguish between the two disorders based on the presence of these symptoms. However, SAD and PD differ in two notable ways. First, the anxiety in SAD is specific to social or performance situations and the fear of embarrassment when in these situations (31). There is no significant fear of having panic attacks and being unable to get help, which is a central feature of PD. In addition, if panic attacks are present in SAD, they are situational as opposed to spontaneous. These same two features distinguish specific phobia from PD: patients with specific phobia do not fear having panic attacks, nor do they experience spontaneous attacks (31).

The other major anxiety disorders include posttraumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), and generalized anxiety disorder

(GAD). Unlike PD, PTSD develops as a result of an actual threatening event (31). Anxiety and attacks of panic occur because the event is re-experienced through memory or flashbacks; thus, they are not spontaneous but rather have a specific trigger. In OCD, anxiety and panic are directly related to the obsessions and compulsions (31). In GAD, patients experience anxiety with no discernible cause (31). There is no specific trigger, as in PTSD, nor is the fear related to having panic attacks, as in PD.

The use of certain substances can evoke panic-like symptoms and should be considered before a diagnosis of PD is made. Such substances include caffeine, amphetamines, and decongestants, as well as marijuana and cocaine. Panic attacks can occur as a result of substance use in both PD patients and healthy individuals, although they are more likely to occur in PD patients. If patients who experience panic attacks following substance use do not also experience spontaneous panic attacks, then they can be diagnosed with substance-induced anxiety disorder (1).

Medical Differential

The appropriate diagnosis of PD is complicated by the fact that the symptoms of PD often resemble those of medical disorders, such as cardiac impairments or seizures. In addition, panic attacks can be triggered by medical conditions or medications used to treat these conditions. These panic attacks may subside once the illness has been appropriately treated or once the medication has been stopped; however, it is also possible that PD will develop. Comorbid medical conditions are also common in PD and can further obscure the diagnosis.

Cardiac

Chest pain is one of the most common symptoms of panic attacks. Patients experiencing chest pain generally present to emergency rooms and are convinced that they are having myocardial infarction. However, only 16% of patients presenting with chest pain are actually diagnosed with cardiac disease (79). In fact, in the majority of cases, no organic cause is found (80). Panic disorder is actually more common than cardiac disease in patients presenting with chest pain in cardiological settings (80). In one study, the prevalence of PD in a total chest pain population was nearly 40%, compared to a prevalence of 16% for coronary artery disease (80).

Distinguishing between panic attack and cardiac disease without testing can be difficult. However, there may be some differences in the type of pain experienced that can aid in appropriate diagnosis (1,80). Like myocardial infarction patients, PD patients may experience severe chest pain that radiates down the arm, but PD patients generally describe the pain as "sticking," whereas myocardial infarction patients describe it as "crushing" (1). One study also found that pain in area 16 (i.e., the right palm) of the Dermatome Pain Map was a predictor of PD in cardiology unit patients presenting with chest pain (80–81). Screening instruments have also been developed that can aid in appropriate diagnosis (80–81). The Agoraphobia Cognitions Questionnaire (ACQ), the Short Form McGill Pain Questionnaire (SF-MPQ) affective pain subscale, and the Symptom Checklist 90 Revised (SCL-90-R) somatization subscale can predict the presence of PD (80). In addition, three specific items from these scales (ACQ item 2, SCL-90-R item 12, SF-MPQ item 12) can be used to identify between 59% and 85% of patients as PD or non-PD (80).

Endocrine

It is possible that hypoglycemia could result in symptoms of panic; this can be assessed with serum glucose testing (1). Another endocrine disorder in the differential diagnosis of PD is pheochromocytoma. Pheochromocytoma is a rare disorder that results in tachydysrhythmias and extreme anxiety (82).

Pheochromocytoma can be lethal if not treated early, and thus it is important that it be considered in the differential diagnosis. Some differences in symptoms exist between PD and pheochromocytoma. In pheochromocytoma, sweating is generally more on the torso than on the extremities or forehead, and head pain is described as "exploding" (1). Also, patients with pheochromocytoma generally feel the need to remain still during their symptoms, whereas PD patients experience a desire to flee (1).

Neurologic

Complex partial seizures, especially those with a temporal lobe focus, can result in many panic attack symptoms, including fear (1,73). In fact, fear is often a central feature of seizures (83–89), in many cases prompting a misdiagnosis of PD (84–87,89). Similarly, the symptoms of panic attacks may be mistaken for neurologic disorders, in particular seizure disorders (90–92). Both panic attacks and seizures have sudden onset and may manifest as tingling, dizziness, palpitations, derealization, hyperventilation, and abdominal distress, as well as symptoms of fear and anxiety (9,93).

The similarities between PD and seizures are not surprising in light of the fact that key brain structures, such as the amygdala, and a key neurotransmitter, GABA, appear to be involved in both disorders. As

discussed earlier, the amygdala has efferent and afferent connections to brain structures involved in the different symptoms of panic attacks, and electrical stimulation of the amygdala results in many of those symptoms (67,68,73). Abnormal electrical activity of the amygdala is also associated with seizures (94). Reduced GABA levels have been found both in patients with PD (36) and in patients with epilepsy (50), and GABA agonists both reduce anxiety (35) and suppress seizures (50). Furthermore, pharmacologic agents that increase GABA levels are used to treat both PD and seizure disorders. Benzodiazepines have long been used to treat both disorders (25,50), and anticonvulsants that are used to treat epilepsy are increasingly being considered as potential treatments for PD as well (37–39).

The overlap of symptoms between panic attacks and seizures makes it difficult to derive an accurate diagnosis without the use of electroencephalogram (EEG) and other medical testing. However, despite their many similarities, distinguishing features can aid in appropriate diagnosis. Several symptoms of seizures are uncommon in panic attacks, including motor automatisms, transient amnesia, psychosensory symptoms, urinary or fecal incontinence, convulsions, and complete loss of consciousness (79,95–96). Panic attacks generally last between 5 and 30 minutes, whereas seizures are rarely longer than 2 minutes in duration. Other differentiating features include risk factors such as a family history of panic and anxiety versus epilepsy, as well as a personal history of separation anxiety versus febrile convulsions, head injury, or central nervous system infection (95–97).

TREATMENT

Serotonin Selective Reuptake Inhibitors

The serotonin selective reuptake inhibitors (SSRIs) are currently first-line treatment for PD. Three of the SSRIs, paroxetine, sertraline, and fluoxetine, have been specifically approved by the Food and Drug Administration (FDA) to treat PD. These drugs have proven efficacy in PD including prevention of relapse, are safe for long-term use, and have no abuse potential (25). Other SSRIs such as citalopram, escitalopram, and fluvoxamine may also be effective in PD. However, onset of action with SSRIs is usually delayed for days or even weeks, and at the start of treatment patients may actually experience a transient worsening of anxiety (25).

Other Antidepressants

Several of the tricyclic antidepressants (TCA) have been studied and shown to be effective in PD, including imipramine, desipramine, and clomipramine (18). The primary disadvantage to using TCAs is the side effect profile, which includes anticholinergic effects, weight gain, and hypotension. A recent meta-analysis (98) compared the SSRIs and the TCAs on four dimensions of PD (panic, agoraphobia, depression, general anxiety) and found that effect sizes were comparable for the two drug classes. However, the number of drop-outs was significantly greater in patients receiving TCAs, suggesting that SSRIs are better tolerated (98).

The monoamine oxidase inhibitors (MAOIs), in particular phenelzine, are effective in treating PD (99). Unfortunately, MAOIs require dietary restrictions (i.e., a low-tyramine diet). The dietary restrictions, as well as some of the side effects associated with MAOIs, such as orthostatic hypotension and weight gain, may lead to reduced compliance. However, reversible inhibitors of monoamine oxidase A (RIMAs) such as moclobemide may be as effective as the older MAOIs but tolerated better and without the dietary restrictions (100). In fact, moclobemide has been shown to be effective and well tolerated in panic disorder (101,102).

Venlafaxine is a dual serotonin and norepinephrine reuptake inhibitor (SNRI) that is approved by the FDA to treat major depression and generalized anxiety disorder. Preliminary data suggest that venlafaxine is efficacious in PD as well (103,104). Other antidepressants that may be effective in PD include nefazodone (105,106), mirtazapine (107,108), and reboxetine (109).

GABAergic Agents and Anticonvulsants

Two of the benzodiazepines, alprazolam and clonazepam, are approved by the FDA to treat PD, and other benzodiazepines have been shown to be effective as well (25). As mentioned earlier, benzodiazepines bind to the GABA-A receptor complex and increase the output of the inhibitory neurotransmitter GABA. The benzodiazepines have a rapid onset of action; however, they are likely to cause sedation at the start of treatment. Patients receiving benzodiazepines may also develop physical dependence, the risk of which increases with time (25). To avoid withdrawal symptoms, benzodiazepines should be tapered slowly.

Some anticonvulsant agents are being tested for their safety and efficacy in anxiety disorders. These include valproate (37,110,111), gabapentin and pregabalin (38), and tiagabine (39). Carbamazepine has also been tested in PD, but the evidence has been mixed (112,113).

Cognitive-Behavioral Therapy

Although patients can receive either cognitive or behavioral therapy for PD, it is common for the two to be com-

bined. Cognitive behavioral therapy is very effective in PD, with or without agoraphobia (114,115). Cognitive and behavioral therapies include patient education, cognitive restructuring, exposure therapy, and relaxation therapy. It is important to educate the patient on the disorder so that he understands that although the symptoms of panic attacks are certainly distressing, they are not in fact life-threatening. This involves cognitive restructuring, in which the patient's cognitive distortions, such as the belief that the bodily sensations are dangerous, are challenged. Exposure therapy involves modifying the patient's response to panic-provoking stimuli, and can be situational or interoceptive. In situational exposure therapy, patients are exposed to panic-provoking situations such as driving, whereas in interoceptive exposure therapy patients are exposed to the physiologic sensations of panic. Interoceptive exposure therapy is contraindicated in certain medical conditions, such as asthma.

Combination Treatments

Combination treatment can refer to either the combination of pharmacologic treatment and psychosocial treatment or to the combination of two different pharmacologic agents. There has been some concern that adding pharmacologic therapy, particularly benzodiazepines, to psychosocial therapy may adversely affect the outcome of psychosocial treatment. However, recent data do not support this for benzodiazepines (116) or for antidepressants (117–120). In fact, several studies that have compared psychosocial treatment alone to psychosocial treatment plus an SSRI have actually shown the superiority of combination treatment (117–120). In addition, adding cognitive behavioral therapy during the discontinuation of SSRIs may help to maintain remission (121). Cognitive behavioral therapy initiated during the discontinuation period of benzodiazepines may also be beneficial. Otto et al. (122) compared the effects of benzodiazepine discontinuation alone to benzodiazepine discontinuation with cognitive-behavioral therapy. They found a notable increase in panic attacks during tapering of the last 50% of the dose for patients without cognitive behavioral treatment, whereas those receiving cognitive behavioral treatment did not experience rebound panic.

Combining pharmacologic agents may also be superior to single-agent treatment, at least at the beginning of therapy. Since both serotonin and gamma aminobutyric acid projections are involved in the inhibition of anxiety, combining these methods of treatment may be synergistic (123). In fact, there is evidence that early anxiety associated with the initiation of an antidepressant is decreased with concomitant use of a benzodiazepine (124–126). In contrast, antidepressants may prevent and treat depression with benzodiazepines (127,128). Most of the studies assessing a combined use of an SSRI with a benzodiazepine have been in depression (124,125,127,128). However, there is a PD study in which combination treatment was superior to SSRI alone early in treatment (126).

Treatment-Refractory Patients

Predictors of nonresponse to treatment include longer duration of illness, higher baseline phobic avoidance and anxiety scores, and the presence of comorbid disorders (129). However, nonresponse or inadequate response to PD treatment may not reflect actual treatment-resistance, but rather insufficient dose or length of treatment, treatment intolerance, or inaccurate diagnosis. It should be kept in mind that the time to remission is generally longer for PD patients who also have agoraphobia (130). If the dose and duration of treatment are appropriate, and the patient is compliant with treatment, then careful reassessment of the diagnosis and potential medical conditions is warranted.

PROGNOSIS

Panic disorder is associated with significant physical and psychosocial impairment. In addition, comorbidity rates for both psychological and physical illness are high in PD patients. Ensuring adequate treatment duration is important, as relapse rates are high for patients who stop treatment within 6 months of symptom resolution. Medication discontinuation can be tried in patients who have been asymptomatic for 6 months to a year; however, PD is a chronic illness that most often requires indefinite maintenance therapy. Despite the chronicity of the disorder, if diagnosed and treated appropriately, PD patients can experience significant improvements in quality of life, with substantially reduced costs in terms of healthcare costs and psychosocial and physical suffering.

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