Seizures and Epilepsy: Pathophysiology and Principles of Diagnosis

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**INTRODUCTION**

Epileptic seizures are among the most common neurologic symptoms in all human populations. Over 5% of Americans have at least one epileptic seizure during their lifetimes. At any point in time, 1% to 2% of Americans have epilepsy. Cumulative lifetime incidence of epilepsy exceeds 3%. These statistics are similar across large human populations, although the incidence and prevalence of epileptic seizures and epilepsies can be higher in certain smaller groups (for example, in populations exposed to military combat due to high rates of traumatic brain injury [TBI]).

This article is the first of a 6-part review of epilepsy diagnosis and management. It provides an overview of the pathophysiology of epileptic seizures and classification systems for seizure and epilepsy and summarizes key features of established types of epilepsies. Subsequent articles in this series will discuss the techniques, interpretation, and applications of electroencephalography (EEG) and video-EEG (Part 2) and structural and functional brain imaging (Parts 3 and 4). Part 5 focuses on selection, dosing, adverse effects, and therapeutic monitoring of antiseizure medications. Part 6 will review both epilepsy surgery, including the role of neuropsychological testing in planning for epilepsy surgery, and the application of neuropsychological testing in initial diagnosis and rehabilitation of patients with epilepsy.

**DEFINITIONS**

Seizures are defined as paroxysmal events of transitory alteration in consciousness or other signs or symptoms that can be due to brain dysfunction. Epileptic seizures are seizure events that are caused by excessive, abnormally synchronized, localized or widely distributed neuronal electrical discharges; usually these electrophysiological correlates are presumed by indirect evidence, although electrophysiological recordings sometimes are performed during seizures. Nonepileptic seizures are seizure events that are not caused by such electrocerebral discharges; usually these electrophysiological correlates are presumed by indirect evidence, although electrophysiological recordings sometimes are performed during seizures. Nonepileptic seizures are seizure events that are not caused by such electrocerebral discharges. Nonepileptic seizures are sometimes divided into categories of organic nonepileptic seizures, such as atypical syncope and parasomnias, and psychogenic nonepileptic seizures, such as...
conversion symptoms and dissociative states. Many clinicians use terms such as “spell” or “event” to help the patient more clearly understand that these are not epileptic seizures.

Epilepsy is a condition in which persisting cerebral dysfunction causes recurring epileptic seizures without the need for immediate insults to provoke each seizure\(^2\); exacerbants such as sleep deprivation can increase seizure frequency in epilepsy, however. Acute symptomatic seizures are generalized tonic-clonic seizures that occur in the absence of epilepsy in response to a wide range of provoking insults, such as hyponatremia and other electrolyte disorders and fever in infants and young children.\(^3\)

**Figure 1.** Paroxysmal depolarization shift (PDS). When a PDS occurs as an abnormally prolonged run of action potentials during sustained membrane depolarization in a single neuron, as shown in the upper trace in B, the event is detectable only with microelectrodes; increased glutamate concentration is associated with influx of cations initially, followed by increased GABA concentration with efflux of potassium. When PDSs in a large number of neurons are synchronized for less than 200 ms, as shown in A, these electrical potentials may summate as a spike-wave complex that is recorded with macroelectrodes, as shown in the lower trace in B. When sustained repetitive firing of PDSs in a large number of neurons becomes synchronized for many seconds or longer, an electrographic seizure occurs, as shown in C. (Adapted with permission from Holmes GL, Ben-Ari Y. Seizing hold of seizures. Nature Med 2003;9:994–6.)

**NATURE OF EPILEPTIC SEIZURES AND EPILEPSIES**

**NEUROBIOLOGY OF EPILEPTIC SEIZURES**

The *paroxysmal depolarization shift* (PDS) is the pathophysiological cellular phenomenon that underlies all types of epileptic seizures (*Figure 1*) and interictal epileptiform electroencephalography (EEG) abnormalities (“spikes”).\(^5,6\) PDSs are cellular events in which rapidly repetitive action potentials are not followed by the usual refractory period, thereby generating a prolonged membrane depolarization (which is more prolonged than typically occurs in response to normal excitatory postsynaptic potentials [EPSPs]). An interictal spike is caused by PDSs in large numbers of neurons that are synchronized such that each involved neuron generates one PDS at the same time. An electroclinical seizure occurs when large numbers of neurons in one or more brain regions are repeatedly generating PDSs, in sustained repetitive firing with synchronization. Repetitive neuronal firing probably underlies the interictal and ictal unit and local field recording of high-frequency oscillations.\(^7\)

The tendency of individual neurons to enter pathological states in which PDSs are generated
can be based on intrinsic neuronal properties, such as dysfunctional ionophores in the genetically determined channelopathies (Figure 2), or on extrinsic mechanisms such as inadequate inhibitory neurotransmitter concentrations or exposure to excessive concentrations of excitatory amino acids or exogenous excitotoxins. However, large groups of neurons must generate PDSs simultaneously to account for the episodic nature of seizures. In experimental models of generalized epilepsies, this widespread epileptic synchronization of interictal and ictal PDSs is based on intrathalamic synchronization that drives thalamocortical relay neurons to synchronize the bihemispheric cortical neuronal discharges (Figure 3).8

In experimental models of partial epilepsies, intracortical mechanisms of synchronization operate during ictal discharges (Figure 4).8 There is evidence that in certain epilepsies specific channelopathies operate to initiate PDSs in individual neurons and produce seizures through normal mechanisms of interneuronal synchronization, while other epilepsies appear to require abnormal interneuronal pathways to generate pathological synchronization.

**EXPERIMENTAL MODELS OF SEIZURES AND EPILEPSY**

Experimentally induced seizures and animal models of epilepsy have been used extensively to...
study the nature of seizures and epilepsy and to
develop new therapies for epilepsy. For much of
the 20th century, potential new antiseizure medi-
cations were tested in rodents with the maximal
electroshock model and the penttylenetetrazole
model. Most experimental epilepsy research has
been performed with acute seizure and epi-
lepsy preparations, although amygdala kindling
and post-status epilepticus models offer chronic
epilepsy models, as do genetic rodent models of
epilepsy.

CLASSIFICATION OF SEIZURES

TYPES OF EPILEPTIC SEIZURES

The starting point in diagnosis of seizures and
epilepsy is to determine the type(s) of seizures
that the individual has sustained, or at least
generate a hypothesis regarding the type(s) of seizures. Consensus by experts of the International League Against Epilepsy (ILAE) established an electroclinical classification of seizure types (Table 1) that has been widely used for over 3 decades.10 A new classification of seizures proposed by the ILAE (Table 2) is similar to the earlier classification with regard to generalized-onset seizures, but the new classification abolished the subtypes of partial-onset seizures, instead considering altered awareness and generalized convulsive activity to be descriptors for focal seizures with evolution into generalized convulsive activity.

**TYPES OF NONEPILEPTIC SEIZURES**

Organic nonepileptic seizures are paroxysmal events caused by a nonepileptic condition. These events are grouped as nonepileptic seizures mainly because they can mimic epileptic seizures, not because they have a common pathophysiology. Seizures caused by other organic conditions usually are confused with epileptic seizures because patients cannot describe their own behaviors during events that cause loss of consciousness, and because witnesses usually can provide only limited information about behaviors during the events.11 (In contrast, expert review of ictal behaviors on video-EEG recordings affords detailed and accurate
information regarding movements and responsiveness.) For example, when syncope is not preceded by lightheadedness and postsyncopal confusion occurs, other diagnoses must be entertained. Atypical presentations of syncope and incompletely observed parasomnias are among the most common organic nonepileptic seizures.\(^{12,13}\)

Psychogenic nonepileptic seizures (PNES) can mimic essentially any type of epileptic seizure, as described to the neurologist by the patient and lay observers of the seizure events.\(^{14,15}\) Recording of habitual events on video-EEG not only shows absence of electrocerebral discharges of types expected for epileptic seizures with similar behaviors, but also provides an opportunity for detailed analysis of the behaviors themselves. Specific psychiatric syndromes do not appear to have relationships with patterns of event behaviors. Current understandings of PNES is that conversion-type reactions and dissociative states are not under direct conscious control, and these represent the majority of PNES. Conversion-type PNES can occur in individuals with persisting somatiform disorders who have evidence of other nonorganic dysfunctions, but many conversion-type PNES occur in isolation. Dissociative-state PNES often occur in individuals with a history of physical, sexual, or other abuse in the setting of post-traumatic stress disorder; this group of PNES patients may be the most responsive to cognitive-behavioral forms of psychological therapy. While malingering with consciously controlled events of unresponsiveness can occur, this scenario appears to be rather uncommon as a cause of repeated PNES. Many epileptologists who diagnose PNES routinely refer for psychiatric consultation first, to be certain that additional psychiatric diagnoses are not missed, and next to a clinical psychologist for therapy.

**Table 3** summarizes the commonly encountered types of nonepileptic seizures that cause loss of consciousness or an event with unresponsiveness and subsequent amnesia for the event, together with epileptic seizure types, descriptions of motor behaviors at the level of detail usually achieved by nonmedical witnesses of seizures, and typical diagnostic tests. Transitory events without impaired awareness have very different diagnostic considerations, which include simple partial epileptic

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**Table 1. ILAE 1981 Classification of Seizures**

I. Partial (focal, localization-related) seizures
   A. Simple partial seizures
      1. With motor signs
      2. With somatosensory or special-sensory symptoms
      3. With autonomic symptoms or signs
      4. With psychic symptoms
   B. Complex partial seizures
      1. With impairment of consciousness at onset
      2. Simple partial onset followed by impairment of consciousness
   C. Partial seizures with secondary generalization
      1. With simple partial seizures evolving to generalized seizures
      2. With complex partial seizures evolving to generalized seizures
      3. With simple partial seizures evolving to complex partial seizures evolving to generalized seizures

II. Generalized seizures
   A. Absence seizures
      1. With impairment of consciousness only
      2. With mild clonic components
      3. With atonic components
      4. With tonic components
      5. With automatisms
   B. Myoclonic seizures
   C. Clonic seizures
   D. Tonic seizures
   E. Tonic-clonic seizures
   F. Atonic (astatic) seizures

seizures, a large range of organic movements (including dystonias, tics, positional clonus, and blepharospasm), a very large range of organic subjective sensations and experiences (including vertigo, tinnitus, and abdominal sensations), a large array of psychogenic movements, and an even larger array of psychogenic sensations-perceptions and mental experiences. Frequently recurring movements without loss of consciousness often can be video-recorded to diagnose movements that fit established patterns of movement disorders or other organic conditions; however, care must be taken not to equate bizarreness of movements with psychogenicity, given the propensity of frontal lobe epilepsies and REM behavior disorders to cause peculiar movements. In general, the laboratory tests listed in Table 3 are more likely to provide definitive diagnostic evidence for the nature of transitory events that are associated with impaired consciousness, or at least with abnormal movements, than they are for transitory events during which baseline responsiveness is maintained.

**Table 2. ILAE 2010 Classification of Seizures**

<table>
<thead>
<tr>
<th>I. Focal seizures</th>
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<tbody>
<tr>
<td>Descriptors of focal seizures:</td>
</tr>
<tr>
<td>A. Without impairment of consciousness or awareness</td>
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<tr>
<td>1. With observable motor or autonomic components</td>
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<tr>
<td>2. Involving subjective sensory or psychic phenomena only</td>
</tr>
<tr>
<td>B. With impairment of consciousness or awareness</td>
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<tr>
<td>C. Evolving to a bilateral, convulsive seizure</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Generalized seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Tonic-clonic seizures</td>
</tr>
<tr>
<td>B. Absence seizures</td>
</tr>
<tr>
<td>1. Typical</td>
</tr>
<tr>
<td>2. Atypical</td>
</tr>
<tr>
<td>3. Absence with special features</td>
</tr>
<tr>
<td>a. Myoclonic absence</td>
</tr>
<tr>
<td>b. Eyelid myoclonia</td>
</tr>
<tr>
<td>C. Myoclonic</td>
</tr>
<tr>
<td>1. Myoclonic</td>
</tr>
<tr>
<td>2. Myoclonic atonic</td>
</tr>
<tr>
<td>3. Myoclonic tonic</td>
</tr>
<tr>
<td>D. Clonic</td>
</tr>
<tr>
<td>E. Tonic</td>
</tr>
<tr>
<td>F. Atonic</td>
</tr>
<tr>
<td>G. Unknown</td>
</tr>
<tr>
<td>1. Epileptic spasms</td>
</tr>
</tbody>
</table>


**HISTORY, EXAMINATION, AND LABORATORY TESTS**

The common risk factors, historical associations, and examination findings for epileptic seizures are listed in Table 4. The risk factors for nonepileptic seizures generally differ from those for epileptic seizures, including prior history of hysteriform paralyses or movements and prior history of childhood sexual abuse or other psychological trauma. An important exception is TBI, which is highly associated with both epilepsy and psychogenic seizures. Potentially epileptogenic insults usually should have occurred months or years before onset of the habitually recurring epileptic seizures, giving rise to the typical temporal pattern of an initial precipitating event followed by a latent period (during which the epileptic seizures have not yet begun to occur) and lastly the phase of active epilepsy. Epileptic seizures that occur during or within a week after a cerebral or systemic insult are generally considered provoked seizures that are not indicative of epilepsy. Among the exceptions to these patterns are conditions in which seemingly unprovoked forms of status epilepticus occur at onset of a condition that later manifests as sporadically recurrent seizures, such as the hemiconvulsion-hemiplegia-
Epilepsy syndrome (see Hecovulsion-Hemiplegia-Epilepsy section below).

Brief, interictal EEG recordings with scalp electrodes (routine EEGs) can record interictal epileptiform activities (spikes) and nonepileptiform abnormalities. Interictal spikes are valuable signs of epileptic excitability. In most epilepsies, interictal spikes can occur intermittently, such that prolonged EEG recordings often detect spikes missed with routine EEGs. Ambulatory EEG can detect interictal spikes and electrographic seizures that occur infrequently. Focal interictal spikes tend to occur in partial epilepsies, and generalized interictal spikes often occur in generalized epilepsies, but exceptions to this principle are common. Normal interictal EEGs are common in many epilepsies, as are interictal focal and generalized slowing without spikes.

Video-EEG monitoring is highly valuable in diagnosis of paroxysmal events with impaired consciousness or with abnormal movements and behaviors. The EEG data can fully distinguish epileptic seizure discharges (with phenomena specific to partial-onset versus generalized-onset epileptic seizures), pathological generalized slowing and depression of electrocerebral activities (of syncope and organic encephalopathies), onset of unconscious behaviors during sleep (specific to REM-onset versus slow-wave sleep onset), and absence of change from waking or drowsy baseline EEG activities (in psychogenic events). The synchronized audio-video record-

<table>
<thead>
<tr>
<th>Movements during period of unresponsiveness</th>
<th>Bilateral, repetitive, rapid flexion-extension, jerking or shaking movements</th>
<th>Sudden fall or droop, without jerking or shaking</th>
<th>Staring spell, with movements more complex and localized than jerking or fall</th>
<th>Staring spell, without jerking, fall, or other movements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epileptic seizure types</td>
<td>Generalized tonic-clonic</td>
<td>Generalized tonic</td>
<td>Complex partial</td>
<td>Complex partial</td>
</tr>
<tr>
<td></td>
<td>Generalized clonic</td>
<td>Generalized atonic</td>
<td>Atypical absence</td>
<td>Typical absence</td>
</tr>
<tr>
<td>Organic nonepileptic event types</td>
<td>Rigors</td>
<td>Syncope</td>
<td>REM behavior disorder</td>
<td>Atypical arousal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vertebrobasilar TIA</td>
<td>Somnambulism and other parasomnias</td>
<td></td>
</tr>
<tr>
<td>Psychogenic nonepileptic seizure types</td>
<td>Psychogenic convulsion</td>
<td>Psychogenic swoon</td>
<td>Psychogenic fugue state</td>
<td>Psychogenic stare or catatonia</td>
</tr>
<tr>
<td>Most frequently indicated tests</td>
<td>EEG or video-EEG, routine or prolonged Brain MRI (CT emergently)</td>
<td>ECG, routine or prolonged Tilt-table test Brain MRI/MRA</td>
<td>EEG or video-EEG, routine or prolonged Brain MRI Polysomnography</td>
<td>EEG or video-EEG, routine or prolonged Brain MRI</td>
</tr>
</tbody>
</table>

CT = computed tomography; ECG = electrocardiography; EEG = electroencephalography; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; TIA = transient ischemic attack.

Adapted with permission from Henry TR, Drury I. Non-epileptic seizures in temporal lobectomy candidates with medically refractory seizures. Neurology 1997;48:1374–82
Table 4. Summary of Risk Factors, Historical Associations, and Examination Findings for Diagnosis of Epileptic Syndromes

Risk factors and historical associations often provided by the patient or lay care givers:

- Family history of epilepsy or seizures
- Family history of genetic conditions that are potentially epileptogenic in family members without seizures (e.g., neurofibromatosis type 1)
- History of gestational or perinatal injury, febrile convulsions, developmental delay, stroke, meningitis, encephalitis, significant traumatic brain injury, ethanol or other drug abuse, or other epileptic predispositions
- Reported seizure-provoking factors: photic stimulation-flashing lights, hyperventilation, sleep deprivation, ethanol use or cessation, use of carbamazepine or other antiseizure medications known to exacerbate specific epileptic seizure types, catamenial exacerbation, numerous other possible seizure triggers and exacerbants

Risk factors and historical associations often provided by the medical chart (e.g., previously diagnosed clinical-imaging conditions) and conditions which the epileptologist will find on further evaluation:

- Primary or metastatic cerebral neoplasm (glioblastoma and lower-grade glial tumors, ganglioglioma and gangliocytoma, dysembryoplastic neuroepithelial tumor, others)
- Primary or metastatic extra-axial, intracranial neoplasm (meningioma, meningeal carcinomatosis, others)
- Cerebral infarction or hemorrhage, chronic (including residua of posterior reversible encephalopathy syndrome)
- Cerebral infection, remote or chronic (including cysticercosis, bacterial-myocobacterial-fungal cerebritis or abscess, bacterial meningitis, herpes or other viral encephalitis, retroviral encephalopathy, prion disease, others)
- Post-traumatic encephalomalacia (particularly with retained skull or metal fragment or hemosiderin deposition)
- Cerebrovascular lesion (arteriovenous malformation, cavernoma)
- Malformation of cortical development (lissencephaly, schizencephaly, hemimegalencephaly, perisylvian or other polymicrogyria, band or nodular heterotopia, focal cortical dysplasia, others)
- Genetic disorders of neurocognitive development (Aicardi syndrome, fragile X syndrome, Angelman syndrome, Rett syndrome, Down syndrome, trisomy 12p, ring 20 chromosome syndrome, Alpers’ disease, progressive encephalopathy with edema-hypsarrhythmia-optic atrophy [PEHO syndrome], others)
- Inherited metabolic disorders (mitochondrial diseases including pyruvate dehydrogenase deficiency and MELAS [mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes], neuronal storage disorders including Lafora disease and neuronal ceroid lipofuscinosis, peroxisom al disorders, cerebral calcinosis due to celiac disease, glycine encephalopathy, propionic acidemia and other organic acidurias, pyridoxine dependency, phenylketonuria and other aminoacidopathies, urea cycle disorders, disorders of carbohydrate metabolism, disorders of biotin, folate, or B12 metabolism, glucose transporter protein deficiency, Menkes disease, glycogen storage disorders, Krabbe disease, fumarase deficiency, Sanfilippo syndrome)
- Neurodegenerative conditions of adult onset (Alzheimer disease, Huntington disease, others)
- Neurodegenerative conditions due to neurotoxin exposure (organic solvents, lead, mercury, others)
- Other cerebral conditions of adult onset (e.g., multiple sclerosis, neurosarcoidosis, sequelae of lupus cerebritis, sequelae of paraneoplastic limbic encephalitis)
- Other encephalopathies of unknown etiology (e.g., autism and other developmental syndromes, neuropsychiatric encephalopathies of later onset including schizophrenia).
- Neurosurgical instrumentation (e.g., ventricular shunt, deep-brain stimulation electrode)

Examination findings

- Cutaneous stigmata of phakomatosis or neurocutaneous syndrome (adenoma sebaceum, ash leaf spots, shagreen patches, or periungual fibromas of tuberous sclerosis, multiple large café-au-lait spots or axillary freckling of neurofibromatosis, facial angiom a of encephalotrigeminal angiomatisis, others)
- Oculoretinal stigmata of storage disorders (cherry red spot of sialidosis, iris hamartoma of neurofibromatosis, others)
- Craniofacial dysmorphism of neurodevelopmenal syndromes (Down syndrome, others)
- Cranial defects suggesting unreported trauma or neurosurgical intervention
- Static abnormalities of the neurological examination indicating cognitive deficits, psychosis, and cerebral motor or sensory dysfunction
- Episodic abnormalities of the neurological examination including interictal spontaneous or startle-induced myoclonus and witnessed ictal manifestations
ing of behaviors is highly informative, and even when myogenic and kinesigenic artifacts obscure the EEG recording, the recorded behavioral data frequently in itself supports definitive seizure diagnosis.

**CLASSIFICATION OF EPILEPSIES AND EPILEPTIC SYNDROMES**

### 1989 CLASSIFICATION

There are many highly individual aspects of the seizures, interictal dysfunctions, and associated cerebral and systemic conditions experienced by persons with epilepsy. Nonetheless, it is obvious that some of these characteristics cluster across individuals as particular types of epilepsy. Ideally, every person with epilepsy could be assigned to one type of epilepsy, and the various types of epilepsy could be classified into a neurobiologically based, clinically relevant organizational schema of the epilepsies. This ideal taxonomy of the epilepsies has yet to be devised, and clinical epileptologists must use the current epilepsy classifications to guide diagnostics and therapeutics.

At this time, the most widely accepted classification of epilepsy types is that published by the ILAE in 1989 (Table 5). In addition to defining accepted epilepsy types, this taxonomy used 2 dichotomous principles to organize the epilepsy types. The partial (or focal, or localization-related) versus generalized dichotomy was determined by whether the individual had partial-onset or generalized-onset seizures, respectively. The idiopathic (or primary) versus symptomatic (or secondary, or acquired) dichotomy was determined by whether the individual had seizure intrinsic to his or her brain structure-function in the absence of any brain insult, or had a brain insult that precipitated epileptogenesis, respectively. A special category of the symptomatic group was persons with seizures of cryptogenic etiology who had indirect evidence of having had a causative brain insult, although the precise insult could not be determined. Characteristically, the idiopathic epilepsies had no interictal evidence of brain injury, so interictal intelligence and other functions typically are normal or nearly normal. Symptomatic partial epilepsies often feature interictal dysfunctions localized to the injured area, which includes the ictal onset zone, with mental retardation or developmental delay in many of those with symptomatic generalized epilepsies (eg, delayed verbal recall deficits in those with left-sided mesial temporal lobe epilepsy-hippocampal sclerosis, a symptomatic and usually cryptogenic partial epilepsy).

### 2010 CLASSIFICATION

Ongoing efforts to improve epilepsy classification were most recently summarized in 2010 (Table 6). The partial-generalized and idiopathic-cryptogenic dichotomies were discarded, and the epilepsy types were organized by typical developmental stage at seizure onset (eg, neonatal, childhood) and etiology. The established types of epilepsy are mainly the same as those recognized by the 1989 classification, although more developed and specific syndromes of neonatal seizure onset are included in the 2010 classification. The new epilepsy classification has been described as multifactorial and flexible, with emphases on age at onset and etiology, and also as a work-in-progress and incomplete. Epileptologists will need to track this transitional period in epilepsy classification systems, but fortunately the core knowledge of classification continues to be in recognition of the individual epilepsy types.

### SPECIFIC SYNDROMES OF EPILEPSY

A number of epilepsies are established as clinically distinguishable from epilepsy as a whole, with
Table 5. ILAE 1989 Classification of Epilepsies

1. Localization-related (focal, local, partial) epilepsies and syndromes
   1.1 Idiopathic (with age-related onset)
       · Benign childhood epilepsy with centrotemporal spikes
       · Childhood epilepsy with occipital paroxysms
       · Primary reading epilepsy
   1.2 Symptomatic
       · Chronic progressive epilepsia partialis continua of childhood (Kojewnikow syndrome)
       · Syndromes characterized by seizures with specific modes of precipitation
       · Temporal lobe epilepsies (amygdalo-hippocampal, lateral temporal)
       · Frontal lobe epilepsies (supplementary motor, cingulate, anterior frontopolar, orbitofrontal, dorsolateral, opercular, motor cortex)
       · Parietal lobe epilepsies
       · Occipital lobe epilepsies
   1.3 Cryptogenic (same syndromes as for symptomatic localization-related epilepsies, but without known etiology)

2. Generalized epilepsies and syndromes
   2.1 Idiopathic (with age-related onset)
       · Benign neonatal familial convulsions
       · Benign neonatal convulsions
       · Benign myoclonic epilepsy in infancy
       · Childhood absence epilepsy (pyknolepsy)
       · Juvenile absence epilepsy
       · Juvenile myoclonic epilepsy
       · Epilepsy with grand mal (GTCS) seizures on awakening
       · Other generalized idiopathic epilepsies not defined above
       · Epilepsies with seizures precipitated by specific modes of activation
   2.2 Cryptogenic or symptomatic
       · West syndrome
       · Lennox-Gastaut syndrome
       · Epilepsy with myoclonic-astatic seizures
       · Epilepsy with myoclonic absences
   2.3 Symptomatic
       2.3.1 Nonspecific etiology
           · Early myoclonic encephalopathy
           · Early infantile epileptic encephalopathy with suppression burst
           · Other symptomatic generalized epilepsies not defined above
       2.3.2 Specific syndromes
           · Epileptic seizures that complicate a specific disease state

3. Epilepsies and syndromes undetermined whether focal or generalized
   3.1 With both generalized and focal seizures
       · Neonatal seizures
       · Severe myoclonic epilepsy in infancy
       · Epilepsy with continuous spike-waves during slow wave sleep
       · Acquired epileptic aphasia (Landau-Kleffner syndrome)
       · Other undetermined epilepsies not defined above
   3.2 Without unequivocal generalized or focal features. All cases with generalized tonic-clonic seizures in which clinical and EEG findings do not permit classification as clearly generalized or localization related, such as in many cases of sleep grand mal (GTCS) are considered not to have unequivocal generalized or focal features.

4. Special syndromes
   4.1 Situation-related seizures (Gelegenenheitsanfälle)
       · Febrile convulsions
       · Isolated seizures or isolated status epilepticus
       · Seizures occurring only when there is an acute metabolic or toxic event due to factors such as alcohol, drugs, eclampsia, nonketotic hyperglycemia

Adapted with permission from Proposal for revised classification of epilepsies and epileptic syndromes. From the Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 1989;30:389–99.
diagnostic criteria by (1) seizure types, (2) age at onset, and (3) EEG and imaging findings, and in many instances supplemented by information regarding (4) associated cerebral and systemic conditions, (5) interictal cerebral dysfunctions, and (6) typical responses to specific medications or

### Table 6. ILAE 2010 Proposal for Classification of Epilepsies

<table>
<thead>
<tr>
<th>Organizational Group</th>
<th>Electroclinical Syndrome</th>
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<tbody>
<tr>
<td>Neonatal onset group</td>
<td>Benign familial neonatal epilepsy (BFNE)</td>
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<tr>
<td></td>
<td>Early myoclonic encephalopathy (EME)</td>
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<tr>
<td></td>
<td>Early myoclonic encephalopathy (EME)</td>
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<tr>
<td>Infancy onset group</td>
<td>Epilepsy of infancy with migrating focal seizures</td>
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<tr>
<td></td>
<td>West syndrome</td>
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<tr>
<td></td>
<td>Myoclonic epilepsy in infancy (MEI)</td>
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<tr>
<td></td>
<td>Benign infantile epilepsy</td>
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<tr>
<td></td>
<td>Benign familial infantile epilepsy</td>
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<td></td>
<td>Dravet syndrome</td>
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<td></td>
<td>Myoclonic encephalopathy in nonprogressive disorders</td>
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<tr>
<td>Childhood onset group</td>
<td>Febrile seizures plus (FS+) (can start in infancy)</td>
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<tr>
<td></td>
<td>Panayiotopoulos syndrome</td>
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<tr>
<td></td>
<td>Epilepsy with myoclonic atonic (previously astatic) seizures</td>
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<td></td>
<td>Benign epilepsy with centrotemporal spikes (BECTS)</td>
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<tr>
<td></td>
<td>Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)</td>
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<tr>
<td></td>
<td>Late onset childhood occipital epilepsy (Gastaut type)</td>
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<td>Epilepsy with myoclonic absences</td>
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<td></td>
<td>Lennox-Gastaut syndrome</td>
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<td></td>
<td>Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)</td>
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<td></td>
<td>Landau-Kleffner syndrome (LKS)</td>
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<td></td>
<td>Childhood absence epilepsy (CAE)</td>
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<td>Adolescence – Adult</td>
<td>Juvenile absence epilepsy (JAE)</td>
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other therapies that had been used before the current attempt to diagnose the individual’s epilepsy type. Successful classification of epilepsy type usually supports the physician’s efforts to establish a prognosis regarding remission of active epilepsy. Many individual patients have epilepsy with specific seizure types but lack other information that permits diagnosis of an established epilepsy syndrome. When seizure types can be diagnosed but the overall epilepsy cannot be classified, the physician’s ability to make an accurate prognosis is limited. The following list of epileptic syndromes is derived from the current ILAE consensus on classification,20 grouped by age at seizure onset.

NEONATAL PERIOD

Benign familial neonatal epilepsy (BFNE) is an autosomal dominant condition in which brief (1–2 sec) generalized events include tonic, apneic, and other features.21–24 Seizures usually begin within the first days after birth and remit in over 80% within the first 6 weeks. Those whose seizures do not remit may have a few seizures in adulthood. Several potassium channelopathies appear to be responsible for BFNE. The prognosis for neurocognitive development is good.

Early myoclonic encephalopathy (EME) is a neonatal syndrome with frequent myoclonia and focal motor seizures and is associated with a burst–suppression pattern on EEG.25–27 Various metabolic syndromes are the most common etiologies. Some children with EME recover with normal or nearly normal neurocognitive development.

Ohtahara syndrome, or early infantile epileptic encephalopathy with burst-suppression (EIEE), is a neonatal syndrome with frequent tonic seizures and is associated with burst–suppression on the interictal EEG.28–30 This syndrome often evolves into the West syndrome and subsequently into the Lennox-Gastaut syndrome, and is most often associated with brain structural abnormalities including unilateral or bilateral cerebral hypoplasia and other developmental malformations. The prognosis for neurocognitive development is grim.

INFANCY

Epilepsy of infancy with migrating focal seizures is a rare, severe, and progressive focal epilepsy in which focal seizures arise in multiple bihemispheric regions and are refractory to medications.31,32 Brain magnetic resonance imaging (MRI) studies initially are normal but show progressive atrophy. Many of these children die in the first year, and most continue to have refractory seizures throughout childhood, with severe developmental delay and microcephaly.

West syndrome is an uncommon electroclinical syndrome of multiple etiologies characterized by the triad of infantile spasms, hypsarrhythmia on EEG, and developmental regression.33–40 Tuberous sclerosis is the single most common cause; other causes include focal cortical dysplasias, other malformations of cortical development such as lissencephaly, perinatal asphyxia and infarction, prenatal and postnatal brain infections, and various other cerebral structural lesions and metabolic syndromes. A small number of these patients have no identifiable cause; this “idiopathic West syndrome” has a more favorable prognosis for cessation of seizures and normal development. Many West syndrome patients evolve into the Lennox-Gastaut syndrome and other generalized epilepsies with mental retardation. The spasms are difficult to treat with medications, including adrenocorticotropic hormone (ACTH) and vigabatrin, and multilobar resections have been used when one hemisphere predominates in malformation or epileptiform activity, in some cases with reportedly good functional outcomes.
Myoclonic epilepsy in infancy (MEI) is a rare syndrome in which subtle or massive myoclonic jerks occur in clusters of a few seconds’ duration or somewhat longer. The interictal EEG is normal, while during jerks there are generalized fast spike-/polyspike-wave discharges. No other types of seizures occur; the myoclonic seizures usually are controlled with valproate, and most patients with MEI have no seizures later in life.

Benign infantile epilepsy and benign familial infantile epilepsy feature partial seizures with or without secondary generalization that most often begin between 6 months and 2 years of age. The interictal EEG usually is normal, although some have midline spikes during slow-wave sleep. Ictal EEG recordings show clear focal onsets, most often with either temporal or centroparietal maxima across this population (but a single ictal onset pattern in an individual patient). Brain imaging is normal. Often patients have an associated viral gastroenteritis, without encephalitis. Acute therapy with antiseizure agents may be unnecessary. Seizure recurrence later in life is rare and normal intellectual development is expected.

Dravet syndrome is a rare and progressive epileptic encephalopathy that usually begins with febrile and afebrile generalized and unilateral clonic or tonic-clonic seizures in infancy, when the EEG is normal interictally. Ongoing seizures and developmental delay are associated with findings of generalized spike- and polyspike-wave and diffuse theta slowing on the waking EEG by 2 years. This syndrome can occur with GEFS+, but in these instances is rarely familial, as new mutations account for most cases of GEFS+ with Dravet syndrome.

Myoclonic encephalopathy in nonprogressive disorders (also termed myoclonic status in nonprogressive encephalopathy) is usually evident by the end of the first year of life, manifesting as developmental delays that will constitute severe mental retardation and as refractory myoclonic absences. Irregular and fragmented spike-wave discharges and low-amplitude multifocal spikes occur with generalized slowing of the waking EEG. Most of these patients have a genetic developmental disorder, with Angelman syndrome predominating over the 4p-deletion syndrome (Wolf–Hirschhorn syndrome) and Rett syndrome, but perinatal anoxia also can cause this electroclinical syndrome.

CHILDHOOD

Childhood absence epilepsy (CAE) or “pyknolepsy” is the most widely recognized form of epilepsy in childhood, but not the most common, with a prevalence of less than 10% in children with epilepsy. Seizure onset is usually at 3 to 8 years of age in children with normal development. Most have only absence (petit mal) seizures, often occurring multiple times daily before treatment, but some also rarely experience generalized tonic-clonic (GTC) seizures. The interictal EEG is usually normal except for brief bursts of generalized 3-per-second spike-wave discharges, which are provoked with photic stimulation and hyperventilation; often there is also occipital intermittent rhythmic delta slowing. Generalized 3-per-second spike-wave discharges usually last 10 to 20 seconds during the seizures. Brain imaging is generally considered unnecessary, as no lesional or acquired epilepsies cause these types of seizures with these EEG findings. Ethosuximide is usually effective for absences, and valproate for both absences and GTC seizures. Seizures cease by the teens in over 90% of patients, and those whose seizures persist most often evolve into the juvenile myoclonic epilepsy syndrome.

Lennox-Gastaut syndrome (LGS) begins at
age 3 to 8 years or rarely later, but in perhaps 20% of cases is preceded by the West syndrome. This archetypal symptomatic or cryptogenic generalized epilepsy is defined by mixed seizure types, generalized slow spike-wave discharges and generalized slowing on waking-drowsy interictal EEG, generalized paroxysmal fast activity on sleeping interictal EEG, and developmental delay. The typical seizure is a medically refractory drop attack as a generalized tonic seizure. Atypical absences and GTC seizures are very common. Generalized atonic, generalized clonic, generalized myoclonic, and focal seizures often occur. Later age of onset and relatively normal intellect sometimes are observed. Etiologies include the phakomatoses, various malformations of cortical development, early diffuse anoxic and focal ischemic injuries, and others as for the West syndrome. Cryptogenic LGS with normal brain MRI accounts for perhaps one-third of cases. Valproate, zonisamide, and other agents are typical of the polytherapy needed to avoid status epilepticus, but only infrequently is full seizure control achieved in childhood. By adulthood, the interictal EEG often evolves away from generalized slow spike-wave, so technically the individual no longer has LGS, but often has the same types of seizures under improved control. Focal seizures occur in some patients with LGS, and the interictal EEG may show more focal spike elements. Intellectual prognosis is poor, and psychosis, episodic dyscontrol, and other disabling behavioral disorders are common.

**Benign epilepsy with centrotemporal spikes** (BECTS) is the most common benign partial epilepsy of childhood, and the single most common form of epilepsy in childhood. Seizure onset is usually at 3 to 13 years of age in children with normal development. Most patients with BECTS have nocturnal events that eventually are diagnosed as focal seizures with sensory and motor facial or glossopharyngeal seizures, often with grunting or drooling. Diagnosis often occurs after a first nocturnal GTC seizure. The interictal EEG most often shows single and repetitive unilateral or bilateral independent spike-wave complexes of centrotemporal maximum, without focal delta slowing at the spike site(s), but sometimes with generalized 3-per-second spike-wave discharges. Atypical clinical or EEG features may indicate the need for brain imaging. When therapy is needed, carbamazepine or other agents usually control the seizures at modest doses. Epilepsy almost always remits within several years of onset.

**Benign epilepsy with occipital spikes** (Panayiotopoulos syndrome) is the second most common benign partial epilepsy of childhood. Focal seizure onset is usually at 3 to 6 years of age in children with normal development, although a large minority has a preceding history of febrile convulsions. Most have focal seizures with gaze deviation, emesis and other autonomic signs, and impaired consciousness, with nocturnal predilection. Hemiconvulsions and GTC seizures are common. Interictal EEGs show normal background activities with high-amplitude occipital spike-wave complexes on eye closure, and spike activation by sleep with unilateral or bisynchronous occipital spikes; some also have other foci of spikes or generalized spike-wave bursts. Most have only a few seizures, but paradoxically these few seizures frequently generate status epilepticus. Carbamazepine and valproate are usually effective, although many do not require medication. Focal seizures consistently cease within 2 years of onset.

**Late onset childhood occipital epilepsy** (Gastaut type) is a rare condition that features focal seizures beginning at age 6 to 12 years, with visual hallucinations or blindness, often with gaze devia-
tion or eyelid fluttering, and often followed by post-ictal migraine headaches. The focal seizures often evolve into hemiconvulsions or GTC seizures. The interictal EEG typically shows unilateral or bi-synchronous occipital spikes of high amplitude with fields extending over adjacent parietal and temporal areas, and with attenuation on eye opening. Brain MRI is normal. Seizures often are medially refractory, but tend to remit by the late teens.

**Epilepsy with myoclonic atonic (astatic) seizures** (Doose syndrome) is a rare syndrome with onset at 2 to 5 years of age, usually in developmentally normal children. The initial seizures typically are repetitive GTC seizures, with only isolated GTC seizures thereafter, but followed by persisting epileptic drop attacks. The drop attacks are generalized myoclonic-atonic (or “myoclonic astatic”) seizures with components both of increased and decreased muscle tone. The interictal EEG is abnormal due to generalized slowing in waking with high-amplitude atypical generalized spike-wave complexes at sleep onset. The ictal EEG may be similar but with more and higher amplitude slowing and spiking, and often with greater rhythmicity of slow waves and spikes. Brain MRI is normal. Valproate can reduce seizures, which usually remit after several months. Some of these patients have persisting cognitive deficits.

**Autosomal-dominant nocturnal frontal lobe epilepsy** (ADNFLE) is a rare syndrome with seizure onset in middle childhood and adolescence in the majority of affected patients. The disorder was once considered to be “paroxysmal nocturnal dystonia,” but with the advent of video-EEG, ictal recordings established the epileptic nature of the events. These focal seizures have been termed “hypermotor” because of their vigorous but rather variable movements, which can be low- and high-amplitude, synchronous or asynchronous or alternating, and axial or appendicular. Untreated, these seizures often occur repeatedly on many nights. Most patients have no other type of seizure, a normal interictal EEG, normal intelligence and neurologic examination, and normal brain MRI. Even the ictal EEG may be difficult to interpret, often with anterior or diffuse attenuations or rhythmic slow waves rather than sharply construed or high-amplitude focal discharges. Known causative mutations code for subunits of neuronal nicotinic receptors. Most patients with ADNFLE attain seizure control with carbamazepine or other agents, but a sizeable minority do not attain seizure control and may have increased risk of chronic neurobehavioral sequelae.

**Epilepsy with myoclonic absences** is a rare, idiopathic generalized epilepsy with onset at age 1 to 12 years of myoclonic absences as the sole seizure type, or as myoclonic absences with other seizure, particularly GTCs. Myoclonic absences briefly impair awareness, with proximal arm and other jerks during transitory increases in tone that cause the arms to elevate for a few seconds, rarely with falling. The interictal and ictal EEG shows generalized 3-per-second spike-wave discharges. Prognosis for medication control and later remission is generally good.

**Epileptic encephalopathy with continuous spike-and-wave during sleep** (CSWS), also known as electrical status epilepticus in sleep (ESES), is a rare cryptogenic syndrome in which various focal or generalized (including absence) seizures can occur in early-middle childhood. The requisite EEG feature is occurrence of generalized spike-wave discharge during greater than 85% of the non-REM sleep recording. Global cognitive decline occurs and usually leaves permanent deficits, despite relative ease of medication control of seizures and later remission of epilepsy.
Landau-Kleffner syndrome (LKS) is a rare cryptogenic syndrome that is highly associated with CSWS, as the same non-REM spike-wave discharges occur, with similar types of seizures and medication responsiveness as in CSWS.\textsuperscript{106,107} A progressive loss of previously acquired language function defines LKS, and after epilepsy remits permanent auditory agnosia and aphasia are common.

Febrile seizures plus (FS+) (more often termed generalized, or genetic, epilepsy with febrile seizures plus, or GEFS+) is an electroclinical-genetic syndrome with a starting point of febrile convulsions of early childhood or infancy, but a wide range of subsequent epilepsy manifestations that have considerable overlap with other electroclinical syndromes.\textsuperscript{108,109} These syndromes include myoclonic-astatic epilepsy, Dravet syndrome, various generalized epilepsies, and familial temporal lobe epilepsy TLE with or without hippocampal sclerosis. Some affected individuals have only febrile seizures. Early publications reported genes whose products disrupted neuronal sodium channel function at the ionophore’s alpha subunit (SCN1A mutations), but other sodium channel components, and in some cases GABA\(_\alpha\) receptor subunits, are affected by more recently reported genes that cause GEFS+.

**ADOLESCENCE–ADULT**

Juvenile absence epilepsy (JAE) is somewhat more common that CAE.\textsuperscript{58–67} Many authorities consider CAE and JAE to be a continuum. Seizure onset is usually at 8 to 12 years of age in children with normal development. In addition to absence seizures, which tend to occur less frequently before treatment in JAE than in CAE, most also occasionally experience GTC seizures. Interictal and ictal EEGs in JAE are highly similar to those of CAE. Valproate may be most effective for both absence and GTC seizures, but concerns with teratogenicity in young women often favor use of lamotrigine or other agents. Seizures cease in the late teens in over 80\% of patients, with more than 10 lifetime GTC seizures being a negative prognostic sign. As with CAE, most nonremitters evolve into JME.

Juvenile myoclonic epilepsy (JME) probably is the second most common epileptic syndrome across all ages, after mesial TLE, and accounts for perhaps one-sixth of adult epilepsies.\textsuperscript{110–114} Seizure onset is usually at ages 12 to 18 years in individuals with normal development, and may follow on CAE or JAE. Myoclonus in early waking states is positive or negative, and segmental or massive; massive negative myoclonus can cause an injurious fall without loss of consciousness. Occurrence of at least 1 GTC seizure has been a formal requirement for this diagnosis, but GTC seizures should be rare after medication initiation with good compliance and avoidance of the principal precipitants (sleep deprivation and ethanol). Approximately one-third of those with JME have absence seizures. The interictal EEG typically is normal except for brief, generalized, fast (4–6-per-second) spike-/polyspike-wave discharges, often increased with photic stimulation and hyperventilation, or sometimes with generalized 3-per-second spike-wave discharges. Jerks often coincide with polyspikes, but ictal recordings are rarely if ever needed for diagnosis. Valproate (in those without child-bearing potential), zonisamide, lamotrigine, and other agents usually can control seizures fully in patients with good medication and lifestyle compliance. Unlike other idiopathic generalized epilepsies, prognosis for remission is very poor, with reports of GTC seizure recurrence in elderly JME patients on medication withdrawal after decades of seizure freedom.
Epilepsy with generalized tonic-clonic seizures alone is clearly a common situation. As an epileptic syndrome, it suffers from a paucity of published research, with no defined age-range of onset and no established diagnostic criteria to fully distinguish the syndrome from recurrent GTC seizures of other causes.\textsuperscript{115,116} Seizure frequency and relationship to seizure-provoking factors is poorly defined. Interictal EEG sometimes shows generalized 3-per-second spike-wave discharges. Brain MRI presumably is normal in this idiopathic epilepsy. Medications are chosen for seizure type rather than epilepsy type, and prognosis for remission is unclear.

Progressive myoclonus epilepsies (PME) are a well-defined set of etiologies with a common clinical syndrome, which unfortunately is most often untreatable and progressive to early death.\textsuperscript{117–121} The syndrome consists of myoclonus, mixed GTC and other seizures, dementia, and usually other progressive neurologic deficits, including ataxia. Onset is usually in late childhood or adolescence, depending on the etiology. The interictal EEG shows generalized and multifocal slowing, multifocal spikes often with posterior predominance, and atypical generalized spike-/polyspike-wave discharges. Depending on the age of degeneration, cerebral atrophy is present on MRI. Causes include Lafora disease, neuronal ceroid lipofuscinosi, myoclonus epilepsy and ragged red fibers (MERRF), sialidosis, and other neurodegenerative storage diseases, each with specific biochemical or tissue studies allowing diagnosis. Seizures are refractory and decline is inexorable, except in Baltic familial myoclonus epilepsy (Unverricht-Lundborg disease), an autosomal recessive condition that probably occurs in most human populations, although somewhat less rarely near the Baltic Sea. Most cases involve mutations in genes encoding cystatin B, a cysteine protease inhibitor, with some mutations developed for clinical tests. Baltic familial myoclonus epilepsy features cognitive decline that can be stabilized if seizures are controlled, which also prolongs survival. Valproate and zonisamide are the medications most frequently used for seizure control in PME.

Autosomal dominant epilepsy with auditory features (ADEAF) is a rare TLE of teenage or early adult onset, characterized by auras with unformed auditory hallucinations and frequent GTC seizures.\textsuperscript{122,123} The interictal EEG is normal or shows interictal spikes of posterior temporal maximum. Brain MRI is normal or may show subtle enlargement of lateral temporal cortex without clearly dysplastic features. Seizures generally are easily controlled with medications.

Other familial TLEs are uncommon, and are often associated with febrile convulsions before onset of auras, focal seizures with impaired awareness, and GTC seizures similar to those of mesial TLE with hippocampal sclerosis.\textsuperscript{124–127} Interictal and ictal EEGs are similar to those of mesial TLE with hippocampal sclerosis, and some individuals have hippocampal atrophy on MRI. Clear distinction of familial from sporadic mesial TLE probably will require genetic tests that are yet to be developed.

LESS SPECIFIC AGE RELATIONSHIP

Familial focal epilepsy with variable foci is a rare syndrome with variable onset in childhood or adulthood. In this syndrome, each affected individual has focal epilepsy limited to one invariant focus, but the family has individuals with different foci in frontal, temporal, and occipital lobes.\textsuperscript{127,128} Focal seizures are defined by semiology and EEG abnormalities, as brain MRI is consistently normal.

Reflex epilepsies must be differentiated from reflex seizures.\textsuperscript{129–131} Many forms of epilepsy feature
generalized or focal seizures that sometimes occur immediately on photic stimulation, startle, or other particular stimuli, but these seizures also occur spontaneously in the absence of the potentially ictogenic stimulus. In reflex epilepsy, the seizures should occur only in response to a specific set of stimuli. The prototypical example of reflex epilepsy is primary reading epilepsy. In this very rare and quite remarkable syndrome, the patient can predictably induce focal seizures by reading complex material for prolonged periods of time, after which mandibular myoclonus or orofacial sensations or movements occur. If the individual persists in reading, a GTC seizure consistently ensues. Interictal EEG and brain MRI are normal, but bilateral or unilateral EEG spikes of left temporoparietal predominance occur during the focal seizures.

DISTINCTIVE CONSTELLATIONS AND LESS SPECIFIC AGE RELATIONSHIP

Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) is probably the single most common form of epilepsy, if one allows for limitations in detection of very mild hippocampal sclerosis by current clinical MRI techniques. Habitual seizure types often are preceded by febrile convulsions. The typical auras, focal seizures with impaired awareness and with or without automatisms, and afebrile GTC seizures can begin by 2 or 3 years of age, but more often begin in middle childhood or well into adulthood. Psychic and autonomic auras can include dreamy states with perceived unreality or déjà vu or jamais vu phenomena, gustatory or olfactory hallucinations, epigastric rising sensations, and a variety of other symptoms. With more widespread ictal discharges, an initial motionless staring spell often is followed by chewing, swallowing, nonspecific hand movements, and various other automatisms. Evolution into a GTC seizure may be immediately preceded by oculocephalic version. Typical interictal EEG findings include unilateral or bilateral anterior temporal spikes or runs of intermittent rhythmic delta activity (specific TLE discharges), nonspecific focal temporal or generalized slowing, or a persistently normal interictal EEG. Typical ictal discharges are focal frontotemporal rhythmic discharges that can be sinusoidal or sharply contoured and evolve in field, frequency, and morphology, or similar discharges that are nonlocalizing at onset and sometimes develop later temporal maximum. Brain MRI can be normal or nonspecifically abnormal (with subcortical white matter signal alterations, for example), but the classic signs are unilateral or rarely bilateral hippocampal atrophy and $T_2$ signal increase. This syndrome is medically refractory in perhaps 50% of individuals, but is more likely to be amenable to surgical resection than are most other epilepsies.

Rasmussen syndrome is an electroclinical syndrome of epilepsia partialis continua with progressive atrophy of the affected cerebral hemisphere and profound medication refractoriness. Characteristic onset is in early to middle childhood, but considerably later onset is recognized, as are variants with aphasic or other focal seizures rather than focal motor seizures. The clinical and EEG abnormalities are highly lateralized, with EEG slowing, spikes and seizures continuing over months and years, usually with limited response to tolerable or intoxicating polypharmacy. Serial brain MRI shows progressive atrophy of the affected hemisphere, correlating with progressive hemiparesis. Brain tissue shows characteristic microglial proliferation and nodularization, perivascular lymphocytic cuffing, and neuronal loss and gliosis in the affected hemisphere. T-cell dysfunction and other lines of evidence support various anti-inflammatory and
immune-modulating therapies, which possibly blunt the severity of cerebral degeneration over the years of ongoing seizures. Functional hemispherectomy may allow the other hemisphere to develop more normally, with seizure control, in selected children.

Gelastic seizures with hypothalamic hamartoma is a rare syndrome of focal seizures with mirthless laughter and GTC seizures that is specifically associated with a neuronal-glial hamartoma of the hypothalamus. Precocious puberty, ictal semiology, and brain MRI findings are diagnostic. Interictal and ictal EEG epileptiform findings are variable. Seizures often are intractable, but resective or radiosurgical procedures have significant efficacy.

Hemiconvulsion-hemiplegia-epilepsy (HHE) is a rare syndrome most often of early childhood onset. The first manifestation usually is hemiconvulsive status epilepticus lasting one to several hours, or longer if untreated. After status ends, a new postictal hemiplegia persists. After a latent period of 1 to 4 years, focal seizures begin to occur as complex partial seizures (focal seizures with impaired awareness), focal clonic seizures, or other types of focal seizures. These seizures may be controlled with medications, or sometimes with resective surgery. The optimal therapy is aggressive management of all childhood status epilepticus, and with improving health care delivery the incidence of HHE appears to have declined.

BOARD REVIEW QUESTIONS
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