SECOND EDITION

# A to Z Epilepsy

A CONCISE ENCYCLOPEDIA

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## A Concise Encyclopedia
## Second Edition

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# Contents

# Preface

This book was designed to provide health care professionals with a quick and easy way to find short answers to questions that revolve around terms and language commonly used within the field of epileptology. To this end we have listed common terms and topics and have arranged them alphabetically with a brief discussion and key references when necessary. The goal of this new edition of *Epilepsy A to Z*, is to provide a "bullet" of information pertaining to essential topics that are intermediate between a definition obtained from a dictionary and a textbook discussion. Since this is essentially a "working" dictionary, this book is not meant to be exhaustive, but rather a functional source for the clinician to use to find common terms utilized in epilepsy evaluation and management. Within the text, the contents are arranged alphabetically. The references provided have been chosen because of their relative importance to the topic. Many excellent works and authors have not been included due to the size constraints of this work.

Cross-referencing has been used so that the reader can easily find a subject. Antiepileptic drugs have been listed by generic and common trade names, provided they are available or are active in clinical trials. Other abbreviations will appear throughout the text and reflect common representative applications.

We hope this guide to the diction of epilepsy assists all who seek rapid access to the common "lingo" and relevant information used within the field. We sought to fulfill the learned words of Albert Einstein: "simplify as much as possible, but no more."

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*Pierre Jallon, MD*

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# Epilepsy A to Z

# A

## ABDOMINAL AURA

Epileptic auras are a common manifestation of partial epilepsy. Abdominal auras represent partial seizures characterized by an abrupt viscerosensory sensation of an epigastric feeling-sometimes described as "moving in a roller coaster" or "butterflies." The visceral quality may initially suggest a gastrointestinal origin, although abdominal auras are neurally mediated simple partial seizures. An abdominal aura usually emanates from the epigastrium, but it may also be sensed in the lower chest area. It may rise up to the throat or the top of the head but rarely moves in an irregular fashion. Less frequently, unpleasant sensations such as nausea, tightness, or frank abdominal pain may occur. While abdominal auras are not specific to a single region of the brain, they are very frequently a common feature of auras in patients with mesial temporal lobe epilepsy. Abdominal epilepsy is an older descriptive term used in individuals having epilepsy with prominent abdominal auras.

## ABSCESS, CEREBRAL

Seizures are common in the face of a cerebral abscess, occurring in up to nearly 70% of those affected. Partial seizures and secondarily generalized tonic-clonic (GTC) seizures, as well as status epilepticus, are potential neurologic sequella. Common microorganisms include both anaerobic and microaerophilic bacteria. The causative organism depends upon the individual clinical setting. *Staphylococcus* is common in surgical or patients with open wounds, *Streptococcus* more so in head trauma, *Pseudomonas* and *Candida* species in burn patients, and fungals and parasitic causes in AIDS. Neuroimaging has prompted rapid improvement in detection for early surgical incision and drainage in addition to protracted organism-appropriate intravenous medication.

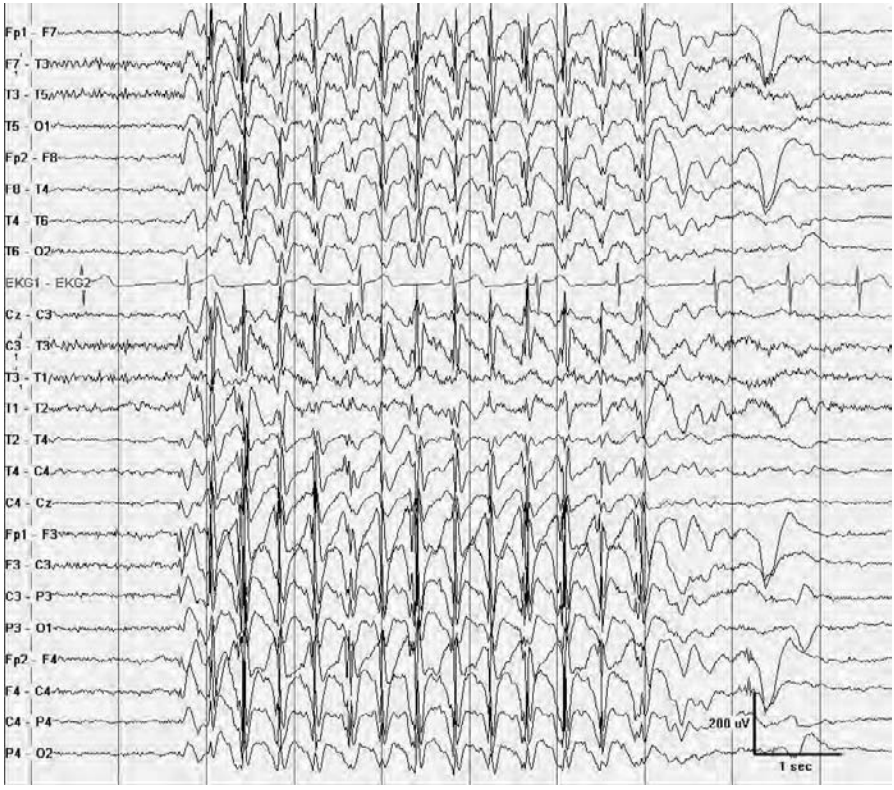
## ABSENCE EPILEPSY (*see also* PETIT MAL)

Absence seizures are the prototype for the idiopathic ("primary") generalized epilepsies (IGE). A typical absence seizure is characterized by an alteration in consciousness alone (simple absences) or with additional features (complex absences) such as myoclonus, atonia, or prominent automatisms. The age of onset

reflects the epilepsy classification or syndrome associated with absence seizures. Childhood absence epilepsy ("pyknolepsy") is most common. However, other epilepsy syndromes that include absence seizures include juvenile absence epilepsy and juvenile myoclonic epilepsy, which begin at a later age with a mixture of other seizure types such as GTC and myoclonic seizures. Absence seizures are characterized by an abrupt arrest of ongoing activities, stare, eye fluttering, and brief impairment of consicousness and lack a postictal state. The typical duration is approximately 10 seconds, but ranges from 1 second to nearly 2 minutes. The clinical manifestations during an absence seizure become more obvious with longer duration. Seizures greater than about 10 seconds cause greater impairment in reaction time on tests requiring concentration, but bursts of generalized spike-and-wave (GSW) of more than 3 seconds can usually be noticed or demonstrated with clinical testing of response time. Subtypes of typical absence seizures are recognized by the International League Against Epilepsy (ILAE) and include absence associated with impaired consciousness alone as well as those with (mild) clonic features, atonic features, tonic components, and those with automatisms or autonomic phenomena. Proper identification of the frequency of the subtypes is a direct reflection of the rigorous degree of observation and the group of patients selected. In addition, the incidence of additional features increases with more intense scrutiny and greater duration of seizure. Simple absence with impairment of consciousness only or those with subtle clonic features of the face, neck, or upper limbs are by far the most commonly recognized types. Those with more robust clonic jerks, such as those with forward jerking of the neck and upper limbs (*see also* Epilepsy with Myoclonic Absence) or in association with myoclonic jerks (*see also* Juvenile Myoclonic Epilepsy), have indistinct boundaries between absence with complex features and individual epilepsy syndromes. Absences with automatisms, those with mild atonia, and mixed forms occur far less frequently, although they are probably underrepresented by discovery by clinical means alone without videotape review. Absence seizures may include several of the above features, and a single patient may show different types of absence seizures at different times. While absence seizures may be precipitated by inactivity, emotional stimuli, intellectual effort, hypoglycemia, and drowsiness, hyperventilation and photic stimulation are both consistently and characteristically associated triggers and are therefore integrated into routine EEG recording. The diagnosis of absence is usually easy and virtually never occurs after only a single event. The principal differential diagnostic challenge is to differentiate absenced from complex partial seizures. Because automatisms associated with absence may include licking of the lips, brief smacking or pursing of the lips, and even swallowing, humming, or mumbling, complex partial seizures (*see also* Complex Partial Seizures) must be considered. However, the lack of an aura, greater duration of impairment of consciousness, prominent or unilateral automatisms, and a postictal state help differentiate complex partial seizures from absence. Additionally, EEG helps by demonstrating a generalized discharge from a focal discharge. Fluctuation in concentration and attention and attention deficit disorder may

mimic absence seizures in school-aged children, while transient global amnesia, uncomplicated memory lapses, or "blackout spells" from alcohol abuse appear during middle age or in the elder years and may require ictal recording to differentiate seizures in these populations. Similarly, some patients with various cognitive or psychiatric disorders have nonepileptic behaviors that include staring or appearing "absent" that make diagnosis challenging without video-EEG monitoring of the habitual event. Autonomic features associated with absence, including brief changes in respiration, blood pressure, heart rate, or pupil size, and even bowel or bladder incontinence, may be a distraction from the diagnosis of absence and suggest alternative seizure types (i.e., complex partial seizures) or nonepileptic physiologic events (i.e., syncope). When staring spells are reported in school or by parents, a concomitant EEG that shows a 3 Hz GSW pattern makes the diagnosis straightforward (*see* figure).

The EEG of absence seizures has a robust association with a generalized 3 Hz spike-and-slow wave discharge. Interictal EEG consistently demonstrates this pattern as single complexes and more prolonged bursts. Bursts often begin at 3-4 Hz and slow to 2.5-3 Hz by the end of a burst. Ictal EEG during absence




EEG with generalized spike-and-slow-wave discharge and absence seizures in an otherwise normal 8-year-old male. (From Tatum WO, Husain A, Benbadis SR, Kaplan PW. The Handbook of EEG Interpretation. New York: Demos Medical Publishing, 2008.)

seizures shows the same generalized, 3 Hz spike-and-slow wave bursts, which are symmetric, bifrontally predominant, and synchronous, with spike amplitudes that vary between 150 and 1200 uv. When absence seizures are very brief, alteration in consciousness may require more sophisticated techniques for response testing. Bursts are characteristically induced by hyperventilation, and testing may be optimized during this time. Photic stimulation may precipates a photoparoxysmal response as well but is a less potent activator for both the clinical and EEG features of absence. Other features in EEG typically include normal background electrocerebral activity. Clinical observation often underestimates the frequency of seizures, and more precise quantification is enhanced by prolonged EEG recording. When bursts of generalized spike-and-slow waves last longer than 3 seconds, it is usually possible to demonstrate a clinically detectable change in the level of responsiveness. The treatment of absence is generally ethosuximide when unassociated with additional seizure types such as GTC seizures. Valproate and lamotrigine are alternatives that have demonstrated efficacy. Still others, such as topiramate, benzodiazepines, acetazolamide, and possibly leviteractam or zonsiamide, may yield benefit in some patients [1].

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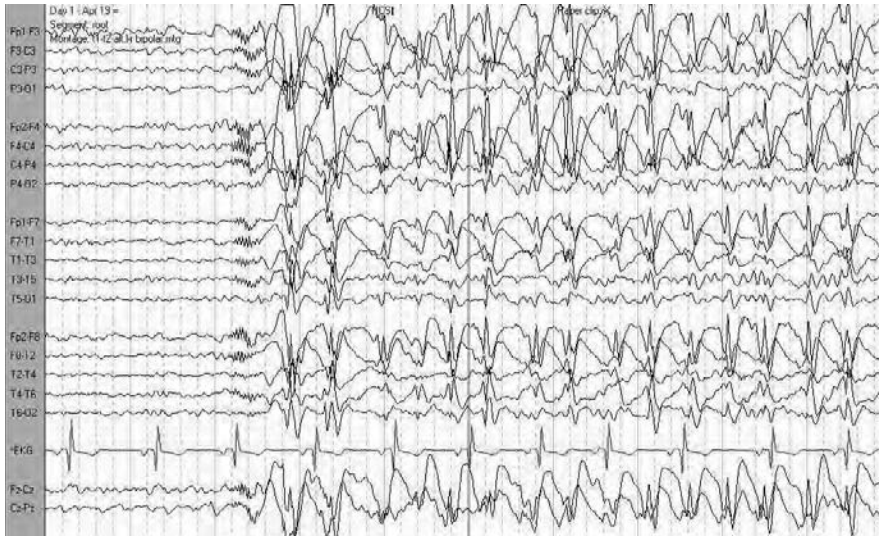
## ABSENCE, ATYPICAL

Compared to typical absence, atypical absence has a more gradual onset of alteration in consciousness with a longer and more variable duration, usually 1-2 minutes. As with typical absence, common features include staring, eyelid fluttering, and interruption of activity or conversation with immediate resumption following cessation of the spell. Complex automatisms, sudden loss of postural tone, head drop, and falls are more common in atypical absence. Absence seizures associated with falls may be classified as atonic, myoclonic, or myoclonic-atonic.

Atypical absence can be difficult to distinguish from complex partial seizures or other seizure types including tonic seizures (especially when they are associated with faster rhythmic ictal discharges on EEG). Nonepileptic events may be confused with atypical absence. However, nonepileptic inattention is readily distinguished by ictal EEG. Typical absence seizures tend to occur in a younger age group, manifest a quicker recovery of cognition, show more regular generalized spike-and-wave discharges on EEG, and respond better to treatment with ethosuximide or valproic acid. Mental retardation and behavioral disturbances often make the clinical diagnosis more challenging, and video-EEG monitoring is sometimes required. Atypical absence seizures are associated with encephalopathic generalized epilepsies. They may appear as cryptogenic or symptomatic seizures. Atypical absence is often associated

with Lennox-Gastaut syndrome, but they may also occur with any static or progressive epileptic encephalopathy of childhood, including perinatal injury, inborn errors of metabolism, and storage diseases of the CNS.

Atypical absence seizures are associated with an irregular generalized 1.5-2.5 Hz spike-wave discharge that is much more irregular. Compared with typical absence seizures, there is less abrupt onset and greater degree of assymetry, the frequency is often 1.5 Hz, and the epileptiform discharges are often sharp waves. In addition, the background is slow with abnormal mixtures of theta and delta and may include focal or mutifocal spikes or sharp waves appearing in prolonged runs during sleep. Other patterns less characteristically seen with atypical absence include low-voltage fast activity at approximately 20 Hz, a rhythmic burst of high-voltage 10 Hz polysharp waves, as well as the classic "slow" (fewer than three per second) spike-and-wave discharge.



EEG demonstrating 1.5-2.5 Hz generalized slow spike-and-waves in a patient with encephalopathic generalized epilepsy and atypical absence seizures. Note the brief polyspikes prior to onset of the burst.

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## ACETAZOLAMIDE (DIAMOX®)

Acetazolamide is a weak carbonic anhydrase inhibitor with mild diuretic activity that is used as an adjunctive antiepileptic drug (AED). The antiepileptic properties may be related to its induction of a mild transitory metabolic aci-

dosis. Tolerance may develop if used chronically. It is effective against a variety of different seizure types, including generalized tonic-clonic seizures, myoclonic seizures, and particularly absence seizures. In addition, acetazolamide is frequently used for patients with partial seizures and catamenial exacerbation and can be initiated for 10-14 days beginning several days prior to menses and continued until after menses is completed. The drug half-life is 6-12 hours, and it is 90% protein bound and comes in 250 and 500 mg tablets. Effective plasma concentrations range from 1 to 22 mg/L, but they are not usually measured. Tolerance to the antiepileptic effect is common. Significant side effects are rare, but may include increased urination, paresthesias, anorexia, drowsiness, headache, rash, confusion, renal calculi, and rare instances of agranulocytosis, leukopenia, and thrombocytopenia.

## ACETYLCHOLINE

Acetylcholine (Ach) may be involved in initiation of seizures and has been associated with activation of epileptiform discharges on EEG. Some animal models of epilepsy use pilocarpine as a cholinergic agonist to produce experimental status epilepticus. In humans, defects in Ach have been associated with focal epilepsies such as nocturnal frontal lobe epilepsy [1].

### Reference

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## ACTION POTENTIAL

Action potentials (and synaptic potentials) are basic chemo-electrical signals that are regulated by ion channels within a biologic membrane and are fundamental to neurotransmission within the CNS. Intrinsic electrical properties of neurons are reflected in biologic signals that can generate spontaneous activity modifying responses of adjacent cells. During an action potential, elective ion channel "gating" permits the influx of positively charged ions (primarily sodium) into the interior of a cell to supercede the resting membrane potential, and depolarization occurs. The resultant action potential is responsible for an "all-or-none" electrophysiologic current that continues independent of the triggering stimulus, although different neurons can have very different patterns of electrical excitability. Hodgkin and Huxley described the equations governing axonal membrane permeability in the generation of the action potential. Despite its importance in neuronal signaling, action potentials are only slightly reflected in the EEG because of their brief duration (less than 2 msec) and limited synchrony. Repolarization occurs when termination of the action

potential is prompted by inactivation of the sodium channels and opening of the potassium channels. Intrinsic mechanisms that are mediated through action potentials are important in integrating information within neural tissues within the body but have also been the foundation for patch clamp recording in the basic science of epileptology.

## ADENOSINE

Adenosine is an inhibitory neurotransmitter that modulates synaptic and postsynaptic excitatory neurotransmission. During seizures, brain adenosine increases dramatically and may occur as part of a cascade leading to seizure termination and postictal suppression of neural activation.

## ADHERENCE (COMPLIANCE)

Adherence, also known as compliance, is generally defined as the extent to which patients' treatment-related behaviors correspond to health professionals' advice. Adherence includes taking medication as directed as well as co-administering vitamin supplements and behavioral modification such as not operating a motor vehicle. Adherence in epilepsy is arguably of more immediate concern than in other chronic diseases because a lapse in adherence (compliance) may lead to breakthrough seizures, injury to self and others, and loss of driving or work privileges. Breakthrough seizures reflect treatment "failures" that result from a patient-induced condition most commonly due to low AED concentrations after missed medication. Similarly, adhering to behavioral modifications such as avoiding sleep deprivation, drugs and alcohol, environments with flashing lights (i.e., concerts or discos), and other unique triggers may be especially important for patients with epilepsy to optimize therapy. The reasons for nonadherence may be multifactorial and include deliberate (e.g., cessation due to side effect or fears of side effects) or unintentional causes (poor memory, poor medicine access, etc.), although encouragement from medical professionals is key to ensure tight control. While nonadherence is common, simplification of daily dosing regimens may help facilitate better compliance. In one study using continuous electronic monitoring to measure compliance, once-a-day dosing was found to result in a mean compliance rate of 87%; twice a day, 81%; three times a day, 77%; and four times a day, 39% [1]. There may be variances in patient-stated compliance compared to actual medication intake, as has been demonstrated in pregnant women with epilepsy by measuring hair AED content and comparing to drug compliance diaries. Pregnancy, in particular, involves reduced adherence because of side effects (nausea) and hidden as well as overt fear of medication effects on the fetus. Direct measures of adherence lie in measuring AED levels. Indirect measures include self-report, pill

counts, documenting appointment attendance, medication refills, and seizure frequency [2]. Adherence may be increased through patient education on the importance and advantages of such behavior balanced against an informed risk of the consequences of seizures on person, profession, and driving.

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## ADRENOCORTICOTROPIC HORMONE (ACTH)

The initial benefits of adrenocorticotropic hormone (ACTH) in the treatment of childhood seizures appeared in the1950s. The epilepsies that respond to steroids are typically age-related and begin during early childhood during critical times of brain maturation. Infantile spasms or West syndrome, Lennox-Gastaut syndrome, Ohtahara syndrome, and Landau-Kleffner syndrome are a few of the encephalopathic generalized epilepsies in which ACTH may play a role. However, improvement in EEG abnormalities (e.g., electrical status epilepticus of slow sleep [ESES]) has also been described. A wide variety of steroids and different doses have been used. The biologic activity of ACTH may be different when it is a natural compound that is derived from pituitary extracts enhancing the benefit-to-risk ratio when compared to synthetic compounds. Hydrocortisone, prednisone, prednisolone (Medrol®), and dexamethasone (Decadron®) are other commonly used steroids; ACTH appears superior to oral steroids. Dosages of ACTH are represented in international units (IU). The effect of ACTH may be independent of the effect upon the cortical-adrenal axis to stimulate steroidogenesis and may have a direct effect on brain function. Great variability in the duration and modality of treatment exists. Natural ACTH appears superior to oral steroids in the treatment of infantile spasms. The most effective dose remains controversial. ACTH is purported to have a rapid effect-within a week-but relapses may occur. While prospective studies have shown that high doses of ACTH (150 IU/m2 or 60 IU/d) demonstrate excellent short-term results [1], the differences between high- and low-dose effects have not been consistently reproducible [2], and the optimal dose may lie between 50 and 200 IU/m2/d. One approach may be to begin at lower doses and increase to high doses with a suboptimal response. Treatment durations also vary from 3 to 9 weeks, although more than several months of treatment may be required if relapse occurs.

High doses of ACTH or those administered by depot formulations in doses commonly used for infantile spasms may have marked side effects. Lowered immune resistance with a high rate of infection, Cushingoid facies, obesity, gastrointestinal disturbances, electrolyte abnormalities, hyperglycemia, hyperten-

sion, agitation, insomnia, adrenal suppression, and insufficiency are some of the more common adverse effects that may occur.

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## ADRENOLEUKODYSTROPHY (ALD)

ALD is an X-linked hereditary disorder of peroxisomal biogenesis that results in a defect in very long-chain fatty acid (VLCFA; 24-30 carbon chain length) metabolism. A deficiency of a single peroxisomal enzyme results in deposition of fatty acids in the central nervous system to produce clinical manifestations that may include seizures. Children are most frequently affected. In women, the myelopathic clinical form predominates, although males may present with various clinical features. The neonatal syndrome is an autosomal recessive disorder with a pathophysiology that resembles X-linked ALD. While no characteristic EEG patterns are evident, hypsarrhythmia may appear and mimic West syndrome. Seizures may be intractable and manifest as tonic-clonic, clonic, tonic, and myoclonic. Later-onset ADL has progressive neuropathy and spastic paraplegia, with Addison's disease, blindness, dysarthria, encephalopathy, and mood liability appearing frequently. The phenotypic presentation is variable, but in the juvenile form in males seizures are usually a later manifestation in the course of the disease. The diagnosis is possible based upon the typical clinical characteristics, measurement of VLCFAs in the serum (or tissue), and prominent white matter disease or leukodystrophy on MRI. Dietary therapeutic lowering of VLCFA levels over 1-2 years using Lorenzo oil does not measurably improve CNS dysfunction.

## ADVERSIVE SEIZURES

*see* Versive Seizures.

## AFFECTIVE SYMPTOMATOLOGY

Affective symptomatology is most often seen during simple and complex partial seizures. They may be associated with either cryptogenic or symptomatic localization-related epilepsies and most commonly occur as a manifestation of temporal lobe epilepsy. A wide variation in affective symptomatology ranges

from extreme pleasure to extreme displeasure during an epileptic seizure. Affective symptoms may occur with a change in affect that is typically unpleasant (e.g., fear, anxiety, panic). Ictal fear is the most frequent symptom. It is often quite dramatic, with intense displays of terror and objective autonomic signs of sweating, screaming, pupillary dilatation, flushing, and tachycardia. Unlike panic attacks associated with primary psychiatric conditions, epileptic seizures that manifest as anxiety are unprovoked episodes lasting only seconds to minutes. Like epileptic seizures, epileptic panic attacks or anxiety may have a postictal state, abnormal EEG with interictal epileptiform discharges, and be associated with other, more apparent seizures types such as GTC seizures. Anger and depression are extremely rare affective symptoms as an ictal phenomenon, although hostility may appear in the form of provoked or resistive violence in the postictal period. Similarly, patients may even become psychotic in the postictal state after a cluster of seizures, which state may last for hours or even days if left untreated. Rarely, pleasurable symptomatology may occur including euphoria, ecstasy, or even sexual pleasure that includes orgasm. Other clinical manifestations include visual phenomena of monocular or binocular illusions of form, distance, or perception such as micropsia or macropsia, distorted images or sounds, or feelings of depersonalization, derealization, or even out-of-body experiences (autoscopy). Frank hallucinations may also occur and consist of formed or unformed alteration of perception. Visual, auditory, olfactory, gustatory, or somatosensory hallucinations with alteration in perception of size, weight, or pain in an "affected" limb may be present.

## AGE OF ONSET

The age of onset is significant in establishing both a diagnosis and classification of some well-established epileptic syndromes as well as in determining the etiology and initiating treatment and providing a prognosis. The bimodal distribution of incidence seems to be specific for epileptic seizures and epilepsy. The highest rates of recurrence of unprovoked seizures are observed in children and in the elderly, with 69.9 /100,000 in children less than 10 years of age, 36.6 in adolescents and young adults, and 82 in the elderly [1]. A similar distribution has been noted for first seizures, although this has not been observed in developing countries probably due to the associated higher mortality rate [2].

Incidence rates show a slow decrease in children but a striking increase in the elderly. In developed countries, more than 25% of the first seizures are observed in patients older than 65 years. In the Rochester study [1], the incidence rate in the elderly increased from 44 to 110/100,000 between 1935 and 1984. The cumulative incidence at age of 80 has been estimated at 5%, although the rate is less than 1% in persons younger than 20 years of age [1].

This epidemiologic feature is not as clear with regard to prevalence. In the Rochester study, the prevalence rate in children remained stable between 1960 and 1980 at 3.75-6.25/1000 people, implicating either a decrease in mortality

(which has not been established) or improvement in management. The prevalence rate in the elderly is approximately 10/1000.

Certain epileptic syndromes, such as febrile seizures, West syndrome, and sometimes Lennox-Gastaut syndrome, are observed in children with the time of onset and the cause conferring prognostic value.

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## AGRANULOCYTOSIS (*see also* ANEMIA, APLASTIC)

Agranulocytosis is also referred to as granulocytopenia. It is one of the most feared hematologic complications of AED use and reflects a severe deficiency of the granulocytes (polymorphonuclear white blood cells). When the absolute granulocyte counts fall lower than 500/mm3, this predisposes the patient to mucosal ulerations and opportunistic infections. Fortunately, agranulocytosis is an uncommon complication of AED therapy. In one study, only 1.4 per million were affected by agranulocytosis when treated with carbamazepine.

## AICARDI'S SYNDROME

Aicardi's syndrome is an epileptic syndrome that is only seen in females. It usually appears in the first year of life, but also occasionally in the neonatal period. The syndrome typically presents with infantile (flexor) spasms that may be asymmetric, isolated, or associated with other seizure types. In addition, partial or complete agenesis of the corpus callosum and multiple chorio-retinal lacunae are found. Other associated cerebral malformations have been reported, including ventricular heterotopia, microgyria, and pachygyria. Vertebral malformations have been seen in 50% of cases. EEG demonstrates diffuse abnormalities with an asymmetric burst-suppression pattern independently in both hemispheres and hypsarrhythmia. The prognosis is characteristically associated with a poor outcome.

## AIDS (Acquired Immune Deficiency Syndrome)

The human immunodeficiency virus (HIV) is one of a group of retroviruses that has a predilection for the CNS and results in a potentially fatal outcome from the acquired immunodeficiency syndrome (AIDS). Direct nervous sys-

tem invasion by the HIV group of viruses as well as by opportunistic infection with AIDS result in neurologic complications in most cases by the time of demise. Seizures are both a common presenting sign and chronic condition at any stage of HIV disease. Seizures occur in about 7-11% of patients seropositive for HIV but who do not have AIDS [1]. AIDS occurs when symptoms associated with immune deficiency occur and has protean manifestations when HIV attacks the nervous system. Cerebral complications of AIDS include seizures as an important sign to identifying CNS involvement of HIV. Toxoplasmosis, cryptococcal meningitis, and lymphoma are but a few of the opportunistic infections that may occur in an immunocompromised host during the course of AIDS, though in over 40% of patients with HIV infection who present with seizures, no cause other than HIV is discovered. Seizures are more frequently seen with toxoplasmosis or lymphoma and more rarely with encephalopathy or meningitis. Seizures occur in approximately one third of cases of AIDS. Seizure types include GTC, although focal seizures also predominate and status epilepticus may occur as a presenting symptom. Early treatment with AEDs is recommended given the high likelihood of a symptomatic basis with the first seizure (*see* First Seizure). AED therapy may be problematic as patients may develop hypersensitivity reactions, worsening leukopenia, or drug interactions that impair antiretroviral agents when enzyme-inducing antiepileptic drugs (EIAEDs) are utilized. The newer AEDs may be preferred due to the lack of drug-drug interactions and favorable pharmacokinetics (*see* Treatment).

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## ALCOHOL, EFFECTS OF

In clinical practice, alcohol remains one of the most important causes of seizures and epilepsy. Seizures can occur during either the acute phase of alcohol intake,or alcohol withdrawal after a relative alcohol intake cessation in the setting of chronic alcohol abuse. Single seizures or a series of generalized tonic-clonic seizures most often occur, although rarely partial seizures or even status epilepticus has been reported. Any lateralizing seizure semiology that occurs should always prompt a search for a focal cerebral lesion such as CNS infection or posttraumatic encephalomalacia. Seizures related to abrupt cessation of alcohol are generalized tonic-clonic seizures. Seizures are usually single, but two or more may also occur. Status epilepticus suggests a coexisting disorder (e.g., subdural hematoma or drug withdrawal). Seizures occur during the initial 48 hours of withdrawal from alcohol intoxication and are most common between the hours 12 and 24 after a drinking binge. The symptoms of alcohol withdrawal range from tremulousness, hallucinations, seizures, and finally delirium tremens, occurring within 48-96 hours. Seizures that occur more than 6 days following ab-

stinence should not be ascribed to ethanol withdrawal. The EEG is usually normal, but it may show nonspecific and nonepileptiform patterns.

Alcohol abuse is also a risk factor for developing epilepsy, depending on the duration and amount of alcohol being consumed. The incidence of alcoholism in epilepsy is no higher than in the general population, although alcoholics have a higher incidence of seizures [1]. Alcohol abusers are at higher risk for head trauma during intoxication and intracranial infections, which may predispose them to epilepsy. Excessive intake of alcohol in persons with or without epilepsy can increase the frequency of seizures by creating metabolic changes (e.g., hypoglycemia, hyponatremia), variation in the levels of some AEDs (e.g., through increased AED renal clearance), sleep deprivation during bouts of drinking, and poor adherence to recommended antiepileptic treatments. Some studies have shown that limited acute alcohol intake or "social" drinking do not adversely affect seizure frequency or produce EEG abnormalities in persons with epilepsy (PWE) [2].

Treatment depends on the underlying causation for the seizure(s). Electrolyte imbalances (e.g., sodium, glucose, magnesium) should be corrected. Administering thiamine *prior to* glucose administration will minimize the risk of developing Wernicke-Korsakoff syndrome. Initiation of treatment with lorazepam, diazepam, chlordiazepoxide, or clorazepate is pursued prior to primary management of substance abuse to minimize the risks of delirium tremens. Treatment with chronic AEDs is unnecessary unless a concomitant epileptogenic lesion or mechanism exists and spontaneous partial-onset seizures are suspected to recur [1-3].

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## ALOPECIA

Alopecia is the loss or thinning of hair. Infrequently, patients on valproic acid, topamax, lamotrigine, and zonisamide may develop alopecia [1]. Even fewer patients taking carbamazepine, ethosuximide, or other AEDs may also experience hair loss. Hair usually regrows with reduction or discontinuation of medication, although vitamin therapy with zinc, selenium, and B vitamins has been utilized.

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# ALPERS' DISEASE

Alpers' disease is a syndrome that reflects a genetically determined disorder composed of rapidly progressive encephalopathy with intractable seizures associated with diffuse neuronal degeneration of uncertain etiology. It was first described as a progressive form of infantile diffuse neuronal degeneration. The onset is usually before the age of 1 year in the absence of a toxic, metabolic, or other structural cause. The syndrome is characterized by progressive hypotonia, cognitive deterioration, and respiratory problems; a subgroup with hepatic insufficiency is recognized. The first sign of the disease begins early in life with generalized seizures. Progressive brain atrophy is seen on serial neuroimaging of the brain. Seizure types include myoclonic, partial, and generalized tonic-clonic seizures. The patient may develop focal as well as convulsive status epilepticus. EEG may demonstrate continuous high-voltage, anterior predomint 1-3 Hz polyspikes and spike-and-slow waves. A gene mutation has been proposed with an underlying metabolic defect suspected. A definitive diagnosis is possible only with brain biopsy or autopsy, and no treatment exists to slow progression. The course is progressive and most patients die within the first decade of life with intractable seizures that often lead to death.

# ALPHA RHYTHM

Alpha rhythm is an electrocerebral rhythm seen in the normal EEG of children and adults. It remains the starting point to analyze clinical EEG. The *frequency* of alpha lies within the bandwidth of 8-13 Hz. The alpha *rhythm* is attenuated ("blocked") during eye opening and is maximal during the relaxed, awake state with the eyes closed. A transient increase may be noted immediately after eye closure, referred to as alpha "squeak." It is normally best detected over the posterior regions of the head and is part of the resting background activity. During normal development, the alpha rhythm appears by age 3 and persists as a stable rhythm of 8 Hz or more even into later life. In approximately one fourth of normal adults the alpha rhythm is poorly visualized and in < 10% low voltages of < 15 V may be seen [1]. Voltage asymmetries of > 50% and left-right differences of > 1 Hz should be regarded as abnormal [1]. Slowing or disruption of the alpha rhythm may suggest an underlying diffuse or posterior cerebral disturbance. Idiopathic epilepsies are characterized by a normal alpha rhythm; symptomatic epilepsies by abnormally slow background frequencies. Slowing of the alpha activity may be seen with some AED toxicity. Preservation of alpha rhythm during a generalized seizure is supportive evidence for nonepileptic seizures.

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# AMBULATORY EEG

Ambulatory EEGs exists as a means of recording of EEG patterns for prolonged periods (e.g., 24 hours) during normal routines of daily living at home, work, or school. It serves to fill the gap between routine EEG and in-patient video-EEG monitoring. Only 20-30 minutes of recording are obtained during routine EEG, yet abnormal paroxysmal episodes or interictal epileptiform discharges (IEDs) may appear infrequently. Ambulatory EEG monitoring has been shown to be more productive when compared to routine EEG, especially when seizure monitoring is essential [1]. Newer digital computer-assisted ambulatory monitoring systems have nearly the same technological advances that fixed inpatient video-EEG monitoring units possess, yet the application differs relative to greater cost, hospitalization, and ancillary testing capabilities associated with inpatient recordings. Most systems use spike- and seizure-detection software. In older ambulatory EEG studies using cassette recording, when compared to in-patient video-EEG monitoring, the diagnostic yield for detection of interictal and ictal abnormalities was nearly 85% [1,2]. However, artifact identification, ancillary behavioral and ancillary testing, continuous video-EEG recording, and detailed localization of interictal epileptiform discharges and seizures with multiple channels of recording have greater capability with inpatient monitoring. Ambulatory EEG has been limited in the past by the lack of a video correlation, although newer systems are now capable of obtaining video during discontinuous ambulatory EEG. As newer-generation computer-assisted EEG technology advances and costs of inpatient long-term monitoring increase, the use of ambulatory EEG will likely increase in the differential diagnosis of recurrent "spells" that are frequent, aid in the classification of interictal epileptiform abnormalities, and be used to characterize patients' seizures for the purpose of resective epilepsy surgery [2].

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# AMMONIA

Ammonia is generated by the metabolism of urea and amino acids and may be associated with seizures in those with inborn errors of metabolism. Hyperammonemia is a common finding in patients receiving valproate (VPA) and may be more likely to occur when coadministered with an enzyme-inducing AED. The mechanism that results in increased serum ammonia may occur by inhibiting ammonia transport across the mitochondrial and cell membranes. Hy-

perammonemia may lead to a clinically evident encephalopathy, although more commonly it is asymptomatic and occurs without an increase in the serum hepatic transaminase levels. Asymptomatic rises of serum ammonia levels from VPA are of uncertain clinical significance, and routine serum monitoring is not required. Chronic treatment with VPA has been associated with lower carnitine concentrations. Supplemental L-carnitine may reduce hyperammonemia by facilitating transport of ammonia across mitochondrial membranes, but the clinical benefits, while suggested [1], remain to be confirmed.

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## AMNESIA

Amnesia is a loss of memory stemming from organic processes that usually involve the temporal lobes. This may occur with intoxication or withdrawal from drugs or alcohol, dementias, brain trauma, brain tumors (especially temporal lobe), and especially temporal lobe epilepsy (TLE). Patients with complex partial seizures may frequently be unaware that they have had a seizure even in their home environment [1]. The degree of retrograde and anterograde manesia is variable, and postictally a form of Todd's phenomenon may affect the mesial temporal structures in TLE to create amnesia that may persist and mimic other disorders with memory loss such as dementia. Memory loss is a concern following temporal lobectomy for intractable epilepsy, although amnesia is rare when Wada testing demonstrates bilateral memory function. Cases of amnesia are rare; however, H.M., a patient who underwent bilateral temporal lobectomy for intractable epilepsy, developed amnesia as a result, underscoring the importance of memory in those undergoing resective temporal lobe surgery. Wada testing is therefore performed prior to surgery to prevent amnesia. Loss of memory from psychological causes is called *dissociative amnesia* [2]. Usually there is sudden anterograde loss of an emotional event after severe physical or emotional stress. If after an acute stress the patient suffers a severe memory loss, leaves home, and acts like a different person, *dissociative fugue* is present.

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## AMNESTIC SEIZURES

These partial seizures produce distortions of perception and memory. This may induce an altered sense of time including the feeling that a new experience has already been seen (*déjà vu*), already heard (*déjà entendu*), or already lived (*déjà vecu*). When a prior sensation that has been experienced is perceived as never having been experienced, in the case of visual stimulation this is referred to as *jamais vu*, or *jamais intendu* when an auditory experience is involved. There may be "panoramic vision" in which the patient experiences episodes in his or her life in rapid succession a form of "forced thinking." Amnestic hallucinations occur when the patient reexperiences minutiae of previous experiences. According to some authors, these features are the result of the simultaneous ictal involvement of Ammon's horn and the external temporal cortex and may be regarded as hallucinatory, ideational, dysmnestic illusions. Some seizures consist of recurrent episodes of anterograde amnesia, resembling transient global amnesia or dementia when recurrent subtle amnestic seizures occur.

## AMYGDALA

The amygdala is a large complex of gray matter nuclei in the dorsal anterior-medial temporal lobe. It is classified as part of the limbic system and of the olfactory system through established connections. The amygdala is situated immediately anterior to the hippocampal formation and lies lateral to the temporal horn of the lateral ventricle. Considerable study has been devoted to the phenomenon of amygdalar kindling (*see* Kindling) as a model for partial seizures. The amygdala is a favorable target because of its large size, ease and ability of the region to kindle, and accessibility to placement of stimulating-recording electrodes. This experimental model, best elicited by repeated electrical stimulation of the amygdala, is initially subconvulsive, ultimately resulting in partial and convulsive seizures.

Seizures arising from the amygdala are characterized by a sensation of rising epigastric discomfort, nausea, oral automatisms, chewing, fear, panic, and marked autonomic features: facial flushing, pupillary dilatation, belching, and borborygmus (*see also* Abdominal Aura). Depth EEG recording revealed localized seizure onset in the amygdala in a minority of patients with temporal lobe epilepsy with spread to adjacent hippocampal structures, the hypothalamus, and fronto-orbital region. The etiologies of amygdalar seizures are the same as those for seizures arising from the temporal lobe.

## AMYGDALOHIPPOCAMPECTOMY

Selective amylgdalohippocampectomy has been proven to be an effective treatment for patients with medically intractable mesial temporal lobe epilepsy.

Seizure freedom has been equivalent to standard en bloc anterior temporal lobectomies in comparative trials [1]. Targeted surgical resection to excise more limited tissue has been postulated to result in more favorable neuropsychological outcomes [2]. Because both seizure freedom and neuropsychological outcome influence health-related quality of life, selective amygdalohippocampectomy for mesial temporal lobe epilepsy has become a favored technique in resective temporal lobe epilepsy surgery (*see* Surgery for Epilepsy).

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## ANEMIA, APLASTIC (*see also* AGRANULOCYTOSIS)

Hematologic adverse reactions associated with AED therapy for epilepsy encompass a wide range of abnormalities. Asymptomatic effects may occur, ranging from mild anemia, leukopenia, or thrombocytopenia to aplastic anemia with a potentially fatal outcome. Megaloblastic anemias commonly occur and have been seen with carbamazepine, phenytoin, primidone, and phenobarbital. Aplastic anemia reflects a severe, often irreversible dysfunction of the bone marrow stem cells. It is readily detected on a complete blood count (CBC) by demonstrating a reduction in the blood volume of all hematopoietic cell lines. Abnormal reduction of the white blood cells, red blood cells, and platelet count are observed. Drug-induced aplastic anemia is often fatal when it occurs. Unfortunately, the occurrence of aplastic anemia cannot be anticipated by routine hematologic monitoring. Agranulocytosis appears during the initial course of aplastic anemia when the stem cells are first injured, probably due to the brief half-life of a normal granulocyte (6-12 hours). The platelet counts are the second cell line to be affected (1). Several AEDs, including acetazolamide, carbamazepine (CBZ), ethosuximide, felbamate, and mephenytoin, have been associated with aplastic anemia during the course of treating epilepsy. While the incidence is rare, with a case incidence of 5.1 per million (for CBZ), the mortality rate may be as high as 33-50% [1]. A review of felbamate-associated aplastic anemia in the United States demonstrated a high risk on the order of 27-209 per million compared to 2-2.5 per million in the general population [2]. The treatment of aplastic anemia includes bone marrow stimulant drugs and transplantation.

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# ANESTHESIA

No changes in AED dose are required before or after anesthesia when oral agents are able to be continued. Oral intake of AEDs suspended during general anesthesia should be safely resumed when the patient awakens and bowel motility is restored. Higher dosing prior to surgery, benzodiazepine coverage during surgery, and initiation of alternate formulations following surgery are dependent upon the specific AED and formulations available. Intravenous formulations are available for phenytoin, phenobarbital, valproate, and levitiracetam substitution, when applicable, although conversion differences may exist from p.o. to i.v. (i.e., phenytoin). There appears to be negligible risk in PWE using local anesthesia at routine doses. However, local anesthesia with lidocaine, if injected intravenously, will have epileptogenic effects, and seizures have been rarely reported to occur. Nevertheless, both local (*see* Lidocaine) and general anesthesia have been used to effectively treat recurrent seizures and refractory status epilepticus. General anesthesia may produce significant alteration in EEG background activity, including the presence of epileptiform activity [1]. Propofol, etomidate, and barbiturates are general anesthetics that have been shown to affect the electrocorticogram (Ecog). Some anesthetics carry a higher risk in patients with epilepsy, with abnormalities that can occur both on Ecog and behaviorally with the occurrence of seizures [1]. Spikes may be augmented or "activated" through the use of methohexital not only as titrating boluses but also with stable doses to produce anesthesia; however, anesthetic agents that produce epileptiform and nonepileptiform cerebral activity are often of nonlocalizing clinical value. Some combinations of inhalant anesthetics with nitrous oxide may introduce slower frequencies during Ecog but may generate epileptiform abnormalities, while other specific combinations, such as fentanyl with isoflurane, may result in spike reduction. The use of total intravenous anesthesia using propofol and small amounts of narcotic (i.e., sufentanil) has made "awake" craniotomy easier for both the patient and the neurosurgeon [2].

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# ANEURYSMS, ARTERIAL

Unlike angiomas, seizures do not occur with aneurysms except in the case of giant aneurysms or aneurysmal rupture and hemmorhage. Seizures occur in

10-25% of patients who have undergone surgical intervention for aneurysm repair. A higher incidence of seizure is seen with larger aneurysms and particular localizations (medium-sized cerebral arteries). The presence of a hematoma, postoperative vasospasm, or hydrocephalus in the face of an unclipped aneurysm has prompted the use of preventative AED therapy during the perioperative time course, often extended until convalescence is completed.

## ANGELMAN SYNDROME

Angelman described the clinical features of this epilepsy syndrome in 1965. Epilepsy, mental retardation, unprovoked laughter, jerky movements of the trunk and limbs, and ataxia were known by the pejorative term "the happy puppet syndrome" [1]. Angelman syndrome is a genetic syndrome that is inherited by approximately 1/15,000 children [1]. The diagnosis is based upon history, clinical features, behavior, EEG, and genetic testing abnormalities. Following normal birth, developmental delay with growth failure and prominent difficulty with speech and gait occur within the first year. Minimal or no use of language occurs, with one or two words at most and retention of only basic comprehension for commands. The distinctive characteristics include a happy appearance, smiling and laughing with an open mouth, protruding tongue, drooling, and irregular jerky movements of the body with hand flapping [1]. Microcephaly and light head and eye color typically occur, although the syndrome has been identified in African Americans. Seizures are common, occurring in > 80% of patients within the first year of life and persisting into adulthood, and include both generalized and partial seizures types. Infants may present with infantile spasms, and adult-onset patients usually present with generalized tonic-clonic seizures. Atypical absence, myoclonic, and generalized tonic-clonic seizures occur in most patients, though partial seizures may also occur. Neuroimaging is nonspecific with diffuse cerebral atrophy. The characteristic EEG abnormality that occurs in virtually all patients with Angelman syndrome in early childhood includes 1-3 Hz slowing with a notched or triphasic waveform with the appearance of a slow sharp-waved complex [1]. Discharges have also been reported in the occipital regions, which are facilitated by eye closure. Generalized high-amplitude 4-6 Hz theta is seen in children, and prolonged runs of 2-3 Hz delta may have irregularly intermixed high-amplitude, posterior-predominant spikes [1]. Nearly continuous rhythmic myoclonus of the face and hands has been noted to be accompanied by a 5-10 Hz rhythm, although laughter is without EEG correlate. *Maternal* deficiency of UBE3A is the primary biochemical and molecular defect, with a mutation of the E6-AP ubiquitin-protein igase gene (UBE3A) in Angelman syndrome found within the 15q11-13 region [2]. Deletions in the long arm of chromosome 15 occur in 65-75% of patients [2]. No specific therapy exists, and seizure-specific treatment with AEDs is required.

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# ANIMAL MODELS OF THE EPILEPSIES

Important knowledge of the processes by which epilepsy is generated has been learned via animal models. There are ethical and practical limits on the investigational study of epilepsy in human subjects, and much of what is known about mechanisms of epilepsy and of potential antiepileptic drugs has been learned via animal models of the epilepsies. No one animal model suffices for study, since none perfectly replicates the clinical epilepsies, and different types of epilepsy require different models. An experimenter chooses a model based on the experimental question, familiarity, cost, and completeness of information about the chosen model. Epileptogenesis is acquired epilepsy following an initial insult to the brain, prior to the silent period of epileptogenesis, and finally the onset of spontaneous recurrent seizures. Provocation by the inciting event causes a restructuring of the neuroanatomy by reorganization through formation of new synapses in the surviving cellular region surrounding the site of neural injury [2]. By understanding the mechanisms that promote epileptic seizures, facilitation of selective preventative or interventional strategies may become evident.

Acute partial seizures have been modeled in rodents, cats, and monkeys by deposition of a variety of convulsant compounds on the surface of the brain. The application of penicillin directly to the cortex antagonizes GABA receptors and is commonly employed in acute focal models. Additionally, metals such as aluminum in gel compounds, cobalt, tungsten, and iron can be applied to the brain to produce chronically recurring partial seizures.

Because of their increased prevalence, complex partial seizures of temporal lobe origin have been modeled by several methods. The excitotoxic glutamate analogue kainic acid can be injected systemically, intraventricularly, or intrahippocampally to produce seizures that originate in hippocampal structures, although the development of a febrile seizure model dissociates proepileptogenic processes from excitotoxicity [1]. *Kindling* is a process by which repeated, brief electrical stimulations of brain (often amygdala) result in progressively more complex afterdischarges and eventually seizures originating from the limbic system. Kindling can serve as a model not only of epilepsy, but also of the plasticicty in the brain leading to the genesis of epilepsy. Considerable advances in our understanding of epilepsy mechanisms have derived from study of in vitro *hippocampal slice preparation*. Brain slice model systems sacrifice realism for control over numerous experimentally important variables

but have been pivotal in the development of several important hypotheses.

Generalized seizures have been modeled sucessfully by maximal electroshock in rats and mice, which predicts a putative anticonvulsant's efficacy against tonic-clonic epilepsy. Generalized seizures can also be produced by systemic administration of chemoconvulsant drugs, such as pentylenetetrazol, picrotoxin, strychnine, bicuculline, and a variety of other agents. Since certain epilepsies have a genetic component (*see* Genetics), study of genetically prone strains of mice and rats has been of particular interest as models of absence and tonic-clonic seizures. Parenteral administration of penicillin in cats produces spike-wave discharges on the EEG with behavioral manifestations that appear similar to absence seizures in humans. Gamma-hydroxybutyrate (GHB) is a GABA metabolite that may also be used to chemically model human absence seizures.

Despite the existence of many models for the epilepsies, an abbreviation of the different forms is given above. There is still great need for more accurate and convenient models to more precisely replicate the human condition of epilepsy so that further knowledge moving toward improved treatment applications may be discovered.

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## ANOXIA/HYPOXIA

A severe, diffuse, anoxia in adults produces a variety of neurologic disorders including seizures (*see also* Hypoxia). These include partial onset seizures, generalized tonic-clonic seizures, and myoclonic seizures, including convulsive and nonconvulsive status epilepticus [1]. The EEG provides essential diagnostic and prognostic information in cases where coma is present. EEG patterns that reflect hypoxia/anoxia include low-voltage diffuse slowing into the theta or delta range, burst suppression, and electrocerebral inactivity. Generalized periodic epileptiform discharges including generalized sharp and spike-and-slow wave complexes may overlap with nonconvulsive status epilepticus [2]. Additionally, a unique EEG pattern of patients in coma following hypoxic/anoxic insult may also include a widespread, unreactive alpha activity that portends a poor prognosis (alpha coma).

Comatose survivors are often encountered in the hospital setting with seizures occurring after resuscitation from hypoxic-ischemic injury. While the underlying insult appears to be most reflective of prognosis, status myoclonus has a poor prognosis after global hypoxic-ischemic injury [1,2]. In neonates, hypoxic-ischemic insult is the most common cause of seizures that occur in the

first 48 hours of life, and isolated seizures may be followed by clusters of seizures or status epilepticus in the newborn. The prognosis is poor, with less than half of children developing normally associated with a fivefold increase in the incidence of epilepsy.

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## ANTIEPILEPTIC DRUG (AED) LEVELS

Antiepileptic drug (AED) levels may be obtained from whole blood, plasma, serum, blood cells, saliva, tears, urine, cerebrospinal fluid, or tissues. Blood levels are usually used to monitor AED concentrations to predict therapeutic impact. For every AED there is probably an optimal concentration for maximal effectiveness and minimal toxicity-the so-called therapeutic level. Ranges for the older AEDs have been established as the concentrations within which the majority of patients have seizure control without side effects. Levels above this concentration are more likely to produce side effects ("toxic" levels). However, some studies of therapeutic monitoring of AED levels demonstrate no apparent impact on either side effects or seizure control [2]. Furthermore, some individuals may have optimal control of epilepsy with serum concentration outside of the therapeutic levels or experience side effects within the desired concentration. Therapeutic ranges are provided by the laboratory performing AED assays. These may be used as a guide in management, but treatment must be adapted to the patient's needs. Not infrequently, higher- or lower-than-therapeutic level ranges are needed to control an individual's seizures or avoid toxicity. Often supratherapeutic levels may be reached in an individual without clinical toxicity, but providing the requisite seizure control.

Many of the newer AEDs have wide therapeutic ranges or pharmacodynamic effects at the CNS receptors that make pharmacokinetic measurements less applicable. The goal of treatment is to eliminate seizures, not to produce a therapeutic AED drug value.

Brain and blood concentrations are expected to be similar, though in fact they may differ among different (especially pathologic) brain regions. The dosage in mg/kg needed to provide optimal blood levels may vary markedly, however, from patient to patient. When multiple AEDs are used, drug interactions may be predicted in general, but the degree of interaction is more difficult to predict. Certain pathologic states, including hypoalbuminemia or hepatic or renal insufficiency, may change the equilibrium or elimination rate of the AED, leading to a higher likelihood of toxicity. AED monitoring is es-

sential in verifying compliance. The AED levels can only be compared if they are measured at the same time. For AEDs with sustained-release formulations or with long half-lives, the serum concentrations should not deviate by more than 20-25% once steady state is achieved when there is adherence to treatment. For AEDs with short half-lives, concentrations may vary by 50% or more. Therefore, AEDs such as gabapentin, levetiracetam, pregabalin, or valproate DR or carbamazepine dosed bid should not be interpreted as demonstrating nonadherence when values differ by > 50%.

Chromatography, radioimmunoassay, and immunoenzymatic monitoring are methods used to measure serum concentrations. Typically the total plasma AED level is measured, which does not distinguish between the free and protein-bound fractions. If there is reason to believe an increase in the free fraction of a particular AED exists (i.e., combined highly protein-bound AEDs such as VPA and phenytoin (PHT)), then free or unbound drug levels may be measured. Such testing may be beneficial for certain patient populations such as those with hypoalbuminemia, on renal dialysis, or during pregnancy, where a shift in protein binding occurs and AED elimination increases. When blood samples are difficult to obtain (e.g., in children), salivary levels may be helpful. Measurement of drug metabolites may be made in blood or urine, though such measurements are not clinically useful on a routine basis (e.g., 10,11 epoxide intermediatry of CBZ).

Laboratory values must always be interpreted in the light of the patient's clinical state. Noncompliance may produce lower-than-expected blood levels, as may poor gastrointestinal absorption, altered distribution or metabolism from co-administered medication, or increased clearance (genetic factors, enzyme induction, or measurements taken before a steady-state concentration is achieved). Additionally, normal fluctuation of serum concentrations occurs during the course of the day. Higher-than-expected levels may be seen due to faulty compliance or decrease in renal clearance (due to genetic factors, drug interactions, hepatic insufficiency, renal insufficiency). In certain metabolic states, such as renal insufficiency, AED levels may not correlate with seizure control or toxicity. In uremia, for example, the free (unbound) and therefore active fraction of phenytoin may be significantly raised, resulting in toxicity, even though total phenytoin levels are within the therapeutic range. Similarly, half the therapeutic level of total phenytoin may be sufficient to control seizures. Assays for the free fraction of an AED are commercially available.

Assays are now routinely available for most AEDs and should be used with the intent to assist in clinical treatment. Such measurement may be beneficial in the following clinical situations: (1) to assess patient compliance, (2) to correlate drug toxicity (*see* Antiepileptic Drug Levels), (3) to establish an individual, clinically therapeutic concentration, (4) to guide dosage adjustments when pharmacokinetic variability exists (i.e., AED formulation switches, treating young or elderly patients or those with comorbid disease states), (5) to assist treatment when potentially altered pharmacokinetic changes may occur (i.e., pregnancy or polypharmacy), and (6) to assist management when narrow

therapeutic ranges or dose-dependent pharmacokinetics are present (i.e., phenytoin) [1].

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## ANTIEPILEPTIC DRUG MECHANISMS

The earliest antiepileptic drug, bromide, was accidentally discovered when an erroneous theory designed to treat sexual dysfunction in epilepsy resulted in seizure reduction [1]. Phenobarbital was then discovered by serendipity when seizure reduction was seen after it was used as a medication designed to serve a sedative function. Over 21,000 chemical compounds were subsequently screened for activity against the maximal electroshock (partial seizures) and pentylenetetrazole (generalized absence seizures) models of epilepsy [1]. Newer models such as the genetic absence epilepsy rats from Strasbourg (GAERS), the lethargic mouse, or the GABA rat model may have greater predicitive value [1]. Additionally, the acute models of MES and PTZ may be ineffective mechanistically for active compounds (i.e., levitiracetam) unless valid chronic models bring to light more comprehensive models that include newer AED mechanisms. By understanding the basic mechanisms of the epilepsies (*see* Basic Mechanisms of the Epilepsies), AED development design based on rational theory has been pursued. The GABA degradation inhibitor vigabatrin and other GABAergic agents, including progabide and tiagabine, have been developed by this approach.

Current AEDs were developed on the basis of their ability to protect against seizures in animal models [1]. Because most antiepileptic drug development has been empirical, understanding of AED mechanisms remains incomplete. New mechanisms are continuing to be discovered (i.e., leviteracetam), and several mechanisms may exist within a single agent (i.e., topiramate). Synaptic transmission is usually antegrade and requires presynaptic release of neurotransmitters or neuromodulators to act at the postsynaptic receptors. The brain uses GABA as the main inhibitory neurotransmitter. Enhancement of GABAergic synaptic inhibition appears to be an important mechanism of benzodiazepines and barbiturates. Inotropic (ligand-gated ion channels) GABAA receptors gate a chloride channel and under most conditions result in hyperpolarization. Metabotropic (modulate ion channels or intracellular messengers by coupling to G proteins) GABAB are also linked to hyperpolarization and reduced Ca2+ conductance through presynaptic inhibition and decreased neurotransmitter release. Barbiturates enhance GABAA binding at the respective pentameric receptor binding site and increase mean chloride channel opening time, while benzodiazepines facilitate mean chloride channel frequency opening time. Valproic acid can an-

tagonize the metabolic degradation of GABA, especially at supratherapeutic concentrations. Gabapentin and pregabalin have no direct effect on the GABA or other known neurotransmitter systems, but appear to act on a gabapentin-specific binding site (alpha-2-delta subunit of the L-type calcium channel) to modulate seizure activity. Vigabatrin acts as an irreversible "suicide" inhibitor of GABA breakdown via GABA transaminase to increase brain GABA concentrations.

Phenytoin, carbamazepine, valproic acid, and phenobarbital inhibit sustained repetitive firing of neurons in a seizure focus. Blocking of the sodium channels appears to be the mechanim important in inhibiting epileptiform cellular bursting. However, certain AEDs, such as phenytoin, may in some circumstances diminish seizure propagation without eliminating synchronous epileptiform discharge at the focus. Lamotrigine also has activity at the voltage-sensitive sodium channels to inhibit presynaptic release of glutamate. Glutamate is the main excitatory neurotransmitter in the CNS and is the principal mediator of synaptic excitatory neurotransmission with receptors that may be categorized as inotropic (NMDA, kainic acid, AMPA) and metabotropic (L-AP4 and ACPD) receptors. The prototypic antiglutamate drug of this class is MK-801, although newer compounds are in development. Topiramate and zonisamide have already demonstrated activity at the AMPA receptor as one of their mechanisms of action. In addition, several AEDs can also inhibit calcium currents in certain model systems, perhaps relating to their antiepileptic actions. The anti-absence agent ethosuximide appears to inhibit the T-calcium channel in thalamic neurons involved in rhythmic thalamic activity as the primary mechanism of action.

As advances in our understanding of the mechanisms of AEDs evolve, newer pharmacologic approaches will become available for the treatment of patients with epilepsy.

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## ANTIEPILEPTIC DRUGS (AEDS)

For years, the treatment options for epilepsy were limited, but after 1993 an explosion of new-generation AEDs became available for patients with seizures [1]. AEDs are available for monotherapy or as adjunctive therapy in patients with idiopathic, cryptogenic, or symptomatic seizures and include both new- and older-generation AEDs for inpatients and outpatients in addition to intravenous formulations for the treatment of status epilepticus. The AED of choice varies with experience, personal preference, desire to avoid particular side effects, cost convenience issues, and seizure type for an individual patient (*see* Treatment) [2]. Other promising AEDs that are still in development at

this time include clobazam, vigabratin, lacosamide, talampanel, rufinamide, retiagabine, and brevetiracetam.

### Antiepileptic Drugs (AEDs) Available for Clinical Use in the United States

**Hydantoins**
Phenytoin* (Dilantin®)
Ethotoin (Peganone®)
Mephentoin (Mesantoin®)

**Barbiturates**
Phenobarbital* (Luminal®)

**Primidone* (Mysoline®)**
Mephobarbital (Mebaral®)
Methabarbital (Gemonil®)

**Carboxamides**
Carbamazepine* (Tegretol®)
Oxcarbazepine* (Trileptal®)

**Succinimides**
Ethosuximide* (Zarontin®)
Methsuximide (Celontin®)
Phensuximide (Milontin®)

**Carbamates**
Felbamate* (Felbatol®)
Phenyltriazine derivative
Lamotrigine (Lamictal®)

**Sulfonamide AED**
Zonisamide (Zonegran®)

*Of major clinical importance.

**Oxazolidinediones**
Paramethadione (Paradione®)
Trimethadione (Tridione®)

**Phenylureas**
Phenacemide (Phenurone®)

**Carboxylic acids**
Valproic acid* (Depakene®)

**Carbonic anhydrase inhibitor**
Acetazolamide (Diamox®)

**Benzodiazepines**
Diazepam* (Valium®)
Clonazepam* (Klonopin®)
Lorazepam (Ativan®)
Chlorazepate (Tranxene®)
Midazolam (Versed®)

**GABA analog**
Gabapentin (Neurontin®)
Pregabalin (Lyrica®)

**Structurally distinct**
Topiramate (Topamax®)
Leviteracetam (Keppra®)
Lacosamide (Vimpat®)
Rufinamide (Banzel®)

## Pharmocokinetics

Pharmacokinetics is the study and mathematical expression of the drug course in the body, including absorption, distribution, metabolism, and excretion. Pharmacokinetics (and pharmacodynamics) differ between the AEDs [3]. *Absorption* occurs after the ingestion of a single dose; the half-life of an AED can be extrapolated from absorption and decay curves obtained from repeated blood levels. The highest point of the curve represents peak concentration and the speed of absorption, whereas the area under the curve reflects bioavailability. Intravenous AED administration produces total and immediate absorption. Oral ingestion requires penetration of the gastrointestinal mucous membrane and passage through enterohepatic circulation before reaching the systemic circulation. This process usually involves passive diffusion of the nonionized portion of the anticonvulsant. Many factors affect distribution, including molecular size, lipid solubility, membrane concentration of anticonvulsant, gas-

trointestinal contents, and gastric emptying. Solubility may vary from one formulation of a drug to another. Bioavailability of an AED may be determined by measuring the area under the curve produced by intravenous or oral administration. Rectal administration of some drugs in solution results in excellent absorption. Conversely, certain AEDs (i.e., phenytoin given intramuscularly) may bind to muscle proteins and create irregular absorption. In blood, *distribution* is a balance of absorption, excretion, and entry into the extravascular tissue compartment. Immediately after intravenous injection, blood drug concentrations fall exponentially, since it is the total plasma volume that is cleared in a given time. After oral administration, the serum concentration increases and subsequently decreases by the same mechanism. For most AEDs, the rate of clearance is proportional to the serum concentration (first-order kinetics). For other AEDs (e.g., phenytoin at high serum concentrations), clearance is limited by the rate of biotransformation, with a clearance rate independent of serum concentration (zero-order kinetics). In the case of zero-order kinetics (nonlinear) with phenytoin, high serum levels may take a much longer time to clear than lower levels. When a medication is taken frequently in repeated doses, some portion remains in the intravascular compartment, leading to an accumulation or increase in blood concentration. With first-order kinetics, clearance is proportional to the concentration, and equilibrium is achieved between input and output. With zero-order kinetics, and with an intake that exceeds the maximum rate of clearance, serum concentrations continue to rise. Whatever the means of administration or the number of doses, concentration falls when intake stops. The apparent clearance half-life is the time needed for the serum concentration to fall by one half. As a general rule, achievement of steady state on the rising phase of drug administration requires about five half-lives. For any given medication, an equilibrium is produced between a free and a protein- or tissue-bound fraction. The free fraction is the ratio of the free concentration to the total concentration. Molecules bound to proteins provide a "drug reservoir" and may disassociate so as to maintain a constant free drug level. Only the free fraction can cross the vascular endothelium to reach the brain. The apparent volume of distribution (Vd) is the hypothetical volume required to produce the same concentration as in the blood compartment. Vd represents the proportion of the blood concentration to the amount administered. For a given drug, this varies according to physiologic state (i.e., pregnancy) or pathologic state (i.e., obesity, hypoalbuminemia). In the extravascular compartment, the free fraction distributes itself into the various organs. AEDs are distributed evenly between the blood and intracerebral compartments. *Elimination* of a drug from the body proceeds in the form of biotransformation (metabolism) and clearance (excretion). Biotransformation of AEDs begins in the liver with oxidation, reduction, and hydrolysis. Drugs are transformed into numerous metabolites: some active, some inactive, and some potentially toxic. The cytochrome P450 system of the hepatic endoplasmic reticulum plays a major role in metabolism. Age, humoral, and genetic factors may all modify the activity of the P450 system. After hepatic

metabolism, the water-soluble (usually conjugated) metabolites are renally excreted by glomerular filtration and tubular secretion. Many drug interactions occur between the various AEDs, as well as between AEDs and other drugs. Absorption of some AEDs can be diminished by certain antacids. Competition may exist between drugs for a protein binding site: for example, with bilirubin, aspirin, nonsteroidal anti-inflammatory drugs, heparin, and several others. One drug may increase the free fraction of another without significantly altering the total level. During biotransformation, drug interactions may occur via induction of the hepatic cytochrome P450 system and increased metabolism of other drugs. Phenobarbital, phenytoin, and carbamazepine are potent P450 inducers. Oxcarbazepine and topiramate are weaker inducers. Conversely, certain drugs can inhibit the biotransformation of others, either by competition for the same enzyme system or by inhibition of a metabolic enzyme. Valproic acid increases serum barbiturate levels by about 30% via inhibition of barbiturate metabolism. Felbamate increases phenytoin, valproate, and carbamazepine-epoxide levels while lowering carbamazepine levels. During excretion, modifications in urinary pH may alter clearance.

## Toxicity

AEDs are generally less toxic than many other drug groups. Side effects may be grouped according to the drug responsible, the target organ, or the parent mechanism. Acute or subacute overdoses are dose-dependent. When too high a dose is prescribed, too large a dose is taken, or unexpected decreases in clearance occur-for example, by interaction with another drug (e.g., CBZ and erythromycin)-toxicity may occur. Intercurrent infection such as hepatitis may also result in drug accumulation and toxicity. Typical clinical signs include drowsiness, dizziness, ataxia, nystagmus, and occasionally a paradoxical increase in seizure frequency. An individual patient's tolerance of chronic AEDs may be more important than the amount of drug taken. In most cases, signs of toxicity are seen with high doses and high serum levels. In some susceptible patients, these signs and symptoms may appear even when doses and AED levels lie within the so-called therapeutic range. Therapeutic ranges are based on monotherapy, and polypharmacy may lead to the accumulation of metabolites with consequent side effects. Patients may appear sedated, lethargic, and somnolent with decreased verbal output and psychomotor retardation. All of the above features may adversely affect professional or scholastic performance.

These effects are more commonly seen with phenobarbital and primidone than with valproic acid or carbamazepine. Side effects may appear insidiously and be attributed to other factors (i.e., epilepsy, environmental, or psychological factors). Side effects may be noted only when the drug is stopped and symptoms resolve. Other side effects reported include weight gain or loss, gastrointestinal problems, endocrine abnormalities, acne, a fall in serum folate, leukopenia, macrocytosis, osteoporosis, and an increase in hepatic enzymes (gamma GT). Idiosyncratic adverse events are rare, unpredictable, and fre-

quently serious side effects, occasionally leading to death, including leukopenia and aplastic anemia (*see also* Anemia; Agranulocytosis), severe exfoliative dermatitis (occasionally leading to Stevens-Johnson syndrome), hepatitis, and pancreatitis. A serum sickness may appear 1-8 weeks after starting treatment and usually resolves if the drug is stopped immediately. Felbamate was found to be an effective broad-spectrum AED but has become associated with aplastic anemia and irreversible liver failure and has rarely been associated with fatalities (*see* Felbamate). Despite considerable research, the precise mechanism of action of most AEDs remains poorly understood (*see* Antiepileptic Drug Mechanisms) and exacerbation of seizures by AEDs may infrequently exist as a consequence of drug therapy [4].

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## ANTIEPILEPTOGENESIS

The search for antiepileptogenesis is one of the most fundamental and important areas of epilepsy research. The search for therapies that provide prophylaxis against developing epilepsy before the cascade of seizure-related burdens is encountered is at the forefront of applied basic science in the field of epileptology. Neuroprotection is invariably tied to antiepileptogenesis by virtue of the multitude of injuries that create both neurologic and cognitive deficits associated with epilepsy. Prior clinical trials with various AEDs have failed to demonstrate antiepileptogenesis [1]. Traumatic brain injury and ischemic cerebral infarction are areas where the concepts of neuroprotection and antiepileptogenesis have overlapped in epileptology. To date, phenytoin and valproate have failed to convincingly demonstrate antiepileptogenesis [1]. Additional trials with magnesium sulfate have also failed to demonstrate its benefit as both an antiepileptogenic or neuroprotective agent in randomized double-blind trials [2]. Thus far, no clinical evidence of antiepileptogenesis has been shown in human subjects, and deleterious effects may potentially occur with treatment.

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## ANXIETY

Mood disorders have long been recognized as a complicating factor in patients with epilepsy. In patients with psychogenic non-epileptic seizures (PNES), after conversion disorders anxiety disorders are the most common etiology and thus remain important in patients with seizures. Anxiety has been a frequent comorbidity factor in patients with mood disorders both with and without epilepsy. In one multicenter study of patients with epilepsy, 73% with a history of depression also met the DSM-IV criteria for an anxiety disorder [1]. Patients with acute episodic anxiety attacks may be manifesting partial seizures of temporal lobe origin and should be suspect when the episodes are unprovoked, associated with impaired consciousness or postictal state, and of very brief (seconds to 1-2 minutes) duration. After epilepsy surgery, approximately one third do not change from preoperative anxiety or mood disorders and persist, although most improve and, rarely, new symptoms develop after surgery [2].

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## APHASIA, ACQUIRED EPILEPTIC (LANDAU-KLEFFNER SYNDROME)

The rare syndrome of "acquired epileptic aphasia with convulsive disorder in childhood" was first reported by Landau and Kleffner in 1957. This condition is rare, of unknown etiology, and begins in early childhood, resulting in progressive deterioration of language function over several years. Acquired aphasia occurs with male predominance, with 70% occurring before age 6. Clinically, a verbal auditory agnosia associated with a reduction in spontaneous speech output becomes manifest as loss of auditory comprehension for nonverbal sounds such as responding to a knock at the door. The aphasia is usually noted gradually over days but is progressive, variable, and fluctuant, with relapses that make the child appear either deaf or autistic. Additionally, cognitive and behavioral disturbances may also commonly occur with hyperactivity, aggression, and personality disturbances noted in about two thirds of patients. Neuroimaging failed to demonstrate a causative structural lesion, though PET may reveal asymmetric bitemporal hypometabolism that disappears following remission.

EEG may demonstrate bilateral synchronous epileptiform discharges, multifocal spikes, or focal temporal ictal activity. While epileptiform abnormalities are usually maximal over the left temporal region, significant activation occurs during sleep. This syndrome overlaps the clinical features of "epilepsy with continuous spikes and waves during slow sleep" and "epilepsy with electrical status epilepticus during slow sleep" (ESES). Over several years, epileptiform activity becomes more continuous. Generalized tonic-clonic and partial motor seizures appear in about 70% of patients, although usually infrequent and responsive to AEDs. Landau-Kleffner syndrome with acquired epileptic aphasia may be unassociated with clinical seizures at all. The seizures typically appear at the onset of language dysfunction and remit in adolescence, as do the epileptiform discharges on EEG. Seizures appear not to affect the prognosis, and by 10 years of age only 20% persist with seizures. Aphasia persists until after the seizures have ended, although usually disappearing before adulthood in most cases. The prognosis appears more favorable when late onset of aphasia occurs and when aggressive speech therapy is undertaken.

## APHASIC SEIZURES

Aphasic or dysphasic seizures involve the impairment of language function due to an ictal discharge in the region of the *dominant* inferior posterior frontal lobe (nonfluent or expressive aphasia) or the temporoparietal region (fluent or receptive aphasia). Ictal speech is a reliable indicator of nondominant hemispheric onset in patients with complex partial seizures. Accurate determination of aphasia in partial seizures is difficult because of (1) its brevity, (2) the ictal involvement of other cortical regions, which may bring about nonlateralizing speech arrest or ictal vocalization that is not truly aphasic in nature, and (3) the expressive and comprehensive difficulties resulting from impairment of consciousness. Ictal aphasia in patients with simple partial seizures may demonstrate regional cerebral hyperperfusion on functional neuroimaging studies such as SPECT to assist with confirmation of the ictal origin. Postictal aphasia must be distinguished from ictal aphasia but, when present in TLE, is a lateralizing sign to the dominant hemisphere.

## APNEA (*see also* RESPIRATION)

Apnea as well as hypopnea may be seen in complex partial seizures as a postictal phenomenon and less frequently as an ictal phenomenon. It is frequently associated with other autonomic symptoms when it occurs. It is a constant feature of tonic-clonic seizures when muscles of respiration are ineffective due to muscular contraction during the tonic phase. In neonates and infants, apnea may be the only clinical correlate of an otherwise subtle seizure semiology that is manifest as motion arrest (*see* Neonatal Seizures).

## APOLIPOPROTEIN E

Apolipoprotein E has widespread importance in neurology, including the area of epilepsy. Better known as ApoE, this lipoprotein transports lipids, maintains synaptic and dendritic homeostasis, and functions in neuronal repair. Chromosome 19 codes for three isoforms referred to as alleles 2, 3, and 4. When the e4 allele is present, this compromises the function of ApoE and impairs its ability to protect and repair neurons after injury. The principal source of ApoE in the brain is the astrocytes, although neurons are capable of producing ApoE in response to injury, and mRNA may be found in the hippocampus as well as the cortex. Clinically, patients with longstanding temporal lobe epilepsy and the e4 allele are at greater risk of verbal learning deficits [1]. Earlier age of onset, insults early in life, and longer durations of epilepsy have been seen in patients with the e4 allele and epilepsy [1]. The e4 allele, when present, appears to confer lower verbal and nonverbal memory when a long duration of epilepsy is encountered despite temporal lobe resection [2] and suggests that repetitive seizures may be damaging when normal repair mechanisms are encountered.

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## APOPTOSIS

Apoptosis is the process that results in cell death. Innate "programming" of the cellular pool is an inherent effect that is both genetically determined and influenced by secondary events that may affect the brain. Apoptosis is different than a sudden destructive force that results in cell death such as may occur from traumatic forces or ischemic injury. Rather, it may occur in undifferentiated cells early in life to facilitate a balance between cellular proliferation and degeneration. This balance is modulated through neuropeptides, hormones, and suppressor genes that inhibit the expression of apoptosis. Secondary apoptosis may also occur in differentiated cells in response to pathophysiological or degenerative conditions in epilepsy [1].

### Reference

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## ARACHNOID CYSTS

Arachnoid cysts are intra-arachnoidal collections of cerebrospinal fluid (CSF) with little or no communication with normal arachnoid spaces. They are seen in

the temporo-Sylvian, suprasellar, and posterior fossa regions. Cysts may remain asymptomatic and be discovered as an incidental finding on neuroimaging (especially in adults), or they may present with intracranial hypertension or seizures (especially in childhood). Seizures may occur in up to 20% of cases, although they are frequently assymptomatic. Indications for surgical excision of arachnoid cysts depend on the size, presence of mass effect, a rapid rate of growth, as well as the presence of neurologic signs, especially if progressive. Shunting procedures to divert CSF from the cyst to the peritoneal cavity may be performed, although cyst evacuation may not necessarily eliminate ongoing seizures.

## ARITHMETIC SEIZURES

Rarely in PWE, performing mathematical calculations may reflexively lead to a seizure [1]. Seizures may be myoclonic, tonic-clonic, or absence and are usually associated with idiopathic generalized epilepsy, although partial seizures may also be precipitated by performing mathematics or by the decision-making process involved.

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## ARRHYTHMIA

Cardiac arrhythmias may be the result of excessive autonomic nervous system discharge in patients with epilepsy with consequences that range from benign to a lethal effect [1] (*see also* Mortality). The sudden unexplained death in epilepsy (SUDEP) may have arrhythmia as the mechanism [2]. Also, cardiac arrhythmias resulting in loss of consciousness (Stokes-Adams attacks) may occur, with convulsive syncope associated with generalized posturing or a series of myoclonic jerks that mimic epileptic seizures (*see* also *Syncope*; Autonomic Seizures).

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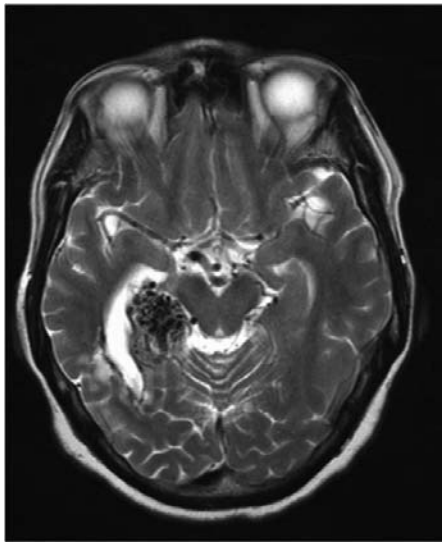
## ARTERIOVENOUS MALFORMATION (AVM)

Arteriovenous malformations are usually discovered when they bleed, although seizures may be a presenting feature, and asymptomatic lesions may be discovered by incidental or coincidental detection. Ischemia, gliosis, and he-



Right AVM in a 42-year-old patient with memory loss and medically intractable complex partial seizures successfully treated with surgical resection.

mosiderin deposition is the principal substrate for seizures. A steal phenomenon resulting in ischemia and injury with hemorrhage in the surrounding cortex may be seen leading to neurologic deficits [1]. They may occur at the time of hemorrhage or following surgical intervention. Seizures have been reported to lead to the discovery of AVMs in up to 31% of cases, and approximately 60% of AVMs may give rise to seizures [2], the risk increasing with the size and superficial localization of the AVM and the youth of the patient. AVMs have been implicated in secondary epileptogenesis in the mesiotemporal regions, anatomically distant from the malformation [2]. Surgical resection of the AVM and surrounding epileptogenic cortex produces a favorable result in patients with medically intractable epilepsy (*see* figure), although freedom from seizures has also been seen following radiosurgery.

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## ASPARTAME

Aspartame (Nutrasweet®), which is produced from L-phenylalanine and aspartame, is an extremely popular low-calorie peptide used as a sweetener in the United States. It is estimated that many millions of Americans consume aspartame every year. Because aspartame is chemically related to the excitatory amino acids (glutamate and aspartate-*see* Aspartate; Glutamate) associated with seizures and neurotoxic changes, concern has been raised about the use of aspartame by individuals with epilepsy [1,2]. Aspartame may increase EEG spike-waves in absence epilepsy [1] and in massive amounts might precipitate clinical seizures [2]. Review of the animal and clinical literature to date provides no definitive evidence for convulsive or neurotoxic effects from aspartame when used in reasonable quantities.

### References

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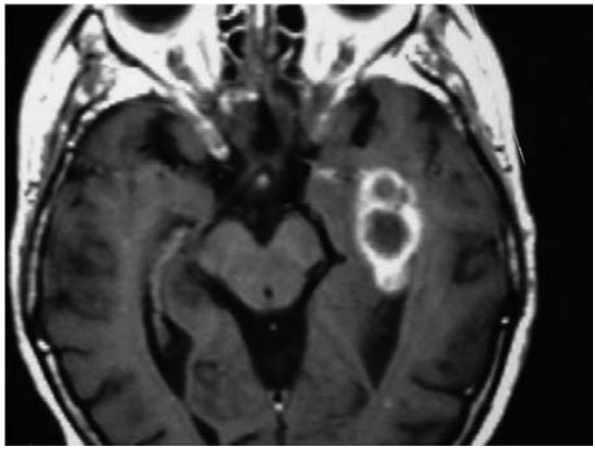
## ASPARTATE

Aspartate is a four-carbon dicarboxylic amino acid found in high concentrations in the brain, spinal cord, and other tissues. Aspartate and glutamate are important excitatory neurotransmitters involved in regulating the functions of the central nervous system (*see also* Glutamate).

## ASTROCYTOMA (*see also* TUMORS OF THE BRAIN)

Patients with slow-growing, locally invasive tumors (*see also* Tumors of the Brain) such as low-grade gliomas or astrocytomas may present with persistent focal or secondarily generalized seizures [1]. Seizures may precede other clinical features, such as headache or focal weakness, by several years. Malignant change to glioblastoma may occur over time. The optimal management-resective surgery with or without radiotherapy or chemotherapy versus conservative treatment in patients presenting with long histories of epilepsy-has not been resolved and is directed by the "grade" of the lesion based upon the radiographic and clinical course [2].



Anaplastic astrocytoma in a 46-year-old male with new onset of recurrent complex partial seizures.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# ASYSTOLE (ICTAL)

A variety of serious cardiac arrhythmias have been seen during or immediately following seizures. Ictal asystole is rare and in a recent large inpatient video-EEG monitoring study was seen in fewer than 0.5% of patients diagnosed with epilepsy [1]. This is likely an underestimation of those with recurrent seizures, however, and in a smaller study of ambulatory patients implanted over several months with a EKG loop recorder, up to 21% of patients with epilepsy were found to have at least one episode of ictal aystole [2]. Ictal asystole has been most prevalent in temporal lobe epilepsy, is a rarity for generalized epilepsy, and occurs without respect to lateralization or the degree of ictal propagation on EEG [1]. Confusion with syncope may occur when asystole is prolonged and the initial partial seizure is subtle. Ictal asystole may represent a potential link between sudden unexplained death in epilepsy and explain why those with otherwise structurally normal hearts die without a witnessed seizure [1].

### References

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# ATAXIA

Cerebellar function is important in epilepsy for several reasons, including association with a primary epilepsy syndrome or as an effect of AEDs. Ataxia is a frequent presenting complaint in patients with AED toxicity. Phenytoin, carbamazepine, and primidone are the more frequent causative agents, although newer agents, including gabapentin, lamotrigine, and oxcarbazepine, may also cause ataxia in sensitive patients or at higher doses. Ataxia may not strictly correlate with "toxic" AED levels and should be considered especially in seniors with epilepsy. Patients with "therapeutic" levels may be ataxic despite the "normal" results from laboratory testing [1]. Transient ataxia may occur as a result of chronic or acute AED intoxication. Irreversible cerebellar atrophy may be seen with prolonged exposure to pheytoin [1] but may even occur following acute overdose. Anatomic pathologic abnormalities of the cerebellum in PWE may be clinically evident or appear radiographically without clinical signs. The cerebellum may be atrophied with characteristic degeneration of the Purkinje cells, atrophy of cerebellar cortex, occasionally vermian atrophy, and rarely unilateral in patients with localization-related epilepsy (LRE).

Ataxia may occur in both progressive and nonprogressive encephalopathies that are associated with epilepsy or myoclonus where cerebellar signs appear in-

termittently or continuously in association with seizures (*see also* Alpers' Disease; Baltic Myoclonus; Ceroid Lipofuscinoses; Ramsay Hunt Syndrome).

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## ATIVAN® (LORAZEPAM)

Intravenous solutions of lorazepam (*see also* Lorazepam) are used as a treatment of choice in status epilepticus (*see* Status Epilepticus). Oral preparations are rarely used for chronic seizure prophylaxis given the tendency for tachyphylaxis. Proprietary formulations include oral tablets in doses of 0.5, 1, and 2 mg. Injectable lorazepam is available in vials of (after dilution) 1 mL 2 mg/mL or 4 mg/mL. Oral solutions (lorazepam intensol) have been used for termination of acute repetitive seizures in selected patients and may have a faster onset of action than sublingual or oral doses.

## ATONIC SEIZURES

Atonic seizures are generalized seizures that result in a sudden loss of postural tone. This may involve the sudden forward drop of the head or a global loss of postural skeletal muscles tone that results in a fall. Cataplectic seizure, apoplectic seizure, inhibitory seizure, and akinetic seizure are terms no longer used, and *drop attack* is the preferred term to designate falls from atonic or tonic seizures where precise classification is difficult. Atonic seizures usually are brief, lasting 1-2 seconds, begin suddenly without warning, and result in a fall. An initial head drop lasting approximately 250 milliseconds is followed by truncal and leg collapse that occurs within 800 milliseconds [1]. A pure atonia is unusual, and frequently additional motor components such as a myoclonic jerk will accompany the atonia. The EEG shows a diffusely slow posterior dominant rhythm, with interictal burst of polyspikes or slow spike-and-waves. During atonic seizures, EEG reveals a generalized polyspike-and-wave discharge or less regularly a generalized irregular slow spike-and-wave burst [1]. The loss of tone occurs with the onset of polyspike-and-wave discharges. Myoclonic-atonic seizures with bilateral myoclonus and polyspike activity on the EEG occur in the encephalopathic generalized epilepsises such as Lennox-Gastaut syndrome and patients with epilepsy with myoclonic-astatic seizures of childhood. A type of atonia with prolonged atonic seizures and loss of consciousness with generalized hypotonia lasting several minutes may occur. The child may fall to the ground and remain immobile ("akinetic seizures") (*see also* Absence Epilepsy) Drop attacks may also atypically occur in partial seizures of frontal lobe origin when the "negative motor areas" are involved (*see* Frontal Lobe Epilepsy) [2]. The differential diagnosis also includes sleep disorders with cataplexy and syncope.

### References

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## ATTENTION DEFICIT DISORDER

Attention deficit disorder affects approximately 10% of children with epilepsy and occurs with a male predominance [1]. This disorder may reflect underlying brain abnormality but may have persistence into adulthood and be associated with psychosocial dysfunction (*see* Psychosocial Problems). When ordinary periods of inattention are repetititive, the behaviors may be misdiagnosed as absence or complex partial seizures. When normal children have staring spells with a normal EEG, most staring spells will be nonepileptic in origin. Clues to help differentiate a nonepileptic basis include immediate preserved responsiveness when stimulated as well as the absence of repetitive motor movements, motion arrest, and urinary incontinence [2]. Stimulant medication is usually effective, and AEDs are usually ineffective.


### References

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2. Rosemon F, Wyllie E, Kotagal P, et al. Staring spells in children: descriptive features distinguishing epileptic from nonepileptic events. J Pediatr 1998;133:660-663.


## ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER (ADHD)

There is a high prevalence of attention-deficit/hyperactivity disorder (ADHD) symptoms in children with epilepsy [1,2]. In tertiary care centers, ADHD is the most common disorder of children with new-onset seizures compared to controls, affecting 31% of preschoolers and 63% of school-age children [2]. In contrast to the general population, where a greater number of boys are affected, in patients with epilepsy ADHD has an equal representation between boys and girls. ADHD can occur in children with different types of epilepsy, from those that are medically intractable epilepsy to those that are controlled. In addition, ADHD may be associated with idiopathic, cryptogenic, and the symptomatic epilepsies. While ADHD may occur with different seizure types, including absence and complex partial seizures, those with frontal lobe discharges on EEG may be more associated with ADHD symptoms. Certain types of epilepsies may predispose to ADHD-like behavior. Frontal lobe epilepsy syn-

dromes often share behavioral features with ADHD, including impulsivitiy, disinhibition, and excitement or irritability, although site of seizure onset and type do not appear to be predictive.

There is evidence that symptoms associated with ADHD may predate the onset of epilepsy in children, appearing twice as often as in those without epilepsy [1]. In patients with epilepsy, the subtype of ADHD is more likely to include the inattentive type as opposed to that experienced in the general population with combined deficits of impulse regulation and attention. This may be the result of multiple risk factors in patients with epilepsy, including recurrent seizures, effects of AEDs, and underlying brain and cognitive abnormalities. However, like the general population with ADHD, children with epilepsy tend to have an age-related expression, with fewer symptoms as children age.

### References

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2. Dunn DW, Kronenberg WG. Childhood epilepsy, attention problems, and ADHD: review and practical considerations. Sem in Ped Neurology 2006;12:118-222.

## AUDIOGENIC SEIZURES

Audiogenic seizures are reflex seizures produced by an auditory stimulus and may have different precipitating mechanisms. A sudden unexpected sound may cause a startle or jump—"startle epilepsy" (*see* Movement). However, rhythmic or monotonous sounds without the element of surprise (e.g., the sound of a running motor) may also produce seizures referred to as audiogenic seizures.

Musicogenic epilepsy is rare, althugh seizures may be induced by virtue of hearing unique tones and melodies present in music. In musicogenic epilepsy, partial seizures are usually of temporal lobe origin and may be precipitated by specific melodies, certain types of music, or repetition of music [1]. The music that acts as a trigger is specific to the individual PWE without unique epileptogenic qualities to the sounds. In some cases, the sound frequency appears to be important, but in most cases it appears that the affective significance of the music is of greater importance. Some focal seizures may be induced by a particular voice without a startle effect [1]. Right temporal localization has been demonstrated in musicogenic epilepsy with SPECT [2], although complex musical pieces probably evoke activation of cortical and subcortical networks bilaterally within the auditory processing systems.

### References

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## AUDITORY SEIZURES

Focal epileptic seizures may produce a subjective perception of sounds. Simple auditory tones or tinnitus, including the dulling of sounds, whistles, rhythmic or rumbling sounds similar to the sound of a motor or a cicada may occur with auditory seizures. Abnormalities may involve first the posterior temporal lateral neocortex in the dominant hemisphere around Heschl's gyrus. Other illusions such as altered auditory perception with respect to intensity, distance, rhythm, tonality, and timbre may occur and be due to lesions in the superior temporal cortex near the auditory association areas. *Palinacousis* is a complex auditory illusion in which external auditory stimuli such as speech, music, or noises are perseverated internally in a paroxysmal fashion; it has been identified as an interictal, ictal, and postictal phenomenon in patients with localization-related epilepsy. Formed auditory hallucinations may also occur where there is the perception of words, sentences, conversations, songs, and melodies, suggesting involvement of the auditory association areas adjoining Heschl's gyrus. Most reports of auditory hallucinations in patients with epilepsy and without psychiatric disorders have been described during interictal or postictal psychosis.

## AURA

Aura is a term used to identify the initial clinical symptoms that warn an individual that a seizure will occur. Use of the term is restricted to patients with partial-onset seizures. Clinical symptoms that occur are a reflection of the site of onset within the brain. The clinical features of an aura represent a simple partial seizure. Aura refers to the behavioral symptoms that occur at seizure onset and may immediately precede the impaired or lost consciousness associated with complex partial seizures or seizures that are secondarily generalized or occur independently.

## AUTISM

Autism includes a wide spectrum of conditions in children, and therefore autism spectrum disorder (ASD) is used clinically to describe a group of behaviorally defined neurodevelopemental disorders characterized by deficits in verbal and nonverbal communication, poor social skills, a restricted repertoire of interests, and repetitive behaviors [1]. ASD is a central nervous system disorder that is evident in children who have greater than average head circumferences and larger brain volumes. The defective underlying connections of the neural substrate may have a predisposing genetic mutation that is responsible for the manifestations of the disorder [2]. The high frequency of seizures was important in initially serving to identify autism spectrum disorder as a neuro-

biologic condition. In children with autism, approximately one third have epilepsy, although frequency ranges widely-from 5 to 38.3% [1,3]-and more recent population-based studies have demonstrated a prevalence of 6-7% when onset of seizures occurs in the first year of life [3]. Seizure onset has a peak incidence in early childhood, usually in the first year of life, and may be associated with either partial-onset or generalized seizures, including infantile spasms. Most of these patients have been mentally retarded or have learning disabilities, with associated medical conditions occurring in 10-15%. The association of epilepsy with mental retardation (MR) and autism may have a common etiologic basis, because most age-specific incidence of epilepsy in childhood is highest during the first year of life and is more often symptomatic than are epilepsies that begin later in childhood [3]. However, because epilepsy is usually diagnosed prior to autism and MR, an influence of seizures themselves on the developing brain has been suggested [1]. A clinical regression in autism (pervasive developmental disorder) has been noted in association with epileptiform discharges on the EEG, though the ASD is not considered an epileptic encephalopathy. There is insufficient evidence at this time to recommend performing a routine screening EEG on children with autism. EEG should be considered when there is a clinically evident regression in social or communicative function that may suggest an electrophysiologic contribution to the regression (*see* Landau-Kleffner syndrome).

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## AUTO-INDUCED SEIZURES

Autoinduction of seizures occurs when a patient voluntarily triggers a seizure. This may be brought about by an interrupted exposure to light (usually of direct sunlight or other intense light sources) by rapidly moving one's fingers or hands between oneself and the light source, by shaking one's head while facing the sun, by looking through venetian blinds, by looking directly at flickering television screens, or by rapid eye blinking. Less frequently, seizures may be brought on by hyperventilation. Absence seizures are most frequently seen, though occasionally myoclonic seizures or generalized tonic-clonic seizures follow. The auto-induced seizures are usually classified in the group of photosensitive idiopathic generalized epilepsies but may occur with focal seizures, especially when associated with sexual auras. Although half of patients may be mentally subnormal, patients with normal intelligence may also elicit their own seizures. Self-induced photosensitive epilepsy is usually seen at the age of 5

years and is often discovered accidentally. For reasons not clearly understood, seizures may continue to be induced during childhood and adolescence.

## AUTOMATISMS

Automatisms are involuntary movements that occur during a seizure (ictal automatisms) or following the seizure (postictal automatisms). Video-EEG recording may be required to distinguish nonictal, ictal, or postictal behavioral automatisms. Automatisms may occur with either focal or generalized seizures, and be categorized according to their appearance (i.e., a sequence of patterned movements), which may be normally, poorly, clumsily, or too vigorously carried out. Automatisms represent a continuation of an ongoing activity or the appearance of a new pattern of activity (de novo automatisms), which are adapted involuntary movements. Stereotypic patterned movement or movements in response to exterior stimuli may be evident. According to characteristic patterns *eating* automatisms are the most frequent. Activities such as lip-smacking, licking of the lips, or chewing reflect oroalimentary automatisms due to involvement of the amygdala and swallowing movements with supra-insular propagation that occurs frequently in TLE [1,2]. Automatisms may reflect the *emotional* state of the patient, with expression of emotions such as ictal fear. Simple *gestural* automatisms, such as scratching, fidgeting, or fumbling with an object seen in seizures involving the limbic circuits, or complex gestures, such as unbuttoning clothing (disrobing), moving or arranging objects, or complex organized automatisms with both the hands and feet (bimanual-bipedal), may be seen in frontal lobe seizures or temporal lobe seizures. Automatisms are usually common movements reflecting the environment or sensation at the time of the seizure. Simple or complex *verbal* automatisms lateralize to the nondominant temporal lobe when ictal speech is present [1]. Verbal automatisms with repetitive violent motor movements and little or no demonstrable impairment of consciousness often localize to the orbitofrontal regions.

The differential diagnosis of episodic behavior that occurs with automatisms includes; sleepwalking, hypersomnias with automatic behaviors such as walking, transient global amnesia, night terrors, emotional states of panic or anxiety, acute confusional states, and toxic-metabolic or neurodegenerative conditions. These non-epileptic physiologic episodes may possess automatic behaviors that mimic automatisms associated with complex partial seizures.

The term "automatism" is not synonymous with focal seizures alone, as generalized seizures such as absence may be associated with simple oro-alimentary automatisms too. Generally, chewing or lip-smacking automatisms are more suggestive of temporal lobe seizures, whereas complex gestural automatisms occur with frontal lobe seizures, and simple gestures may be seen in both. Automatisms occurring during complex partial seizures typically cannot be recalled, though they may rarely involve no alteration in the level of conscious-

ness [2], and patients with frontal lobe seizures may complain of movements or gestures that are not under their control (forced automatisms).

### References

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## AUTONOMIC SEIZURES

Autonomic disturbances are frequently a component of partial seizures. Autonomic phenomena include oropharyngeal and epigastric discomfort, sweating, flushing, pallor, pupillary dilatation, piloerection and cold shivering, salivation, bradycardia and tachycardia, palpitations, and changes in respiratory rate and blood pressure. Autonomic auras have included a wide range of symptoms with overlap, may involve multiple auras with autonomic features, and may be measurable through other mechanisms. The presence of palpitations, for example, is a common autonomic symptom reported during partial seizures and may be measured by EKG, yet palpitations may also represent the experiential phenomenon associated with ictal fear [1]. Epigastric sensations have been postulated to result from autonomic involvement (*see also* Abdominal Aura) and reflect a common aura of frequently of temporal lobe origin.

Autonomic dysfunction may also be seen with other disorders, including generalized forms of epileptic seizures (e.g., absence and tonic-clonic seizures), as well as being associated with nonepileptic causes such as pallid and cyanotic syncope and psychiatric disorders. Seizure-induced dysautonomias that include cardiac dysrhythmias have been implicated in sudden death (*see also* Arrhythmia; Mortality; Syncope).

### Reference

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## AXON

The axon is a specialized, elongated neuronal process involved in the signaling of information over relatively long distances. The axonal membrane consists of a lipid bilayer, with embedded protein molecules that serve as ionic channels and enzymes. Axons may be coated with additional lipid material (myelin), serving to insulate the axon and provide greater efficiency through salutatory conduction of electrical activity. The internal milieu of the axon is composed of high concentrations of potassium, chloride, and inorganic an-

ions. The extra-axonal fluid consists of high concentrations of sodium, calcium, and chloride. Axonal membrane permeability to cations markedly increases during an action potential.

# B

## BALTIC MYOCLONUS

Baltic myoclonus, identified in Finland, is a form of progressive myoclonic epilepsy with a prevalence of 1 in 20,000. Inheritance is by an autosomal recessive pattern. Onset occurs between 6 and 15 years (mean 10-11 years). Myoclonic movements are characteristic: segmental, widespread, and induced by effort, movement, stress, or sensory stimuli. Generalized tonic-clonic seizures are also frequently seen. Intention and rest cerebellar ataxias usually appear late in the course. Mental decline is slowly progressive. The EEG is abnormal, with slow and disorganized background rhythms, spikes, polyspikes, and slow waves. Degenerative lesions are found, but no Lafora bodies are seen. Its existence as a separate syndrome is arguable, as similar clinical pictures have been described in other regions in the world [1]. The clinical presentation is the same as that of the Unverricht-Lundborg syndrome.

### Reference

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## BAND HETEROTOPIA (SUBCORTICAL LAMINAR HETEROTOPIA)

This neuronal migrational disorder reflects an arrest of migratory neuroblasts in the subcortical white matter to form a band of gray matter that appears as a "band" and has been referred to as "double cortex" [1]. Regions of dysplasia and poor lamination are seen. The double-cortex syndrome has female predisposition caused by a defective gene, doublecortin (DCX), and patients are clinically mentally retarded with severe epilepsy [1].

### Reference

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## BARBITURATES

The barbiturate class of AEDs includes phenobarbital (Luminal®, Gardenal®), mephobarbital (Mebaral®), and primidone (Mysoline®). Two groups of barbi-

turates with variable duration of action are used in the treatment of seizures: those with an intermediate onset used in status epilepticus (*see* Status Epilepticus) and those with a long duration of action used in chronic epilepsies. Of the latter, phenobarbital is the oldest AED and has been available for the treatment of epilepsy since 1912. Other long-acting barbiturates are used in other countries (e.g., mephobarbital). The barbiturates are now considered a third-line AED given their potential for sedation and cognitive impairment (*see* Treatment). Ultra-short-acting barbiturates such as methohexital or thiopental may have a convulsant effect and have been used to demonstrate a focal loss of beta activity (*see* Beta Activity) in individuals undergoing presurgical evaluation for intractable epilepsy (*see* Electrocorticography).

## BASIC MECHANISMS OF THE EPILEPSIES

Analysis of surgically resected tissue and the development of animal models to characterize the various epilepsies have furthered our understanding of the basic mechanisms in the cellular neurophysiology of epileptogenesis [1-4]. However, limitations in our understanding exist as a barrier to fully appreciating the interaction between normal brain function and cellular hyperexcitability associated with epilepsy [3]. Several factors may contribute to reconciling this barrier. First, animal models used to simulate human epilepsies are imperfect representations of the clinical disorder (especially IGE) [1]. Second, epilepsy is a heterogeneous disorder and not a single process, and thus the results in one type of epilepsy do not necessarily apply to another type. Third, epilepsy is a complex disorder, and single cell eletrophysiologic models do not fully represent the diffuse electrophysiologic neuronal networks involved in the expression of different seizure types [2]. Despite these limitations, certain general principles have been established.

Epilepsy reflects an imbalance between normal excitation and inhibition, such that specific subpopulations of neurons fire synchronously [1,2]. Normally, excitatory neurotransmitters open membrane channels (*ionophores*) and allow influx of sodium ions and subsequent depolarization of the neuronal membrane. Inhibitory neurotransmitters such as gamma aminobutyric acid (GABA) open chloride channels and hyperpolarize neurons. Inherent in the hyperexcitability for epileptogenesis is the capability of pacemaker neurons of *burst firing*, recurrent excitatory synaptic connections, and reduced inhibition through a relative reduction of GABA [1,2]. Membrane hyperexcitability remains the most important excitatory influence through the excitatory postsynaptic potential, mediated primarily by glutamate or aspartate (*see* Glutamate). However, multicellular synchronization involving neurons as well as glial and supporting cells is necessary to generate the electroclinical spectrum of seizures. In focal seizures, GABAA receptors have been shown to be reduced in patients undergoing resective epilepsy surgery, while other forms may result from a genetic predisposition to decreased GABA-mediated inhibition [4]. Furthermore, a decrease in

GABA inhibition can induce epileptiform discharges in the EEG. However, disinhibition does not appear to be the mechanism in all types of epilepsy. In absence seizures, inhibitory function may be increased, possibly because inhibition plays a crucial role in synchronizing neuronal populations. Hence, synchronization of neuronal populations may be more important than an absolute level of inhibition or excitation for some PWE.

Cellular mechanisms underlying seizures are complex. Intracellular recordings from cortical neurons in experimental seizure foci show giant depolarizations called *paroxysmal depolarization shifts* (PDSs) [1,2]. These PDSs represent a combination of synchronous excitatory post-synaptic potentials (EPSPs) generated from neurons within the epileptogenic zone (*see* Epileptogenic Zone) initiated by intrinsic membrane calcium currents activated by neuronal depolarization. A few neurons with burst firing and recurrent excitatory collaterals to neighboring neurons can recruit a large population of cells into participation in a seizure discharge. An interictal-ictal transition occurs when a critical mass is achieved, when inhibitory mechanisms become insufficient to limit spread of the discharge, or via a variety of additional synaptic and extrasynaptic mechanisms. Glial cells appear to have an important role in preventing ictogenesis [2]. A seizure produces significant ionic changes in the extracellular milieu, with an increase in potassium (potassium has a critical role in neuronal excitability) and a decrease in sodium and calcium concentrations [2]. At the cellular level, these ionic changes can depolarize neighboring neurons and facilitate seizure elaboration and propagation.

### References

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## BATTEN-VOGT-SPIELMEYER DISEASE (SPIELMEYER-VOGT DISEASE OR LATE-ONSET BATTEN DISEASE, NEURONAL CEROID LIPOFUSCINOSIS TYPE III)

Batten-Vogt-Spielmeyer disease was the first of the neuronal ceroid lipofuscinoses to be described and is the juvenile form of this disorder (previously described as familial amaurotic idiocy). It is transmitted as an autosomal recessive trait, and localization to chromosome 16q12.1 is seen. The onset occurs at ap-

proximately age 5-10, marked by a decrease in visual acuity due to retinitis pigmentosa, behavioral problems, and slow cognitive decline (*see* Ceroid Lipofuscinoses). Myoclonic and generalized tonic-clonic seizures occur later. Progression is slow, with death usually occurring 6-8 years after the onset of symptoms. The histologic diagnosis is based on finding intracellular and curvilinear inclusions with fingerprint inclusions, believed to represent an accumulation of lipopigments.

## BEHAVIOR, ABNORMALITIES OF

Most patients with epilepsy exhibit normal behavior. There is now emerging evidence on the epileptic substrates underlying abnormal behavior. Much of the information has been gleaned from animal models of epilepsy, including the environmental and social aspects, kindling models, and the effects of AEDs. Mechanisms imputed have been those of neuronal sprouting and plasticity and amygdalar neuroregulation effects on emotional behavior.

Behavioral manifestations may be classified as ictal, interictal, and perictal. Ictal behavior directly correlates with seizure occurrence. Complex automatisms (e.g., biting) and inappropriate behavior (e.g., sexual automatisms) may occur ictally during complex partial seizures (or status epilepticus) or postictally as part of limbic involvement or effect to promote apparent psychiatric manifestations associated with a peri-ictal confusional state. Interictal manifestations include multifactorial behavior problems that may reflect the causative brain lesion, effect upon adjacent brain regions from repeated seizure spread (particularly the limbic or frontal structures) [1], AED side effects [2], poor self-image in PWE, and co-dependent overprotection or rejection by family or friends [3]. Some treatments, including AEDs and the vagus nerve stimulator, may have a beneficial effect upon behavior [2]. Sources of stress and anxiety may be from seizures with a strong affective component of fear, seizures that occur in public, the constant need for antiepileptic medication, and the effect of consequent professional or scholastic frustrations and failures. In the past, physicians identified "the epileptic personality," characterized by several of the following features: verbosity, hypergraphia, obsequiousness, viscosity, adhesiveness, humorlessness, dependence, obsessional tendencies, exaggerated interest in particular ideas or concepts, hyperreligiosity, interest in philosophic or cosmic themes, hyposexuality, moodiness, irritability, explosiveness, and violence (*see* Violence) [1]. Although this picture may occur, other conditions such as obsessionality and obsessive-compulsive disorder were said to exist. Personality disorders have been attributed particularly to epilepsies involving the temporal lobe, since the limbic system and temporal lobes are involved in affect. While isolated characteristics as described above may be found in people with chronic epilepsy, there is no "epileptic personality" per se, only a predisposition to behavioral characteristics that are multifaceted [1].

Patients commonly have comorbid interictal mood disorders such as anxiety, depression, bipolar disorder, and psychosis, which may warrant psychiatric intervention. Behavioral abnormalities may be due to low IQ. Widespread cortical lesions may account for both seizures and promulgate the effects of primary mental retardation. Variable IQs are found in PWE ranging in different reports from 35 to 165, and comorbid behavioral issues may be a function of mental capacity as well as social environment. Additionally, epilepsy surgery, location-specific malformations of cortical development, chromosomal abnormalities, brain tumors (especially temporal and frontal lobes), and the autistic spectrum disorder may challenge the clinician to separate structure from functional components to altered behavior. Special factors to account for behavior changes in PWE may be seen in nonconvulsive status epilepticus, reflex epilepsies, Landau-Kleffner disease, and epilepsy with continuous spike-waves during sleep. These conditions may have a notable behavioral component due to the primary effect of seizures and epilepsy on cognition, memory, perceptual function, and emotion.

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## BEMEGRIDE® (MEGIMIDE)

This is a proconvulsant drug previously utilized to activate clinical and electrographic seizures to help classify and characterize patients with recurrent seizures. Because of false-positive effects due to activation at a nonhabitual epileptogenic zone in the normal population, proconvulsant drugs have fallen into disuse in the presurgical evaluation of patients with intractable epilepsy.

## BENIGN EPILEPSY

The benign nature of an epileptic disorder is ultimately determined by its outcome. This would include (1) the permanent remission of seizures, either spontaneously or noted after an extended period without treatment, or (2) complete seizure control enabling normal social integration even on treatment. Certain partial epilepsies of childhood possess clinical and EEG characteristics indicative of a more benign course. Some idiopathic localization-related epilepsies of

childhood possess clinical and EEG characteristics that indicate an excellent prognosis and may be considered benign. These benign conditions share common patterns of seizure onset between the ages of 2 and 10, normal neurologic examination and intelligence prior to presentation, interictal EEG with a normal background, as well as infrequent seizures that respond well to treatment. Even with frequent and drug-resistant seizures, the overall long-term outcome is excellent, and patients enter remission in mid-adolescence. The IGEs including childhood absence epilepsy (CAE) and IGE with GTC seizures that occur in adolescence that are likely to remit after control is obtained on AED therapy. Even patients with cryptogenic epilepsy (generalized or focal) may be able to achieve rapid seizure control after seizure onset and will become successful candidates for AED taper and ultimate remission reflecting a lifelong benign outcome. However, benign acting epilepsy accounts for less than a third of all the epilepsies, and an idiopathic (or cryptogenic epilepsy) is not necessarily synonymous with a benign course with respect to treatment.

## BENIGN FAMILIAL NEONATAL CONVULSIONS

Benign familial neonatal convulsions constitute an epilepsy syndrome inherited by autosomal dominant transmission, a condition caused by a novel mutation of the potassium-channel gene KCNQ2 on chromosome 20 [1]. Convulsions begin within the first week of life and spontaneously resolve in most cases by a few weeks to months of age, with < 20% of patients continuing with seizures beyond that time [1]. Identifying benign familial neonatal convulsions in the neonatal period is critical to predict the favorable prognosis that provides reassurance for the family that a good outcome is anticipated.

### Reference

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## BENZODIAZEPINES

At least two dozen benzoediazepines have been used clinically, including the antiepileptic benzodiazepines diazepam (Valium®), clonazepam (Klonopin®), clorazepate (Tranxene®), lorazepam (Ativan®), and midazolam (Versed®). Structurally, a benzene ring is attached to a diazepine seven-membered ring as the central structural component with activity at the GABAA receptor benzodiazepine binding site. Benzodiazepines are the drug of choice in the treatment of status epilepticus, flurries of seizures, and prolonged seizures. They are adjunctive therapies in the chronic epilepsies, especially myoclonic epilepsies.

## Pharmacokinetics

Oral bioavailability ranges from 75 to 100%, with peak plasma levels reached 1-4 hours after oral intake. Depending on the formulation, the Cmax is reached more rapidly with intravenous administration and occurs faster with solutions than with tablets or syrups. Protein binding is high and ranges from 80 to 98% with half-life ranges from 20 to 95 hours or longer when both parent and metabolites are included. Steady-state levels are typically achieved in 4-7 days. Hepatic enzyme induction is usually minimal, though metabolism is increased in the presence of enzyme-inducing AEDs. Despite similar mechanisms of action, a variety of clinical indications, tolerability, and pharmacokinetics and pharmacodynamic interactions exist.

## Dosage

The dose depends on the individual benzodiazepine. Typical regimens vary from one to three or four times per day, depending on the serum half-life. A gradual increase in dose over 2-4 weeks is often required to minimize sedative side effects.

## Side Effects

Sedation occurs in 10-50% of patients, with neurocognitive problems and deficits of attention, concentration, and memory often seen [1]. Attention deficits including excitation and agitation in children may occur paradoxically with an overall hyperkinetic state. Acute psychotic episodes may develop, and delirium and confusion are common even at routine doses, especially in the elderly PWE. Systemic adverse effects of increased bronchial secretions and drooling may occur as can weight gain due to resultant sedation and inactivity. Very rarely, benzodiazepines may cause seizures, though attempts at taper or abrupt withdrawal are most frequently associated with seizure breakthrough or even status epilepticus. The principal problem with the use of chronic benzodiazepines is the development of dependence, tolerance, and tachyphylaxis with long-term exposure, limiting their usefulness as a long-term treatment in epilepsy [1].

## Indications

Lorazepam, diazepam, clonazepam, clobazam, clorazepate, and nitrazepam have played a significant role in the treatment of epilepsy. While chronic use of benzodiazepines such as diazepam has not been proven to be consistently beneficial, clobazam appears to be less sedating and has been used adjunctively in the treatment of epilepsy outside of the United States. Although benzodiazepines have a striking, immediate impact upon seizures, they typically lead to tolerance and breakthrough seizures within 6 months of therapy. Breakthrough seizures may be seen as early as the second week in half the patients.

Increasing the dose usually does not decrease seizures, but increases the possibility of toxicity. Furthermore, the occurrence of seizures after abrupt withdrawal of benzodiazepines often necessitates discontinuing this form of therapy. Lorazepam i.v. and midazolam i.m. (or intranasal) are effective in status epilepticus and are available in the United States. In Europe, i.v. clonazepam and diazepam have been a preferred drug of first choice for the treatment of status epilepticus, frequent seizures with brief intervals between them, and prolonged seizures in childhood.

### Reference

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## BETA ACTIVITY (*see also* EEG)

Beta activity refers to EEG activity in the frequency range above 12 Hz. It is a normal component of the waking and sleeping EEG, often increased by sedative medications. Diffuse decrease in beta activity may suggest a diffuse encephalopathy involving the cortical gray matter and a focal decrease, a local cortical disturbance. Focal high-voltage beta activity occurs with some cortical dysplasias but is an expected and normal finding in patients with breach of the skull from craniotomy or skull penetration.

## BILATERAL SYNCHRONY, SECONDARY

Normally, generalized spike-and-slow waves appear nearly simultaneously (within about 50 msec) over both sides of the head. A primary bilateral synchronous and symmetric interictal or ictal EEG pattern is expected with generalized tonic-clonic or absence seizures, though minor degrees of asymmetry are not uncommon. Secondary bilateral synchrony (SBS) is a term used to describe an apparent generalized epileptiform discharge on the EEG with a focal onset. Diffuse bursts are best distinguished as SBS when a "lead-in" of > 400 msec is seen [1]. In addition, focal interictal epileptiform discharges may be seen independently as well as initiating burst of the generalized epileptiform discharges. The best examples of SBS occur in patients with medial frontal seizures, such as supplementary motor area, medial convexity, or cingulate gyrus, because of their proximity to the corpus callosum. Midline electrodes represented on the EEG are important to detect epileptiform abnormalities in these regions. The disappearance of generalized seizures and bilateral spike-and-slow wave discharges after ablation of a focal lesion has been the best argument in favor of SBS [2], though bilaterally independent intracarotid injections of amobarbital has also been effective in eliminating generalized bursts from a lateralized chemically mediated inactivation.

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## BIOFEEDBACK

Biofeedback involves patient-guided self-regulation of the EEG recording via real-time feedback to train one to achieve a specified level of cerebral activity believed to be beneficial relative to an associated seizure threshold [1]. The feedback loop usually utilizes multielectrode quantitative EEG that is decomposed into frequency components in an audiovisual display with a paradigm to create patient-generated strategies to modify his or her EEG to achieve targeted parameters. While phasic oscillations may reflect an inhibitory state of the sensorimotor rhythm, operant learning of the sensorimotor rhythm production results in an upregulation of excitatory thresholds within the thalamocortical sensory and motor circuitry, which in turn is associated with reduced susceptibility to seizures [1]. The *neurofeedback* training through *operant conditioning* of the sensorimotor rhythm in the EEG involves weekly training for several months and has been utilized most in patients with pharmacoresistant epilepsy manifest as recurrent complex partial seizures [1]. While clinical benefit from neurofeedback has been addressed in double-blind controlled clinical trials, this technique has not been widely accepted or practiced because of the perceived time- and cost-intensive commitment [2].

### References

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## BIPOLAR DISORDER

There is a robust association between bipolar symptomatology and epilepsy, more so than for other medical conditions such as diabetes, asthma, or migraine, occurring in approximately 9% of PWE [1]. Symptoms may go undetected and untreated (similar to depression) for years, but some AEDs may be effective for treating both conditions. Both valproate and lamotrigine have received regulatory approval for the maintenance of bipolar disorder, while yet others have undergone evaluation.

### Reference

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## BIRTH CONTROL

More than1 million women with epilepsy in the United States are of childbearing potential in their active reproductive years [1]. This accounts for the more than 24,000 babies each year born to mothers with epilepsy, with 40% of pregnancies in the United States being unplanned [2]. However, approximately twice as many individuals are exposed to AED use for other reasons. Many of the enzyme-inducing AEDs that induce the hepatic P450 enzyme system also metabolize the contraceptive sex steroids resulting in increased renal clearance and subsequently reduced efficacy. Higher-dose estrogen-containing oral contraceptive pills (OCPs) have been recommended [3] when co-administered with an EIAED, and while progestins are likely the efficacious hormone involved in preventing contraception, most higher-dose estrogen containing OCPs also contain higher doses of progestins. Intramuscular injections of medroxyprogesterone may provide higher doses of progestins, although the frequency of administration prompts dosing at every 8-10 weeks rather than at 12-week intervals. Similarly, the vaginal ring and transdermal patches appear to have higher failure rates, and a combined use of a barrier method (i.e., condoms or diaphragm) is recommended to provide maximal contraceptive protection. The AEDs that do not affect the efficacy of hormonal contraception include ethosuximide, valproate, gabapentin, lamotrigine (AED affected by hormonal contraception in a one-way fashion), levitiracetam, zonisamide, and pregabalin. Other AEDs such as phenobarbital, phenytoin, carbamazepine, primidone, topiramate, and oxcarbazepine have the effect of lowering hormonal levels leading to a greater risk of inefficacy due to their associated mechanism of hepatic enzyme induction of the P450 system [1].

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## BOLD (*see also* FUNCTIONAL MRI)

Blood oxygenation level-dependent (BOLD) signals are the basis for generating images created using functional MRI (fMRI). In epilepsy, there is neu-

rovascular coupling to define the relationship between epileptiform neuronal activity that is able to be measured by various techniques including SPECT and PET in addition to fMRI. During an increase in neuronal activity there is a simultaneous increase in the cerebral metabolic rate of glucose and oxygen. Greater regional cerebral metabolic rates result in an increase in regional cerebral blood flow and volume to compensate for the increased demand for oxygen. The robust blood supply delivered to the active region of the seizing brain produces an "uncoupling" between the baseline physiologic cerebral metabolic rate of oxygen and the cerebral blood flow by delivering an increased oxygen load. The difference between the rate of oxygen metabolism and cerebral blood flow forms the basis of the BOLD technique used in generating brain fMRI.

## BONE HEALTH

Bone health may be compromised by the use of AEDs because of adverse effects on bone metabolism, although the precise mechanism is not fully known. The best evidence that epilepsy increases the risk for bone disease stems from a differential effect that may occur especially with AEDs such as phenytoin and phenobarbital that induce the hepatic P450 enzyme system [1]. This relationship may be seen in children and adults as well as in men and women [1,2]. About 50% of PWE under age 50 who take an EIAED have evidence of bone loss on dual x-ray absorptiometry (DEXA) [2]. Children with epilepsy appear to sustain significant bone mineral density deficit as early as 1 year of treatment which progressively worsens thereafter [3]. A relationship between higher dosing with AEDs and polytherapy has been seen to further heighten the risk for fractures [2]. Breakthrough seizures, AED toxicity, or neurologic physical impairments may lead to potentially injurious falls. Induction of the hepatic P450 enzyme system to metabolize vitamin D by these AEDs gives rise to inactive metabolites incapable of facilitating calcium absorption. As a result, osteopenia or osteoporosis may result from intrinsic osteoclastic activity that secondarily liberates calcium from bone for maintenance of cellular function [1,2]. Still, additional mechanisms including direct effects upon bone homeostasis have been proposed to explain why non-enzyme inducing AEDs such as VPA may lead to similar effects. Osteopenia is defined as a T score of -1.0 to -2.5, while osteoporosis has T scores of less than -2.5 on DEXA bone density evaluation. Concomitant risk factors besides AEDs include age, genetic predisposition, Caucasian, slender frame, female sex, inactivity, smoker, and certain medications (i.e., glucocorticoids). Evidence is surfacing that supplemental calcium and vitamin D may reduce the risk of bone fracture. All PWE should have adequate daily calcium and vitamin D. Calcium intake of 1200 mg/d (with vitamin D) has been recommended, and DEXA bone density scans every 2 years when osteopenia or osteoporosis develops. Issues that deal with timing, precise calcium/vitamin D dosing, means of monitoring bone health, and timing of introducing alternative antiepileptic therapies when bone loss occurs are being established.

**References**

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## BRAIN

The brain is the physical substrate for behavior and for paroxysmal disorders of behavior and physiology, including epilepsy. Regional variations in brain function correlate with different manifestations of partial (focal) seizures-for example, motor seizures with abnormal electrical discharges in the precentral gyrus, visual distortions with occipital seizures, and inappropriate emotional expressions with mesial temporal foci. John Hughlings Jackson, the father of modern epileptology, called epilepsy a "spotlight on the brain," since clinical observation of seizures could provide insight into brain function.

## BREAST-FEEDING

Breast-feeding is encouraged in women with epilepsy, and most believe the benefits of breast-feeding outweigh potential problems from the fraction of AED reaching the breast milk postpartum. Postpartum concentrations are less than the complete exposure delivered to the fetus during pregnancy, and therefore the potential benefits conferred by breast milk probably outweigh the risks [1]. All of the AEDs taken by the mother are found in breast milk to a variable degree, but the levels are less than maternal serum concentrations. The amount expressed is dependent upon the degree of protein binding [2]. An inverse relationship between protein binding and degree of expression is found with highly protein bound AEDs having a lower concentration in breast milk [2]. Other factors such as lipid content are also important with AEDs such as benzodiazepines that concentrate in breast milk to a higher degree than would be reflected through protein binding alone. Additionally, the degree of ionization and free diffusion of the unionized portion of the parent AED across the placenta influences concentrations in breast milk. The majority of infants have no AED-related adverse effects from exposure to breast-feeding. Postpartum sedation, feeding difficulties with poor suck, hypotonia and floppy infants, as well as respiratory insufficiency have been described; these are usually apparent in the immediate postpartum period and disappear within 2 weeks when the breast-feeding is discontinued. Sedative AEDs, such as primidone and phenobarbital, are most likely to lead to these manifestations in the neonate. Conversely, discontinuation of barbiturates and benzodiazepines can

lead to withdrawal problems with "jitters" or tremulousness, myoclonus, hyperactivity, excess crying, or vomiting [2,3]. If the baby appears sedated or irritable after initiating breast-feeding, then a substitute method of feeding should be sought with the need to restart breast-feeding reassessed.

### References

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## BREATH-HOLDING SPELLS

Breath-holding spells are nonepileptic paroxysmal events seen in approximately 4% of children younger than 5 years of age [1]. The onset usually begins in the first year of life, and recurrent episodes may persist up until age 6. Episodes present as cyanotic syncope brought on by fear, pain, surprise, anger, or frustration. During breath-holding spells, after several wails, respiration halts reflexively in the expiratory phase with loss of consciousness, flaccidity, cyanosis of the lips, and a few brief clonic jerks before consciousness is regained. Although the episodes frequently resolve spontaneously, symptoms may progress to include atonia or hypertonicity, including posturing with and without jerking movements, and incontinence with prolonged episodes. However, breath-holding spells can be distinguished from generalized seizures by several features [2]. First, the diagnosis of a breath-holding spell is nearly exclusively based upon a thorough history, which will include the obligate presence of an inciting emotion or event, such as anger, frustration, fear, or injury. Additionally, most spells are brief, lasting less than 1 minute, and are marked by rapid sudden return of consciousness. The EEG shows a diffusely slow background typical in the face of transient cerebral hypoxia, but IEDs are not typically present.

There are two categories of breath-holding spells-*pallid* (acyanotic) and *cyanotic*-both of which are common causes of syncope and "seizure" in children [1,2]. The syndrome of pallid syncope (reflex anoxic seizure) may be brought on by benign trauma, resulting in loss of consiousness with or without crying, marked pallor, and tonic spasm (*see also* Atonic Seizures). Pallid breath-holding spells are thought to represent a hyperreflexive vagal response, resulting in an anoxic or asystole with a loss of consciousness. These are more commonly precipitated by mild injury and pain. In contrast, cyanotic episodes are multifactorial, primarily involving respiratory factors of hyperventilation, expiratory apnea, elevated intrathoracic pressure, and other intrinsic pulmonary mechanisms. Anger and frustration are more common precipitants for cyanotic spells.

The preponderance of children who experience breath-holding spells will recover without consequence and eventually outgrow the spells. In this majority, parental reassurance and prevention techniques are the cornerstones of therapy. However, an investigation for cardiac abnormalities may be indicated, particularly in children with prolonged loss of consciousness. Rarely, breath-holding spells can progress to true anoxic-epileptic seizures [1]. Video monitoring may be useful in identifying this subset. However, routine electroencephalography is not required with a typical clinical history because of the potential impact of false-positive results in healthy children [1].

### References

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## BROMIDES

Bromides are recognized as the first AED used to treat patients with seizures as early as 1857. The mechanism of bromides is unknown, and they were initially employed to reduce sex drive and to temporize hysterical tendencies in patients with epilepsy. While hypothesized to promote hyperpolarization of postsynaptic membranes, their principal use has been in the treatment of GTC seizures with lesser efficacy on other seizure types. Bromides have been reported to be most effective in generalized tonic-clonic seizures and less effective for other seizure types [1]. Bromides are usually administered as a triple bromide solution containing a combination of sodium, postasssium, and ammonium bromide salts. No drug interactions with other AEDs have been noted. Although occasionally effective, bromides can have marked side effects ("bromism"), including effects on the skin (rash, lesions, ulcerations) and GI tract (anorexia, dyspepsia, constipation) in addition to the CNS (confusion, encephalopathy, headaches, irritability, and psychosis). Acute adverse effects on hearing and renal function have also been noted. Bromides fell out of favor in 1912 after the discovery of phenobarbital. However, due to the porphyrogenic potential of most AEDs, bromides were used in patients with seizures and porphyria up until the the last several decades, when new AED development led to reports of safe use.

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# C

## CALCIUM CHANNEL BLOCKERS

The role of calcium in epileptogenesis is linked to its capacity as a second messenger for neurotransmitter release. Calcium exerts an effect upon membrane plasticity with activation of phospholipases A2 and C, which in turn trigger enzymatic lipid degradation involved in phosphatidyl inositol metabolism, thus activating proteolytic enzymes. In addition, calcium directly affects synaptic transmission, since the presence of calcium in the presynaptic terminal is required for release of synaptic vesicles. Calcium is also involved in synaptic reuptake of glutamate and GABA. Certain inhibitory potentials, such as the postburst afterhyperpolarization, are dependent upon calcium influx into the postsynaptic neuron. Calcium thus exerts complex excitatory and inhibitory effects on outflow currents of neural systems. Different types of calcium channels exist: high-voltage activated channels (i.e., L and N type), and low-voltage activated (i.e., T type) channels. The L-type calcium channel also has subtypes that act as the substrate for gabapentine and pregabalin as primary AEDs. The T-type calcium channels (slowly deactivating channels) are central to the bursting of the pacemaker cells that occurs within thalamic neurons central to the generation of absence seizures. Certain calcium channel blockers, including verapamil, nifedipine, cinnarizine, and flunarizine, have a demonstrable anticonvulsant property in animal models of epilepsy. Nifedipine, nimodipine, and flunarizine have exhibited limited antiepileptic effects in humans.

## CAPGRAS' SYNDROME

Capgras' syndrome, a type of delusional misidentification syndrome, is a relatively rare condition usually seen in the context of schizophrenia. It involves the belief that familiar people and objects have been replaced by imposters. Capgras' syndrome has been described as part of an interictal and postictal psychosis in case reports on patients with epilepsy and is believed to have its foundation in a disrupted dorsal pathway from visual cortex to the limbic system via the inferior parietal lobule [1].

### Reference

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# CARBAMAZEPINE (CBZ, TEGRETOL®, CARBATROL®, EQUETRO®)

Carbamazepine, an AED related to tricyclic antidepressants, is useful in the treatment of partial and secondarily generalized seizures. Carbamazepine is an AED of first choice in partial seizures because of its efficacy and the paucity of side effects that has been established in randomized controlled clinical trials [1]. While effective for focal seizures, carbamazepine may exacerbate absence and myoclonic seizures. Carbamazepine has also been used as a treatment in bipolar disorder and neuropathic pain.

Carbamazepine has linear kinetics, but there is uneven absorption following oral administration (70-75%), resulting in peak plasma levels 2-8 hours after ingestion, but as long as 24 hours later. Marked variability in blood levels may occur between two doses. About 70-75% of the ingested dose is bound to protein. Carbamazepine half-life is 5-16 hours for adults, 8-19 hours for children. Steady-state serum levels are reached in 3 days. The volume of distribution (Vd) is 0.8-2 L/kg. As an enzyme inducer, Tegretol increases the biotransformation of other drugs, both endogenous and exogenous, and also induces its own metabolism during the first month of therapy (a dose increase may be required). Clearance may be diminished by isoniazid, the macrolide antibiotics triacetyloleandomycin and erythromycin, and propoxyphene, with a risk for toxic serum levels. The major metabolite is a carbamazepine 11-epoxide which has AED properties but is potentially more toxic than CBZ. Carbamazepine is taken twice a day as an extended-release preparation (Tegretol XR and Carbatrol), although three to four times a day is often required for less fluctuation of the immediate-release formulation between doses to minimize the risk of breakthrough seizures. Suggested therapeutic blood levels are 4-12 mg/L. Acute or subacute toxicity is associated with dizziness, diplopia, nausea, nystagmus, ataxia, "drunkenness," obtundation, and confusion. General fatigue, lightheadedness, malaise, hepatotoxicity, alterated immune system function, a lupus-like reaction (which rarely involves the CNS), dyskinesias, worsening seizures in encephalopathic generalized epilepsies, hyponatremia, occasionally with headaches and vomiting, and, commonly, mild leukopenias are frequently seen, with rare agranulocytoses noted with an incidence of 40 per million. Skin rashes appear 8-10 days after onset of treatment in 5-10% of cases [2]. Because of the risk of bullous epidermolysis, hypersensitivity syndromes, and Stevens-Johnson syndrome, the treatment should be stopped if these rashes are encountered. People of Asian ancestry should take a genetic test before they are treated with AEDs that contain carbamazepine to minimize the potential risk of serious rash. Studies have reported that because of an inherited variant of the HLA-B* 1502 gene found almost exclusively in PWE of Asian ancestry, these persons are at higher risk for developing skin reactions to carbamazepine [3]. A study from Taiwan found that 98% of persons who developed a cutaneous reaction possessed the gene, while only 4%

with no reaction were positive for this genetic marker [3]. As with any AED, care should be taken to withdraw carbamazepine due to the possibility of withdrawal effects.

There are three formulations available, including immediate-release, extended-release, and oral suspension. Tegretol®(Novartis Pharmaceuticals), Equetro® (marketed for psychiatric use), Tegretol-XR® (an extended-release formulation), and Carbatrol (another extended-release formulation; Shire Pharmaceuticals), are available in addition to Tegretol® oral suspension.

### References

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## CARISBAMATE

Carisbamate (RWJ-333369) has a chemical formula of S-2-O-carbamoyl-1-o-chloropheyl-ethanol and is a novel neuromoduloator under development at this time for the treatment of epilepsy. It has demonstrated efficacy in animal models as well as in phase II trials and is currently undergoing phase III trials for adjunctive use in adults with partial epilepsy [1].

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## CATAMENIAL EPILEPSY

Catamenial seizures are seizures that are clustered around the time of menstruation, reflecting the dynamic influence of the ovarian sex steroid hormones estrogen and progesterone with menses in addition to a compromise in AEDs due to alteration in drug metabolism [1]. Estrogens possess convulsant properties and progestogens anticonvulsant properties, both in animal models and the human cortex, that may be seen clinically and on EEG [1]. The sex steroid hormones modulate cortical excitability thorugh several mechanisms. In clinical practice, a primary AED is usually a first-line approach. Breakthrough seizures are most likely to occur 2-3 days prior to menses but are also possible

during the period and at ovulation [2]. Simply increasing the maintenance dose of the standard AED premenstrually may prove beneficial for some women.

No FDA-approved drug has an indication specifically for catamenial epilepsy. Peri-menstrual acetazolamide may be used as an adjunct treatment. Due to tolerance issues, a short course of treatment (e.g., 250-500 mg p.o.bid) for 10-14 days around the cycle may be beneficial, with attention to sedation, headache, frequent urination, and GI upset as limiting side effects. Hormone therapy is conducted with a gyncecologist using a natural progesterone or, less frequently, an antiestrogen preparation. Synthetic progestins appear to be ineffective in catamenial epilepsy, and even i.m. medroxyprogesterone may be ineffective despite chemically induced amenorrhea [2]. Natural progesterone may be effective especially if inadequate luteal-phase cycles (i.e., progesterone levels < 5 ng/mL) are demonstrated at doses of 100-200 mg tid [3]. Side effects of hormone therapy are underrepresented but may occur, including dysfunctional uterine bleeding, apathy, asthenia, breast tenderness, acne, and depression. While the antiestrogen drug clomiphene reduces seizures, side effects may be limiting, and newer antiestrogen drugs and receptor modulating agents are in development for women with hormone-sensitive seizures [3]. Ganaxolone, an orally active GABAA receptor-modulating synthetic neuroactive steroid, and a brain-derived neurotrophic factor (BDNF) anatognist for use during the periovulatory period are promising investigational treatments for catamenial epilepsy. A comprehensive treatment may need to address both the estrogen and progesterone contributions to catamenial epilepsy. Since the different patterns may respond differentially to therapeutic intervention, treatment choices are likely to be complex.

### References

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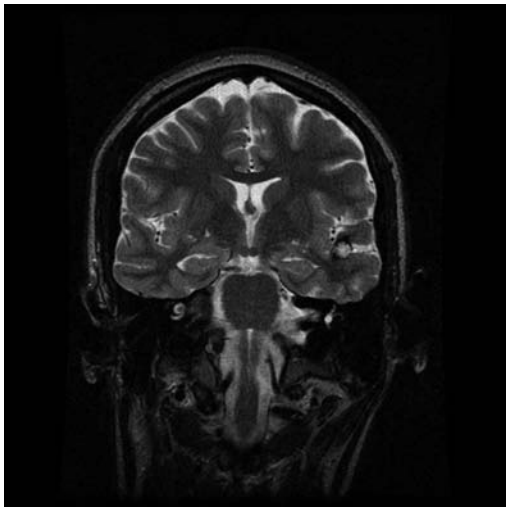
## CATAPLEXY

Cataplexy refers to a paroxysmal brief loss of body tone that may result in a fall that can mimic a seizure. Cataplexy is a nonepileptic attack brought on by strong emotional stimuli such as surprise, anger, or pleasure. It is seen as a less common part of the tetrad of symptoms in patients with narcolepsy (*see* Narcolepsy) occurring in about half of patients and is virtually diagnostic when it occurs in patients complaining of excessive sleepiness. Cataplexy is distinguished from epileptic seizures with drop attacks by its preservation of consciousness, associated clinical features, and lack of additional seizure types (i.e., tonic-clonic seizures) as well as normal EEG.

# CAVERNOUS ANGIOMA, CAVERNOUS HEMANGIOMA, CAVERNOMA

Cavernous angiomas ("cavernomas") are frequently encountered in PWE refractory to AEDs. Due to the breakdown products of blood that include hemosiderin-associated gliosis around the lesion, they are very epileptogenic. They have a characteristic appearance on brain MRI (*see* figure) with a central zone of increased intensity and surrounding rim of decreased signal when visualized on T2-weighted images and a multilobulated "mulberry" appearance of increased signal on T1-weighted images without edema or significant mass effect. The smaller size of the vascular channels and minimal or absence of flow make them difficult to detect angiographically [1]. These vascular malformations possess histologic features of fine vascular walls and no elastin lining consisting of an abnormal mixture of normal tissue elements, which may then develop subsequent calcification, thrombosis, or microhemorrhages or rarely predispose to spontaneous frank bleeds. The yearly risk of hemorrhage is less than 2.7%, with the risk of rebleed highly variable. Most cavernous angiomas are supratentorial and predominate in the temporal or rolandic regions and may produce seizures as a presenting or even sole feature with the clinical picture depending on site of seizure onset and propagation [1]. Familial forms of cavernous angiomas are seen, with autosomal inheritance occurring in fewer than 25% of patients. Seizures are partial onset with complex partial and secondarily generalized seizure types, with breakthrough seizures occasionally associated with micro-bleeds. The response to AEDs is poor, and surgical resection may be highly effective [2]. Treatment is frequently surgical. How much tissue requires removal is in dispute, but several surgeons have argued for a conservative removal of only the cavernoma and visibly abnormal surrounding rim of tissue.



T2-weighted image with cavernous angioma of the left temporal lobe in a patient with localization-related epilepsy and medically intractable complex partial seizures.

## References

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## CELLULAR BASIS OF EPILEPSY

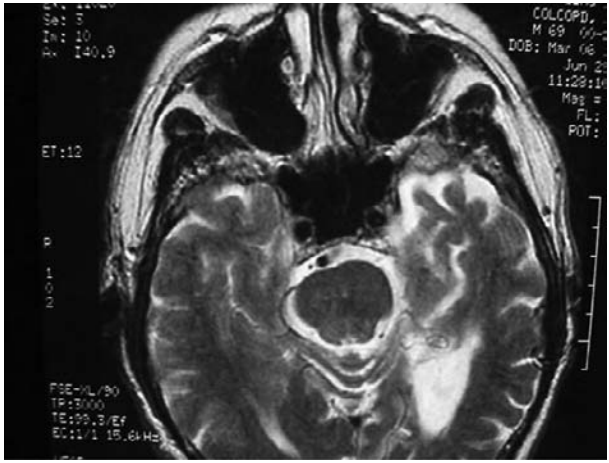
The cellular basis for epilepsy is often referred to as an imbalance between hyperexcitability and insufficient inhibition. Disruption of cellular activity has been shown to occur with alteration of normal ion channel function, which is associated with epileptic seizures. Neurotransmitter dysfunction underlies the basic mechanisms in epilepsy (*see* Basic Mechanisms of the Epilepsies)with defects of glutamate and GABA well demonstrated in patients with recurrent seizures in addition to other modulatory second-messenger systems that help to regulate the balance of neuronal excitability.

## CENTRENCEPHALIC SEIZURES

"Centrencephalic" is an old term referring to anatomic involving the *central encephalon*, which included the nonspecific nuclei of the thalamus, the diencephalon, the mesencephalon, and the rhombencephalon. Certain seizure types were attributed to discharges in the deeper structures, although this was never proven. The generalized epilepsies (*see* Classification of Seizures and Epilepsies) were cited as examples of centrencephalic seizures. However, the pathophysiologic term "centrencephalic" has fallen from use and has been replaced by the "thalamo-cortical" theory of connections that are operational in the IGEs and serve to emphasize pathologic cortical hypreexcitability as the basic mechanism for epileptogenesis.

## CEREBRAL PALSY

Cerebral palsy (CP) refers to a group of nonprogressive perinatal neurologic conditions associated with heterogeneous deficits of motor or movement function. The incidence is low; the prevalence of CP is about 0.2% but it accounts for approximately 2-8% of pediatric neurology patients. Spastic CP is the most common type, although ataxic and athetoid CP are common variants and assessments for diagnosis are available [1]. Most causes of CP are not associated with asphyxia-> 80% of cases are associated with prenatal complications, although congenital, genetic, anoxic, traumatic, and toxic-metabolic causes have been noted. Motor disabilities include spasticity (quadriplegia, hemiplegia, and diplegia) with or without movement disorders that may occasionally mimic seizures. Seizures usually appear within the first year of life. Partial seizures are more common in children with spastic hemiplegia (*see* figure), which is usually associated with a perinatal ischemic infarction within a major vascular ter-




Left hemispheric (temporal lobe) atrophy in a patient with right hemiparetic CP and localization-related epilepsy.

ritory resulting in porencephaly. Quadriplegic (or tetraplegic) CP is less common and is usually associated with a widespread global hypoxia that may give rise to encephalopathic generalized epilepsy and multiple mixed seizure types. The management of epilepsy in patients with CP may be difficult, especially when large structural lesions are responsible, and a trial of AED taper in more restricted forms is often associated with a higher risk of failed withdrawal.

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# CEREBROVASCULAR DISEASE

Cerebrovascular disease is the most common serious neurologic condition in all age groups. Isolated or recurrent seizures may be seen following cerebrovascular disease, including ischemic infarction, hemorrhagic infarction, or intracerebral hemorrhage.

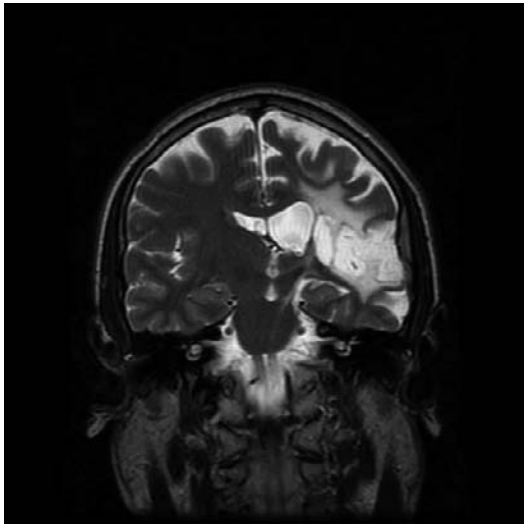
## Seizures Occurring in Proximity to Ischemic Cerebral Infarction

*First seizures*: The presentation of a single seizure or new-onset epilepsy in the face of abnormal brain MRI with evidence of cerebral vascular disease was 25-39% [1]. In addition, in patients older than 60 years of age presenting with partial seizures of cryptogenic origin there is a significant risk of developing an ischemic infarct compared to patients without seizures. Focal seizures predominate in the elderly, with seizure sometimes remaining undiagnosed for

prolonged periods of time given their manifestations of acute confusion or memory dysfunction, which may mimic other neurologic conditions. Alternatively, focal seizures with Todd's paralysis may be misdiagnosed as a cerebral infarction despite the absence of abnormality, which is evident on brain MRI. Seizures may precede the obvious manifestations of cerebral infarction.

*Seizures occurring with cerebral infarction*: In a large prospective analysis, 8.6% of patients developed seizures after ischemic cerebral infarcts, half of which occurred within the first day after the stroke [2]. In the Veterans Cooperative Study in elderly patients, 38.3% manifested complex partial seizures, 14.3% simple partial seizures, 7.5% had both, and of the 40% with generalized seizures one third had a definable partial onset, making partial seizures by far the most common seizure type in the elderly [3]. The incidence of early seizures (within 1 week of stroke) is about 6%. In nearly 90%, seizures were the presenting feature of the stroke, and in stroke 78% occurred in the first 24 hours [4]. The seizures do not necessarily herald an epileptic substrate, with only 8.9% developing late seizures after 10 years [4]. The risk of early and late seizures was more favorable with a younger age at the time of the stroke, although status epilepticus imparts a poor prognosis.

*Late seizures after cerebral infarction*: Late seizures appearing after the first week poststroke up until more than a decade later were seen in 11.5% of patients in a community stroke project in 675 patient over 6 years [5]. A higher risk for postinfarction seizures exists, with cortical infarcts (especially for those infarctions in the territory of the middle cerebral artery) a frequent cause of epilepsy in the elderly. The pathogenesis is poorly understood, but this may be due to glial scarring, iron deposition in the cases of hemorrhagic infarction, or hemodynamic factors. Even in the absence of clinical symptoms, diffusion-weighted sequences with brain MRI may reveal evidence of ischemic infarction.



Left MCA infarction noted on coronal T2-weighted brain MRI in a 44-year-old male with localization-related epilepsy following herpes zoster opthalmicus.

## Seizures and Intracerebral Hemorrhage

*Early seizures* may herald the onset of intracranial hemorrhage or may follow it by several hours. They correlate to the lobar localization of hemorrhage or cortical extension or the presence of blood in the meningeal or intraventricular regions. Seizures are usually partial-onset secondarily

generalized seizures, although status epilepticus is a frequent occurrence. Electrographic seizures are also frequently observed when ICU EEG monitoring is employed.

*Late seizures* occurring after intracerebral hemorrhage are also relatively frequent due to the presence of hemosiderin products containing iron, and they usually require chronic AED treatment. Seizures are more frequent after intracerebral hemorrhage than with infarction, occurring in up to one quarter of cases.

## Seizures and Subdural Hematomas

Although subdural hematomas are caused by head injury in most cases, the incidence of seizures is low in patients with chronic subdural hematoma [6].

## Neonatal Cerebral Infarction or Hemorrhage

With the development of neuroimaging, there has been an increase in the early identification of neonatal cerebral infarction. Partial or generalized seizures, occurring singly or in clusters, usually have a good response to early treatment. Neurologic examination may confirm the presence of cerebral infarction, typically in the territory of the middle cerebral artery. There may be an eventual progression to chronic epilepsy that merits long-term therapy.

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# CEROID LIPOFUSCINOSES

Neuronal ceroid lipofuscinosis (NCL) is a term applied to a group of neurologic disorders that result in the storage and accumulation of lipopigments in the lysosomes present in the brain and other tissues. These genetic diseases are inherited as autosomal recessive conditions that present at different ages with

recognized subgroups and variations. The etiology is unknown, and no universal enzyme defect has been identified. The clinical and EEG features of NCL are those of progressive myoclonic epilepsy.

There are four classic syndromes in NCL comprised of the early infantile (Santavuori-Haltia disease), late infantile (Jansky-Bielchowski disease), juvenile (Spielmeyer-Vogt disease), and adult forms (Kufs disease). Type I, or the early infantile form, differs from the late infantile NCL (Type II) in that a Finnish predisposition is not present, and chromosome 11 instead of chromosome 1 is affected in Type II. The late infantile form (Jansky-Bielchowski) has an onset at age 2-4 years instead of 1-2 years. Intractable mixed seizure types develop composed of myoclonic, atonic, GTC, in addition to other seizure types with cognitive decline, ataxia, and visual failure. The neurophysiology in the late infantile form of NCL includes giant visual evoked potentials and somatosensory evoked potentials. Type III (Spielmeyer-Vogt) begins at 5-10 years of age, is localized to chromosome 16, occurs without ethnic predisposition, like Type II, and manifests as progressive cognitive decline, visual failure, and seizures. Occipital spikes are not characteristically evoked by low-frequency photic stimulation as they are in Type II NCL. Kufs disease is the adult form of NCL and is slowly progressive with frequent generalized seizures including myoclonus and GTCs that may be refractory to AEDs. In contrast to Type III, these do not appear with optic atrophy, although they do exhibit extreme photic sensitivity on low-frequency photic stimulation. Other variations of NCL have also been described. The diagnosis is made by finding inclusion bodies in different organs, e.g., sweat glands, muscle, rectal mucosa, and neurons. These inclusions contain excessive amounts of ceroid or lipofuscin lipopigments. Chromosomal abnormalities have been identified.

## CHOREOATHETOSIS, PAROXYSMAL

Paroxysmal choreoathetosis is a rare condition manifest as a disorder of paroxysmal dyskinesia that begins in childhood or adolescence. Attacks are multiple and brief, lasting 1-2 minutes and occurring daily. They are brought on by sudden movement of the legs, for example, upon standing, beginning to walk, or accelerating pace. Often abnormal movements present distally in one foot with tonic intorsion followed by spread up the leg with flexion or extension of the knee, elbow flexion, hemifacial spasm, and impairment of speech. In more prolonged episodes there may be torsion, chorea, and athetosis. Consciousness is preserved and ictal, and ictal EEG are normal. The neurologic examination is normal. Half of the published cases have a family history, although sporadic types may also occur. Attacks usually cease by 20-40 years of age.

Paroxysmal kinesiogenic choreoathetosis was previously thought to be a variant of movement-induced reflex epilepsy. Because of its resemblance to the episodic semiology of partial motor seizures, paroxysmal dystonic choreoa-

thetosis has been treated with and shown responsiveness to AEDs such as carbamazepine. A relationship with frontal lobe epilepsy has become established with greater frequency as opposed to its classification as an extrapyramidal syndrome [1].

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## CIRCADIAN RHYTHMS

Circadian rhythms represent a biologic pacemaker that normally regulates physiologic fluctuation based upon a near 24-hour time period [1]. Circadian rhythms are found in all organisms, including human beings, with the most potent stimulus being light. The suprachiasmatic nucleus in the hypothalamus of the brain acts as the master circadian biologic "clock" to regulate important human behaviors such as sleep. Seizures may occur with consistency and regularity during different phases of intrinsic circadian rhythms (e.g., sleep, menstrual cycle).

## CLASSIFICATION OF SEIZURES AND EPILEPSIES

Classification systems attempt to provide a common language for all epileptologists, thus simplifying research and epidemiology. The International League Against Epilepsy (ILAE) has proposed several classification systems for seizures [1] and epileptic syndromes [2]. These classification systems replaced the initial proposal for a formal classification system suggested by Gastaut in 1970 [3]. This classification system sought to take a *differential* approach to distinguish the focal (partial) from generalized epilepsies, primary from secondary forms, and applied EEG, pathophysiology, and demographic information to a final classification. The subsequent classification system for the epilepsies in the revised proposal of 1989 applied a *syndromic* approach to the cluster of seizure signs and symptoms on a clinical basis, radiologic basis (with CT and MRI), EEG, etiology, and severity of illness, and reclassified them as localization-related (focal) and generalized epilepsies that were either idiopathic (primary), symptomatic (secondary), or cryptogenic. In 2001 the ILAE proposed a *diagnostic syndrome-oriented* five-dimensional classification system to identify and approach common ictal semiology terms as well as a tiered system to further identify the spectrum of focal (partial) and generalized epilepsies. This system is based upon prior proposals to identify a syndrome-oriented classification encompassing the five axes of ictal semiology, epileptic seizure type, epilepsy syndrome, etiology, and degree of impairment [4]. The advantages include an emphasis on ictal semiology, accepted syndromic diagnoses, refine-

ment of terminology, and EEG features to provide a greater breadth of epilepsy as a spectrum and symptom of a brain condition. Independent seizure classification systems have been utilized baed solely upon semiology [5] and are applied to the second dimension of the 2001 system. An alternative *patient-oriented* five-dimensional classification system was developed to refine issues of axes overlap, age, and syndrome concept and class to highlight the location of the epileptogenic zone, seizure classification, etology, seizure frequency, and related medical conditions [4]. The advantages of the patient-oriented classification include independent and universal characterization of each patient with epilepsy with respect to identifying the epileptogenic zone based upon observation and history in addition to permtting research perspectives by its use. The 1981 seizure classification [1] has provided a common language in the past.

**Partial (Focal, Local) Seizures**

A. Simple partial seizures (consciousness not impaired)
   1. With motor signs:
      - Focal motor without march
      - Focal motor with march (jacksonian)
      - Versive
      - Postural
      - Phonatory (vocalization or arrest of speech)
   2. With somatosensory or special-sensory symptoms (simple hallucinations, e.g., tingling, light flashes, buzzing):
      - Somatosensory
      - Visual
      - Auditory
      - Olfactory
      - Gustatory
      - Vertiginous
   3. With autonomic symptoms or signs (including epigastric sensation, pallor, sweating, flushing, piloerection, and involving dilatation)
   4. With psychic symptoms (disturbance of higher cerebral function). These symptoms rarely occur without impairment of consciousness and more commonly occur as complex partial seizures:
      - Dysphasic
      - Dysmnesic (e.g., déjà-vu)
      - Cognitive (e.g., dreamy states, distortions of time sense)
      - Affective (fear, anger, etc.)
      - Illusions (e.g., macropsia)
      - Structured hallucinations (e.g., music, scenes)

B. Complex partial seizures (with impairment of consciousness)
   1. Simple partial onset followed by impairment of consciousness:
      - With simple partial features (A1–A4) followed by impaired consciousness
      - With automatisms

2. When they start with impairment of consciousness:
   - With impaired consciousness only
   - With automatisms

C. Partial seizures with secondary generalization
   1. Simple partial seizures (A) evolving to generalized seizures
   2. Complex partial seizures (B) evolving to generalized seizures
   3. Simple partial seizures evolving to complex partial seizures, evolving to generalized seizures

**Generalized Seizures**

A. Absence type seizures
   1. Typical absence seizures:
      - Impairment of consciousness only
      - With mild clonic components
      - With atonic components
      - With tonic components
      - With automatisms
      - With autonomic components
   2. Atypical absence may have:
      - Changes in tone more pronounced than in A1
      - More gradual onset and/or cessation

B. Myoclonic seizures
C. Clonic seizures
D. Tonic-clonic seizures
E. Atonic seizures (astatic)

**Unclassified Epileptic Seizures**

## Classification of Epileptic Syndromes

The purpose of the classification system of epileptic syndromes was to organize epileptic seizures based on EEG and clinical criteria of the seizures and their localization. "An epileptic syndrome is an epileptic disorder characterized by a cluster of signs and symptoms customarily occurring together; these include such items as type of seizure, etiology, anatomy, precipitating factors, age of onset, severity, chronicity, diurnal and circadian cycling, and sometimes prognosis" [2]. However, epileptic syndromes are empirically defined and may not share common etiologies such as EEG and clinical characteristics of the seizures indicating a focal or generalized disturbance or their etiologies. Idiopathic epilepsies (previously called primary epilepsies) typically evolve in a predictable fashion. These generalized epilepsies have specific clinical and EEG characteristics, are age-dependent, without a known cause, and are genetically mediated. Cryptogenic epilepsies have no underlying cause that can be determined using present diagnostic techniques. Symptomatic epilepsies are caused by known or suspected, static or progressive lesions or are secondary to inborn errors of metabolism. The 1989 classification of epileptic syndromes [2] codifies on an empiric basis the most common epileptic syndromes, thus pro-

viding a common scientific basis for research. This allows comparison between studies and a standardized approach to prognosis and treatment. Its disadvantages, however, include the fact that the classification system does not necessarily take into account the underlying mechanisms for the seizures, multifactorial causes, or any "grey areas" of overlap between epileptic "syndromes." In attempting to be complete and exhaustive, it includes, on the one hand, rare syndromes and, on the other, syndromes that have been discarded. Furthermore, the different syndromes overlapped. The complexity makes epidemiologic studies, student teaching, and the education of the public more difficult. Additionally, it does not take into account more recent advances in molecular biology or advances in genomics of the inherited forms of epilepsy.

The 1989 classification [2] includes the following:

**Localization-Related (Focal, Local, Partial) Epilepsies and Syndromes**

1. Idiopathic (with age-related onset)
   - Benign childhood epilepsy with centrotemporal spikes
   - Childhood epilepsy with occipital paroxysms
   - Primary reading epilepsy
2. Symptomatic
   - Chronic progressive epilepsia partialis continua of childhood (Kojewnikow's syndrome)
   - Syndromes characterized by seizures with specific modes of precipitation
   - Temporal lobe epilepsies
   - Frontal lobe epilepsies
   - Parietal lobe epilepsies
   - Occipital lobe epilepsies
3. Cryptogenic
   - Cryptogenic epilepsies are presumed to be symptomatic, but with unknown etiology. This category thus differs from the previous one by a lack of demonstrable etiology.

**Generalized Epilepsies And Syndromes**

1. Idiopathic (with age-related onset-listed in order of age)
   - Benign neonatal familial convulsions
   - Benign neonatal convulsions
   - Benign myoclonic epilepsy of childhood
   - Childhood absence epilepsy (pyknolepsy)
   - Juvenile absence epilepsy
   - Juvenile myoclonic epilepsy (impulsive petit mal)
   - 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. Cryptogenic or symptomatic
   - West syndrome (infantile spasms, Blitz-Nick-Salaam Krämpfe)
   - Lennox-Gastaut syndrome

- Epilepsy with myoclonic-astatic seizures
- Epilepsy with myoclonic absences

3. Symptomatic

*Nonspecific etiology*

- Early myoclonic encephalopathy
- Early infantile epileptic encephalopathy with burst suppressions
- Other symptomatic generalized epilepsies not defined above

*Specific syndromes*

- Epileptic seizures may complicate many disease states. These include diseases in which seizures are a presenting or dominant feature.

**Epilepsies and Syndromes Undetermined Whether Focal or Generalized**

1. With both generalized and partial seizures
   - Neonatal seizures
   - Severe myoclonic epilepsy of childhood
   - Epilepsy with continuous spike waves during slow wave sleep
   - Acquired epileptic aphasia (Landau-Kleffner syndrome)
   - Other undetermined epilepsies not defined above
2. Without unequivocal generalized or focal features
   - This includes generalized tonic-clonic seizures in which clinical and EEG findings do not permit their classification as being either clearly generalized or localization-related.

**Special Syndromes**

1. Situation-related seizures
   - Febrile convulsions
   - Seizures occurring only with acute metabolic or toxic disturbances due to factors such as alcohol, drugs, eclampsia, or nonketotic hyperglycemia.
2. Isolated seizures or status epilepticus

For the details of the 2001 proposed classification, the readers are referred to the diagnostic schemes reported by the ILAE Task Force [4]. Examples of the application of the five-axis syndrome-oriented system would appear as follows:

**Axis 1 (ictal semiology):** generalized tonic-clonic seizure

**Axis 2 (underlying mechanism of seizure types):** generalized tonic-clonic seizures

**Axis 3 (epilepsy syndrome):** epilepsy with generalized tonic-clonic seizures on awakening

**Axis 4 (etiology):** genetic causes

**Axis 5 (impairment):** based upon the revised International Classification of Functioning, Disability and Health rating (http://www.who.int/icidh).

Using the five-tiered patient-oriented classification, the above patient according to the 2001 ILAE proposal would be classified as follows:

**Dimension 1 (epileptogenic zone):** generalized (epilepsy with generalized tonic-clonic seizures on awakening)

**Dimension 2 (semiologic seizure classification):** generalized tonic-clonic seizure
**Dimension 3 (etiology):** unknown
**Dimension 4 (seizure frequency):** persistent (one per year)
**Dimension 5 (related medical information):** seizures triggered upon awakening

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## CLINICAL TRIALS

Antiepileptic drug development has ranged from serendipity to designer AEDs based upon proposed pharmacologic mechanisms. Since the 1960s AED development has been required through clinical testing to demonstrate efficacy prior to marketing. Animal models have been utilized to screen potential AEDs through the NIH Antiepileptic Drug Development Program such that by 2002, more than 24,000 potential antiepileptic agents had been screened [1]. Another method besides model-based screening is mechanism-based screening. For example, the AED topiramate was discovered through model-based screening, and tiagabine was discovered through mechanisms-based screening. Two principal animal models employing maximal electroshock and subcutaneous pentylenetetrazol have been used. Differentiation based upon mechanisms has used chemoconvulsants like bicuculline (GABA antagonist), picrotoxin (Cl-channel blocker), kindling, and others [1]. The ILAE has established several guidelines [2]. For new drugs, an initial trial of their effectiveness as AEDs and the absence of toxic side effects must be established in animal studies. The drug is then administered to humans in a sequence of stages:

- Phase I: The purpose is to determine the pharmacokinetics of the drug in humans, the maximally tolerated dose, and the dose at which toxicity first appears. Healthy adult volunteers take various amounts of the drug either as a single dose or in repeated doses with a limited number of individuals studied. Later, phase I trials may evaluate the antiepileptic effective-

ness, toxicity, pharmacokinetics, and interactions with other drugs. In adults with uncontrolled seizures, the new drug is used as an add-on treatment in either open or closed study conditions for 1-2 months.

- Phase II: The objective is to determine the efficacy and toxicity of the new drug. The first efficacy trials are usually referred to as the proof of principle (or concept) trials and are often smaller open-label trials. Controlled trials using double-blind, placebo-controlled design may be made with the new drug as add-on therapy in poorly controlled adult patients with epilepsy and may last 3 months and are performed in parallel groups or as a crossover study.
- Phase III: The objective is to determine, with, more precise safety and efficacy; the clinical indications for the new AED within the therapeutic armamentarium, and its specific role in treatment of special epilepsy populations or syndromes such as in children, monotherapy, or Lennox-Gastaut syndrome. Phase III trials usually involve large numbers of patients (100-150) tested for at least a year in a placebo-controlled trial or a comparator AED in a controlled fashion. These "regulatory" trials are required for FDA approval, and two adequate and well-controlled clinical trials must demonstrate efficacy and adequate safety prior to submission for a New Drug Application (NDA) status. These trials are usually referred to as "pivotal" trials relative to final approval for marketing and clinical use.
- Phase IV: After the drug reaches the market, phase IV investigations may be used to evaluate the advantages and disadvantages of the AED under community conditions. This postmarketing testing usually involves less homogeneous groups of patients in "real-life" settings. These trials often expand new uses to include alternative indications and applications.
- Phase V: Investigator-generated trials based upon a sole hypothesis of the investigator postmarketing that involves a trial that is open-label or controlled to seek new off-label uses of the compound.

In all these trials, patients are examined in a blinded fashion according to specific standards that determine drug toxicity and effectiveness, thus ensuring patient safety. The inclusion and exclusion criteria are strictly defined, usually with the exclusion of a large number of patients with epilepsy from particular studies due to the strigent criteria for study entry. Most of the information that is available on the AEDs has been made possible through clinical trials. Newer study designs (e.g., monotherapy designs) will likely evolve, and greater detail of terminology, observation through neuropsychology, and quality-of-life ratings will no doubt become useful adjuncts to standard safety and efficacy paradigms that make up current clinical trials design.

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## CLOBAZAM (FRISIUM®)

Clobazam is a 1, 5-benzodiazepine producing less sedation than other drugs within the benzodiazepine class (*see* Benzodiazepines). It is used outside of the United States as an adjunctive therapy in typical absence seizures and in partial epilepsies, and it has also been used for its anxiolytic properties. It is usually divided into two or three doses per day. Favorable short-term results have been achieved with clobazam, but relapses may occur, as with other benzodiazepines, due to tolerance, and an intermittent "pulse" course of therapy may be helpful. If there has been little response after 1-3 months, further use is probably unhelpful.

## CLONAZEPAM (KLONOPIN®, RIVOTRIL®)

Clonazepam is a benzodiazepine unlike others that is frequently used in the treatment of seizures, both acute and chronic (*see* Benzodiazepines). It is available in an intravenous form that has been an effective treatment for status epilepticus in Europe, and it has been used for frequent seizures, prolonged seizures, and febrile convulsions. Administration of clonazepam is by intravenous injection of 0.01-0.09 mg/kg over 2-5 minutes. The drug may also be given by rectal administration. Clonazepam is available only as an oral preparation in the United States. It is very lipid soluble, has little hepatic enzyme induction, and has a half-life of 19-42 hours. Clonazepam is particularly useful in myoclonic epilepsies (benign and progressive), absence seizures, and photosensitive seizures. It is effective in a broad spectrum of seizure types, although side effects often limit its usefulness. Studies in children with severe epilepsies treated with multiple AEDs have shown it to be effective in neonatal seizures, infantile spasms, and the Lennox-Gastaut syndrome. Withdrawal seizures and even status epilepticus may occur upon discontinuation of clonazepam refractory to conventional AEDs, and suggested taper schedules have included safe reduction by 0.04 mg/kg/week [1]. Sedation occurs in approximately half of patients, although tolerance to side effects may occur with time, and up to 85% of children have reported drowsiness, which required drug termination in a quarter of children. Respiratory or cardiovascular depression and increased bronchial secretions may occur with intravenous use, especially in children and the elderly. Dysarthria, incoordination, ataxia, and dizziness may occur with initial use or with higher doses. Behavioral worsening and eating disorders have occurred in children, and a peculiar "burning mouth syndrome" has also been described with the use of clonazepam. Oral dosing is 0.01-0.02 mg/kg/d in children and up to 8 mg/d in two to three divided doses in adults.

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## CLONIC SEIZURES

Clonic seizures are characterized by rhythmic clonic jerks, which may be focal or generalized, with varying amplitude, frequency, and distribution during the seizure [1]. Convulsive seizures may occasionally lack a tonic component and are best described as clonic seizures. Clonic seizures typically occur in young children with symptomatic epilepsies and with febrile seizures. Over the age of 3, the clonic movements are typically regular and symmetric. In the younger age groups, unilateral or asymmetric jerks may be seen (hemibody jerks, unilateral, hemiclonic), and jerks may "migrate" or shift from one side to the other. The EEG correlate of clonic seizures is classically one of repetitive irregular focal or generalized spike-and-slow waves. Generalized clonic seizures cause an immediate loss of consciousness followed by a postictal phase that is usually brief [1]. IGE may include seizures that begin with a clonic phase and progress to a clonic-tonic-clonic seizure semiology that is characteristic of an IGE. In hemiclonic seizures, consciousness may be preserved or only mildly affected, and they are often associated with a symptomatic localization-related epilepsy. Clonic seizures may last seconds to hours and when restricted to a limited area on one part of the body may manifest as epilepsia partialis continua (*see* Kojewnikow's syndrome). A variable postictal hemiplegia is commonly seen, with seizure onset or region of activation or propagation typically extratemporal and most often the dorsolateral frontal lobe.

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## CLONIC-TONIC-CLONIC SEIZURES

Clonic-tonic-clonic seizures are primary generalized seizures beginning with massive bilateral myoclonic jerks occurring at seizure onset before consciousness is lost. They are then followed by a tonic-clonic seizure. These seizures are usually seen in juvenile myoclonic epilepsy and signify an IGE. The line to distinguish myoclonus that evolves to a tonic-clonic seizure and a clonic-tonic-clonic seizure has not been precisely demarcated. In addition, asymmetric or even unilateral jerks may cause a misdiagnosis of focal epilepsy in patients with clonic-tonic-clonic seizures and juvenile myoclonic epilepsy (JME).

## CLORAZEPATE (TRANXENE®)

Clorazepate has been used as an adjunctive AED in chronic epilepsies. It has most frequently been used in the treatment of anxiety or in association with al-

cohol-related seizures. Its use in refractory epilepsy has been in refractory patients, though the application is often limited by tolerance. Initial starting doses have been 0.3 mg/kg/d given 7.5 mg tid with slow titration to a maximum of 1 mg/kg/d in adults. Chlorazepate has been used due to the reduced sedation compared to other benzodiazepines, although sedation is the most frequent side effect in addition to dizziness, gait difficulties, depression, and withdrawl symptoms on taper. In Europe, an intravenous formulation has been used in the treatment of status epilepticus. In addition, a sustained-release formulation is available (Tranxene-SD).

## COCAINE

Cocaine is a central nervous system stimulant and one of the most abused recreational drugs in the United States with a high risk of seizures when used [1]. Even a single intake may precipitate seizures, and up to 10% of patients may experience seizures, often within 1½ hours of use [1]. Seizures are usually solitary and generalized convulsive when they occur, but when previous seizures have occurred an even higher percentage of patients may experience exacerbation of their seizures with cocaine use. When cocaine-induced seizures are focal or repetitive, an underlying structural brain complication such as intracerebral or intraventricular hemorrhage must be strongly considered. The majority of seizures have been associated with smoking "crack" cocaine or with intravenous use as compared to intranasal "snorting" [1,2]. Body "stuffing" and "packing" with cocaine may result in delayed toxicity including seizures. Attention to fluids, electrolytes, and acid-base balance, with judicious use of benzodiazepines, has been the treatment of choice for cocaine-induced seizures. AEDs are required for comorbid epilepsy complicating cocaine use.

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## COGNITIVE SEIZURES

Some partial seizures can involve cognition during evoluation. These partial seizures often consist of a dreamy state in which the patient is aware of an alteration in perception of real events or hallucinates because of mild confusion. These manifestations usually are associated with temporal lobe abnormalities. Additionally, forced thinking in which an unshakable perception is noted by the patient is another cognitive phenomenon of partial seizures and usually reflects a temporal localization though involvement of the mesial or inferior frontal lobes.

The association of epilepsy and an increased risk of cognitive deficits have long been known [1-3]. The issue of whether an epilepsy in effect reflects a progressive brain disease is complex, and variability is reflected by the different causes and types of epileptic seizures. In prospective controlled population studies, compared to healthy individuals, patients with epilepsy demonstrated a significant decline in retention of new verbal and visual-spatial information as well as in performance aspects of general cognition [1]. In contrast, others emphasize a lack of overall cognitive decline for up to 10 years [2]. However, in addition to animal studies and studies of surgically treated patients, these data suggest that seizures can have a direct adverse effect on cognition and that good seizure control even after years of intractability can have a favorable impact on cognition [3].

### References

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## COMMISSUROTOMY

The corpus callosum is the largest interhemispheric commissure with axons that stem from all parts of the neocortex, and surgical therapy to abolish the bilateral epileptiform activity and motor manifestations of seizures was first introduced around 1940. However, it is not the only fiber tract that interconnects homotopic regions of the hemispheres. The anterior and posterior commissures, thalamus, and brainstem also play a role in interhemispheric propagation. The anterior commisure mainly interconnects the anterior temporal lobes and has been a target in surgical therapy of pharmacoresistant epilepsy. The efficacy of surgical disconnection through section of commissural tracts (commissurotomy) has been shown as a means of providing palliative therapy in PWE and refractory epilepsy (most often SGE) that incur recurrent injury from seizures. Surgical intervention is aimed at diminishing the frequency of the most debilitating seizures, drop attacks with tonic or atonic seizures. Besides partial (i.e., two thirds division) and complete division of the corpus callosum, section of the fornix, the anterior commissure, and the fields of Forel in the subthalamic region have been attempted with suboptimal results. Radiosurgery has been proposed to avoid complication of open commissurotomy.

## COMPLEX PARTIAL SEIZURES

Complex partial seizures are the most prevalent seizure type in an unselected adult population of patients with epilepsy (*see* Classification of Seizures and Epilepsies). This type of seizure presents with simple partial seizures (auras) in 50% of cases and frequently an arrest of activity, staring, fumbling automatisms (automatisms are present in the majority), and blunting of awareness or recall (occurs in all cases, by definition) when associated with TLE. The term "complex" applies to a focal seizure that is associated with an alteration or degree of *impairment* in the level of consciousness (*see also* Consciousness) as opposed to simple partial seizures with no impaired level of consciousness or generalized tonic-clonic seizures with a loss of consciousness. Complex partial seizures most commonly arise from the temporal lobe, but they may originate in any region of cortex in the brain capable of harboring an epileptogenic zone.

## COMPLIANCE

Compliance is another term for adherence (*see* Adherence) and refers to the manner in which a patient follows medical advice adhering to prescribed recommendations including the dosage and timing of medication intake. It is one of the most important factors in failure of AED therapy and may lead to pseudo-intractability where it appears as if AEDs are ineffective.

## CONCUSSION

The American Academy of Neurology defines concussion as a trauma-induced alteration in mental status that may or may not involve loss of consciousness. Few prospective studies have been done comparing incidence of accidental injury in PWE compared to those without epilepsy [1]. Only a mild increase was found in PWE and most were minor, consisting of closed head trauma with soft tissue injury. Many retrospective studies have claimed a higher incidence with more serious injury from seizures and include submersion and near-drowning (especially in children), fracture, burns, and falls causing concussion [1].

### Reference

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## CONFUSION

Confusion is a common neurologic symptom that carries a wide differential diagnosis. Migraine, transient global amnesia, and epilepsy may present with an

acute confusional state. Confusion may occur in PWE for several reasons. In the interictal period, confusion may occur because of toxic or metabolic encephalopathies (i.e., AED toxicity or hyponatremia) or comorbid psychiatric conditions (i.e., acute psychosis) or be associated with the underlying etiology of seizures from brain tumor, encephalitis, dementia, cerebral infarction, or head trauma. Brief ictal confusion is frequently seen with complex partial seizures, especially of temporal lobe origin where the nondominant hemisphere is affected and ictal speech may occur. Confusion following a seizure has been attributed to the postictal effects that occur within the mesial temporal structures bilaterally and is commonly the hallmark of a seizure when gradual recovery is evident. It is seen as a result of impairment of consciousness and may last from several hours to 1-2 days. Clinically, it can be difficult to distinguish a postictal confusional state from ongoing ictal confusional states seen with complex partial or generalized nonconvulsive status epilepticus unless an EEG is performed simultaneously. The treatment for confusion associated with seizures is directed toward determining the underlying etiology, optimizing use of AEDs, and ensuring adequate recovery.

## CONNECTIVE TISSUE DISEASE

Seizures occur with greater incidence in patients with connective tissue disease (CTD). Rheumatism is an older euphemism for rheumatologic connective tissue disease. Vasculitis is the means by which CTDs lead to the development of seizures. The CTD with the highest association with seizures is systemic lupus erythematosus (SLE). Seizures are the most common manifestation of lupus, with an incidence in flares of CNS lupus of 10-50% (*see* Lupus). Seizure types include focal and GTC seizures, although status epilepticus may also occur. Seizures may occur as the presenting feature preceding the development of systemic symptoms by several years. Patients with Sjögren's syndrome and Behçet's syndrome may occasionally be associated with seizures, especially during flares, although rheumatoid arthritis, scleroderma, and mixed connective tissue disease due to CNS involvement is rare.

Lupus-like reactions with arthralgias may occur with some AEDs including barbiturates, phenytoin, carbamazepine, ethosuximide, and valproate. In drug-induced disorders, complements and anti-DNA antbodies are normal in contrast to those with SLE as a CTD. The status of the new AEDs is yet to be defined.

The barbiturates, including phenobarbital and primidone, have been implicated in arthralgias, adhesive capsulitis, Dupuytren's contracture, and Peyronie's disease. The incidence of these adverse effects has been estimated to be between 5 and 38% [1]. Barbiturate-related connective tissue disorders may appear from 4 weeks to 20 years after the initiation of treatment, but usually appears in the first year of therapy. Resolution usually occurs upon stopping the barbiturate, although persistent sequelae are possible (*see also* Dupuytren's Contracture).

**Reference**

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## CONSCIOUSNESS

Consciousness during seizures refers to the degree of *awareness* and *responsiveness* available to react to an external stimulus with an ability to partially recall internal or external events that have occurred. Responsiveness refers to the ability to follow commands, while awareness refers to recall of the events performed. Impairment of consciousness during a seizure is usually demonstrated by impaired responsiveness to ictal testing and amnesia for the duration of the seizure. Patients may seem to be conscious or even partially responsive to others during seizures yet be unaware that one has even occurred. If the loss of consciousness is brief, patients may not only be unaware of their seizure, they may even deny it.

Consciousness depends upon perception, memory, cognition, and voluntary motor capabilities. Evaluation of the level of consciousness during a seizure may be difficult, especially in infants. Consciousness may be preserved in simple partial seizures or myoclonic seizures. However consciousness is impaired during complex partial seizures and in generalized seizures (other than myoclonic seizures). Complex tasks may be required to reveal mild alteration in consciousness or level of alertness, which may be demonstrated with more finite endpoints such as during auditory response testing with absence seizures. The inability to speak during a seizure should not be confused with an alteration in the level of consciousness.

## CONTRACEPTION

Nearly 40% of pregnancies in the United States are unplanned, and the potential impact of the inactivation of contraception involves two people: the mother and the infant (*see* Pregnancy) [1]. Several surveys suggest that a large percentage of healthcare professionals have limited knowledge about optimizing contraceptive efficacy in women with epilepsy and therefore do not receive information about inactivation of hormonally based contraception [2]. All methods of birth control that involve preparations containing steroidal contraceptives are at risk for contraceptive failure when co-administered with AEDs [3]. These forms include oral contraceptive pills, transdermal applications, and injections. Because of the common use of low-dose estrogen preparations, this has been a primary focus for the majority of young females of childbearing potential. Enzyme-inducing AEDs such as phenytoin, phenobarbital, primidone, carbamazepine, felbamate, oxcarbazepine, and topiramate interfere with the metabolism of hormonal contraceptives via the CYP 450

enzyme system to decrease hormonally based contraceptive effectiveness [1]. Recommendations have included higher-dose combinations of ethinylestradiol or mestranol to ensure adequate delivery of progesterone components to prevent pregnancy [4]. Frequently these are contained in 50 μg tablets when oral routes are preferred, but in spite of current guidelines that suggest higher-dose estrogen-containing pills, it is the progesterone component that provides contraceptive efficacy through prevention of ovulation [3].

Valproate, benzodiazepines, ethosuximide, gabapentin, levetiracetam, vigabatrin, and zoisamide are AEDs that do not interfere with contraceptive effectiveness. The newer AEDs as a group are less likely to interfere with the efficacy of hormonally based contraceptives. Of the newer AEDs, topiramate has a theoretical concern for potentially interfering with the efficacy of hormonal contraception in a dose-related fashion when doses exceed 200 mg/d. Conversely, oral contraceptives can alter serum protein-binding characteristics and change the efficacy of a given AED regimen. Lamotrigine has a demonstratable interaction where hormonal contraception may significantly reduce its serum concentration and result in compromised efficacy and breakthrough seizures through steroid-induction of the UDP-glucuronosyltransferase system, the principal pathway for elimination of lamotrigine [3]. Therefore, because the potential for drug interactions with AEDs and hormonal contraceptives appears high, recommendations for oral contraceptives that contain 1 mg of norethindrone, 0.15 mg of levonorgestel, or 0.3 mg of norgestrol should be included in the formulations used to ensure adequate birth control. All hormonal contraceptives that contain 50 μg of estrogen can be recommended as they also contain high doses of progestin. The contraceptive patch should not be used by women receiving EIAEDs because it is a low-progestin-containing formulation. On the other hand, copper-containing intrauterine devices provide a highly effective means of contraception for women with epilepsy. Additionally, 150 mg of depomedroxyprogesterone acetate (Depo-Provera) given i.m. every 3 months is an effective means of contraception for women who are nonadherent or at risk for problems with estrogen and may also be beneficial for seizure control.

## References

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## CONVERSION DISORDER

A conversion disorder is a symptom complex that is composed of nonphysiologic complaints or findings properly categorized as a somatoform disorder. *Conversion disorder with seizures* is a common diagnosis responsible for 20-30% of patients admitted for definitive diagnosis to epilepsy monitoring units and is a specific diagnosis contained within the *Diagnostic and Statistical Manual* published by the American Psychiatric Association. Conversion disorders or somatoform disorders (*see* Somatoform Disorders) are not diagnoses of exclusion but rather are based upon specific characteristics and with regard to seizures are diagnosed with excellent sensitivity and specificity with video-EEG monitoring [1].

### Reference

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## CONVULSION

The term "convulsion" refers to a generalized seizure (*see* Classification of Seizures and Epilepsies) with generalized motor movements that occur with jerking movements and loss of consciousness (*see* Consciousness) during the seizure. The term has been used more loosely as a general descriptive term that includes tonic, tonic-clonic, clonic-tonic-clonic, and repetitive myoclonic seizures when they create the appearance of a generalized tonic-clonic seizure.

## CONVULSIVE SYNCOPE

The request to differentiate syncope from seizure is a common one, although the clinical features are distinctive, with the majority that experience syncope manifesting a flaccid collapse during intial syncopal episodes. However, motor symptomatology is very common in those who manifest cerebral hypoxia caused by cardiac arrest, orthostatic hypotension during head-up tilt testing, syncope during electrophysiologic studies, and in normal individuals who undergo valsalva maneuvers [1]. Convulsive syncope describes the rapid, brief, and often asymmetric limb flexion that appears concurrently, shortly after the fall to the ground, and which may be confused with a brief tonic-clonic seizure. Tonic posturing may also occur. A distinct evolution is noted on EEG during syncope with normal background evolving to low-amplitude diffuse slowing and ultimately suppression of all background electrocerebral activity. Syncope may occur in patients with partial seizures if ictal asystole comorbidly occurs.

Additionally, prolonged syncope may result in electroclinical seizures when significant anoxia occurs [1,3]. Additionally, distinguishing characteristics include triggers by known precipitants such as cough, pain, or emotional triggers such as during phlebotomy, hot environments, exerecise, or micturition or defecation. Concomitant dizziness, pallor, diaphoresis, nausea, and the brevity and relationship of the motor symptoms to syncope may help differentiate syncope. The character and more prolonged duration of the convulsive manifestations, head turning or lateralizing features, urinary incontinence, tongue biting, and postictal confusion make epileptic seizures more likely. A simple point scoring system of historical features has been developed to help distinguish syncope from seizures with a very high sensitivity and specificity [2].

### References

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## CORPUS CALLOSTOMY

Section of the corpus callosum (*see also* Commissurotomy) is a palliative operation initally performed nearly 70 years ago, which gained popularity in the late 1970s to decrease uncontrolled seizures. The best response has been seen in PWE and drop attacks due to refractory atonic and tonic seizures [1,2]. In addition, medically refractory encephalopathic generalized epilepsy (especially the Lennox-Gastaut syndrome or West syndrome) has been a common target for treatment directed with callostomy for those with recurrent seizure-induced injury [2,3]. Partial (anterior two thirds) and total sections of the corpus callosum are performed in adults and children with refractory epilepsy and are typically performed serially, sectioning the anterior and then the posterior portion to minimize the potential complication of the disconnection syndrome [1-3]. Section of the anterior two-thirds section of the corpus callosum as an intial treatment appears to induce little neuropsychological impairment when compared to complete corpus callostomy, which is not performed as a two-stage procedure [1]. Quality of life appears improved, although improvement in alertness and responsiveness and clinical improvement did not always correlate with seizure reduction [3]. Brain MRI and EEG are not reliably predictive of seizure outcome, but an electrodecremental response may suggest a more favorable response in adolescence. While atonic seizures appear to respond most favorably, tonic, myoclonic seizures, and generalized tonic-clonic seizures may also be reduced [1,2]. Patients with complex partial seizures are less likely to respond to callosotomy, and for those with infantile hemiplegia, Rasmussen's syndrome, hemimegalencephaly, and other large hemispheric lesions, corpus callosotomy is performed as a part of modified hemispherectomy.

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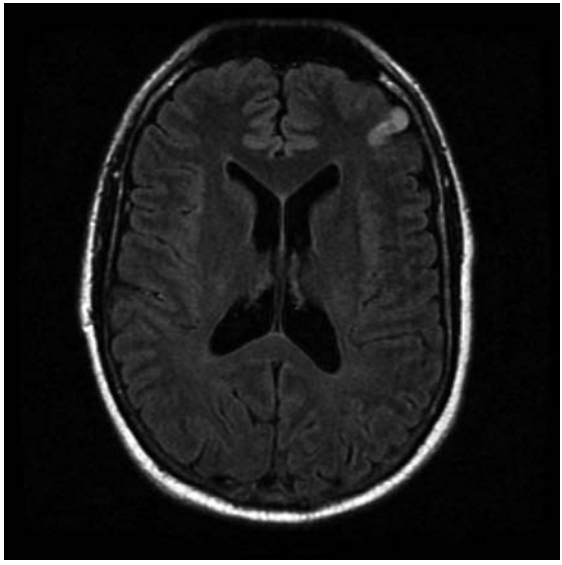
## CORTICAL DYSPLASIA

Focal cortical dysplasias and diffuse cortical dysplasias are heterogeneous groups of developmental disorders defined by an abnormal cerebral cortical cytoarchitecture. Focal cortical dysplasia (FCD) is the most common form of focal developmental disorder, diagnosed in 20-30% of patients with medically intractable localization-related epilepsy. The clinical features are variable but usually become evident when seizures occur [1]. Seizures are often complex partial or secondarily generalized, with the semiology reflective of the brain region where they begin, and are commonly refractory to multiple AEDs. Most patients have extratemporal cortical dysplasia, often involving the frontal lobe (*see* figure), although temporal lobe focal cortical dysplasia has also been reported. MRI has greater resolution than CT imaging and demonstrates abnormal gyral thickening with underlying T2-weighted white matter changes [2]. EEG may reveal focal spikes or polyspikes, but are often less circumscribed than those seen with TLE due to mesial temporal sclerosis (*see* Mesial Temporal Sclerosis). The association of cortical dysplasia in the temporal lobe with mesial temporal sclerosis is known as *dual pathology*. Inherited genetic syndromes such as Miller-Dieker or X-linked lissencephaly, subcortical band heterotopias, and tuberous sclerosis may be encountered [3]. In addition, nongenetic causes including hypoxic-ischemic encephalopathy, traumatic brain injury, and CNS infections may also be asso-



Brain MRI demonstrating focal cortical dysplasia of the left frontal lobe in a patient with medically intractable localization-related epilepsy and recurrent complex partial seizures.

ciated with cortical dysplasias. Focal cortical dysplasia represents a spectrum of histopathologic features. The characteristic features include disruption of the cortical ribbon with poorly differentiated glial cell elements. In the most pronounced form, giant neurons, cortical dyslamination, balloon cells (type II), and astrocytosis are seen [3]. Balloon cells are probably the result of proliferation of abnormal cells in the germinal zone. Patients are often refractory to AEDs, and surgical therapy is very effective when the entire lesion is able to be resected.

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## CORTICECTOMY

The aim of a corticectomy is to eradicate seizures by resecting the epileptic focus. Much of the early work was done by the group in Montreal, Canada. The indications for corticectomy are for patients with progressive lesions and partial seizures inadequately controlled by AEDs. Corticectomy is performed for the epileptogenic zone when resection does not place the patient at risk of deficit greater than that of the seizures themselves and where AED therapy has failed (*see* Antiepileptic Drugs) [1]. The initial approach to surgical resection is confirmation of a diagnosis of epilepsy and identification of the seizure focus using scalp or intracranial EEG when an extratemporal focus is suspected. Common resection of cortex occurs with a standard temporal lobectomy, mesial temporal resection, or amygdalohippocampectomy. Selective focal resections (topectomies) and corticectomy are guided by intraoperative or extraoperative electrocorticography with intracranial electrode arrays of combinations of implantable depths, strips, and grids. Results depend on the precision of seizure localization and the nature of the population under study. With accurate localization, seizures may be eliminated in 55-70% of temporal lobe epilepsies and 40-60% of patients with extratemporal epilepsies, and a significant seizure reduction may be seen in the majority of the remainding patients [2].

### References

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## COST

The annual cost of the 2.3 million epilepsy cases in the United States has been estimated to be $12.5 billion dollars ($11.1 billion for incident cases) (1995 population figures) [1]. The expense is associated with direct costs attributed to medical care, AEDs, and diagnostic testing (i.e., MRI, EEG, laboratory studies), with a high mean cost of all medical services estimated to be $9,617 per year [2]. Different patient profiles vary, with mean annual cost ranging from $4,362 to $43,333, dependent upon the number of procedures from none to those requiring invasive diagnostic procedures [2]. Indirect costs may represent 85% of the total and, with direct costs, are concentrated in patients with medically intractable epilepsy. Indirect costs reflect intangible costs such as restricted activity days and loss of wages, excess unemployment and reliance on governmental support, reduced taxation accountability, and excess mortality. Even greater expense is incurred when seizures are not controlled, resulting in inflated costs to pursue proper diagnosis or surgical intervention. Additionally, those with PNES incurred expense despite the lack of an epilepsy diagnosis (*see* Psychogenic Nonepileptic Seizures).

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## CRYPTOGENIC

The Commission on Classification Terminology of the International League Against Epilepsy reserves the term "cryptogenic" epilepsy for partial or generalized epilepsies in which neither the history, clinical examination, nor ancillary investigations reveal a lesion accounting for the seizures. However, clinically apparent cryptogenic epilepsy may become reclassified as a symptomatic epilepsy following application of higher-resolution neuroimaging; for example, when a patient with a normal head CT scan and focal seizures with no historical cause is subsequently discovered to have a foreign tissue lesion on high-resolutoin brain MRI. Cryptogenic epilepsies are thus based on negative criteria, whereas idiopathic epilepsies are defined by positive criteria that include genetic transmissibility of the seizure syndrome.

## CUMULATIVE INCIDENCE

Cumulative incidence (CI) is defined as the ratio of incident cases to the at-risk population at the beginning of the observation period (when losses to follow-

up are nonexistent). CI determines a frequency, in percentages, that measures the risk that any seizure or epilepsy could occur at a specific age. For instance, the CI for provoked and unprovoked seizures at 75 years of age is between 5.8 and 7.0 % [1].

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## CURE

The use of the term "cure" is controversial because of the ever-present possibility of the reappearance of seizures after prolonged seizure freedom without AED. Resective epilepsy surgery in cases of lesional excision carries a high likelihood of seizure freedom, yet those that are "cured" and remain successfully seizure-free without AEDs account for less than half of the surgical successes. The term "cure" has sometimes been used with regard to some idiopathic epileptic syndromes such as childhood absence epilepsy or benign idiopathic partial epilepsy of childhood. These syndromes may be considered to have been "cured" when the seizures remit in adolescence even if other epilepsy syndromes develop later. The term "remission" is preferred even when a nonsurgical seizure-free state exists, especially when continued AEDs are required.

## CURSIVE SEIZURE

Cursive seizures are seizures characterized by ambulatory automatisms involving gait. During a cursive seizure, patients may walk or run into obstacles. These seizures are thought to be due to limbic foci and may be related to gelastic seizures (*see* Gelastic Seizures). Cursive seizures should be distinguished from the automatisms occurring during postictal or ictal confusional periods, during which patients ambulate in a more coordinated and purposeful fashion (*see also* Versive Seizures).

# D

## DACRYSTIC SEIZURES

Dacrystic seizures are characterized by brief episodes of crying, with or without impairment of consciousness, and are rarely seen [1]. Postictal depression with crying may also occur and is especially seen in patients with limbic epilepsy. The epileptogenic zone is frequently in the nondominant anteromesial temporal or mesial frontal regions. Dacrystic seizures may also occur with mesial temporal lobe epilepsy with identical affective semiology reproduced during Wada testing [WOT: personal observation 2007].

### Reference

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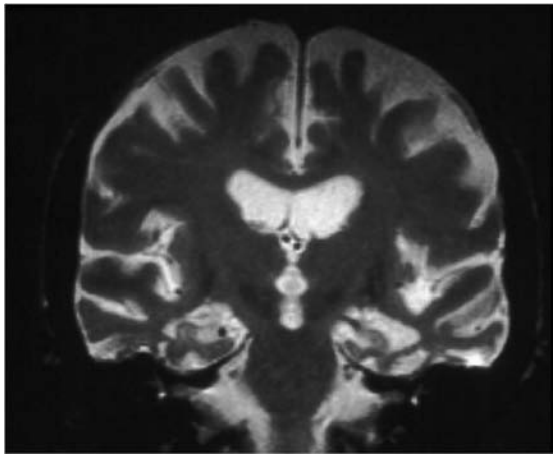
## DELTA ACTIVITY

Delta activity is a frequency bandwidth seen on EEG that occurs with frequencies under 4 Hz (*see also* EEG). In waking nonelderly adult patients, this frequency is abnormal. Diffuse delta activity may be seen with diffuse cerebral dysfunctions such as toxic, metabolic, or infectious encephalopathies, frontal delta activity with midline tumors, hydrocephalus, hypoglycemia, diffuse encephalopathies, and dialysis dementia. Focal delta activity can overlie structural abnormalities such as tumors, intracranial bleeds, or strokes involving subcortical and cortical areas. Occipital delta occurs with childhood absence epilepsy, posterior fossa, and deep midline dysfunctions. Delta activity occurs normally during slow-wave sleep as well as during hyperventilation, especially in the face of hypoglycemia.

## DEMENTIA

Dementia is a common cause of memory loss with aging that occurs in 5-11% of the population by age 65 and up to 50% beyond age 85 [1]. While stroke accounts for the majority of known cases of epilepsy in the elderly, dementia is becoming one of the most common underlying etiologies, especially as people live longer lives. Alzheimer's disease is a major cause of morbidity, the fourth leading cause of death, and a significant concern in the elderly. The elderly



T2-weighted coronal brain MRI in a 72-year-old patient with new-onset seizures and Alzheimer's disease.

comprise the fastest growing segment of the U.S. population. Among all ages, the elderly are more likely to develop epilepsy. The prevalence is 1% for individuals over age 60 and increases with advancing age. Complex partial seizures are the most common seizure types to occur, with generalized tonic-clonic seizures in only about 30%. Seizures may be subtle, associated with unawareness, and be mistaken for TIAs, pseudodementia, or cardiac problems and result in a delay in diagnosis for as long as 25 years [2]. Prolonged EEG monitoring may be helpful when an atypical course of dementia is encountered. The treatment is seizure specific, and AEDs that are effective against focal seizures are selected are being initiated relative to their tolerability and pharmacokinetics. Altered gastrointestinal absorption, delayed renal clearance, and altered metabolism make treatment of the elderly challenging and common issues. While more studies are being completed that compare efficacy and tolerability in the elderly [3], the use of newer AEDs such as lamotrigine, leviteracetam, and gabapentin (pregabalin) with more favorable pharmacokinetics needs to be balanced with the cost of AEDs such as carbamazepine.

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## DENDRITE

A dendrite is the receiving end of a neuron. Neural impulses are propagated via an electrochemical gradient that flows from the axon to the dendrite prior to synaptic connections, which further propagate information. Interactions among axons and dendrites undoubtedly play a large role in the generation of EEG and epilepsy.

# DEPRESSION

Mood disorders and depression constitute the most common category of psychiatric comorbidity in PWE, with prevalence rates that are lower for IGE, controlled, and community-centered studies [1]. Patients with hospitalized, refractory localization-related epilepsy (LRE) may have prevalence rates of depression that reach 20-50% [1]. The incidence of depression has been shown in several studies to be a better predictor for overall health-related quality of life than seizure frequency or severity [2]. The clinical features of interictal depression remain underrecognized and undertreated and do not conform to the primary psychiatric diagnosis of endogenous depression in up to 50% of PWE. Blumer coined "interictal dysphoric disorder," which underscored the differences of interictal depression and includes an intermittency of symptoms, feelings of hopelessness, fear, and prominent irritability, in addition to anhedonia and "feeling down" for the purposes of treatment [1]. Anxiety (*see* Anxiety) often appears concomitantly with depression, and similar to the fivefold increase in suicide encountered in PWE (*see* Suicide), it is more common than in the general population. Postictal symptoms are also commonly observed in contrast to infrequently encountered ictal depression (*see* Dacrystic Seizures). It is not surprising that PWE are more likely to develop depression when seizures are uncontrolled. However, the reverse is also true, indicating a bidirectional effect with depressed patients being more likely to develop epilepsy [1]. Anatomic abnormalities of the mesial temporal lobe have also been demonstrated [3]. Anticonvulsant effects of serotonergic and noradrenergic agents have been demonstrated in animal models. In addition, the incidence of seizures in placebo-treated patients with depression was actually higher in the general population than in those treated with serotonergic agents [4], reemphasizing the relative safety of aggressive antidepressant treatment for those PWE in need of therapy. To combat underrecognition, a screen for depression (the Neurologic Disorders Depression Inventory for Epilepsy [NDDI-E]) taking a mean of 3 minutes to complete has been validated to facilitate detection. Treatment recommendations have included treating depressed PWE with a selective serotonin reuptake inhibitor (SSRI) with agents such as escitalopram or citalopram due to the absence of significant pharmacokinetic interactions with AEDs, thereafter considering a trial of serotonin-norepinephrine re-ptake inhibitors (SNRIs) with venlafaxine or duloxetine should failure be noted [1]. Clomipramine, maprotiline, amoxapine, and bupropion should not be used in PWE, and psychiatry referral should be prompted after failure of one or two agents.

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## DIAGNOSIS

The diagnosis of epilepsy requires two or more spontaneous seizures although it may be anticipated after initial recognition in those with high risk for recurrence (i.e., symptomatic cause, epileptiform EEG, etc). Alternatively, neurologic examination, interictal EEG, and neuroimaging may be normal in PWE, making the correct diagnosis difficult. The routine diagnosis of epileptic seizures (ESs) is predicated upon a good historical account of the direct observation of seizure behavior, yet this information may be vague or secondhand, at odds with the clinical semiology expected with ES, or even misleading at times (i.e., brief lateralizing features in patients with generalized epilepsy). Historical account is the foundation for the diagnosis of seizures, and the clinical impression remains the gold standard. Unfortunately, the witness observing an ES is often able to provide only an inaccurate description of the event [1]. Symptoms including unresponsiveness, left-right confusion, and lateralizing features were often missed by volunteer observers during videotape review of a partial-onset secondarily generalized seizure [1]. Additionally, the reaction of the observer commonly becomes a part of the description beyond clinical observation [2]. Hence, considerable differences in seizure description may be seen between nonphysician observers, and in addition, the quality of a recount of the seizure may be affected due to subsequent mistranslation of descriptive language used [2].

The diagnosis of a seizure will have enormous consequences for a patient, including loss of driving privileges, social limitation of home and work life, and, for some, chronic AED therapy. No validated single clinical criteria exist for the diagnosis of epilepsy, and therefore the diagnosis has proven to be subject to error with considerable interobserver disagreement [3]. In one study, interobserver agreement in adults with a first seizure was moderate (kappa 0.58) when neurologists based the diagnoses solely on clinical judgment, was much higher (kappa 0.73) when references to simple descriptive diagnostic criteria (e.g., loss of consciousness with tongue bite) were used, and still higher when group consensus was used [3]. In children, interobserver agreement was poorer, with moderate agreement (kappa 0.41), improving modestly (kappa 0.45) when comparable, more descriptive criteria were used. However, epileptologists evaluating patients with ES by clinical history compared to video-EEG seizure monitoring demonstrate excellent overall clinical accuracy (94%) with a high sensitivity (96%) for complex partial and secondarily generalized seizures [4]. Weaker specificity (50%) for simple partial seizures and psychogenic nonepileptic seizures (PS) was seen. Despite our rapidly expanding knowledge within the field of epileptology, the quality of the scientific evidence available

to clinicians remains more limited. The optimal technique to provide or validate a clinical diagnosis of epilepsy has been video-EEG. Yet this technique may not be available to many people, especially PWE who suffer infrequent seizures.

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## DIAMOX®

*see* Acetazolamide.

## DIAZEPAM (VALIUM®)

Diazepam was the first benzodiazepine AED used as a drug of first choice in the treatment of convulsive and nonconvulsive status epilepticus, acute repetitive seizures, prolonged seizures, and febrile convulsions, although it has become replaced by lorazepam (*see* Lorazepam) as the principal agent [1]. Diazepam is a highly protein-bound drug (> 90%) and rapidly enters the brain, but due to significant lipid solubility rapidly redistributes into the tissues, resulting in a serum half-life of less than 1 hour with single dosing [2]. Hepatic enzyme induction of the CYP2B occurs with demethylation to nordiazepam (desmethyl-diazepam) with a long half-life of more than 20 hours; temazepam is formed by hydroxylation with a long half-life after conjugation, with renal excretion occurring thereafter. Side effects include somnolence, sedation, fatigue, amnesia, inattention, and respiratory depression. Other difficulties with gait and falls associated with injury may occur in the elderly. Diazepam also causes prominent beta activity on EEG.

Diazepam has several formulations including p.o., i.v., and a rectal gel. The administration of diazepam is an i.v. infusion of 5-20 mg over 2-5 minutes. Problems of precipitation within i.v. bags or tubes merit caution. Diazepam may be given i.v. repeatedly every 20-30 minutes until seizures stop, with the maximal dose in 24 hours. Rectal administration of the gel (0.5 mg/kg) has been effective in adults with refractory epilepsy, and commercial preparations are available for use.

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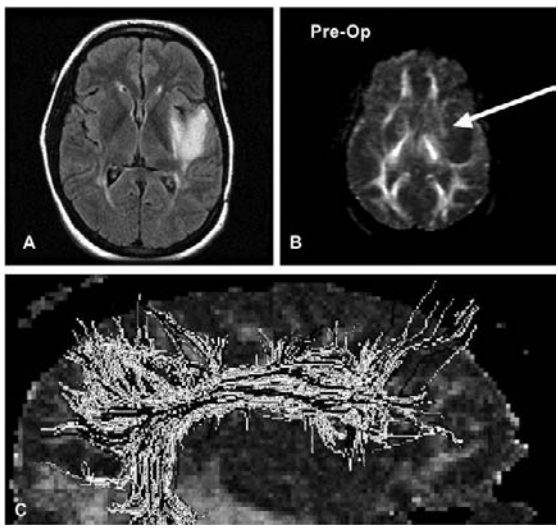
## DIFFUSION TENSOR IMAGING

Diffusion tensor imaging (DTI) is an imaging technique performed on a standard MRI scanner that is more sensitive to white matter injury than conventional brain MR imaging. DTI reflects the myelin integrity in vivo and the inherent properties of the cell membranes of the white matter tracts that restrict the movement of water molecules. Water tends to move preferentially along the horizontal axis of the white matter tracts rather than perpendicular to them (anisotropic diffusion), though the apparent diffusion coefficient (ADC) is the average measure of all directions of water diffusion. The ADC has been considered the surrogate for white matter integrity [1], and DTI may aid in the evaluation of the large fiber white matter tracts. MRI with DTI has the ability to characterize microstructural abnormalities in epileptic foci and to demonstrate the white matte fibers and tracts participating in the epileptic network [2]. This may help further characterize the seizure-induced neuronal injury by revealing the synaptic reorganization and connectivity crucial to understanding what occurs beyond the epileptic focus (*see* Focus) in addition to providing a practical implication to resective epilepsy surgery [2]. Though the technique is still evolving, the affected subcortical white matter has been shown to extend beyond the visible cortical abnormalities in patients with cortical dysplasia in addition to TLE.




(A) Axial T2-weighted brain MRI with left temporal high signal lesion (tumor) that resulted in aphasia and uncontrolled complex partial siezures. (B) DTI performed for preoperative assessment of disruption of the arcuate fasciculus (see arrow). (C) Tractology demonstrating isolation of the white matter tracts. After temporal lobectomy, restoration of the anatomy of the disrupted tract was seen post-operatively on DTI and the aphasia improved.

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## DILANTIN

*see* Phenytoin.

## DIONES (OXAZOLINE-DIONES)

Introduced in the 1940s, the diones (i.e., trimethadione and paramethadione) were the first class of AED to be used in the treatment of typical absence seizures, even though they were frequently associated with adverse effects. They have since been replaced by ethosuximide, valproate, and lamotrigine in the treatment of childhood absence epilepsy due to the greater benefit-to-risk ratio when compared with the poorer safety profile seen with the diones.

## DISCONTINUATION OF AEDs

Approximately 65% of PWE become seizure-free with AEDs. Classification of the epilepsy syndromes is key to the consideration of a trial of AED taper. Discontinuation of AEDs with some of the IGEs (e.g., JME) carry an unacceptable likelihood of relapse, and in these PWEs discontinuation of AEDs is not recommended. Other conditions such as Lennox-Gastaut syndrome almost never achieve prolonged remission with AEDs and are similarly not candidates for discontinuation. On the other hand, some childhood epilepsy syndromes such as benign childhood epilepsy with centrotemporal spikes (BCECTS) almost always achieve remission, and successful discontinuation is anticipated during adolescence even when the interictal EEG remains abnormal [1]. Symptomatic causes appear to carry higher rates of relapse than either idiopathic or cryptogenic etiologies that have a similar prognosis.

Discontinuation of therapy should be considered if patients have been seizure-free for more than 2 years. The likelihood of remaining seizure-free with withdrawal after 2 years as opposed to 4 years appears similar [2], although in some children remission of less than 2 years has been associated with successful AED discontinuation. By convention, slower rates of taper have been utilized. However, evidence of significant difference when comparing a 6-week versus 9-month trial of taper was not found [3]. Certain AEDs (i.e., barbiturates or benzodiazepines) may require longer rates of taper given the potential for withdrawal effects, and abrupt discontinuation should be avoided

with all AEDs given the risk of status epilepticus. After resective epilepsy surgery, successful discontinuation of AEDs may occur in approximately 50-60% of patients and may be considered approximately 2 years following successful operation, with lesional focal epilepsy having a greater success rate than nonlesional cases [4]. Success rates vary, but in well-selected patients overall success rates approach approximately 60-70% over the subsequent 2 years of follow-up.

Counseling patients and families should be undertaken with education about the possibility of the impact of a breakthrough seizure, and they should understand the associated risk. Driving, climbing to heights, swimming alone, or the use of high-voltage electrical or heavy/open machinery should be avoided during a discontinuation of AED and for a reasonable period thereafter. Driving privileges should be restricted according to state policies (e.g., no driving until 3 months after successful taper has been completed). The long-term outcome is not affected adversely when a trial of taper is unsuccessful, and the "nightmare" of controlled epilepsy becoming an uncontrolled one is fortunately rare.

There are also attendant risks of continuing AEDs. Many patients with severe and long-standing epilepsy have endured a gradual increase in AED dosage. Excessive polypharmacy may produce marked side effects and limit the ability to bring a single effective AED to the maximum dose. In this circumstance, one should consider reduction in AED dose over several months. The least effective medication or the most toxic may be chosen as a candidate for initial reduction. Certain patients who have obtained seizure control over a long period of time do not wish to stop treatment. In these instances, potential benefits and risks of medication reduction should be discussed, but patients should not be forced off medications for the sake of principle. Seizure-free patients on AED monotherapy who taper their medication may show improved neuropsychological performance compared to those who continue AEDs, though there is a small risk of psychopathology following AED withdrawal, especially when mood-stabilizing AEDs are utilized [5].

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## DOWN SYNDROME

Down syndrome (DS) is the most frequent chromosomal abnormality causing mental retardation, occurring with an estimated incidence of 1/1,000 live births. Patients with Down syndrome have greater neurologic comorbidities including mental retardation, dementia of the Alzheimer type, hearing deficits, vision impairment, and epilepsy. Seizures occur with greater frequency in those older than 55 years probably due to the early association of DS with Alzheimer's disease. Overall, approximately 5-16% of patients with DS manifest seizures. When seizures occur in children, febrile seizures are rarely observed, and infantile spasms are the primary seizure type seen and may imply a less malignant course than otherwise expected in developmentally normal populations. When seizures occur later in life, generalized tonic-clonic seizures may occur with myoclonus. Reflex epilepsy in the form of startle-induced seizures is more frequent in DS. The EEG typically demonstrates nonspecific slowing of the background, seen in nearly 50% of patients with DS, and is more prominent in the elderly, though interictal generalized spike-and-wave and focal spikes may help characterize the seizure type. Diagnosis is usually straightforward with karyotype analysis and may be acquired antenatally. Treatment with AEDs appropriate for either encephalopathic generalized epilepsy or localization-related epilepsy monotherapy is frequently uncomplicated by DS, though phenytoin should be used with caution, especially in elderly patients with DS due to the potential for side effects even at "therapeutic" serum concentrations.

## DRIVING

There is the potential for danger both to the patient and to others imposed by PWE who drive or operate motor vehicles. Driving is a privilege that is regulated by the individual state or country. The longer the seizure-free duration, the greater the reduction in the risk of motor vehicle accident. Patients with epilepsy have a slight risk for traffic accidents-especially when compared to those associated with alcohol or substance abuse-accounting for approximately 0.04% of all reported motor vehicle accidents [1]. In the United States, there are 7 million car crashes and 3.5 million injury-related crashes per year that has the potential for traumatic brain injury and subsequent post-traumatic symptomatic localization-related epilepsy [2].

Legal restrictions vary from state to state and country to country and have largely been guided based upon duration of seizure freedom. The time elapsed since the last seizure has been used as an index of the likelihood of subsequent seizures. In some places, the required seizure-free interval may be as short as 3 months after the last seizure, and others have been up to 1 year. Trends have developed in the direction of shorter seizure-free intervals and to individualized

clinical features such as allowances for purely nocturnal seizures and a provision to allow prolonged and consistent auras [3]. Commercial driver's licenses are usually regulated under stricter standards than are individual licenses. In most areas it is the obligation of the patient, rather than the physician, to inform the Bureau of Motor Vehicles that a seizure has occurred, but California, Delaware, Nevada, New Jersey, Orgeon, and Pennsylvania still require the physician to report patients that have seizures and/or epilepsy. Reporting has been enlisted to attempt to identify the large number of PWE who do not self-report, though it has been criticized for compromising the physician-patient relationship and felt to be counterproductive overall. An open and frank discussion between patients and doctors may be of greatest value, and physicians should in all cases clearly inform patients of the risks of driving with seizures and document their discussions in the medical record. The American Academy of Neurology has stated their position on reporting and driving and include optional reporting of individuals with seizures, stricter driving and reporting standards for people who provide professional driving services, policy clarification of physician immunity for reporting and nonreporting, as well as promoting safe driving evaluations, public transportation resources, review of the individual laws, and collaboration with other specialties to improve public safety [4].

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## DROP ATTACKS

Epilepsy received early distinction as "the falling sickness" due to the falls that occur with seizures. Drop attacks are seizures that encompass the spectrum of atonic and tonic seizures that ultimately result in fall, frequently with injury. Atonic seizures are generalized seizures with a sudden loss of postural tone that predispose an individual to epileptic falls. Tonic seizures are associated with falls less consistently than atonic seizures, because the leg muscles are often not involved or have an increased extensor tone to maintain an upright posture. Seizures that result in falls are not synonymous with atonic seizures and may also occur with tonic, myoclonic, generalized tonic-clonic, and partial seizures. Myoclonic and atonic seizures often coexist during a single event or individually in the same patient (i.e., myoclonic-astatic epilepsy). Video-EEG monitoring may be necessary in order to classify the individual seizure type.

# DRUG ( NON-AED) POISONING

Seizure emergencies due to drug overdoses account for an almost threefold lesser incidence than those related to alcohol consumption.. The most common agents causing seizures associated with poisoning or drug overdose in a recent retrospective review from a poison control center were bupropion, diphenhydramine, tricyclic antidepressants, tramadol, amphetamines, and venlafaxine [1]. In these cases almost 70% had only one seizure. Drugs of recreational abuse associated with seizures have included cocaine, amphetamines, heroin, and phenylcyclidine (PCP) in addition to methylenedioxymethamphetamine (MDMA) and gamma hydroxybutyric acid (GHB) [2]. Cocaine and the amphetamines increase the release of norepinephrine and serotonin and have a high risk of seizures, possibly due to the associated sympathomimetic effects of the drug. GHB may cause both an intoxicating or withdrawal effect of seizures. Ethanol (*see* Alcohol), benzodiazepines, and baclofen may all cause seizures upon withdrawal, including both oral and parenteral routes of administration. Both the balcofen pump and treatment with the benzodiazepine antagonist flumazenil for benzodiazepine overdose have been associated with seizures. Buproprion, tricyclic antidepressants, selective and serotonin reuptake inhibitors (e.g., citalopram), and serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine) all produce seizures in overdose. Of the antipsychotics, the traditional antipsychotic agents (e.g., chlorpromazine) are more established in producing seizures in overdose, though reports of the atypical antipsychotics (e.g., olanzapine) have also been noted [3]. Of the analgesics, the opioid mepederine (and its metabolite normeperidine) has been associated with myoclonus and seizures, in addition to tramadol and propoxyphene overdoses. The AEDs (e.g., phenytoin and carbamazepine) also have been reported to paradoxically act as proconvulsants in excessive doses, worsening seizures and producing status epilepticus [4]. The treatment of drug- or toxin-associated seizures (*see* Self-Medication and Alternative Medication) includes a detailed history to identify the source following immediate attention to airway, breathing, and circulation. A systematic approach to stabilizing serum chemistries (especially glucose) and acid-base balance is key prior to additional testing, emptying the gastric contents, and enhanced elimination. A specific antidote is used depending upon the source of toxic ingestion. Endotracheal intubation to protect the airway and maintain ventilation and neuromuscular blockade with short-acting agents (e.g., rocuronium) with continuous EEG monitoring may be required in patients with chemically induced seizures that include status epilepticus. Lorazepam is utilized for seizure emergencies, though phenytoin is ineffective or may worsen drug-induced seizures from some agents, such as tricarboxylic acid and ethanol withdrawal, in addition to the systemic effects from its use (e.g., hypotension).

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## DUAL PATHOLOGY

Dual pathology refers to two independent pathologic processes in a PWE. In patients with mesial temporal lobe epilepsy, hippocampal sclerosis is associated with a second lesion in approximately 15-30% of cases [1]. In most cases the additional lesion is developmental in origin and may be extratemporal or even contralateral to the epileptogenic zone. Poorer outcomes are encountered when one of the lesions (hippocampus) is resected in the face of a second persistent lesion (i.e., cortical dysplasia), while resection of both lesions in their entirety produces the best response [2]. When the pathology is a glioma or hamartoma, hippocampal formation atrophy is less robust, and therefore resection of the tumor alone may suffice [3].

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## DUPUYTREN'S CONTRACTURE

Dupuytren's contracture consists of fibrosis and contraction of the palmar aponeurosis; it is occasionally associated with long-term phenobarbital treatment. The contracture may improve with discontinuation of the AED. It may coexist with other connective tissue diseases: plantar fibromas (Lederhosen sydrome), juxtarticular nodules, Peyronie's disease, and scapulohumeral periarthritis ("frozen shoulder").

## DYSKINESIAS

Paroxysmal dyskinesias consist predominantly of oral-buccal-facial dyskinesias, but choreic, athetotic, or ballistic movements of the limbs, which may simulate partial seizures, may appear either unilaterally or bilaterally [1]. There may also be dystonic movements of the trunk and limbs with asterixis. Typically,

the abnormal movements persist from several hours to several days and appear episodically, precipitated by stress, startle, or awakening from sleep [1]. Consciousness is preserved and the movements are uncomfortable. Dyskinesia may be familial and be precipitated by movement (kinesiogenic) It appears most frequently in patients with encephalopathy when high AED levels are reached, but may also be seen in the so-called therapeutic range. Alcohol, caffeine, excitement, and AEDs may exacerbate dystonic choreiform movements commonly associated with athetosis (*see* Choreathetosis, Paroxysmal). Although phenytoin is most commonly mentioned, phenobarbital and carbamazepine have also been implicated, and lamotrigine has been associated with tic.

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# E

## EARLY MYOCLONIC ENCEPHALOPATHY

Early myoclonic encephalopathy (EME) is an age-dependent epileptic encephalopathy. It begins in the neonatal period and may be associated with inborn errors of metabolism. Similar to Ohtahara syndrome, seizures begin in the first 3 months of life, although the onset is usually a little later with EME. Frequent focal seizures predominate in EME, unlike the infantile spasms or myoclonus more common with Ohtahara syndrome, though these seizure types may occur with EME as well. An evolution to infantile spasms has been reported with nonketotic hyperglycinemia when it occurs as the underlying etiology [1]. The EEG may demonstrate nonspecific abnormalities during wakefulness that develop into a nonevolving burst-suppression pattern in sleep. Broad-spectrum AEDs (*see* Treatment) are usually first-line approaches such as VPA and LTG, although the prognosis is dismal, with many dying within the first 2 years of life.

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## EARLY INFANTILE EPILEPTIC ENCEPHALOPATHY (OHTAHARA SYNDROME)

Early infantile epileptic encephalopathy was first reported by Ohtahara with a nonfamilial syndromic title bearing his name to describe the earliest of the age-dependent encephalopathies. Seizure onset is within the first 3 months of life, with many occurring on day 1. Clinically, infantile spasms and hypsarrhythmia are noted on EEG, though focal seizures and rarely other seizure types such as myoclonic seizures may occur. EEG demonstrates a characteristic burst-suppression pattern that may be periodic but is present during wakefulness and sleep. The clinical features as well as EEG demonstrate an evolution of the course of time. Bursts of high-voltage spikes and slow waves are punctuated by suppressions that last for several seconds. The infantile spasms may evolve to the Lennox-Gastaut syndrome. No single pathophysiology is consistently identified and neuronal migrational disorders and other structural lesions, as well as associated syndromes (i.e., Aicardi's syndrome), have been reported. A poor re-

sponse to AED treatment is seen, and progressive deterioration of neurocognitive and neurodevelopmental function is encountered with Ohtahara syndrome. Improvement has rarely been reported with ACTH, and while the long-term prognosis is usually unchanged, treatment with ACTH should be administered as for West syndrome (*see* West syndrome).

## ECLAMPSIA

Eclampsia, a condition that is unique to pregnancy, is characterized by the appearance of seizures or coma (usually after the 20th week), without antecedent neurologic conditions such as epilepsy. Seizures usually occur with preeclampsia, which includes one or more of the following: proteinuria (at least 5 g/24 h), widespread peripheral and facial edema, persistent hypertension above baseline (at least 20 mmHg systolic or 10 mmHg diastolic for more than 4 hours). The clinical presentation may include encephalopathy, headache, seizures, or coagulopathy. Typically, single seizures, acute repetitive seizures, or status epilepticus appears after the 28th week of pregnancy, during labor, or in the 24 hours after delivery. Mortality associated with ecclampsia occurs in 1-2%, with a complication rate of 35% [1]. Eclampsia is no more frequent in epileptics than in nonepileptics and does not increase the risk of developing epilepsy. The pathophysiology is unknown, but hypertensive encephalopathy, cerebral edema, cerebral vasospasm, and loss of cerebrovascular autoregulation are clinical features. Therapy is aimed at delivery of the baby, prevention of arterial hypertension during pregnancy (especially near delivery), and treatment of the seizures using rapidly acting AEDs such as intravenous benzodiazepines and/or phenytoin. In the United States, magnesium sulfate has been widely used by obstetricians for preeclampsia and eclampsia, with a randomized, placebo-controlled trial demonstrating benefit with magnesium sulfate when compared to phenytoin [1]. Continued epileptic seizures or altered states of consciousness may require prolonged EEG monitoring and conventional AEDs for seizure control.

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## EEG (ELECTROENCEPHALOGRAPHY)

Electroencephalography has played an indispensable role in the evaluation of seizures and consists of an amplified electrical signal derived from cerebral neuronal activity. When the EEG reveals a paroxysmsal epileptiform discharge during a behavioral episode, this is diagnostic of an epileptic seizure. Interictal epileptiform discharges (IEDs) consistute the primary means of providing sup-

port for a clinical diagnosis. EEG also provides information regarding classification of the seizure type and syndrome as well as characterizing seizures for the purposes of epilepsy surgery.

EEG rhythms are divided into different frequency bands: delta frequencies are < 4 Hz, theta frequency between 4 and 8 Hz, beta frequencies are > 12 Hz, and alpha frequency includes 8-12 Hz. These divisions help to identify components of the normal mixture of frequencies that typifies the human interictal EEG. Classification into these bands facilitates the determination of normal and abnormal waves in clinical EEG. Since frequency provides one of the important criteria for normality, potentials above 12 Hz are fast waveforms and are usually normal, but waveforms less than 8 Hz are slow waves and are usually abnormal in the adult waking EEG. Interictal displays have digital capability for prolonged recording and easier review and storage.

EEG recordings are of prime importance in patients with seizures and provide information that is useful in the diagnosis, classification, prognosis, and management of patients with epilepsy. However, scalp-based EEG recordings are subject to a number of shortcomings, including recording signals at a point distant from the source leading to signal distortion and limitations seen with propagated patterns from a deep focus that may not reach the scalp. Furthermore, the recording time is limited, and therefore events under investigation might be missed, and ultimately the interpretation of the tracing is subjective and generally nonspecific. A sleep recording is desirable and may show IEDs not seen during wakefulness. To minimize the subjective aspect of EEG interpretation, a widely accepted standardization has been developed, and quantitative measurements are now available. Topographical mapping is visually attractive but is not yet accepted for diagnostic purposes and remains a research tool.

For patients that experience a new onset of seizures, an initial interictal EEG that is normal is common and expected even when clinical epilepsy becomes apparent. Following the first EEG, approximately 30-55% reveals IEDs, and even after several EEGs up to 15% of patients will still not manifest IEDs [1]. However, the presence of IEDs is strongly predictive of subsequent epilepsy in adult patients even with unkown etiologies. The 3 Hz spike-and-wave pattern on EEG is strongly suggestive of IGE, although nonspecific for seizure type. It may less frequently occur during EEG in people without seizures appearing as an inherited trait. When 3 Hz bursts are generalized and regular in distribution and are longer than 3 seconds in duration, clinical signs are suspect. Most IEDs associated with IGE have a 3 Hz or greater frequency, increase in drowsiness and non-REM sleep, and may "activate" with hyperventilation (absence) or demonstrate photosensitivity with intermittent photic flash. Some IED-suppressant AEDs (valproate, ethosuximide, benzodiazepines, etc.) may play a role in accurate recovery and lead to "false-negative" interictal EEGs, especially in generalized epilepsy leading to a delayed clinical diagnosis through lack of electrophysiologic support.

The recovery of focal IEDs may be even less in adults that begin, later in life, the extratemporal epilepsies, during wakefulness or REM sleep, and in pa-

tients with infrequent seizures. Errors of EEG interpretation have led to the erroneous diagnosis of epilepsy in patients with PNES [2]. Nevertheless, lower rates of misdiagnoses have been reported when EEG revealed IEDs as compared to when no abnormalities were seen. Ictal semiology adds additional information to ictal EEG to improve lateralization and localization when semiology and EEG are used together in patients with temporal lobe epilepsy evaluated for epilepsy surgery. Concordance of seizure semiology and scalp ictal EEG is high (95%) when used together to localize seizure onset, while ictal EEG used alone (65%) is significantly less useful [3]. Similar features are seen with seizures that are of extratemporal origin though for more precise localization, invasive EEG may be necessary (*see* Invasive EEG). Dense array EEG is a newer method of recording that utilizes many more electrodes (up to 256) to enhance the spatial resolution of scalp EEG. It may prove useful in noninvasive ictal localization when standard methods fail [4]. Some AEDs may change the clinical semiology, with reduced motor movements, automatisms, and tendency to vocalize during the seizure, and, similarly, greater intensification of seizure semiology, duration, and frequency may be noted on withdrawal from different AEDs.

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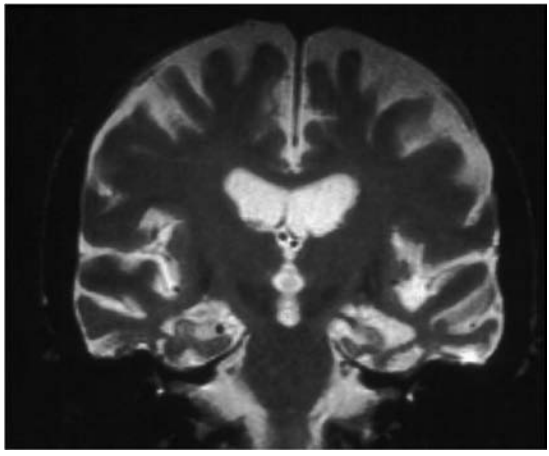
## ELDERLY AND EPILEPSY

Elderly PWE are classified as those at least 65 years of age. The elderly represent the most rapidly growing segment of the population. A second peak prevalence time period, in addition to epilepsy that begins in childhood, occurs in the elderly. Epidemiologic studies of the epilepsies in the community setting demonstrate that the incidence of seizure onset is 52-59/100,000 in the 40- to <60-year age group but more than doubles in those > 60 years of age and older, with an estimated rate as high as 127/100,000 per year. In addition, the overall number of elderly PWE has risen substantially to make this population a significant target for treatment. The elderly residing in institutional settings, such as nursing homes, have an even higher prevalence of treatment targeted toward epilepsy. For the estimated 150,000 (1% of the 1.5 million elderly population) residents in U.S. nursing homes, 10-11% are treated with an AED [1]. Single seizures may carry a higher risk of recurrence given the high predomi-



Coronal brain MRI obtained in a PWE and Alzheimer's disease. Note the prominent amygdalo-hippocampal atrophy bilaterally.

nance of symptomatic seizures in the elderly. Patients with a single unprovoked seizure with a remote symptomatic cause (e.g., stroke) should be treated with AEDs because of the high risk of recurrence. Convulsive syncope, disorders of fluid and electrolyte balance, systemic infections, and drugs all may provoke seizures and do not require AEDs. Seizures of late-life onset are more frequent in males, and those in the 70- to 79-year age group account for the highest prevalence. Partial seizures predominate in this group, with approximately 30% of this population demonstrating generalized tonic-clonic seizures. The cause of seizures is unknown in 25-50%, and stroke accounts for up to 40-50% of cases in the elderly; seizures may also stem from dementia (especially Alzheimer's disease; *see* figure), brain tumor, and brain trauma. Nonconvulsive status epilepticus or serial seizures is not uncommon, and elderly with subtle complex partial seizures without awareness may be undiagnosed for years prior to definitive diagnosis and treatment. Seizures in the elderly, however, are in general mild, infrequent, sometimes isolated events.

Drug treatment may become more complex in the elderly and must always be addressed in the light of multiple medications and health factors. Seniors are especially sensitive to the sedating AEDs, and potential adverse effects upon cognition and gait may have disastrous consequences. In addition, they are increasingly likely to have health problems requiring medications that can interact with their AEDs. Treatment of seizures in the elderly is fraught with potential complications. Because of altered metabolism in the aged, therapy must be modified. Smaller doses of AEDs, AEDs with limited drug-drug interactions, and frequent reevaluation of treatment are helpful because elderly patients are subject to clinical toxicity with polypharmacy and drug interactions. The benefits of the older AEDs include low cost, while those of the newer AEDs include fewer drug-drug interactions and more favorable pharmacokinetic profiles. While phenytoin is the most widely utilized AED, because of its enzyme induction, narrow therapeutic range of tolerability, and nonlinear pharmacokinetics it appears to be a poor choice for the elderly population. Small adjustments in dose and lower doses and serum concentrations may help avert adverse events. Carbamazepine is an effective agent in the treatment of focal seizures, although it produces a higher incidence of side effects in the elderly

than some of the newer AEDs [2]. Adverse effects may become symptomatic (e.g., dizziness) or asymptomatic (e.g., hyponatremia), limiting use. AED or non-AED drug interactions (e.g., warfarin, cimetidine, propoxyphene, erythromycin, ketoconazole) further complicate the treatment of elderly patients who frequently have co-administered polypharmacy. Valproate has the potential for encephalopathy, tremor, and coagulopathy. Phenobarbital should be avoided due to its effects on cognition, behavior, and level of alertness. Newer agents such as levetiracetam, lamotrigine, and gabapentin appear much more desirable agents in the elderly due to their lack of enzyme induction/inhibition, lack of drug-drug side effects, tolerability with respect to cognition and gait, and presumed reduction in increased rates of bone loss and attendant risk of fracture [3]. Epilepsy in the elderly is complex, and the different clinical presentation, altered metabolic function, sensitivity to AEDs, and differential effects of treatment must be kept in mind in the approach to treatment of this rapidly increasing segment of the population of PWE.

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## ELECTROCONVULSIVE THERAPY

ECT is a psychiatric modality of treatment for depression that involves intentionally inducing an electroclinical seizure that may be peformed with unilateral or bilateral stimulation with preferential effects dependent upon the psychiatric condition, although unilateral stimulation may optimize the risk-benefit ratio in patients with refractory depression.

Electroconvulsive therapy (ECT) is a medically acceptable procedure for treatment of severe depression and is not contraindicated in patients with pharmacologically refractory depression. ECT is directly related to epilepsy in several ways: first, ECT is a semiologic model of GTC seizures. Additionally, ECT may be difficult to induce in individuals who are being treated for epilepsy because most of these individuals are on AEDs. Furthermore, the electroshock animal model of epilepsy is a screening procedure for AEDs (*see* Animal Models of the Epilepsies). Therefore, in PWE it may be necessary to reduce or withhold AEDs for a day or two prior to ECT in order to obtain a satisfactory response. The effects of ECT may increase slow 4-8 Hz rhythms on the EEG following treatments, and the short-term increase in theta and delta generally accompanies improvement in depression.

There have been previous concerns that the incidence of epilepsy may occur or increase following ECT, but in clinical studies the influence of ECT on any underlying tendency for epilepsy in clinical practice led to no specific problems and in severe drug-resistant depression may be life-saving. The indications are essentially the same as for those with a primary psychiatric condition.

## ELECTROCORTICOGRAPHY

Electrocorticography (ECOG) refers to the recording of neurophysiologic potentials directly from the brain. ECOG is best appreciated as a technique that is used in the operating room to record EEGs from surgically exposed brain, but it may also be performed extraoperatively. ECOG is composed of the same combination of cortical rhythms found on scalp recording with amplitudes that are 10-fold greater than at the level of the scalp. Spikes are more evident on ECOG than on scalp EEG, and about 25% of patients with TLE have IEDs on ECOG that are not noted on the scalp EEG. Additionally, the area containing IEDs with ECOG is frequently larger than that obtained with scalp recordings. Compared to scalp-recorded IEDs, ECOG-recorded IEDs have greater amplitude (500-1000 μV) and are shorter in duration, sometimes even less than 20 ms [1]. Furthermore, ECOG IEDs may appear in several regions distant from the site of epileptogenicity. Dysplastic cortex often produces a unique pattern of epileptiform abnormalities on ECOG with prominent, widespread IEDs that may be very complex, repetitive, and have polyspike morphology. The evidence to suggest that the preexcision ECOG helps to determine the degree of resection for temporal, extratemporal, lesional, and nonlesional surgeries to provide a favorable clinical outcome has been limited. One case series of pure lesionectomy (normal tissue at the edge of resection) patients reported seizure freedom to be independent of spike distribution or even spike presence on ECOG before or after resection [2]. Another study found no difference with the use of ECOG in patients with temporal lobe epilepsy (TLE), though resection margins may have encompassed the majority of the IEDs [2]. Some locations, such as the posterior parahippocampal gyrus and insular cortex, appear to lack prognostic signifi-

Subdural grid placed over the targeted cortex for determination of ictal onset in a 28-year-old female with extratemporal localization-related epilepsy.

cance when persistent spiking is encountered on the postexcision ECOG. As with the preexcision ECOG, evidence for a beneficial role of the postexcision ECOG in predicting surgical outcome has been inconsistent. Interestingly, in one study of 80 patients with mesial TLE who underwent a resection tailored to remove up to 7 cm of tissue, depending upon the presence of neocortical spikes and eloquent cortex, the presence of neocortical spikes was found to be associated with a more favorable prognosis for postoperative cognitive outcome [3]. Intracranial electrodes surgically implanted in the form of either strips or grids (*see* figure) are capable of performing not only ECOG but also electrical stimulation of the cortex for functional brain mapping.

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## ELECTRODES, SUBDURAL (EPIDURAL)

Subdural electrodes are invasive electrodes used to localize the epileptogenic zone or perform functional brain stimulation studies in the course of treatment for patients with medically refractory LRE. Electrodes may be contained in clear silicone (silastic) with various numbers and sizes of strips and grids to be surgically placed in the epidural or subdural space for intracranial recording. Stainless steel or platinum alloys are the principal compounds composing the electrodes. A grid of electrodes is placed over areas of cortex thought to contain the seizure focus. Commercially available "strips" and "grids" usually contain 2-8 contacts and grids with 4-64 electrodes commonly 5 mm wide and separated by 1 cm for continuous or intraoperative EEG recording over days. Subdural electrodes (epidural electrodes are not used for stimuation) can be used to provide information about "eloquent" brain function (i.e., by demonstrating language, motor, sensory, or visual cortex) by means of electrical stimulation of cortex at the lesion. Depending on the requirements of a particular patient, a certain number of electrodes, grids, or electrode strips may be passed through a bone flap or burr hole and placed over one lobe, one hemisphere, or on several lobes of both hemispheres. Structural lesions (e.g., cortical dysplasia) may be amenable to analysis with subdural electrodes when the cortex is accessible to electrode placement. In one study, bilateral interictal EEG abnormalities, incomplete resection of the ictal onset zone, ictal onset at the edge of a grid, as well as multiple semiologies were predictors of seizure recurrence after epilepsy surgery [1].

The results obtained with invasive subdural or epidural electrodes are more precise, given the limitations of scalp EEG, due to allowing precise evaluation of hemispheric convexities and some areas in cerebral fissures. In expert hands, there are few complications (e.g., infection or hemorrhage). In some cases, the epileptogenic zone may be less accessible to surgical placement (i.e., the amygdala and hippocampus). Thus, stereoencephalography EEG obtained with depth electrodes may be required to access deeper targets where both neocortical and depth electrodes are used together to provide the best "coverage" of the structures and greater likelihood of identifying the epileptogenic zone. In some cases, detection of the epileptogenic zone may be identified with depth electrodes and not subdural electrodes with less accessible and more limited fields of ictal onset [2].

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## EMPLOYMENT

The economic costs of epilepsy for society are largely due to the indirect costs that accrue through loss of employement. Lost wages account for 85% of all epilepsy costs [1]. Newly diagnosed epilepsy does not seem to affect employment rate, but ongoing uncontrolled seizures are associated with a higher level of unemployment [2]. While the 1990 Americans with Disabilities Act was designed to combat discrimination for health reasons in the workplace, many individuals have described prejudice in the workplace that contributes to unemployment (*see* Workplace Issues). In addition, persons with epilepsy may not have the same opportunities to find employment as others. Issues involving transportation greatly hamper access to employment, although individual state requirements exist to approve licensure that permits one to safely operate a motor vehicle. Those with uncontrolled seizures are unable to obtain an operator's permit for a motorized vehicle, and those with controlled seizures may face substantial obstacles when pursuing a commercial pilot's license or commercial driver's license to operate a truck. Work near or in bodies of water or near high-voltage electrical outlets or heavy machinery may be greatly limited for seizure sufferers.

Despite problems during schooling, patients with epilepsy in childhood may have normal professional development, although scholastic success usually determines the ultimate level of employment. Most patients with epilepsy are able to work full time, but in almost 50% of patients the level of skill required at the job is often less than the patient's potential. There are frequent job changes requiring decreasing levels of skill and job terminations because

of the occurrence of seizures in the workplace. Reasons for employment problems include seizures, subnormal IQ, poor neuropsychological test results, lack of self-confidence, diminished motivation at work, social ostracism, behavioral problems, and lack of initial professional qualifications. Adaptation by both the employee and the employer may therefore be more challenging. Fortunately, accidents in the workplace are no more frequent in patients with epilepsy than in persons without epilepsy. To promote the appropriate occupational match, patients should be individually evaluated for particular employment opportunities using psychological, aptitude, and workplace assessments. A scale for occupational levels of risk has been developed by Goodglass et al. [3]:

- **Low risk:** risks are kept at a minimum, focusing in on work at home, or in a protected environment away from machines or moving parts. Immediate access to care exists when seizures arise. Work is performed under conditions in which brief interruptions that might be caused by seizures do not affect productivity.
- **Moderate risk:** jobs requiring interactions with the public. Patients may have a supervisory responsibility as long as continuous surveillance is not an integral part of the work.
- **High risk:** for work at heights, involving a driver's permit (not for an airplane, bus, or other means of public transport), and for jobs requiring responsibility for the security and well-being of others.

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## ENCEPHALITIS (VIRAL)

Encephalitis refers to an acute inflammatory process of the brain parenchyma due to direct (viral) infection. The clinical presentation often includes fever, altered mental status, focal neurological deficits, and seizures. Encephalitis may cause seizures in two clinical contexts: first, in the acute phase of the illness, regardless of age or vector involved, and second, after a variable latent period. Viral encephalitis is reported to account for up to 13% of childhood epilepsies and 5% of adult epilepsies. Seizures occur during the course of encephalitis in 10-20% of patients, and the risk of epilepsy is twofold greater if seizures supervene in the acute symptomatic phase. Epilepsy generally follows directly after the illness, but occasionally occurs months or as much as 5 years before the onset of seizures. With either early or late sequellae of encephalitis, partial-onset seizures predominate.

Specific viral diagnosis can be achieved by demonstrating viral nucleic acid in the cerebrospinal fluid (CSF) or by isolating the virus in brain tissue, though 30-60% remain undiagnosed [1]. Chronic viral infections include latent viral infections with acute exacerbations in which the virus often cannot be isolated (e.g., herpesvirus). The herpes simplex virus is the most common form of encephalitis associated with seizures. Progressively worsening headache, mental status changes, and fever occurs with complex partial seizures, and secondarily GTC seizures, which implicate a febrile illness involving the cerebral cortex. The herpesvirus has a predilection for the temporal lobe and the propensity for developing seizures is therefore not surprising (*see* Herpesvirus). Polymerase chain reaction (PCR) techniques have significantly improved viral detection for individual virological diagnosis [2]. Equine encephalitides as well as St. Louis encephalitis may also manifest focal seizures. There are also chronic viral infections that may produce encephalitis, such as cytomegalovirus (CMV), Epstein-Barr virus, hepatitis B virus, measles, and varicella virus. Late seizures remain more poorly characterized relative to their frequency, course, and prognosis [1]. Slow virus infections may produce seizures associated with encephalitis and may be responsible for progressive deterioration such as subacute sclerosing panencephalitis and other prions. Additionally, other forms of limbic encephalitis have been reported to produce mesial temporal sclerosis, which may be amenable to surgical therapy when seizures become intractable to AED treatment (*see* Mesial Temporal Sclerosis).

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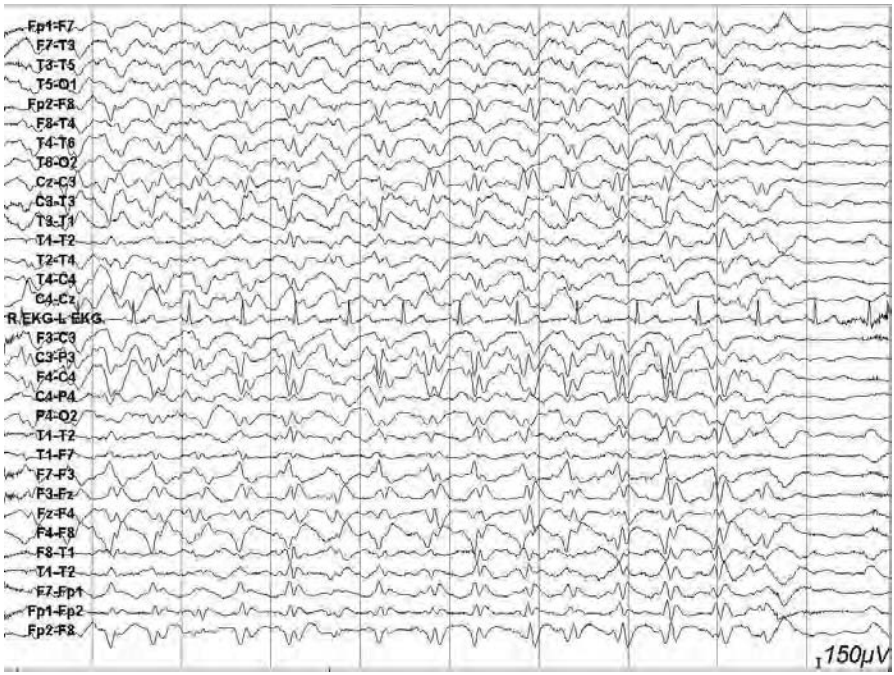
## ENCEPHALOPATHIC (SYMPTOMATIC) GENERALIZED EPILEPSY

The symptomatic generalized epilepsies, in contrast to idiopathic (primary) generalized epilepsy, are a distinct classification used to refer to a number of epilepsy syndromes associated with diffuse structural injury of the brain. Because the symptomatic (encephalopathic) generalized epilepsies are often associated with chronic static encephalopathies, the term encephalopathic generalized epilepsy has also been used to describe epilepsies associated with diffuse structural injury of the brain with seizures, including tonic, atonic, atypical absence, and myoclonic seizures among other partial and generalized seizure types [1]. Notable symptomatic generalized epilepsies include the West and Lennox-Gastaut syndromes. Symptomatic generalized epilepsies are secondary to diffuse structural brain injury and as such have been referred to in the past as secondary generalized epilepsy, though the latter term has been




Slow spike-and-waves at 2 Hz characteristic of the interictal EEG findings in a patient with encephalopathic generalized epilepsy (Lennox-Gastaut syndrome).

abandoned due to the confusion with secondarily generalized seizures, which begin focally and evolve to a convulsive seizure. The EEG has included slow spike-and-waves (*see* figure) as well as diffuse slowing of the background, multifocal independent spike discharges, and generalized paroxysmal fast activity, which may or may not be associated with tonic seizures in encephalopathic generalized epilepsy.

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## ENCEPHALOPATHY

Encephalopathy is a general term that refers to any diffuse cerebral dysfunction, most of which are secondary to the systemic effects of toxic-metabolic, hypoxic (anoxic), degenerative, infectious, inflammatory, or neoplastic causation. Seizures may appear during the course of these disorders, usually in the early stages, and are manifest as convulsive or nonconvulsive seizures precipitated by the underlying pathophysiologic process. Epilepsy may result from

progressive or static encephalopathies when an underlying substate is fixed and capable of epileptogenicity (i.e., hypoxic or degenerative origin). Epilepsy may dominate the clinical picture to an extent such that the term "epileptic encephalopathy" may be utilized, as has been the case with patients who have very refractory epilepsy such as West and Lennox-Gastaut syndrome.

## ENDOSCOPY

There are a few reports of neuroendoscopy used to surgically treat patients with epilepsy. Stereotactically guided endoscopic procedures to visualize intraventricular structures have been performed during resective and disconnection procedures from an intraventricular approach. Surgical resection of hypothalamic hamartomas has probably best been evaluated with the use of endoscopic radiofrequency ablation during ventricular endoscopy [1]. Successful outcomes have been described in a very small number of patients undergoing the procedure, and it has been reported to be an effective adjunct even following unsuccessful open surgical procedures [1].

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## EPIDEMIOLOGY OF THE EPILEPSIES

Descriptive epidemiologic studies have provided information regarding frequency, clinical expression, distribution, incidence, prevalence, and mortality rates of the epilepsies [1,2]. These studies enable assessment of the susceptibility of an individual to the disease and lead to possible hypotheses regarding risk factors. Analytic epidemiology is used to confirm hypotheses based on results obtained from descriptive epidemiology. It enables the determination of risk factors for the appearance of epilepsy. Further strategies can then be developed for cost-benefit assessment, evaluation of the effects of therapy, research, patient and family education, teaching, etc. Disparate results obtained in different studies of epilepsy may be the result of the inherent bias of patient selection in the individual epidemiologic study. Distinguishing the individual measures in PWE includes elucidating the precise definition of epilepsy, the means by which seizures were identified, the source of the study population (e.g., community vs. epilepsy centers), and the means of identifying and stratifying the seizure types relative to including febrile and afebrile seizures, symptomatic and cryptogenic epilepsies, single and recurrent seizures, and those with acute symptomatic seizures and unprovoked seizures—all of which are important characteristics that may lead to discordant results.

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# EPILEPSIA PARTIALIS CONTINUA

Epilepsia partialis continua (EPC) constitutes a continuous epileptic seizure type identified in the proposal for a newer diagnostic classification system of epileptic seizures (*see* Classification) [1]. EPC is a form of focal motor status epilepticus with preserved consciousness. It typically starts as somatomotor simple partial seizures, but may evolve to persistent segmental myoclonus. Initially described in by Kojewnikow in 1894, EPC (Kojewnikow's syndrome) was described after cases of Russian spring-summer tick-borne encephalitis resulted in muscular contractions that affected a restricted part of the body over a prolonged period of time. Focal clonic or myoclonic semirhythmic muscular contraction is limited to somatomotor seizures, which usually involve the distal musculature (hand, shoulder, or hemifacial). The frequency of the jerks may be 1-2 Hz, and the EPC may last for months or years. The epileptogenic zone represents a LRE that often involves the perirolandic cortex but may also involve the sensorimotor cortex; it can be seen at any age and be symptomatic due to circumscribed lesions of various causes (tumor, trauma, stroke, infectious, demyelinating, etc.). The clinical picture, additional seizure types (e.g., GTC), seizure manifestations (e.g., seizures with "jacksonian march") and prognosis are dependent upon the underlying lesion.

EPC type I has focal pathology of the rolandic cortex and EPC type II as a diffuse unilateral encephalitic process [2]. Several focal or multifocal abnormalities affecting the motor cortex can cause EPC. In children, EPC usually results from an infectious source, but it also may occur with congenital brain malformation or migrational disorders of cortical development. An encephalitic form of EPC may also occur in childhood as a part of a progressive syndrome due to chronic focal encephalitis (*see* Rasmussen's Encephalitis). Common causes in adults are strokes, hemorrhagic cerebrovascular disease, and tumors, though metabolic (e.g., diabetic ketoacidosis) and genetic causes (e.g., mitochondrial cytopathies) may also be associated with EPC. The EEG in EPC may be normal and demonstrate focal slowing or focal IEDs (including PLEDs) depending upon the location and size of the epileptogenic zone.

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# EPILEPSY

Epilepsy is defined as two or more unprovoked seizures, although the diagnosis may become apparent after initial presentation of a single seizure where the risk for recurrence is high. Some seizures never present after a single seizure, such as those PWE and absence or myoclonic seizures. Epilepsy is the world's most common serious neurologic disorder, affecting approximately 50 million individuals worldwide, with 25% unable to be controlled despite treatment [1]. Within North America, more than 2.5 million persons have recurrent unprovoked seizures with an incidence of 50 persons per 100,000 per year or a prevalence of 5-10/1000 people [1]. Epilepsy is a chronic disorder of the cerebral cortex with various etiologies characterized by recurrent seizures due to an excessive paroxysmal discharge of cortical neurons, associated with a variety of semiologic manifestations. A single seizure and acute symptomatic seizures during an acute illness or acute injury therefore are not synonymous with epilepsy. Epilepsy is thus defined as a disorder in which repeated seizures arise spontaneously in the same patient. Having more than two seizures carries a high risk of ongoing seizures [2], and though some patients with single seizures have a high risk, epilepsy is arguably evident when two unprovoked seizures occur. For many people seizures represent not only a clinical disorder that requires medical care, but also a condition with an important stigmatizing social impact [3]. Dating from ancient history, apileptic seizures have been linked to religion and have represented a "sacred disease." Today however, misperceptions about epileptic seizures have been perpetuated by the public perception of the "grand mal" seizure as the sine qua non for epilepsy, creating continued misconception. In the media and film industry, seizures have been portrayed as convulsions, with patients "foaming at the mouth" in *The Andromeda Strain*, exhibiting demonic possession in *The Exorcist*, and with psychiatric association in *A Beautiful Mind* to impart a negative connotation for PWE. For many people, seizures produce an even greater adverse reaction than other stigma-provoking conditions, including psychiatric conditions and HIV. Still, there exists the misperception by many Americans that seizures are a form of mental illness or that they may be contagious. For PWE, recurrent seizures have a significant adverse effect upon the quality of the individual's lifestyle—impairing driving, employment, socialization, and cognition [4]—that extends far beyond the independent impact of the medical treatment.

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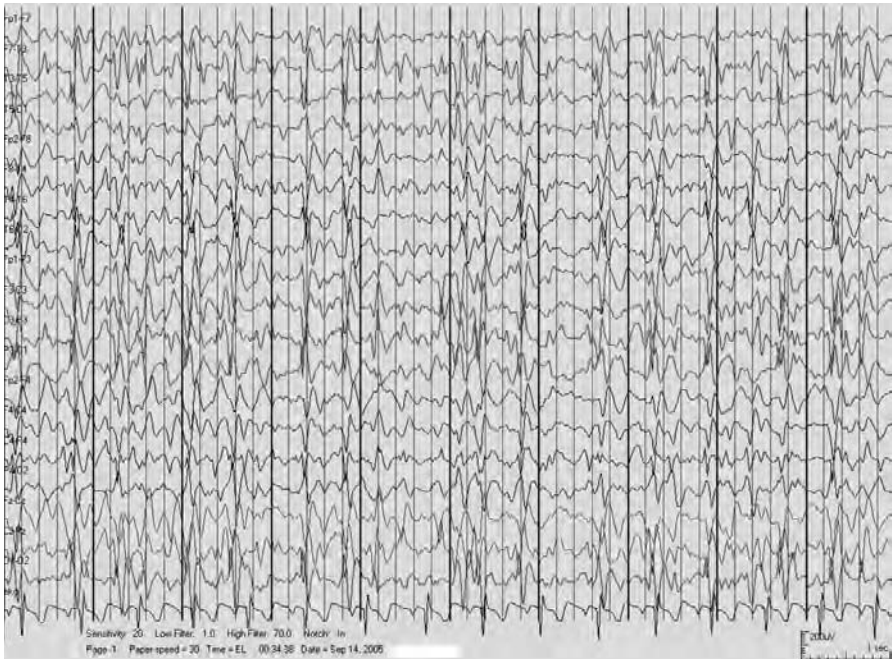
# EPILEPSY WITH CONTINUOUS SPIKE WAVES DURING SLOW SLEEP (ELECTRICAL STATUS EPILEPTICUS DURING SLOW SLEEP)

Continuous spike waves of slow sleep (CSWS) is an epileptic encephalopathy that has clinical features of cognitive and behavioral disturbances that are temporally related to nearly continuous spike-and-wave epileptiform discharges recorded on EEG during slow-wave sleep. Electrical status epilepticus of slow sleep (ESES) has been applied to the EEG abnormalities that include continuous or nearly continuous runs of bilateral synchronous spike-and-wave epileptiform discharges that occur during slow-wave sleep, while CSWS has been defined by both ESES and the clinical features associated [1]. CSWS is rare, with an incidence of 0.5%, and occurs in children around 4-14 years of age with neuropsychological and behavioral disorders. CSWS shares some common features with Landau-Kleffner syndrome (LKS) and probably represents the clinical continuum that includes age-specific electroclinical syndromes that initially appear in childhood, from milder forms of epilepsy (e.g., BCECTS) to those with more severe neuropsychological difficulties (e.g., CSWS and LKS). While language disorders have been well documented with LKS and neuropsychological deficits with CSWS, language can also be altered in CSWS. While the exact nature and severity of the impairment related to this syndrome has been poorly understood, a unique profile including specific dysfunction of pragmatic language and conservation of oral comprehension may be more associated with CSWS [6]. The clinical features include neuropsychological impairment that represents a global loss of cognitive milestones following normal development. Associated language deterioration occurs with expressive difficulties in a subset. Motor impairments may also occur, and seizures are not the major features of CSWS. Focal or generalized seizures occur most frequently during sleep, though multiple seizures types including absence, drop attacks, and myoclonic seizures may also occur between 3 and 5 years, often before the diagnosis is solidified. Seizures remit between the ages of 10 and 15 years, and spike-and-slow wave discharges disappear between 8 and 13 years. Marked neuropsychological abnormalities with language problems have been noted, especially with a previous history of psychomotor retardation.

Spike-and-slow wave discharges occur typically as bilaterally synchronous and symmetrical 1.5-2.5 Hz high-amplitude discharges in prolonged runs dur-



Electrical status epilepticus demonstrated on an overnight recording in a 9-year-old boy with LKS. (From Tatum WO, Husain AM, Benbadis SR, Kaplan PW, eds. Patterns of Special Signficance, In: Handbook of EEG Interpretation. New York: Demos Medical Publishing, 2008:146.

ing slow-wave sleep. Spike-and-slow wave discharges should be seen during 85% of slow-wave sleep (ESES) and persist for three or more recordings for longer than 1 month (*see* figure). The epileptiform discharges are most pronounced during the first cycle of sleep, and the activity disappears during rapid-eye-movement sleep. Aside from the striking EEG epileptiform abnormalities, normal electroencephalographic sleep patterns are preserved.

The differential diagnosis includes benign partial epilepsies of childhood, especially when centrotemporal spike-and-slow wave discharges increase during slow-wave sleep, and atypical forms of benign partial epilepsy without cognitive impairment are difficult to distinguish from this syndrome. The Lennox-Gastaut syndrome may have similar features, particularly when atonic seizures and neurocognitive problems prevail. LKS of acquired epileptic aphasia can present a diagnostic challenge with an overlap of the clinical and electrographic features of ESES (*see also* Aphasia, Acquired Epileptic).

Treatment with a team of neuropsychologist, speech pathologist-therapist, and pediatric neurologist is best for a multidisciplinary approach. Clinical seizures are usually responsive to appropriate AEDs, but none of the standard AEDs are consistently effective in ESES. Limited efficacy with steroids has been achieved, and a trial of oral steroids for 6-12 weeks has been suggested in children with CSWS or LKS who manifest a progressive encephalopathy, ESES,

and seizures, and has been reported to diminish spike-and-slow wave activity and improve language functions [1]. A child with uncontrolled seizures and progressive language or cognitive impairment not responding to steroids and AEDs should be evaluated for multiple subpial transaction of the epileptogenic cortex.

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## EPILEPSY WITH MYOCLONIC ABSENCES

Epilepsy with myoclonic absences (EMA) is a rare childhood disorder accounting for 0.5-1.0% of all epilepsy syndromes. It is classified as one of the generalized epilepsies, although it is indistinct in regard to the cryptogenic or idiopathic mechanism, with clinical features of both. Myoclonic absences are a rare seizure type. Infrequently, other seizures types such as GTC seizures may coexist. A male predominance is in stark contrast to the female predominance in childhood absence epilepsy. A family history may be present. Learning disabilities and mental retardation are common with EMA. The seizures are characterized by absence seizures associated with strong, rhythmic, bilateral, generalized myoclonic jerks and a variable degree of alteration in the level of consciousness. The myoclonic jerks involve the shoulders, arms, and legs. The face is less prominently involved, with signs most readily seen around the eyes and mouth. They may awaken the patient from light sleep and occur with urinary incontinence. There is often a diffuse increase in tone during the seizure as well. The seizures are accompanied on EEG by a 3 Hz generalized spike-and-slow wave pattern that is bilateral, frontally predominant synchronous and symmetric, similar to typical absence seizures. The background electrocerebral activity is normal. While the age of onset may be approximately the same as for CAE, the response to treatment is much less favorable. Treatment with valproate has proven most useful, although a combination of valproate and ethosuximide, lamotrigine, as well as the newer broad-spectrum AEDs may be tried [1].

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## EPILEPSY WITH MYOCLONIC-ASTATIC SEIZURES

Epilepsy with myoclonic-astatic seizures (EMAS) was initially described by Doose [1]. It represents 1-2% of all epilepsies, with onset before 9 years of age.

The disorder may be preceded by febrile seizures, beginning about 2-5 years of age as frequent sudden drop attacks, often resulting in injury. In the typical syndrome the drop attack may result from a sudden myoclonic jerk or abrupt loss of muscle tone or a combination of both. Myoclonic or myoclonic-atonic (or astatic) seizures are seen in 100% of patients, with varying intensity from slight head nods to knee buckling to sudden drops to the ground. The myoclonic seizures are characteristically brief, symmetric jerks of the arms and upper body with enough force often to evoke a fall. A prominent feature is the quick recovery of normal consciousness after the seizure. Other seizure types may be present, including GTC seizures, tonic seizures, and status epilepticus. Initially the interictal EEG may be normal or have intermixed theta. Irregular generalized slow spike-and-wave discharges may appear, principally during sleep or sometimes during ictal recordings. The heterogenous nature of the disorder is reflected in the varying prognosis. Poor prognostic features include early age of onset (< 1 year), asymmetric GTC seizures, myoclonic status, abnormal neurologic examination, and nocturnal seizures [1]. Similarly, treatment responsiveness has been variable with broad spectrum agents including valproate, lamotrigine, topiramate, felbamate, zonisamide, and the benzodiazepines used as initial AED approaches.

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## EPILEPTIC ENCEPHALOPATHY

Epileptic encephalopathy is an older term that has been used in reference to the symptomatic generalized epilepsies (West syndrome and Lennox-Gastaut syndrome) in which the seizures are associated and contribute to other severe neurologic impairment, including cognitive dysfunction. Newer terminology, including encephalopathic generalized epilepsy, serves to classify and provide functional description of the symptomatic generalized epilepsies. Temporal lobe epilepsy has been described as a progressive condition (*see* Temporal Lobe Epilepsy) due to encephalopathic features associated with epilepsy that commonly include memory dysfunction in addition to alteration in concentration, attention, and speed of mental processing.

## EPILEPTOGENESIS (SECONDARY)

The hypothesis underlying this concept involves the repeated bombardment of normal cortex by discharges from a focal epileptogenic lesion or primary focus, which eventually produces a secondary epileptic focus—this, in turn, becomes independent. This hypothesis is supported by the finding of an electrographic "mirror focus" in the homologous hemispheres in animal models, the appear-

ance of secondary bilateral synchrony on the EEG in humans, and the experimental epilepsy model of kindling (*see* Kindling). Primates have demonstrated secondary epileptogenesis, and arguments in favor of secondary epileptogenesis in humans have been evolving [1]. PET (*see* Positron Emission Tomography) has been used to show evidence of the existence of secondary epileptogenic foci in human epilepsy, with persistently larger areas of the brain being incorporated in the the neural networks involved with seizure generation [2]. Concern regarding the potential for secondary epileptogenesis underlies the urge for prompt surgical treatment of medically intractable LRE before it becomes established in the contralateral hemisphere. The frequency with which a secondary epileptogenic zone might be generated is unknown.

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## ETHOSUXIMIDE (ZARONTIN®)

Ethosuximide (ETH) is a succinimide (as are methsuximide and phensuximide) with the greatest efficacy and least toxicity in this class of AEDs. It has been used as a first-line AED in the treatment of typical absence seizures since its introduction in 1958, replacing the diones (*see* Diones). ETH may be used as the AED of first choice in young children, though as puberty approaches the risk of GTC seizures increases, and VPA subsequently becomes the AED of first choice. ETH may be used as adjunctive treatment of typical or atypical absence when monotherapy is ineffective, but it is ineffective in focal seizures. ETH may enable clinical seizure control in up to 80% of cases, and in early studies 95% had at least a 50% reduction in seizures [1]. It has little or no activity in other types of seizures. In animal models, it is more effective against pentylenetetrazol-induced seizures than maximal electroshock seizures.

The bioavailability of ETH is 96-100%, and peak plasma levels are obtained 3-7 hours after oral administration. The drug is not significantly bound to plasma proteins. The half-life of ethosuximide is 40-60 hours in adults and 30-40 hours in children [2]. Despite this long half-life, the drug is often given in divided doses to minimize gastrointestinal side effects, but it can be given once a day. The volume of distribution is 0.7, and the drug causes very little hepatic enzyme induction, though ETH undergoes extensive hepatic metabolism by the CYP isoenzyme system. Steady-state levels are achieved in about 1 week for children and almost 2 weeks for adults. Drug interactions have been clinically limited by ETH affecting other AEDs (except reducing VPA), but the effect of EIAEDs may reduce the concentration of ETH. The use of isoniazide increased ETH, and rifampin reduced ETH when they were used together.

The most commonly encountered side effects of ETH include dose-dependent gastrointestinal problems, and nausea, vomiting, diarrhea, anorexia, and abdominal discomfort may be noted at initiation. Other side effects include headache, dizziness, nervousness, irritability, fatigue, behavioral changes, and confusion. Seizure exacerbation has rarely been described, with myoclonic, GTC, and tonic seizures occurring singly or in clusters. Idiosyncratic side effects include rash, arthralgias, and a lupus-like syndrome and blood dyscrasias including eosinophilia, neutropenia, and rarely pancytopenia [3]. Acute psychotic episodes have been reported, including forced normalization when seizure control has occurred with the use of ETH [3].

In children, a starting dose of 15 mg/kg titrating to 40 mg/kg/d, titrated to a serum concentration of 40-100 (g/mL, should be optimized to achieve seizure control. In older children and young adults, capsules of 250 mg (or syrup with 250 mg/5cc) are available to increase in increments every week up to a target of 750 mg/d or optimized until the desired response is achieved.

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## ETIOLOGY

Etiology may be divided into epilepsies due to genetic (*see* Genetics) and acquired causes and those due to a combination of both, which contribute to the predisposition of recurrent seizures. Genetically determined (idiopathic) epilepsy syndromes appear at particular ages and are not associated with an identifiable cerebral pathology. Nevertheless, even in genetically transmitted epilepsies, previous cerebral injury favors clinical expression. Acquired epilepsies (e.g., posttraumatic epilepsy) and acute symptomatic seizures (e.g., alcohol-related seizures) may be more likely to occur in genetically predisposed individuals. Acquired factors that predispose to epilepsy include a large number of various cerebral injuries as well as many systemic disorders. Clinicians must determine the contribution of a possible predisposing factor to the epilepsy, although many cases may be multifactorial. A few etiologic factors for epilepsy are listed below, though the list is not all-inclusive. In all age groups, the etiology of epilepsy often remains undetermined.

- *Neonatal*: Perinatal injury, hypoxia, hypoglycemia, hypocalcemia, pyridoxine deficiency, and intraventricular, intraparenchymal, or subdural hemorrhage.
- *Children*: Perinatal injury, developmental malformation, febrile seizures, stroke, vascular malformations, head injury, infections, brain tumors,

amino acid disorders, urea cycle disorders, gray matter storage diseases.

- *Adults*: Trauma, tumor, substance abuse or drug withdrawal, drug reactions (stimulants, antihistamines, tricyclics, phenothiazines, butyrophenones, certain antibiotics, aminophylline), CNS infections, stroke, intracranial hemorrhage, vascular malformations, and systemic/metabolic derangements. With new-onset seizures of adolescent onset, trauma is a primary consideration, while in the middle years there is a high risk for neoplasm, and in the group over 65 years for underlying cerebrovascular disease and dementia as a cause.

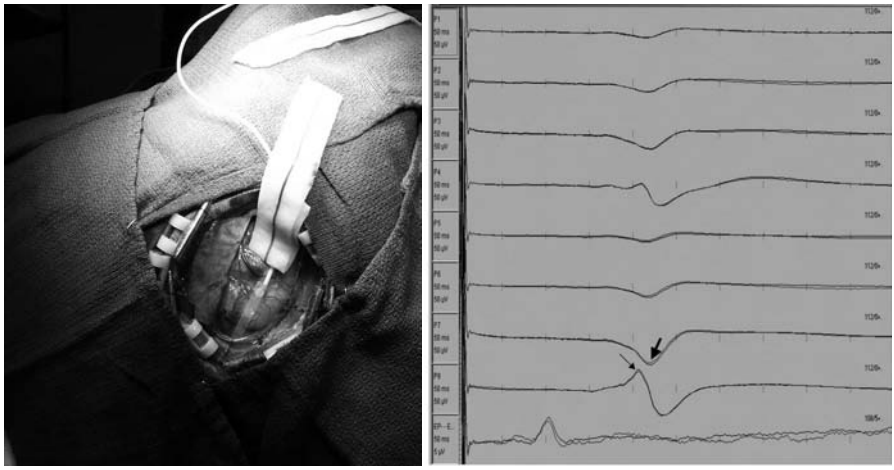
The Classification of Epileptic Syndromes distinguishes between certain epilepsies:

- Idiopathic epilepsy is associated with certain characteristic EEG abnormalities and may be localization-related (e.g., benign childhood epilepsy with centrotemporal spikes) or generalized (e.g., juvenile myoclonic epilepsy). These are the genetic (*see* Genetics) epilepsies that are either presumed or established.
- Symptomatic epilepsy may be symptomatic localization-related (e.g., cerebral palsy due to a perinatal stroke) or symptomatic (encephalopathic) generalized epilepsy (e.g., Lennox-Gastaut syndrome). Symptomatic epilepsy results from a progressive brain lesion or the nonprogressive sequela of any previous injury (e.g., remote symptomatic cause). The etiology is considered symptomatic when there is an identifiable condition that is responsible for epilepsy (e,g,, neuronal migrational disorder).
- Cryptogenic epilepsy may manfest as either focal or generalized seizures without a demonstrable genetic or known acquired cause. The designation may be indistinct in that overlap may appear in certain syndromes between idiopathic and cryptogenic (e.g., GEF+).

A diagnosis of idiopathic epilepsy is based on particular electroclinical characteristics. If a patient does not fit this picture and does not have a clear history of previous cerebral insult, a CT or MRI scan may reveal a potentially epileptogenic lesion. If none is found, the epilepsy is referred to as "cryptogenic." If the seizures are seen in a particular context, the history, clinical examination, and investigation for toxic or metabolic disturbances will help clarify the situation. There is a subtle but important distinction between idiopathic epilepsies and cryptogenic epilepsy believed to be secondary to a lesion not yet identified, which may be clarified as technology advances in the future.

## EVOKED POTENTIALS

Evoked potentials are electrophysiologic modalities where an electrical stimulus is applied to the nervous system to result in an evoked response. Evoked potentials may involve the sensory or motor system and be useful both in and outside the operating room. Evoked potentials are generated with different sensory stimulation to generate evoked responses during visual, auditory, or



(A) An 8 contact subdural strip placed perpendicularly over the central sulcus for motor strip mapping. (B) Intraoperative median nerve somatosensory evoked potentials localizing the motor strip between channels 7 and 8 illustrated by phase reversals between N20 and P22. (From Tatum WO, Husain AM, Benbadis SR, Kaplan PW. Handbook of EEG Interpretation. New York: Demos Medical Publishing, 2008:243.)

peripheral nerve stimulation. Somatosensory evoked potentials (SSEPs) are responses evoked from the large-fiber sensory pathways. Static use has been used to demonstrate conduction delays and infrequently in the diagnosis of epilepsy. However, in the progressive myoclonus epilepsies, SSEPs have been used for diagnostic purposes to show a "giant" cortical evoked response recorded in the central regions after contralateral median nerve stimulation. Therapeutic doses of AEDs do not alter evoked potential latencies. Dynamic use has been employed during resective epilepsy surgery and in the operating room to identify and "map" the motor strip.

During contralateral median nerve stimulation, a phase reversal of the N20/P20 waveforms is seen between the electrodes directly over the motor cortex. Motor evoked potentials are used to demonstrate the integrity of the corticospinal tracts and are frequently used as one modality during spine surgery. Because the cortex is electrically stimulated transcranially with responses over the spinal cord, peripheral nerves, or commonly muscles, caution is advised in patients with epilepsy who are subjected to transcranial motor evoked responses.

Longer latency "cognitive" evoked potentials may be measured, and numerous studies using scalp and depth electrodes provide evidence of widespread long-latency positive and negative waves generated above the brainstem. The P-300 is a symmetric midline positive potential with a latency of approximately 250-600 ms produced by a number of modalities, including the presentation of unpredictable, infrequent stimuli. A hippocampal origin has been postulated. The absence of P-300 is reported to be a predictor of structural or functional abnormalities of the hippocampus in patients with epilepsy originating in the temporal lobe.

## EVOLUTION OF EPILEPSY

The evolution or progression of epilepsy in a particular individual is highly variable and difficult to predict at the onset. However, several patterns can be identified. Single seizures, either acutely symptomatic or cryptogenic, may remain as clinically isolated events [1]. In addition, some epilepsy syndromes have been clearly identified as benign (*see* Benign Epilepsy) due to the infrequent and nonpersistent clinical course. For example, the idiopathic epilepsies of childhood (e.g., benign childhood epilepsy with centrotemporal spikes) may remit and be "cured" by the end of puberty in most cases. Seizures may remit with AED treatment and not reappear when treatment is stopped (*see* Remission; Prognosis), or seizures may respond to AED therapy but reappear when therapy is stopped (e.g., juvenile myoclonic epilepsy [JME]) [2]. Thus the evolution may be predicted by establishing the syndromic classification and responsiveness to AEDs. Finally, up to one third of patients may have seizures that persist despite aggressive AED treatment and represent AED-resistant or medically intractable epilepsy [3]. These different patterns of evolution reflect the heterogeneity of epilepsy from a first seizure that may imply treatment for a lifetime (e.g., JME) or a single event never to recur.

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## EYELID MYOCLONIA WITH ABSENCES (JEAVONS SYNDROME)

Eyelid myoclonia with absences (Jeavons syndrome) is a generalized epilepsy characterized by eyelid myoclonia with or without absences, photosensitivity, and eye closure-induced seizures with paroxysmal epileptiform discharges [1]. The onset of Jeavons syndrome is in childhood, peaking around 8 years of age and predominant in females. Eyelid myoclonia is the hallmark of the syndrome, with retropulsion of the head and upward deviation of the eyes, which occurs multiple times throughout the day and may be associated with clinical absence seizures [1,2]. Photosensitivity, while present in essentially all patients, decreases over time or in response to some AEDs [2]. GTC seizures occur concomitantly in most at some point in the course of the condition. AED therapy with valproate (VPA), ethosuximide (ETH), phenobarbital (PB), levetiracetam (LEV), and the benzodiazepines has been used, though the response to therapy is limited in many patients [2]. Avoidance of precipitants is key, and for

patients with marked photosensitivity, glasses that limit lighting are helpful. Jeavons syndrome is a lifelong disorder with a focus on the myoclonia and a course similar to JME.

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# F

## FAMOUS PEOPLE WITH EPILEPSY

Epilepsy is not necessarily an impediment to achieving a high level of success in life. Many famous people have suffered from epileptic seizures. Great leaders of the world including Napoleon Bonaparte, Julius Caesar, King Charles V, Fyodor Dostoevski, Flaubert, Handel, President William McKinley, Moliere, St. Paul, Peter the Great, Petrarch, and Jonathan Swift have suffered from seizures. It is interesting to note that each of these individuals performed his or her historic functions prior to the availability of effective and nontoxic antiepileptic medication. More modern-day "heroes," including movie stars, sports figures, and governmental officials, also exist with epilepsy. Publicity about persons with the condition is tempered by the stigma that still exists for PWE, though it is noted from time to time in news releases—not surprising given the prevalence of the condition.

## FEBRILE SEIZURES

Febrile seizures (FS) or febrile convulsions are seizures occurring with fever > 38°C seen in neurologically healthy children between the ages of 6 months and 5 years. Febrile seizures usually occur under the age of 2 and in those without the presence of an intracranial infection or previous history of afebrile seizures. FS must be distinguished from seizures that occur in the presence of fever. The prevalence of febrile convulsions is 2-4% of the normal pediatric population; the incidence is slightly higher in males, and seizures may occur at an earlier age. Family history is positive for febrile convulsions in 10-50% of cases and is a risk factor for recurrence of FS [1]. An autosomal dominant transmission with variable penetrance, autosomal recessive, and polygenic mechanisms have all been suggested, though FS are two to three times more common in family members of affected children. Several febrile seizure loci and gene mutations of the sodium channel subunit have been described [1].

Febrile seizures can occur with any childhood febrile illness, but especially with viral upper respiratory tract infections, including childhood illnesses such as measles, mumps, chickenpox, or German measles or following a vaccination (especially for mumps). With fever, the temperature usually rises above 38°C, though the rate of rise of the temperature has been implicated. *Simple* FS are uncomplicated generalized seizures of nonfocal origin that are typically brief GTC seizures or clonic seizures and rarely atonic events. *Complex FS* include those that are prolonged, repeated in the same day, frequently focal, or fol-

lowed by a postictal neurologic deficit. Febrile status epilepticus has been associated with females, and febrile status is not rare and carries a lower risk than it does in adults or with symptomatic etiologies. FS are associated with medically intractable LRE and may produce acute hippcampal edema or neuronal reorganization and evoke mesial temporal sclerosis (*see* Refractory Epilepsy).

Recurrent FS after an initial one occur in approximately 30-40% of cases and are more likely if the patient is younger than 1 year at the time of the first seizure, if there is a family history of febrile convulsions, or if there has been a complex FS. With each recurrent seizure, there is greater chance of recurrence. Severe neurologic sequelae such as hemiconvulsion-hemiplegia-epilepsy syndrome are rare even after prolonged seizures. Recurrent afebrile seizures not associated with fever (epilepsy) are seen in 1.5-4.6% of children with FS, and although it is higher than infants and children, it primarily reflects infants and children with one or more complex FS. The association between prolonged FS and the development of mesial temporal sclerosis continues to remain unresolved, though hippocampal sclerosis is believed to result from asphyxia associated with prolonged FS or febrile status epilepticus.

With simple febrile convulsions, chronic maintenance AEDs are not necessary. Treatment of fever with antipyretics and tepid baths, in addition to treatment of the underlying illness, is sufficient. Furthermore, prophylactic AEDs should not be utilized as the benefits of treatment do not outweigh the risks of the overall benign nature of the condition [2,3]. Rectal diazepam is currently the agent of choice for short-term prophylaxis of FS, though buccal midazolam has also been shown to be effective. When fever appears, diazepam may be given when the temperature exceeds 38.5°C.

Prophylactic therapy with AEDs can be considered with complex FS that carry a higher risk for later epilepsy and is aimed at diminishing the chance for recurrence; however, even those with more than one risk factor (prolonged focal seizure, abnormal neurologic examination, and family history) still have only a 10% risk of epilepsy [3]. Most children do not require treatment with even one of the above risk factors. Treatment with phenobarbital, sodium valproate, or diazepam prevents recurrence of FS, while carbamazepine and phenytoin do not prevent recurrence.

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## FELBAMATE (FELBATOL®)

Felbamate is a novel AED with a chemical structure characterized as a 2-pheny1-1,3-propanediol dicarbamate and is thought to act as a glycine an-

tagonist. Felbamate has efficacy in animal models against both electroshock and pentylenetetrazol seizures, suggesting a broad spectrum of activity against partial and generalized seizures. Absorption is over 90% with a Tmax of 1-4 hours, the Vd is 0.7-0.8 L/kg with 24% protein binding. Elimination is mostly hepatic with a T1/2 of 20 hours as monotherapy and 11-16 hours when used with CBZ or PHT.

The efficacy of felbamate in the treatment of partial seizures and generalized tonic-clonic seizures has been shown in both adjunctive therapy and monotherapy. With the exception of oxcarbazepine and felbamate, all of the new AEDs have received FDA approval for marketing as adjunctive therapy for partial epilepsy. Felbamate is also effective in Lennox-Gastaut syndrome. Side effects include mild, transient nausea and vomiting, insomnia, anorexia, and weight loss, with infrequent cases of hepatic failure and aplastic anemia, resulting in warnings 1 year after its release in 1993 leading to restricted use. While efficacious, the idiosyncratic side effects of aplastic anemia and hepatic failure, occurring in 1/3,000 [1], has limited its use to a third-line agent. Recommendations from the manufacturer include a complete discussion of the risks followed by written informed consent and serial complete blood counts and liver function profiles. Felbatol is available in tablet strengths of 400 and 600 mg and as an oral suspension of 600 mg/5 cc and used in doses of 1200-3600 mg/d in divided doses. Use must be individualized to obtain the appropriate balance between the risks and benefits of treatment compared to the relative risks of uncontrolled seizures.

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## FERTILITY

Reduced fertility is seen in patients with localization-related epilepsy with variable frequency from 0% up to one to two thirds cited with impaired fertility rates [1]. The cause of infertility is probably multifactorial, with possibilities that include sexual dysfunction, anovulatory cycles, and reproductive-endocrine dysfunction. Sexual desire and potency may be compromised in both men and women. Polycystic ovarian syndrome is increased in women with epilepsy with a phenotypic pattern of androgenization (hirsute, acne, and truncal obesity) in addition to serologic abnormalities of LH:FSH ratios [2]. Polycystic ovarian syndrome imparts a risk for hyperlipidemia, diabetes, endometrial cancer, and infertility. In addition, fertility has been shown in men taking EIAEDs with subsequent reduced levels of testosterone and increased circulating levels of sex-steroid binding globulin and impaired spermatogenesis. PWE have fewer children, possibly due to fewer, shorter, or later marriages, in addition to the effect of AEDs on sexuality and fertility [3].

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## FIRST AID FOR EPILEPSY

First aid for epilepsy should be individualized depending upon the person and the situation. As a general guideline, the following are suggested for first aid for individuals having a generalized tonic-clonic seizure. Onlookers and assistants should remain calm and remember the "A, B, Cs" to ensure integrity of the airway, breathing, and circulation. Do not insert anything into the patient's mouth during the seizure because of the risk of biting down on the object and creating dental trauma. The clothing around the neck should be loosened to ensure adequate respiration and the head or body turned to one side to prevent choking on secretions. The patient should be moved away from sharp corners or edges, and a soft object such as a pillow or rolled up coat may be placed under the person's head. During CPSs when the patient is ambulatory, the most important directive of first aid is to ensure the individual's removal from harm's way. It is best to do this without physically restraining an individual to prevent provocation of "resistive violence."

There is an unwarranted fear that individuals having a seizure may "swallow their tongue." Although gagging and respiratory movements become irregular during a seizure, it is impossible to swallow the tongue from an anatomic standpoint. When a seizure continues for longer than 5-10 minutes, the seizure is prolonged and should be approached pragmatically as status epilepticus. Contacting the EMS to arrange immediate medical attention and transport to a medical facility for further evaluation and treatment should at that time be undertaken. Patients with uncontrolled seizures who experience a breakfthrough seizure do not require transport to the emergency department (ED) each time they have a seizure. Discussing when to transport the individual with the patient's neurologist ahead of time to individualize instructions is best. As a general rule, first seizures, prolonged seizures, or seizures without normal recovery of consciousness, associated injuries, cardio-respiratory problems, atypical features, or comorbid concerns (e.g., headache, fever, mental status changes) should prompt immediate evaluation. In carefully selected patients following proper discussion, PWE on stable maintenance AEDs may receive initial abortive treatment with benzodiazepines in the home as a first aid means when they have intractable epilepsy and acute repetitive seizures. After the seizure has terminated, the subject should be protected and reas-

sured as he or she returns to normal awareness. Evidence of injury or atypical features of the recovery should be noted and conveyed to the PWE's physician.

## FIRST SEIZURE

The specific incidence of a first seizure varies according to age, with a biphasic distribution appearing more in children and in the aged, and fewer occurrences in middle years. Symptomatic seizures resulting from an acute cerebral insult should be considered distinct from idiopathic first seizures, since the prognosis and therapy of symptomatic seizures depends largely on the underlying cause. The risk of recurrence after an idiopathic first seizure varies among different studies, in part because of differences in definition of a first seizure. For example, prior unobserved losses of consciousness might or might not be counted, time elapsed between a seizure and evaluation, and variations in testing and treatment strategies and in the clinical judgments by the investigators all may vary. Retrospective studies found a rate of 43% at 2 years, while prospective calculations at 2 years estimated the risk rate of recurrence to be 36% [1]. One study with an extended follow-up of 4 years in 208 patients reviewed recurrence rates of 14, 29, and 34% at 1, 3, and 5 years following the first episode. Patients with abnormal neurologic assessment (pooled relative risk: 1.8; 95% CI 1.5-2.1), abnormal EEG (pooled relative risk: 2.0; 95% CI 1.6-2.6), and those with both an abnormal neurologic examination and abnormal EEG had a risk of 65% (95% CI 55%-76%) recurrence [1]. The risk of recurrence in PWE 2-4 years after diagnosis was 67% recurrence at 1 year and 78% chance within 2 years [2]. In this study of 564 PWE, those with neurologic deficits had high rates of recurrence (100% by 1 year) [2]. In addition, those less than 3 years and more than 60 years of age had an 83% risk of recurrence [2]; the elderly have a higher risk due to the association of structural injury from cerebrovascular disease. Annually, approximately 150,000 adults will present with a first seizure in the United States. In prospective studies, the overall risk of recurrence is 30-40% during the first 12 months [1], and therefore the risk of introducing a selection bias in those studies where a certain time lag separates the first seizure from therapeutic intervention exists and leads to an underestimation of the recurrence rate. Most studies agree that the highest risk of recurrence occurs when IEDs and neurologic deficits are seen on the EEG in PWE. Low-risk patients include those with an acute etiology "provoking" an acute symptomatic seizure, patients with a normal EEG, and those with normal neurologic examinations. Neurologic deficits markedly increase the risk of recurrence, and with symptomatic seizures the risk of recurrence is twice as high. Partial seizures appear to carry a higher risk of recurrence than generalized tonic-clonic seizures (94% vs. 72% at 36 months) [1]. Age at time of the seizure appears to have no effect on recurrence risk in adults and children.

Routine neurologic work-up for adults with unprovoked first seizures should include an EEG and brain CT or MRI [3]. Studies support EEG as a useful tool for prognosis and to predict the risk of seizure recurrence. Generalized or focal IEDs are associated with a greater risk for seizure recurrence, occur on average in almost 30% of cases, and predict a twofold greater risk of seizure recurrence. In one prospective study of 157 patients using EEG to predict recurrence at 2 years, the finding of IEDs was associated with a risk of recurrence of 83% (95% CI 69-97%) as opposed to those PWE and nonepileptic abnormalities in 41% (95% CI 29-53%) and 12% with normal EEG (95% CI 3-21%) [4]. Diffuse slowing or focal slowing are not significant for suggesting seizure recurrence. However, a normal EEG is most frequently seen and does not exclude the possibility of seizure recurrence (epilepsy). Neuroimaging is abnormal in about 10% or more and affect patient management when signs of a stroke, brain tumor, or other structural lesion are discovered. It can determine possible causes of seizures in a significant number of patients (especially the elderly). Lumbar puncture may be helpful in special circumstances when a CNS infection is suspected, such as patients who are febrile or immunocompromised. Further tests with special laboratory, drug screens, and cardiac evaluations should be individualized following history, general, and neurologic examination.

The treatment after first seizures with AEDs reduces the risk of recurrence by about 50%. However, early treatment with AEDs after the first seizure has no impact upon the prognosis of developing epilepsy [5]. Patients have a low risk for recurrence when no symptomatic substrate is found, no remote symptomatology exists, no evidence for focal seizures has occurred, and a normal interictal EEG and neurologic examination are found following a first (and only) seizure. In these situations, most authorities advise that AED therapy be delayed until after a second seizure. The argument against treatment is the relatively low risk of recurrence and the significant incidence (30%) of AED side effects in those treated. However, AED therapy should be considered after a first unprovoked seizure in PWE and a neurologic deficit (or abnormal neuroimaging study), EEGs with IEDs, or in PWE where the risks of a second seizure are unacceptably high (e.g., elderly). The decision as to whether or not to treat children and adolescents who have experienced a first unprovoked seizure must be assessed on a risk-benefit basis that weighs the risk of having another seizure against the risk of chronic AED therapy [6]. The patient's viewpoint should be considered in the decision-making process to treat a first seizure (e.g., in those deferring due to plans for pregnancy). The patient's profession, his or her attitude with respect to seizures, and the certainty of diagnosis are all relevant factors. Treatment after a second seizure is recommended because further seizures are likely.

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## FLUNARIZINE

Flunarizine is a fluorinated derivative of piperazine that has been used in the treatment of epilepsy. The suspected mechanism of action is via the sodium channels or by blockade of calcium channels (*see* Calcium Channel blockers). In clinical trials it has inconsistent antiepileptic properties and may lead to side effects including sedation or extrapyramidal symptoms that limit its use as a primary AED.

## FOCAL SEIZURES

Focal seizure is the term proposed by the ILAE Task Force to define partial seizures in patients with LRE. Focal or partial seizures (*see also* Complex Partial Seizures) may affect sensory, motor, psychic, or autonomic modalities without affecting consciousness (simple partial seizures), impaired consciousness (complex partial seizures), and in those patients with convulsions (partial onset secondarily generalized seizures). Clinical manifestations reflect onset or propagation at the symptomatogenic zone that may or may not be synonymous with the ictal onset zone. A number of factors still merit investigation in order to develop more definitive criteria for distinguishing between different type of focal seizures (e.g., structural lesions, maturational factors, modes of precipitation, and underlying pathophysiologic mechanisms).

The anatomic substrate of different focal seizure semiologies has not been completely elucidated to include this information in the classification systems, though phenomenology is a part of the newer proposal reinforcing the importance of semiology (*see* Classification). Frequent symptomatic causes include structural abnormalities such as trauma and vascular malformations in

younger age groups, tumors in the middle-aged group, and cerebral infarction and dementia in the elderly. Mesial temporal sclerosis is a common pathophysiologic mechanism for those patients who have medically intractable temporal lobe epilepsy. An underlying cause that is not able to be determined is referred to as cryptogenic (*see also* Cerebrovascular Disease; Cryptogenic; Tumors of the Brain).

## FOCUS

The epileptic *focus* is the region of the brain from which epileptic discharges arise, though the term focus is often used to describe the site of focal abnormalities seen with EEG. Excitatory and inhibitory influences interplay among neurons in the seizure focus or *epileptogenic zone* (*see* Epileptogenesis) and in surrounding cortex. The epileptogenic zone is the region from which the seizure discharges arise. The *irritative zone* is the brain region from which IEDs may be recorded at the scalp, at the cortical surface, or with invasive recordings. A particular structural lesion and an epileptogenic focus may not necessarily be congruent and therefore help to distinguish between the "epileptogenic zone" and the "irritative zone." In localization-related epilepsy arising from a particular lesion, the lesion itself shows no ictal activity. Seizures arise in an epileptogenic zone at the border of the lesion or sometimes at a distance from the lesion to express the semiology through the *symptomatogenic zone*. The IEDs may be due to entirely different cellular mechanisms than those generating the ictal discharges, although clearly sites of interictal and ictal discharges are often correlated.

## FOLATE

Folates are water-soluble enzymatic cofactors of DNA synthesis that occur naturally in food. Green leafy vegetables, dried beans and peas, and many other types of vegetables and fruits provide folate. In addition, fortified foods are a major source of folic acid. Foods such as some ready-to-eat cereals are fortified with 100% of the RDA for folate. Even so, some PWE do not consume enough folate in their diet. Folic acid is the synthetic form of folate that is provided in supplements and added to fortified foods. Folate helps produce and maintain new blood cells and is necessary for normal metabolism and maturation of the central nervous system. This is especially important during periods of rapid cell division and growth such as early in the first trimester of pregnancy.

Phenobarbital, phenytoin, carbamazepine, and primidone are associated with folate deficiency, and valproate and lamotrigine interfere with folate metabolism, producing a decrease in serum and CSF folate levels in 50% of patients on long-term AED therapy (particularly with phenytoin). Folate

deficiency may lead to macrocytosis, megaloblastic anemia, and altered mental status (*see also* Anemia, Aplastic). Pregnancy may lead to a decrease in serum folate and increase the risk of fetal malformations and neural tube defects even in nonepileptic women from the general population, who show benefit from supplemental folate during pregnancy [1].

Folic acid is a convulsant in animals but does not appear to cause seizures in humans. Because of a postulated relationship between folate levels and neural tube defects, women at high risk for neural tube defects or those with a family history should receive folate supplementation up to 4 mg/d during pregnancy, even though folate supplementation has not been shown to decrease the incidence of neural tube defects [2] and the registry data have not confirmed a benefit in humans that take preconceptional folate [3]. While maternal use of periconceptional folate has not been associated with a statistically significant risk reduction in major congenital malformations in infants of mothers with epilepsy, the possibility of inefficacy due to lower dosing has been suggested, with up to 5 mg/d recommended during pregnancy for women with epilepsy. However, high levels of folic acid increase the risk of breast cancer and accelerate colorectal tumor growth, and high levels of unmetabolized folic acid have been linked to impaired immune function in women aged 60 and over. Hence, studies of folate indicating both negative and positive effects remain to be validated with long-term, large-scale clinical trials that shed light on the effects on multiple health outcomes.

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## FRACTURE

Both idiopathic and symptomatic epilepsy are associated with reduced bone mineral density (BMD) and the risk of fracture. Symptomatic generalized epilepsy has the biggest decrease in BMD, despite normal ambulating. Fractures are two to six times more common in PWE due to epileptic falls and a generalized decrease in BMD. Fracture risk is associated with decrease in BMD associated with AED treatment, or it may occur with a comorbid condition that results in injurious falls. Fractures result from interplay between accidental trauma, seizure-related falls, and bone strength. Bone mineral density decrease is found to be associated with enzyme-inducing AEDs, specifically phenytoin, phenobarbital, and carbamazapine. Induction of the CYP450 enzyme system results in increased clearance of vitamin D, which results in sec-

ondary hyperparathyroidism and consequent increased bone turnover and reduced bone density. Nonenzyme AEDs (e.g., sodium valproate) can also cause osteopenia. Fractures commonly occur in the fifth and eighth decades [1]. In PWE less than 50 years old, fractures are usually traumatic and seizure-related, while in PWE 70-79 years of age, fractures are usually pathologic [1]. In males, most fractures occur in the 30- to 49-year age group, while in females most pathologic fractures occur between 50-59 and 70-79 years of age [1]. It is important whenever PWE are taking any AED (especially the older drugs) that supplemental calcium and vitamin D be considered in treatment [2]. The specific doses of supplementation, for example, of vitamin D, should be sufficient to normalize biochemical markers of bone turnover and may be supported with DEXA bone density studies [3].

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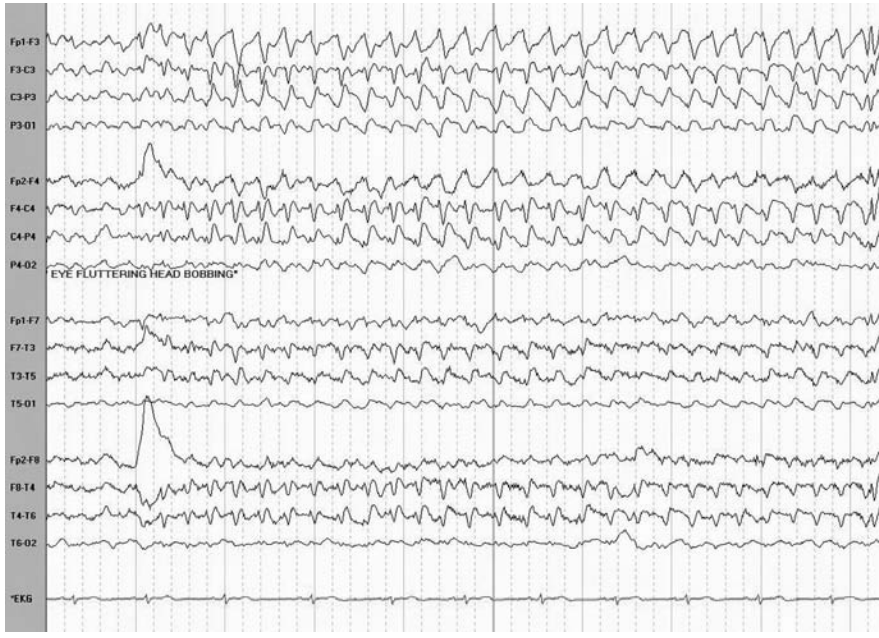
## FRONTAL LOBE EPILEPSY

Frontal lobe epilepsy (FLE) is the second most common site for patial seizures after the temporal lobe. It comprises about 20% of the group of patients with localization-related epilepsy characterized by recurrent simple partial, complex partial seizures, secondary generalized seizures, or a combination. The seizures differ from temporal lobe seizures (*see* Temporal Lobe Seizures/Epilepsy) in that they are associated with motor manifestations that may be associated with complex gestural automatisms or posturing and appear very dramatic and "hypermotor." Loud vocalizations, verbalizations, screaming, or bimanual-bipedal automatisms (bicycling) may occur with head, eye, or body version. A notable focal twitching of a digit or extremity may "march" from a restricted body part and progressively become hemi-clonic when the dorsolateral frontal cortex is involved. If the mesial surface is involved, asymmetric tonic posturing may occur, and the "fencer's posture" may be observed when the supplementary motor cortex is involved. The seizures that originate in the frontal lobe are often nocturnal, arising from sleep, are brief (< 30 seconds) and frequently occur several times a day. Frontal lobe origin of status epilepticus is a frequent associcate. Frontal lobe seizures may be mistaken for psychogenic nonepileptic seizures by virtue of their often bizarre bimanual, bipedal automatisms. Frontal seizures are seen with cryptogenic, symptomatic, or idiopathic etiologies, though the causes of FLE are more diverse than the partial epilepsies of temporal lobe origin. Autosomal dominant frontal epilepsy with brief motor attacks may be confused with a sleep disorder [1]. Frontal

lobe seizures are characterized by relatively preserved awareness and consciousness despite the bilateral motor manifestations and evolve to a secondarily generalized seizure quickly. Little or no postictal confusion is characteristic of frontal lobe seizures.

The interictal scalp EEG in FLE often shows no abnormalities in one third of patients, demonstrating no interictal epileptiform discharges. However, spikes, sharp waves, unilateral frontal spike-and-slow waves, and bilateral frontal spike-and-slow waves, or widespread hemispheric IEDs may appear in FLE. There may also be rapid propagation within the neocortex [2], creating IEDs and seizures that are less localized (*see* figure). Additionally, the IEDs can rapidly propagate in several directions and thus affect cortical areas situated at quite a distance from the seizure origin, often propagating to the temporal lobe. Focal parasagittal slowing may also be seen. The ictal EEG may also be normal, obscured by muscle artifact, or more diffuse fields of the rhythmic fast or slow activity with less dipolar voltage field patterns because of the involvement of larger brain regions. During ictal recordings, when onset electrographically precedes the clinical signs of the seizure, the localizing value is more reliable. The electroclinical localizing value of seizures in FLE is thought to be poor, though this finding depends on the specific areas of the frontal lobe from which the epilepsy originates [2]. Low-amplitude, high-frequency spikes, spike-and-slow waves, or rhythmic slow waves may appear in the frontal re-




EEG demonstrating an electroclinical complex partial seizure in a 17-year-old with right dorsolateral frontal lobe epilepsy due to cortical dysplasia seizure free after topectomy.

gions or other areas, frequently bilaterally. High-voltage sharp waves may occur bilaterally which can then be followed by diffuse suppression. Although rapid cortical spread of seizure activity may affect several frontal regions, making seizure onset identification problematic, particular presentations have been characterized [1-3]:

- •: Fronto-polar seizures may induce forced thinking or early impairment in vigilance, ipsilateral head turning of the head and eyes followed by controversive movements, clonic trunk movements, falls, or changes in affect. Secondary generalization is frequent.
- Orbito-frontal seizures may cause partial complex seizures that appear similar to temporal lobe seizures given the connections with the limbic structures. Early gestural automatisms, screaming, hallucinations, and olfactory illusions (see Olfactory Seizures), and changes in affect may occur. Similar to fronto-polar seizures, ipsilateral head turning may occur.
- Supplementary motor area seizures may cause tonic stiffening of the extremities with extension of one arm and elevation with abduction of the ipsilateral side, followed by head and eye deviation to the same side (i.e., the fencer's posture) and hip abduction and leg flexion, with either verbalization/vocalization or speech arrest. Contralateral head turning is more common than ipsilateral.
- Mesial frontal foci may cause vocalization, laughter, respiratory difficulties, or hand, foot, and trunk movement.
- Cingulate seizures may cause partial seizures with simple motor activities at the onset, leading to complex and elaborate gestural automatisms.
- Opercular seizures (see Opercular Epilepsy).
- Dorsolateral (motor cortex) seizures have their onset characterized by the simple partial phase of the seizure, which correlates clinically with the site of the seizure origin.
  - Basal prerolandic area discharges lead to speech arrest, vocalization or aphasia, contralateral hemifacial tonic-clonic movements, or swallowing automatisms. Generalization is frequent.
  - Rolandic region seizures present as partial motor seizures with or without a jacksonian march (*see* Jacksonian Seizures).
  - Paracentral lobule discharges result in clonic movements of the contralateral leg and occasional tonic contraction of the ipsilateral foot.
  - Kojewnikow's syndrome (*see* Kojewnikow's Syndrome) is a synonym for "epilepsia partialis continua."

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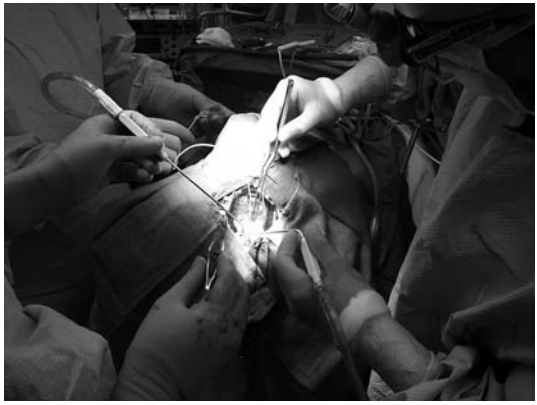
## FUGUE (EPILEPTIC)

An epileptic fugue state is older terminology to describe aimless wandering by a person with epilepsy of which he or she has no memory. It usually lasts several hours and appears during nonconvulsive status epilepticus or as a postictal phenomenon. More prolonged fugue states or states in which complex "intelligent" activities are accomplished are more likely to be nonepileptic in origin.

## FUNCTIONAL BRAIN MAPPING

Electrical stimulation to define the cortical representation of sensorimotor or language function of the dominant hemisphere has been a principal goal of providing a functional brain map. Individual variations of the classic human homunculus are common, especially when lesions are present. One study found variation in the organization of primary motor cortex in 19.4% of 36 patients [1]. In addition, functional overlap between two different areas was found in 11.1% of patients. Stimulation of brain structures has been performed by direct application of electrical current to both cortical and subcortical structures. Functional brain mapping using electrical stimulation can be useful for providing an individualized functional map that identifies areas of eloquent cortex. However, if a site on the map involved with a particular function is accidentally sacrificed during surgery, it does not necessarily imply that there will be a permanent deficit of that function. Often other neural networks are available to compensate for the lost function. Young children are able to demonstrate such plasticity better than adults. Electrical stimulation has been performed in every lobe of the brain. It may be performed extraoperatively at the bedside through implanted electrode arrays or intraoperatively (*see* figure) using handheld probes directed to specific cortical areas of interest by the neurosurgeon. Stimulations are performed sequentially through pairs of adjacent subdural grid or strip contacts, with EEGs recorded simultaneously from other contacts. Stimulation is with constant-current bipolar square-wave pulses delivered at 50 Hz for a duration of 0.5 ms [2]. Initial stimulation intensity is 1-2 mA and is increased by 0.5-1 mA up to maximal settings allowable for the individual stimulator utilized (i.e., 10 mA) and depending on the surrounding AD thresholds [2]. Stimulation is continued for 4-5 seconds, with an AD defined as periodic epileptiform discharges or rhythmic epileptiform activity lasting at least 1 second in at least one contact [2]. ADs are similar to restricted focal seizures and often consist of a sudden onset of recurrent rhythmic or epileptiform discharges that last for seconds to several minutes or more and can involve neighboring contacts. Low-frequency stimulation (i.e., 1 Hz) is less likely to induce seizures than high-frequency (50 Hz) stimulation. However, even with low-frequency stimulation, seizure induction has been noted with



Functional brain mapping with electrical stimulation performed in an operating room for definition of eloquent cortex. The bipolar stimulating wand is being held by the surgeon. A subdural strip on the cortical surface for electrocorticographic recognition of afterdischarges, and sterile numbers in the sterile field are present for developing the "map" of cortical function. Courtesy of Fernando Vale, MD; University of South Florida.

stimulation of temporal lobe white matter as well as the neocortical gray matter. Negative and positive clinical correlates may be noted during functional brain mapping through electrical stimulation of the brain. Stimulation of negative motor areas within the frontal lobe, such as the supplementary motor area, may cause interruption of fine motor movements, focal negative myoclonus, or bilateral atonia. Tingling or phosphenes reflect positive involvement of the somatosensory or visual systems. If negative or positive phenomena are produced with stimulation, a second trial should be conducted for validation. The responses obtained from electrical stimulation of eloquent and "silent" regions of the brain allow the neurophysiologist to design a pictorial map of individualized cortical function that is task-specific. Thus this type of mapping is critical for optimizing postoperative outcomes.

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# G

## GABA

GABA (gamma-aminobutyric acid) is the most well-known and important inhibitory neurotransmitter of the central nervous system. GABA is a four-carbon dicarboxylic acid formed by decarboxylation of glutamic acid under the control of the enzyme glutamic acid decarboxylase (GAD). GABA is metabolized by the mitochondrial enzymes, GABA transaminase and subsequently succinic acid dehydrogenase. A substantial fraction of brain synapses, from 30 to 50%, are GABAergic, and GABA is responsible for fast synaptic inhibition in neurons as a feature of seizure genesis. GABA inhibits neurons by several mechanisms, the most important of which is the opening of chloride channels, resulting in the influx of chloride anions into the neuron with subsequent hyperpolarization of the membrane potential and lowered cell membrane resistance (thereby making excitatory potentials more ineffective).

GABA interacts with neurons via a GABAA receptor complex. The GABA receptor is a macromolecular structure with a chloride channel. Binding sites for GABAA have many different modulatory sites including sites for benzodiazepines, barbiturates, beta-carbolines, picrotoxin, penicillin, and zinc. The GABA receptor that is most widely described in clinical medicine is referred to as the GABAA receptor. Antagonists at the GABAA receptor include picrotoxin, penicillin, and hicuculline. There is compelling evidence that excessive GABA-mediated inhibition may underlie the abnormal electrical activity, initiated in the thalamus, associated with epileptic absence seizures. In particular, the GABAB receptor subtype seems to play a critical role, because its antagonists are potent inhibitors of absence seizures, whereas its agonists exacerbate seizure activity. GABAB is involved in postsynaptic inhibition in certain pathways of the CNS and presynaptic inhibition in the spinal cord. For example, the antispastic drug baclofen is an agonist for the GABAB receptor. Numerous investigators have manipulated the GABA system for therapeutic purposes. GABA may be increased by inhibiting GABA reuptake at the synapse, with agents such as tiagabine, or by inhibiting its breakdown through blocking GABA-transaminanse as with vigabatrin. Use of putative GABA prodrugs, such as progabide, has met with limited success.

The GABA theory of epilepsy is supported by a number of experimental findings (*see* Basic Mechanisms of the Epilepsies). Convulsions may be produced by agents that selectively impede GABAergic transmission, and GABA agonists can play a protective role against seizures. Some human epilepsy has

been shown to involve abnormal GABAergic states [1]. Nevertheless, GABAergic function is increased in some models of epilepsy (*see* Basic Mechanisms of the Epilepsies), and GABA is not the only important neurotransmitter in mediating seizures with GABA metabolism, a key contributor to excitability and tightly coupled to metabolism and to glutamate in the multifactorial condition of epilepsy [2].

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## GABAPENTIN (NEURONTIN®)

Gabapentin (GBP) is a GABA analog developed and used as an AED based on the GABAergic theory of epileptogenesis. GBP has no known interaction with the GABA receptor and acts on a novel binding site that is a gabapentin-specific calcium channel subunit receptor. It is effective as adjunctive therapy for adults with partial and secondarily generalized seizures and has been available for marketing since 1994. Trials using GBP in monotherapy have been mixed [2]. While it is effective as adjunctive use in those over 12 years of age, some studies in the pediatric population have also demonstrated efficacy. There are four class 1 studies demonstrating efficacy of GBP in patients with intractable partial seizures, with up to 26% achieving at least a 50% reduction in seizure frequency [1,2]. There are few side effects noted, with somnolence, dizziness, fatigue, ataxia, weight gain, and pedal edema leading to discontinuation in 3-11.5%.

One attractive feature of GBP is the favorable pharmacokinetic profile. GBP has no significant protein binding, a Vd of 0.6-0.8 L/kg, and linear kinetics; it is 100% renally excreted unchanged, does not interact or alter other AED levels, and is not appreciably metabolized by the liver. The half-life is 5-7 hours, the Tmax is 2-4 hours, and absorption is saturable in a dose-dependent fashion, with reduced absorption seen at higher doses of > 1200 mg. Doses tested in RCTs have ranged from 600 to 1800 mg/d, but in clinical practice doses of up to 3600 mg/da have been used. Gabapentin has been used frequently in the treatment of neuropathic pain.

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## GAMMA-GLUTAMYLTRANSFERASE (GGT)

GGT is a common hepatic enzyme involved in the transport of substances across the cell membrane. An increase in the serum level of GGT may occur with the use of enzyme-inducing AEDs and is one of the first liver function tests to appear elevated. An elevation of GGT alone is not infrequent and of little clinical concern and supports patient compliance with AED drug therapy.

## GAMMA KNIFE RADIOSURGERY

The gamma knife is a radioisotope-based "surgical" system that has been used in the treatment of epilepsy. Radiosurgery utilizes focused radiation to treat patients with medically intractable localization-related epilepsy manifest as uncontrolled seizures. Stereotactic radiosurgery uses high-dose ionizing radiation delivered to stereotactically defined target sites within the brain. It has been utilized in the treatment of mesial temporal lobe epilepsy, targeting the hippocampus as the site of multiple radiosurgically created lesions to ablate seizure generation [1]. The gamma knife has also been used in the treatment of brain tumors, and in epilepsy has been used successfully in the management of hypothalamic hamartomas in patients with gelastic seizures. It has also been used to treat ateriovenous malformations and cavernous angiomas. The goal has been to dessicate or necrose the target lesion to create a nonseizurogenic functional change with minimal effects upon surrounding tissue. The gamma knife is a radioisotope-based photon-beam system that delivers gamma rays. Other techniques employ delivery of x-rays or particles (protons, electrons, neutrons, etc.) for radiosurgical treatment. A primary radionuclide (usually 60Co) is used to create the gamma radiation that is collimated to a fixed focal point in the brain. The dose is regulated by a secondary collimator that are secured on the patients head within a helmet though is often a lower dose of < 20 Gy. Gamma knife surgery is reserved for patients with uncontrolled partial seizures who have a small discrete lesion in inaccessible locations or for those that are not candidates for open resection. However, corpus callosotomy has been performed with radiosurgery as well [2]. There is no histopathology available, capability to visualize anatomical derangements, as well as a delay in seizure improvement when gamma knife radiosurgery is used. Success rates have been reported to be high in the small numbers of patients that have thus far been reported.

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# GANAXOLONE

Ganaxolone is a beta-methylated synthetic analog of allopregnanolone, a neurosteroid exhibiting potent properties in animal models of epilepsy [1]. Ganaxolone represents the class of AEDs known as neurosteroids and acts as an allosteric modulator of the GABAA receptor complex at a distinct site that is different from the benzodiazepine and barbiturate binding sites that augment the GABA-evoked chloride conductance. Ganaxolone has been shown to demonstrate antiepileptic activity in human subjects completing double-blind, randomized, placebo-controlled trial designs. In addition, efficacy has been shown in children and adults in open-label reports using ganaxolone. Somnolence has been the most frequently reported adverse event. Ongoing trials with ganaxolone in epilepsy are in progress to validate the preliminary anticonvulsant potential of this agent.

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# GANGLIOSIDOSIS

Gangliosidosis is a sphingolipidosis caused by an inborn error of metabolism in early infancy that leads to multiorgan deposition of gangliosides. Two forms exist with accumulation of GM1 (Landing disease), and GM2 (Tay-Sachs disease). Deficiency of beta-galactosidase leads to accumulation of GM1ganglioside and degradation products (Landing disease), and deficiency of hexosaminidase A (Tay-Sachs disease) and hexosaminidase A and B (Sandhoff's disease) lead to the accumulation of GM2 ganglioside in the nerve cells as well as other tissues. The clinical picture of a gangliosidosis is one of a progressive encephalopathy and loss of developmental milestones, with facial dysmorphism, visual loss often with a cherry-red spot macula, changes in muscle tone, and neurologic deterioration. Severe, symptomatic generalized epilepsy with myoclonic and atypical absence seizures often develops, and partial seizures may also occur. The diagnosis is made by demonstrating the specific enzyme deficiency.

# GAUCHER'S DISEASE

Gaucher's disease (GD) is a sphingolipidosis (*see also* Sphingolipidoses) that belongs to a group of disease states referred to as the glycosylceramidoses. Glucosylceramide accumulates in the lysosomes of the reticuloendothelial cells and seizures occur as a consequence of CNS involvement. There are three

forms of GD: an adult-onset chronic form, a rare infantile fatal form, and a chronic form with neurologic manifestations. The conditions results from a defective gene on chromosome 1 that codes for beta-glucosidase. In its juvenile form (type III), the onset occurs between age 6-8 years, with epileptic seizures of various types, most commonly GTC seizures and partial motor seizures; it may also appear as a progressive myoclonic epilepsy in adulthood. Neuropsychiatric, ataxia, pyramidal signs, supranuclear palsy, and progressive retardation occur. Early EEG abnormalities consist of widespread synchronous bursts of slow waves predominantly in the posterior regions, an abnormal response to photic stimulation, and slowing of the background frequencies. Paroxysmal features on the EEG may be seen prior to the development of GTC seizures, which worsen as the disease progresses with multifocal abnormalities. Death commonly ensues within 3-10 years of onset. The diagnosis is made by demonstrating enzymatic reduction of leukocyte beta-glucocerebrosidase activity.

## GELASTIC SEIZURES

Gelastic seizures are seizures with the semiologic characteristic of involuntary laughter. A distinction must be made between the ictal origin of gelastic seizures and the postictal origin of seizures with laughter from embarrassment or pleasure as a result of a seizure that occurs independently. The quality of the laughter in gelastic seizures often sounds forced, like a braying, similar to crying, and is without mirth (emotional context). Gelastic seizures are focal seizures associated with ictal semiologies that arise from the floor of the third ventricle, mesial temporal lobe, central regions (forced laughter due to facial muscle contraction). Ictal recordings with intracranial electrodes have revealed seizures arising preferentially from the left anterior cingulate gyrus, and laughter accompanied by other behavioral manifestations of joy or pleasure may result. Electrical stimulation of the fusiform gyrus and parahippocampal gyrus has also produced laughter [1]. Gelastic features may also occur in patients with encephalopathic generalized epilepsy.

Gelastic seizures associated with a hypothalamic hamartoma (*see* Hypothalamic Hamartomas) have been strongly associated with early-onset, brief gelastic seizures that may pass unnoticed in previously normal children. The onset is usually around age 4-10 years, with progression to more prolonged gelastic seizures, other seizure types, and cognitive and behavior problems. This clinical picture is confirmed with an MRI head scan. Prognosis for seizure control and social adaptation is poor unless surgical resection of the hamartoma is performed.

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# GENERALIZED EPILEPSY WITH FEBRILE SEIZURES PLUS

Generalized epilepsy with febrile seizures plus (GEF+) is a rare genetic epilepsy syndrome that includes febrile seizures with generalized seizure types. Typical febrile seizures (FS) (*see* Febrile Seizures) are genetically mediated via polygenetic mode of inheritance, though an autosomal dominant form with a variable seizure phenotype was described in 1997. GEF+ due to a gene mutation in SCN1B [1] located on chromosome 19q13 that encodes the beta subunit of sodium is designated GEF+ type 1. Subsequently, a different locus on chromosome 2q21-33 was found in French families due to a mutation in SCN1A that was designated GEF+ type 2. A GEF+ type 3 due to a GABAA mutation (GABRG2) on chromosome 5q34 has been found, and still others have been reported (SCN2A) in isolated cases. GEF+ has variable phenotypes that are encountered overlapping with IGE in addition to localization-related epilepsies (i.e., temporal and frontal lobe epilepsy). Febrile seizures that are either typical or atypical (i.e., occurring beyond age 6 years) and associated afebrile generalized tonic-clonic seizures in addition to other generalized seizure types have been noted to occur most frequently. Most GEF+ patients have multiple febrile seizures in early childhood (usually about 1 year old) and then overlap with the generalized epilepsies (i.e., CAE, IGE with GTC, JME), though focal epilepsies (e.g., TLE) may also coexist. One phenotype of GEF+ has been associated with TLE with a preceding history of febrile status epilepticus. Variable EEG patterns are encountered, though most frequently generalized IEDs are encountered. Treatment is directed at the afebrile seizure type, and the prognosis is usually favorable. GEF+ with TLE has been associated with the C121W mutation and has been successfully treated with temporal lobectomy in cases of overlap [2].

### References

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# GENERALIZED SEIZURES

Generalized seizures are those in which the clinical characteristics give no indication of focal anatomic localization. However, even in patients with IGE, lateralizing features are not uncommon, occurring in up to 55% of individuals either with observation of the semiology or on EEG [1]. Seizures of nonfocal origin may be convulsive and involve motor manifestations (tonic-clonic, tonic,

and clonic) or nonconvulsive (myoclonic, absence, and atonic). Alterations in consciousness may not be appreciable in some generalized seizures (i.e., myoclonic) or subtle unless testing is performed (i.e., absence). Motor signs are generalized and bilaterally symmetric. Generalized seizures may occur independently (i.e., epilepsy with GTC seizures only) or occur with more than one generalized seizure type and occur as a syndrome (i.e., CAE, JAE, JME, GTC, seizures on awakening). Seizures that are generalized from the onset are seen in both the IGEs and the EGEs, though some syndromes may have an overlap between the two conditions (e.g., GEFs+). Secondarily generalized seizures are discussed elsewhere (*see* Partial Focal Seizures). EEG findings of generalized seizures are also nonfocal, with interictal and ictal EEG findings demonstrating bilateral synchronous and symmetric spikes, polyspikes, sharp waves, and slow waves over both hemispheres.

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## GENERIC ANTIEPILEPTIC DRUGS

Several of the newer AEDs introduced after 1993 (e.g. valproate, lamotrigine, topiramate) have generic versions that are recently available in the United States. Legislation in 1984 was created to encourage pharmaceutical competition; the Hatch-Waxman act sought to promote competition and cost savings effected through generic medication following termination of patent rights to recoup costs incurred during research and development. Hatch-Waxman was able to bypass separate FDA approval of a generic drug as long as bioequivalence to the active ingredient of the brand name was demonstrated. There is concern for PWE taking generic AEDs due to the extreme consequences of having breakthrough seizures. Special precautions may be breached by changes in AED management, with some AEDs demonstrating narrow therapeutic windows, the need for chronic stable serum concentrations over time, and the potential for injurious and psychosocial consequences with failed therapy. However, data and research on the problem of switching name brand to generic AEDs are limited. The therapeutic range accepted by the FDA to show "bioequivalence" of a generic version with a brand name drug is met when a generic drug meets 80-125% of the AUC and Cmax of the brand name drug [1]. This range may be too broad for PWE, allowing for too much variability in levels of the product that controls their seizures. The FDA has previously recognized that some epilepsy drugs may have a "narrow therapeutic index," and therefore the generic version would not be substituted without the agreement of the physician and the patient prompting state-generated "negative formularies" that would prevent pharmacies from substituting certain AEDs. In addition, there may be even further potential fluctuations of serum concentration

and hence efficacy when switching between generic versions of an AED allowing the potential for a second degree of fluctuation initially from brand to generic and then from generic A to generic B. The impact of the "bioavailability" of the generic, furthermore, may theoretically fluctuate and create even greater instability if there are differences in the way a body processes the drug because of other ingredients used to make the generic and name brand drugs. Generic AEDs have the advantage of being less expensive. However, safety limitations for PWE and their cost-effective ratio remain to be further elucidated when coupled with the potential sacrifice in seizure effectiveness [1]. While lower cost may help adherence to AED therapy, 90% of neurologists disapprove of generic AED substitution without being consulted, and until more definitive studies are performed, clinical experience remains the primary determinant of permitting generic substitution. Still, switches from generics back to name brand AEDs were commonly noted in one study compared with other drug classes and may indicate greater toxicity or a reduction in seizure control compared with generics [2].

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## GENETICS

The genetics of epilepsy is complex but plays an important role, with new genes being identified at exponential rates. Seizures may occur through various genetic means of transmissibility or may be one of the inherited clinical traits of a genetically mediated primary neurologic or systemic substrate associated with seizures. Tuberous sclerosis, neurofibromatosis, and Lafora body disease are but some examples of the latter, in addition to other inherited brain malformations, chromosomal abnormalities, and inborn errors of metabolism (*see also* Etiology) that produce seizures in addition to other neurologic deficits. Transmissibility can often be multifactorial, dependent upon the epileptic syndrome, the degree of genetic penetrance, variability of expression, and environmental contributions. Early studies involving monozygotic twins and the study of genetic markers have contributed to our understanding of these issues. A range of types of inheritance patterns varies from polygenetic to single gene modes of inheritance to be associated with seizures. These gene mutations may be responsible for alterations in ion channels or neurotransmitter modulation, at times in concert with environmental triggers (e.g., head trauma) that is the underpinning of epilepsy. Polygenetic transmission exists with multiple genes responsible for the phenotypic expression of seizures, and *complex*

*inheritance* is the basis of the majority of the idiopathic (implying a genetic basis) epilepsies. Complex inheritance patterns often possess a *major susceptibility* gene that interacts with a number of *modifying genes* responsible for the genetic basis for the idiopathic epilepsies [1]. The idiopathic epilepsies produce common phenotypic characteristics, and genetically mediated epilepsy syndromes appear with a specific age of onset and may occur as focal seizures (e.g., BCECTS) or generalized epilepsies (e.g., JME) with complex inheritance that manifest seizures as the only symptom without other neurologic dysfunction. Epilepsy with *single gene inheritance* may occur in a mendelian mode of inheritance less frequently due to a defective major susceptibility gene (e,g,, benign familial neonatal convulsions-chromosome 20). Autosomal dominant frontal lobe epilepsy occurs in families (with variable penetrance) where a mutation of the subunit of the neuronal nicotinic acetylcholine receptor is responsible for the recurrent seizures. Some epilepsies that are inherited have underlying structural disease processes (e.g., the neurocutaneous syndromes), functional neurologic process (e.g., Rett syndrome), or systemic disease processes (e.g., inborn error of metabolism) to account for seizures inherited as a single-gene or autosomal dominant condition. Some single-gene inherited disorders may skip generations within a pedigree despite autosomal dominant inheritance due to *incomplete penetrance*. The variable incidence of the *proband* (affected patient) with inherited epilepsy caused by new mutations may be suspected through family linkage studies prior to identification of the precise molecular defect. Genetic counseling may be offered to a patient and family when an accurate diagnosis of an underlying genetic disorder is found. However, a common gene defect underlying inherited epilepsies may be present in a small proportion of families, and thus diagnosis often relies on the clinical features of the presenting seizure types and clinical inheritance patterns.

Management may be influenced by the knowledge of a genetic mutation. The deficiency in benign familial neonatal convulsions (defect in the potassium channel gene KCNQ2) causes an idiopathic neonatal epilepsy that portends a favorable outcome when this gene is discovered. In contrast, DNA tests that reveal gene mutations in the alpha1 subunit of the sodium channel (SCN1A ) may portend severe myoclonic epilepsy and a poor prognosis.

Neuronal ion channels and neurotransmitter receptor genes play a crucial role in the discovery of genetic foundations of the epilepsies [2]. A PWE due to an idiopathic cause usually has no family history of epilepsy or febrile seizures. Nevertheless, the genetics of the IGEs may involve a wide range of gene mutations involving voltage-gated sodium (generalized epilepsy with febrile seizures plus and severe myoclonic epilepsy of infancy), potassium (benign familial neonatal convulsions), calcium or chloride channels (the IGEs). Additionally, neurotransmitter involvement has included GABAA (IGE; including JME) and acetylcholine (autosomal dominant frontal lobe epilepsy). Thus far, over 50 genetic associations with various idiopathic epilepsy syndromes have been reported, and the number is rapidly increasing [3].

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## GLIA

Epileptogenicity may be influenced by glial proliferation within the epileptogenic zone of patients with focal seizures. Various pathophysiologic lesions (brain tumor, mesial temporal sclerosis, cortical dysplasia) have increased neuronal-glial interdigitation and proliferation that may facilitate hyperexcitabilty occurring with seizures [1]. Glial cells surrounding neuronal populations play a role in uptake and release of glutamate and other ions and neuroproteins, glial-neuronal connectivity through cellular gap junctions, and K+ reuptake during significant neuronal activation [1].


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## GLUTAMATE

Glutamate and aspartate are primary excitatory neurotransmitters that involve a large number of synapses in the CNS (*see also* Aspartate). The neuronal population involved through glutaminergic stimulation will determine the presence and type of normal behavioral effect [1]. Two distinct neuronal glutamate receptor types are found: *ionotropic* and *metabotropic*. Alpha-amino-3-hydroxyl-5-methyl-4-isoxazoleproprionic acid (AMPA) and kainic acid (KA), as well as N-methyl-D-aspartate (NMDA), comprise the population of ionotropic receptors and are responsible for excitatory neurotransmission alone or in combination. Metabotropic glutamate receptors act as second-messenger systems that affect neuronal synapses (and astrocytic connections) and may be responsible for the brain's *plasticity* as well as play a role in epileptogenicity [2]. These receptors have different pharmacologic specificities and are associated with different ionic channels, and excitatory neurotransmission is mediated by receptor(s) stimulation. AMPA channels are responsible for fast excitatory transmission through Na+K+ channels, and N-methyl-D-asparte NMDA (normally blocked by Mg2+) display slow transmissibility to Na+Ca2+ ions. *Long-term potentiation* or depression (dependent upon Ca2+ concentration) through synaptic stimulation via glutaminergic (NMDA) receptor stim-

ulation can occur within hippocampal neurons that may underlie the mechanism for learning and memory (*see* Memory).

Additionally, glutaminergic neurotransmission may play a critical role in pathologic conditions of the CNS including epilepsy [3]. Furthermore, glutamate can act as an excitotoxin, which in excess facilitates neuronal death (e.g., during status epilepticus), and excessive amounts of aspartic, glutamic, and aspartic aminotransferase acids have been found in epileptic cortex. The glutaminergic antagonists, in particular the antagonist of the NMDA receptor, may possess anticonvulsant properties.

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## GRAND MAL SEIZURE (TONIC CLONIC SEIZURE)

A grand mal (GM) seizure represents a generalized tonic-clonic seizure (convulsion). Although colloquial usage of the term GM has referenced a tonic-clonic seizure, other seizures (e.g., generalized tonic with a vibratory component) have had this terminology applied to broadly reflect seizures convulsive in appearance. This usage blurs the important distinction between partial and generalized seizures—each having separate and often very different etiologies, treatments, and prognoses. Literature regarding grand mal epilepsy is similarly confounded by the difficulty, in many cases, of determining from history alone whether the event is a primary or secondary generalized seizure.

Grand mal seizures occur in several epileptic syndromes: the IGEs, the EGEs, and epilepsies of uncertain localization. Some idiopathic generalized epilepsies present only as GTC seizures (e.g., epilepsy with GTC seizures only) or with GTC seizures and other types of seizures including absence and myoclonic generalized seizures (e.g., JME). These constitute clear electroclinical syndromes with etiologic, therapeutic, and prognostic implications.

The general characteristics of IGEs presenting with GTC seizures are:

- Onset in late childhood, adolescence, or early adulthood.
- Increased incidence of an IGE in a family member.
- Frequent co-existence of absence and myoclonic seizures occurring as an IGE syndrome. (JME, JAE, epilepsy with GTC on awakening).
- Seizures triggered by sleep deprivation, excess alcohol intake, fatigue, menses, or photic stimuli.
- Interictal EEG may reveal bilateral, synchronous, symmetric generalized spike- and- polyspike-and-slow wave discharges at 3-6 Hz with a normal background frequency. Photoparoxysmal responses are common.

- Typically, there is an excellent response to AEDs. However, relapses are not infrequent after stopping medication, even after several seizure-free years.

## GUSTATORY SEIZURES

Seizures with gustatory manifestations are focal seizures associated with alteration in taste. The frequency of gustatory auras is low. Gustatory seizures have been associated with foci in the temporal, supra-insular, operculum, rolandic, and parietal extratemporal cortices. Gustatory seizures include the illusion of an increase in the sense of taste (hypergeusia) or produce a hallucination where there is a perception of taste without objective stimulus. Common gustatory auras include unpleasant tastes such as bitterness, acidity, or metallic taste. The abnormal taste in the mouth may persist for several hours after the seizure.

## GYRATORY SEIZURES, EPILEPSY

This is rare form of epilepsy consisting of turning of the entire body in the vertical axis for 180° or more, occasionally in a "ballet-like" manner at the start of the seizure. Gyratory seizures are also known as circular, rotatory, or volvular seizures and involve adversion of half of the body, emanate from the contralateral frontal lobe, and may involve subcortical spread [1]. The mechanism may reflect striatum-induced inhibition that is overcome by ipsilateral thalamocortical influences on the supplementary motor area to produce contraversive movement; stimulation of the caudate in cats has led to circling (*see also* Versive Seizures)[2]. Seizures have been reported to occur with ipsilateral thalamic lesions and in generalized seizures as well.

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# H

## HEADACHE

Different types and timing of headache may be associated with seizures. Migraine headaches and epilepsy are both paroxysmal neurologic events that occur as frequent comorbidities (*see* Migraine), exist in a spectrum of differential diagnostic challenges (*see also* Occipital Lobe Epilepsy), with similar treatments (e.g., VPA and TPM). Migraine, however, is much more common than epilepsy, but acute confusion states, cyclical vomiting (*see* Abdominal Aura), and vertigo may occasionally be challenging to attribute to either headache or seizures.

Prodromal tension-type or vascular headaches may precede a seizure by up to 1-2 days and are generally associated with a concomitant feeling of malaise, fatigue, and moodiness. Ictal headaches are rarely the sole manifestation of a seizure. Sudden, diffuse, severe, throbbing, or sharp and steady, brief headache more frequently is associated with complex partial seizures of amygdalo-hippocampal origin [1]. A lateralized headache has been described ipsilateral to the epileptogenic zone [2]. Headache is rarely the first symptom of a seizure, and a preictal headache should raise a red flag for PNES. Postictal headaches are most commonly seen and may occur in roughly half of patients and are not localizing but rather a reflection of the intensity of the seizure occurring more after generalized seizures and less frequently after partial seizures. The headaches are severe and migraine-like in character and may be unilateral or bilateral, associated with nausea or vomiting, photophobia or phonophobia, and worsened by sudden movement. They may result from the sudden increase in cerebral and cranial blood flow associated with tonic-clonic seizures. In benign epilepsy of childhood with occipital paroxysms and progressive myoclonus epilepsy, headache is often a prominent feature as part of the syndrome, with hemicranial or diffuse headache that may be associated with nausea or vomiting.

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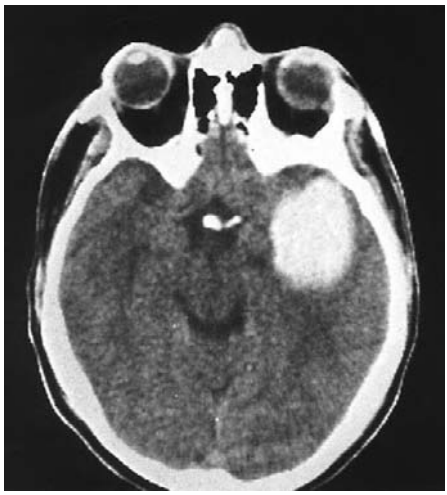
## HEMATOMA, INTRACEREBRAL NONTRAUMATIC

Bleeding may occur in one or more of several intracranial compartments including the epidural, subdural, and subarachnoid "spaces," and intracerebrally



Spontaneous ICH in a patient with medically intractable localization-related epilepsy.

in one or more lobes. Thalamus, basal ganglia, brainstem, and the ventricles are common sites of atraumatic hemorrhage. In adults, seizures are frequently seen with nontraumatic bleeding after aneurysmal and vascular malformation rupture and neoplasms; they are somewhat less common when spontaneous or due to hypertension. Lobar hemorrhages in the frontal and temporal lobes [1] are most commonly associated with seizures (*see* figure). Seizure incidence ranges from 6 to 25% [1-3] for both early- and late-onset seizures and is about 16% in the early posthemorrhage period [2,3], usually within 12 hours of hemorrhage. Subarachnoid hemorrhage results in seizures in 26-35% [2,3] of patients (*see also* Cerebrovascular Disease).

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## HEMICONVULSION-HEMIPLEGIA-EPILEPSY (HHE) SYNDROME

The HHE syndrome is an electroclinical entity described by Gastaut. The syndrome has become less frequent, possibly because of improved management for febrile convulsions and status epilepticus. This syndrome has multiple etiologies, including vascular lesions and encephalitis, or the etiology may be unknown, though fever is an essential trigger.

The HHE syndrome appears in three phases during early infancy or childhood, usually between 6 months and 2 years of age [1]. Hemiconvulsvions occur during the first phase in the face of a febrile illness. The initial phase consists of hemiconvulsions with unilateral clonic jerking that affects one side of the body or at least are predominately unilateral. The duration is typically long, lasting between 1 hour and a few days, manifest as unilateral status epilepticus. The second phase consists of hemiplegia that results in a residual deficit that is longer than a Todd's phenomenon. The third phase is epilepsy in the mani-

festation of the syndrome. Typically partial seizures occur, though secondarily generalized seizures may also appear, usually with a latency of 2-6 years. In about half of the cases experiencing HHE syndrome, partial or generalized epilepsy may appear, usually with a latency of 2-6 years. An association with factor 5 Leiden mutation has been reported. AEDs for focal seizures are utilized, and temporal lobectomy has resulted in successful seizure control.

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## HEMIMEGALENCEPHALY

Hemimegalencephaly is a disorder of neuronal migration that results in a unilaterally enlarged dysplastic hemisphere. Focal seizures occur in the majority and are typically intractable to AEDs. Hemimegalencephaly may occur as an isolated finding or be associated with other conditions including neurofibromatosis, hypomelanosis of Ito, and the linear nevus syndrome. Brain MRI or CT reveals an enlarged hemisphere with cortical dysplasia with thickening of the mantle or gyri, calcification, other neuronal migrational abnormalities such as schizencephalic clefts, and other anomalies such as agenesis of the corpus callosum. While widespread pathologic changes are seen in the affected hemisphere, microscopic abnormalities have also been noted in the seemingly unaffected hemisphere [1]. Anatomic hemispherectomy in hemimegalencephaly has provided effective seizure control and improved neurocognitive outcome [2].

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## HEMISPHERECTOMY

Hemispherectomy is aggressive resective epilepsy surgery that comprises removal of the major portion of a hemisphere for intractable unilateral seizures. Anatomic hemispherectomy, functional hemispherectomy, hemidecortication, and hemispherotomy are variations of respective surgeries to isolate and remove the offensive hemispheric epileptogenicity. Since hemiplegia, hemihypesthesia, and homonymous hemianopsia result, the procedure is typically performed on children with preexisting focal deficits or clearly progressive lesions. Specific conditions amenable to hemispherectomy have included infantile hemiplegia with refractory seizures, hemimegalencephaly, Rasmussen's

encephalitis, Sturge-Weber syndrome in young children, or extensive neoplasm. Hemispheric epilepsy has been used to describe unilateral generalized epileptogenicity of one hemisphere [1]. After hemispherectomy, children can recover to a condition of mild hemiparesis with independent gait and a clumsy but useful hand and forestall some intellectual decline that accompanies continued seizures and their treatment [2]. Early operations performed included anatomic hemispherectomies, though techniques varied; delayed complications of superficial cerebral hemosiderosis were noted. Surgical techniques have been modified to reduce the incidence of late complications due to cerebral hemosiderosis, and functional hemispherectomy has been used to provide improvement in seizure control and behavior, but without the complications [2]. Functional hemispherectomy involves temporal lobectomy, central corticectomy, and corpus callostomy to disconnect the remaining epileptogenic cortex from the contralateral hemisphere [2]. Hemispherectomy is effective in improving seizure control and interictal behavioral problems in 70-90% of cases [2].

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## HEMISPHEROTOMY

Hemispherotomy is predominantly a disconnection rather than an excisional surgical procedure for hemispheric epilepsy. This technique includes intraventriuclar corpus callostomy and resection of opercular and peri-insular tissue including the amygdala to further modify the functional hemispherectomy. Others have pursued a transsylvian approach with even lesser resections but with circumferential hemispheric disconnection [1].

### Reference

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## HERPES
## (*see also* ENCEPHALITIS/ENCEPHALITIDES)

Herpes simplex type 1 encephalitis (HSE) is the most common cause of sporadic viral encephalitis. HSE is associated with seizures in adults, occurring in approximately 3/100,000 persons per year and accounting for 95% of all fatal cases of sporadic encephalitis. HSE usually results from reactivation of the latent virus with heterogeneous clinical manifestations. In children and neonates,

HSV-2 accounts for 80-90% of congenital infections. The virus has a predilection for the temporal and frontal lobes of the brain. Infection is characterized by headache, fever, mild confusion, or behavioral changes but may lapse into obtundation and coma. Olfactory hallucinations, anosmia, and aphasia may occur in addition to frank psychosis, correlating with the propensity of the virus to involve the temporal and frontal lobes and even suggest a behavioral or psychiatric underpinning that may delay diagnosis. Complex partial seizures and secondarily generalized seizures frequently punctuate the clinical picture and may evolve to status epilepticus. There is often aseptic hemorrhagic cerebrospinal fluid on lumbar puncture. With early treatment, 40% of patients recover without significant neurologic deficits; however, despite appropriate diagnosis and therapy, the mortality rate remains approximately 20-30%. Untreated or treated late, the mortality is 70%, with marked residua among the survivors including refractory seizures, dementia, aphasia, and hemi-sensorimotor deficits. Neuroimaging may show unilateral or bilateral frontal and temporal lobe hemorrhage in the parenchyma. The hallmark of herpes simplex encephalitis is the presence of pseudoperiodic slow complexes or periodic lateralizing epileptiform discharges (PLEDs) on the EEG. When unilateral PLEDs are localized to the temporal lobes in the setting of symptoms that suggest a CNS infectious disease, herpes encephalitis must be considered. This feature usually occurs within the first week, repeats with a periodicity of a periodic epileptiform discharge that recurs every 1-2.5 seconds, and abates within weeks. Polymerase chain reaction testing, viral culture, or the finding of microscopic inclusion bodies from biopsied cerebral tissue can confirm the clinical diagnosis. Treatment with acyclovir 10 mg/kg given every 8 hours early in the course of the illness has been reported to lower the mortality rate significantly compared with prior treatment options.

Herpesviruses 6B and 7 may be implicated in some forms of epilepsy. These herpesviruses are the most common causes of febrile seizures in young children. In addition, detection of herpesvirus 6 has been demonstrated more often in mesial temporal lobe epilepsy surgical brain resections compared to those with resections in other regions of the brain [1]. Herpesvirus 6B may be an early acquired infection that becomes latent and with reactivation affects host genes such as glutamate, leading to the development of excitatory neurotoxicity in mesial temporal lobe structures.

### Reference

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## HIPPOCAMPUS

Temporal lobe epilepsy associated with sclerosis of the hippocampus is the most common pathologic finding in adolescents and adults with febrile seizures,

accounting for 70% of cases with intractable temporal lobe epilepsy [1]. The hippocampus is part of the limbic system and is arguably the most epileptogenic region of the brain. It occupies the medial aspect of the temporal lobe and includes the hippocampus proper (Ammon's horn), the dentate gyrus, and the subiculum. The hippocampus is divided regionally into four fields: CA1, CA2, CA3, and CA4, (CA = abbreviation of cornu ammonis).

Febrile seizures and early insults to the brain during the neonatal period or childhood may bring about neuronal atrophy and sclerosis of the hippocampus [1], predominantly involving areas CAI and CA3, with sparing of CA2 subfields, and the dentate gyrus (*see also* Mesial Temporal Sclerosis). In *dual pathology*, the distinct pattern of hippocampal sclerosis is not as evident with more diffuse loss of neuronal in all the hippocampal subfields [2]. The abdominal aura characteristic of mesial temporal lobe epilepsy associated with hippocampal sclerosis (*see* Mesial Temporal Sclerosis) is probably due to involvement of the symptomatogenic zone in the adjacent insular cortex, while ictal fear reflects amygdalar involvement. Mesial termporal lobe epilepsy has characteristic clinical presentations due to hippocampal pathology. Hippocampal sclerosis is probably directly associated with ongoing seizures (as evidenced by success with resection); other pathologies such as end folium sclerosis and amygdalar sclerosis may well represent the epiphenomenon of seizures of extrahippocampal origin.

### References

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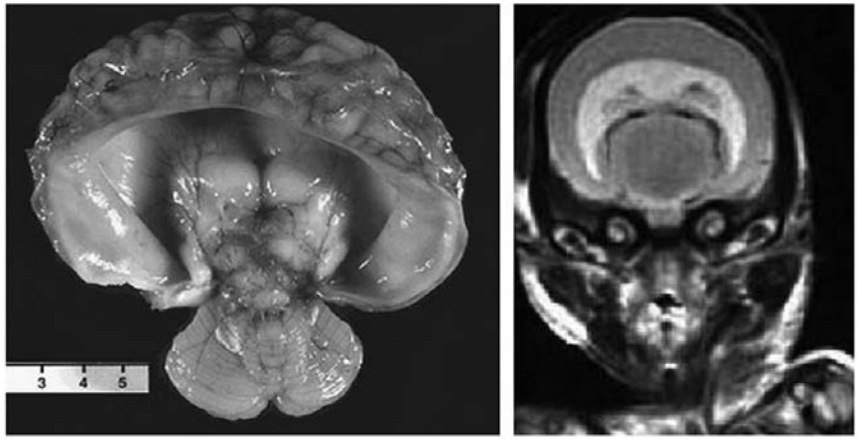
## HIV (HUMAN IMMUNODEFICIENCY VIRUS)

*see* AIDS.

## HOLOPROSENCEPHALY

Holoprosencephaly is a congential brain malformation with early defects in ventral brain development resulting in a single contiguous ventricle due to failure of cleavage of the prosencephalon into two distinct hemispheres [1]. The single ventricle typically exists with associated agenesis of the corpus callosum, olfactory tracts and bulbs, and defects of the hypothalamus (*see* figure). Variants have been recognized with a clinical-neuroradiologic spectrum [1]. The clinical features also vary with facial dysmorphism that frequently includes midface hypoplasia. Other features include mild hypotelorism with or without aplasia of




Pathologic specimen (A) and MRI brain (B) of alobar holoprosencephaly. Note the crecentric ventricle and absence of falx cerebri.

the premaxilla producing a unique midline cleft lip and palate to a single nares, cylopia, proboscis instead of a nose, small mouth, or other midline defects. The malformation is found in 1/15,000 live births and 1/250 spontaneous abortions, making it one of the most frequent malformations [1]. Multiple distinct genetic mutations have been shown with expression manifest as variants along the rostro-caudad and mediolateral planes [2]. The variation with epilepsy additionally is seen with the manifestations of symptomatic generalized epilepsy or partial seizures, with the likelihood of developing intractable epilepsy related to the degree of synaptic disorganization of the cortex. Holoprosencephaly has served as a model for applying genetic approaches to understanding brain development, with mutations causing partial loss of function in regulator genes that result in defective brain morphogenesis [2].

### References

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## HORMONES

Hormones influence epilepsy, and seizures affect the endocrine system. Most studies have included the effects upon women, though men may experience effects of epilepsy and treatment as well. Animal experiments and clinical observations have shown that estrogens decrease seizure threshold and increase

seizure frequency, while progesterone-related agents have the reverse effect (*see* Catamenial Epilepsy). Marked changes in estrogen-progesterone status occur during pregnancy, frequently without having a clinical effect on seizure frequency. Seizures that spread to the limbic system and hypothalamus may increase release of prolactin into the systemic circulation (*see also* Prolactin). There may also be alterations in the release of melatonin, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). These transient increases appear to have no long-term consequence. Basal circulating hormone levels and pituitary stimulation-induced changes are the same for untreated patients with epilepsy and for normal subjects. AED-induced enzyme induction may bring about increased hormone metabolism, thus changing blood levels and the feedback through the hypothalamic-pituitary-ovarian axis. Some AEDs appear to act directly on this axis. Although changes in endocrine function are common, they rarely have any clinical significance.

The hypothalamic-pituitary axis may be altered by patients with epilepsy. Antidiuretic hormone (ADH) may be altered. It may be inhibited by phenytoin (without clinical significance), and increased by carbamazepine (possibly associated with water intoxication and hyponatremia). Prolactin may be inhibited by certain GABAergic and dopaminergic drugs and may be increased by carbamazepine. Growth hormone (GH) may also be increased by the GABAergic and dopaminergic drugs. Corticotrophin-releasing factor (CRF) may be inhibited by valproic acid. Of clinical importance is the effect upon thyroid function that may result from the use of enzyme-inducing AEDs. The T3 and T4 levels may be decreased by phenytoin and carbamazepine, whereas TSH is unchanged, resulting in clinical hypothyroidism. There is a less prominent effect on thyroid by valproic acid, and clinically significant effects are rare. The adrenal gland may be affected with reduction in free cortisol levels by phenytoin and carbamazepine via peripheral inhibition and hypothalamic inhibition, in addition to the increased metabolism via the P450 hepatic enzyme induction. Furthermore, secretion of the 17-ketosteroids may be increased by phenytoin and carbamazepine and lead to circulating steroid-induced binding globulin to reduce circulating sex steroids. Phenytoin, carbamazepine, phenobarbital, and primidone, but not valproic acid, increase specific sex hormone binding globulins (SHBG) that serve as transport proteins. This may result in an increase in total testosterone, a decrease in free testosterone, and an increase in pituitary LH secretion. Testosterone homeostasis may also be altered by AEDs with decreased excretion of androsterone and ethiocholanolone. Insulin metabolism may also be altered. Phenytoin decreases the glucose-induced insulin response but does not affect glucose tolerance. This action is probably due to an inhibition of insulin secretion associated with increased sensitivity to insulin. The effect from PCOS is to facilitate insulin resistance, and this has been suggested to be associated with AEDs such as valproate, though the cause and effect relationship has been subject to controversy.

# HOT WATER EPILEPSY

Epilepsy precipitated by contact with hot water was first known as *hot water epilepsy* but has also been referred to as *bathing epilepsy* or *hot water immersion epilepsy*. While first described in a 10-year-old who was bathing and had seizures, a disproportionate number of cases have been reported from Turkey and India [1]. Most patients experience complex partial seizures during bathing, with or without secondarily generalized seizures, but primary GTC seizures have been described in up to one third of patients [2]. A male predominance has been noted with a wide range of ages with a mean of approximately 13 years of age in some reports, and younger in others. Seizures usually begin before adolescence. Most such seizures occur as a reflex to exposure to hot water, though approximately one third may also be spontaneous seizures that are usually delayed more than 1 year after reflex seizures have been established [2]. The practice of pouring hot water over the head or body with small buckets or bowls may act as the precipitating feature in patients from Turkey or India. Brain MRI is usually normal or infrequently has nonspecific features. The interictal EEG is usually normal, but IEDs have been reported primarily in the temporal regions [1,2]. Treatment is principally to practice avoidance behavior—i.e., avoid pouring hot water over one's head. Patients with spontaneous seizures usually respond to AEDs appropriate for the specified epilepsy type, though benzodiazepines have also been advocated prophylactically prior to bathing [2].

### References

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# HUNTINGTON'S DISEASE

Huntington's disease (HD) or Huntington's chorea is a genetic neurological disease with abnormal choreiform movements, cognitive, and psychiatric manifestations inherited in an autosomal dominant fashion. Juvenile HD (Westphal variant) is seen in children and adolescents and in general progresses more rapidly than the adult form with bradykinesia and rigidity more common than chorea, and commonly associated with seizures. There is no specific EEG or clinical features of seizures in Huntington's disease although low-voltage EEGs and abnormal evoked potentials are common associations and myoclonic seizures have been reported [1]. The Huntington's gene is located on the short arm of chromosome 4 and contains a sequence of DNA bases (cytosine-

adenine-guanine) repeated multiple times. Pre-symptomatic diagnosis is possible by demonstrating alleles containing excessive CAG trinucleotide repeats in blood.

### Reference

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## HYDANTOINS

Following Merritt and Putnam's discovery of the anticonvulsant effects of phenytoin, several hydantoin AEDs were marketed, including mephentoin and ethotoin, though phenytoin is much more widely used (*see* Phenytoin).

## HYDROCEPHALUS

Hydrocephalus (HC) is not a commonly recognized etiology for epilepsy, and a clinical distinction must be made between seizures associated with HC and tonic posturing from brainstem compression associated with acute rises in intracranial pressure. Seizures and HC are more often seen in children than in adults. HC treated by shunting has been associated with an incidence of seizures in shunted children ranging from 20 to 50% [1], though the precise incidence varies depending upon the study examined. Older studies found the risk of epilepsy after ventricular shunting procedures to be approximately 10%, with a higher risk for children under 1 year of age and lower risk for those over 50 years old [1]. Additionally, the incidence of postshunt epilepsy was felt to be higher when the shunt was placed into the frontal lobe (vs. parietal). Retrospective studies have been conducted in various countries with varying results [2]. In a large study of 802 French children treated with VP shunts and followed for a mean of 8 years, 32% of children developed epilepsy [2]. This incidence was higher with the presence of radiologic abnormalities and shunt complications [2]. Seizures were frequently noted at the time the diagnosis of hydrocephalus was made. Another retrospective German study of 283 patients noted a low incidence of postoperative epilepsy (12%). The presence of seizures was determined by the etiology of hydrocephalus, with the onset and clinical presentation (generalized or focal), and EEG changes not predictive for shunt-related epilepsy. Early shunting and poor functional status were associated with a higher risk for epilepsy, while epilepsy was not influenced by the shunt system or by the number of shunt revisions. Patients with hydrocephalus that had either significant cognitive or motor disability were significantly more likely to develop seizures. Intellectual development as an additional feature in PWE and shunted hydrocephalus were found to be an important predictor of poor intellectual outcome in hydrocephalic children with shunts. In patients with shunt revision and seizures, the first seizure occurred in more than half of pa-

tients approximately 1.5 years after shunting, with nearly 3% of visits to the emergency room for seizures culminating in shunt revision and almost 1% of shunt revisions associated with a seizure. Although seizures in shunted patients are not uncommon, a seizure is seldom an indication of shunt malfunction, and the incidence of seizures has not been statistically different in the parietooccipital, parietotemporal, or frontal region [3]. Endoscopic procedures (*see* Endoscopy) may prove helpful in the future to ameliorate the problem of postshunt epilepsy [1].

### References

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## HYPERKEPLEXIA

Hyperekeplexia is a pathologic non-epileptic startle response that is stereotyped in response to an unexpected stimulus. To a certain degree it is a normal reaction, but it becomes pathologic when there is an increased frequency or decreased threshold (*see* Startle Syndromes).

## HYPERGLYCEMIA

Nonketotic hyperglycemia and other hyperosmolar conditions may precipitate spontaneous focal motor seizures or epilepsia partial continua. Ketotic hyperglycemia does not have the same effect, possibly due to the antiseizure properties associated with ketosis [1]. Underlying focal cortical abnormalities may be present. Rarely, stimulation-induced posture-related focal seizures may be precipitated with movement. Seizures usually remit with correction of the underlying metabolic disturbance and do not require chronic AEDs (*see also* Kojewnikow's syndrome; Movement, Seizures Induced by).

### Reference

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## HYPERVENTILATION

Hyperventilation or overbreathing is an activating technique used in clinical practice to represent a stimulus that may trigger abnormalities clinically or on

the EEG. Based upon the degree of physical effort, adequate hyperventilation may induce electro-clinical absence seizures with bilateral synchronous 3 Hz spike-and-slow waves on EEG in up to 80% of patients with idiopathic epilepsy and especially untreated patients with absence epilepsy (*see also* Absence Epilepsy), though < 10% produce focal IEDs in patients with LRE. The mechanism is to create cerebral vasoconstriction through respiratory means of promoting hypcarbia. Hyperventilation normally produces a bilateral increase in theta or delta "build-up" that is frontally predominant and high amplitude. Resolving effects of HV are usually terminated within a minute after cessation. Diffuse slowing of the EEG pattern, especially with low blood glucose levels, occurs frequently in normal individuals. Focal slowing is abnormal if it is focal and persistent and may occur with an underlying structural lesion. Hyperventilation should be avoided in patients with severe cardiac or pulmonary disease, recent cerebral infarction, sickle cell anemia, and pregnancy [1].

### Reference

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## HYPOCALCEMIA

Acute hypocalcemia often follows thyroid or parathyroid surgery though delayed onset of hypocalcemia after surgery has also been noted. However, acute pancreatitis, renal dysfunction, or vitamin D deficiencies may also act as precipitants. Hypocalcemia is uncommon when compared to other electrolyte disturbances, such as hypoglycemia or hyponatremia, and is associated with seizures when severe hypocalcemia is < 6 mg/dL. Seizures may be generalized tonic-clonic, partial motor, or, less frequently, atypical absence or drop attacks. Muscular rigidity may become pronounced, and tentany may raise the possibility of seizures, though the nonepileptic nature is usually able to be separated by preservation of consciousness and clinical course. Calcium administration should be approached with cardiac monitoring in a controlled environment.

## HYPOMAGNESEMIA

Hypomagnesemia is usually associated with seizures when magnesium levels are < 0.8 mEQ/L. Low magnesium in the serum is often correlated with lower levels of calcium [1]. Therefore, as with most metabolic disturbances associated with seizures, the primary underlying cause for the low serum magnesium should be corrected as the principal treatment for seizures. Overaggressive correction may result in skeletal muscle weakness and transient respiratory insufficiency. Concomitant treatment with calcium is often required with low magnesium concentrations.

### Reference

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## HYPOMELANOSIS OF ITO

Hypomelanosis of Ito is a childhood neurocutaneous syndrome associated with irregular hypopigmented lesions associated with hair growth that is also hypopigmented, appearing white or gray. Seizures are often more severe when they occur earlier in life. Infantile spasms or myoclonic seizures occur in early childhood. Mental retardation and epilepsy occur in approximately two thirds of patients, but deafness, blindness from corneal opacitication, hypotonia, macrocephaly, and hemihypertrophy may also occur [1]. Imaging does not demonstrate specific abnormalities, though neuronal migration abnormalities are identified on autopsy, including gray matter heterotopias, though a spectrum of dyslamination of cortical architecture has been shown.

### References

Gordon N. Hypomelanosis of Ito (incontinentia pigmenti achromians). Dev Med Child Neurol 1994;36:271-274.

## HYPONATREMIA

Hyponatremia is one of the most frequent metabolic disturbances that may precipitate seizures. Electrolyte imbalances associated with low serum sodium occur in susceptible individuals resulting from a primary cause. The primary causes range from hypovolemic hyponatremia ("third-spacing" of fluids or sodium wasting nephropathies), euvolemic hyponatremia (SIADH, hypothyroidism, or low cortisol states), to hypervolemic hyponatremia (fluid overload, CHF, cirrhosis, or renal failure). In clinical trials (*see* Clinical Trials), clinically significant hyponatremia has been defined as hyponatremia < 125 mEQ/L. Hyponatremia is commonly seen from AEDs used to treat epilepsy and occurs most frequently as a side effect of carbamazepine and oxcarbazepine [1], especially in adults. An increased risk exists in the elderly and with higher serum carbamazepine concentrations. Seizures are usually generalized, and treatment involves identification of the primary cause and cautious correction of hyponatremia. Rapid correction or overcorrection can cause central pontine myelinolysis through osmotic demyelination and a clinical scenario that changes from varying levels of mental status changes to a comatose individual with quadiparesis or "locked-in state."

### Reference

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# HYPOTHALAMIC HAMARTOMAS

Hamartomas are developmental abnormalities in which histologically normal tissue resides in an abnormal location. Hypothalamic hamartomas are uncommon lesions frequently associated with gelastic epilepsy (*see* Gelastic Seizures) [1]. In addition, developmental delay and precocious puberty may result. Hypothalamic hamartomas frequently begin in childhood and act as a progressive condition leading to cognitive decline and intractable encephalopathic generalized epilepsy, though a more benign course may also occur and present later [2]. The seizure may occur with repetitive mirthless laugher, with ictal onset remaining well localized to the hamartoma. These malformations appear macroscopically as cerebral tumors, either stable over time or slow-growing. Different clinical presentations exist because of their variable anatomic localization. Surgical resection of the hamartoma has proven to be a useful technique for seizure control, though whether there is cessation of the cognitive decline is less well known [1,2].

### References

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# HYPOXIA

Hypoxia may result in a hypoxic-ischemic encephalopathy when oxygenation is compromised to a significant degree and for a prolonged period of time. The perinatal and neonatal periods are vulnerable times during which hypoxia results in severe damage to the CNS associated with mental retardation, fixed perinatal motor deficits (cerebral palsy), and EGE or LRE. In the neonatal period focal motor seizures with tonic or clonic features will typically occur (*see* Neonatal Seizures). However when seizure onset occurs in the first year of life, other seizure types such as infantile spasms, myoclonic seizures, or other generalized and focal seizure types are also encountered. In adults, hypoxia usually results from cardiac or respiratory arrest and may result in partial-onset seizures. In approximately 0.5% of patients who undergo coronary artery bypass surgery, postoperative seizures occur despite an absence of abnormality on neuroimaging [1]. Posthypoxic myoclonus and status myoclonus is associated with a poor prognosis and most die or are severely disabled with survival [2]. Acutely, myoclonus may involve only minimal facial muscles or axial movement, although nonconvulsive status epilepticus may be identified on EEG recording. Posthypoxic action myoclonus is a chronic condition that may also follow respiratory arrest (Lance-Adams syndrome), and more complete recovery may occur when secondary cardiac arrest is absent. The benzodi-

azepines, valproate, levetiracetam, and propofol have been reported to be effective in posthypoxic myoclonus.

### References

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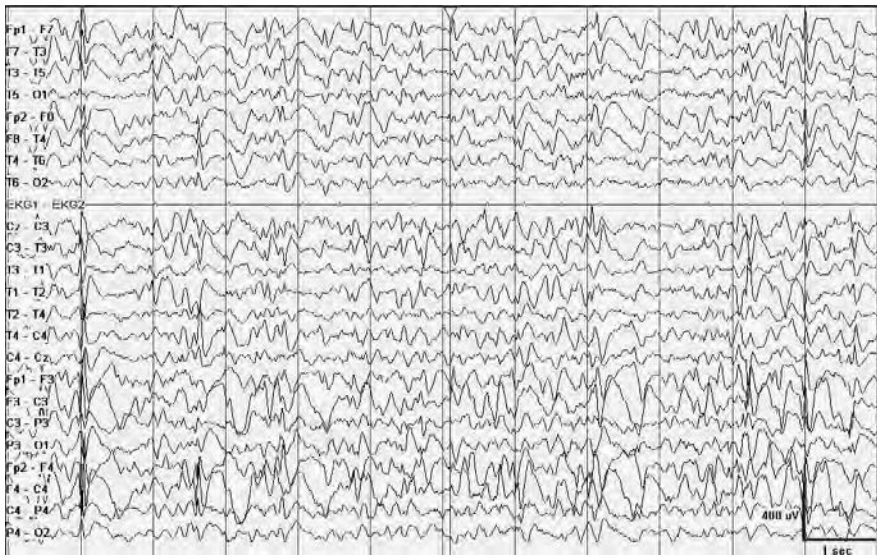
## HYPSARRHYTHMIA

This interictal epileptiform pattern on EEG is a distinctive pattern seen in children and is associated with infantile spasms. Hypsarrhythmia usually occurs in infants under the age of 1 year. It is characterized by a constant abnormal pattern associated with a high-voltage background of asynchronous and synchronous theta and delta frequencies in addition to nearly continuous multifocal spikes and sharp waves constituting a "chaotic" pattern (*see* figure). The greatest abnormalities are usually most prominent during sleep. Modified patterns are less frequently encountered with variations in amplitude and hemispheric predominance. In addition to hypsarrhythmic patterns, generalized periods of attenuation or suppression may be seen that correlate with infantile spasms. Many patients with hypsarrhythmia and West syndrome (*see* West Syndrome) evolve into the EEG findings of Lennox-Gastaut syndrome with diffuse slowing of the background, multifocal IEDs, and slow spike-and-waves.




Hyppsarrhythmia on interictal EEG in a patient with West syndrome. Note the high sensitivity of 400 (V/mm.

# I

## ICTAL

Ictal is a term that refers to paroxysmal events typified by epileptic seizures but also extending to migraine. An "ictal" behavior in epilepsy includes the clinical seizure manifestations, electrographic findings on EEG, as well as the associated cardiovascular and metabolic alterations. It is often difficult to precisely delineate the preictal, ictal, and postictal, phases on clinical history alone from the interictal manifestations. It may be especially challenging to interpret the boundaries between ictal and postictal behaviors and interictal and postictal alteration of consciousness. Similarly, ictal EEG may possess ictal patterns that are especially challenging to interpret in the encephalopathic generalized epilepsies and extratemporal partial epilepsies, blurring precise identification of the interictal-ictal-postictal continuum. Similar manifestations may be encountered with ictal and postictal transitory neuroimaging abnormalities encountered on brain fMRI or peri-ictal SPECT.

## IDIOPATHIC (SEIZURES, EPILEPSY)

The term "idiopathic" in the past referred to any seizure or epilepsy without an apparent cause. The idiopathic or "primary" epilepsies are in counterdistinction to epilepsies caused by a known entity (symptomatic) or suspected cause (cryptogenic). The idiopathic epilepsies include both partial (e.g., BCECTS) and generalized (e.g., JME) seizures and epilepsy. Occasionally an overlap between idiopathic focal and generalized features may occur (*see* figure). The clinical manifestations of idiopathic epilepsies occur in patients with idiopathic epilepsy who are otherwise neurologically normal, with seizures being the only manifestation of the syndrome. Hereditary transmission is not synonymous with idiopathic (e.g., neurocutaneous syndromes), and the term idiopathic is becoming less applicable as gene isolation in epilepsy becomes more commonplace. Primary epilepsy has been suggested [1] as a more appropriate term than idiopathic, and most persons with either idiopathic localization-related or idiopathic generalized epilepsy demonstrate age-specific duration-some at onset and offset (e.g., BCECTS) and some with lifelong predisposition (e.g., JME).

### Reference

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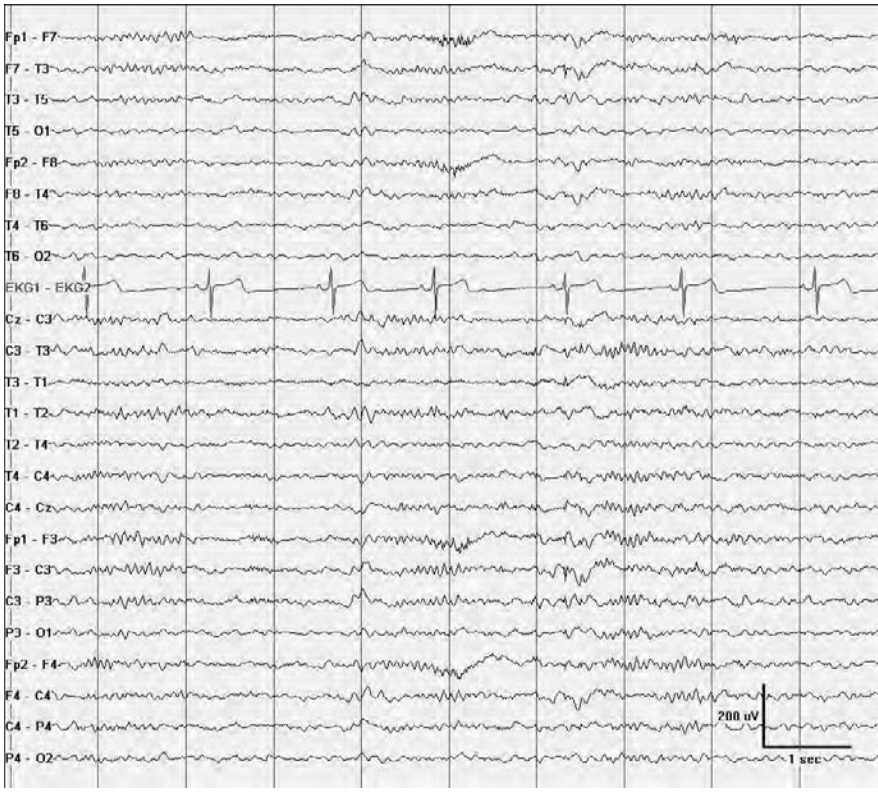


A left centrotemporal spike is seen in the 7th second with phase-reversing spikes at the C3 and T3 electrode derivations. This EEG was obtained in a 12-year-old with a family history of BCECTS that presented with childhood absence epilepsy demonstrated with video-EEG.

## IDIOSYNCRATIC REACTIONS

Idiosyncratic reactions are unexpected side effects of medication seen in patients. Patients experiencing such reactions often have abnormal drug metabolic pathways. Idiosyncratic reactions to AEDs do not exhibit simple dose-response relationships, are host-dependent, are rare (< 0.1% of the general population; 10% of adverse drug reactions), are frequently serious, and occasionally lead to death. They are, by definition, unpredictable (*see* Antiepileptic Drug Mechanisms) and usually cannot be detected in animal models. They can be differentiated into (a) immune-mediated hypersensitivity reactions, occasionally with eosinophilia and systemic symptoms, (b) reactions involving non-immune-mediated individual susceptibility (often linked to defective detoxification of reactive cytotoxic metabolites), and (c)off-target pharmacologic interactions where the drug interacts with pharmacologic systems other that its intended target. The more common idiosyncratic reactions seen

with AEDs involve cutaneous (serious rash), gastrointestinal (hepatic or pancreatic), and hematopoietic (aplastic anemia) systems.

The reactions of greatest concern are the dangerous, often fatal skin reactions such as the spectrum of erythema multiform, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, which call for immediate cessation of the drug. Rarer problems include agranulocytosis, serum sickness, Hodgkins-like lymphoma, lymphosarcoma, aplastic anemia (felbamate-1/7,500), lupus, pancreatitis, and hepatotoxicity. Some somewhat drug-specific problems are pancreatitis (valproate), oligohydrosis (topiramate, zonisamide), acute closed-angle glaucoma (topiramate; zonisamide), and encephalopathy and NCSE (tiagabine). Most older AEDs have been implicated in severe dermatologic reactions: some of these are phenobarbital, primidone, phenytoin (2-5/10,000), carbamazepine (1-4/10,000), valproate, and ethosuximide. Nonserious rash may occur in 5-15% of patients on aromatic AEDs. The newer AEDs appear to have a lesser tendency for severe skin reactions, with the exception of lamictal implemented at a rapid rate of initiation. Felbamate, gabapentin, lamotrigine, topiramate, tiagabine, and oxcarbazepine may all induce allergic dermatitis/rash. Most severe reactions appear within the first 4 months. There is some cross-reactivity among the older AEDs, with 40-60% occurrence of recurrent rash when the patient is switched from one aromatic AED to another [1]. Calculated oxidative protection ratios (COP I and II), gluthathione peroxidase and SOD activities, plasma selenium concentration, and genetic markers show some promise in predicting at-risk patients [2]. Recent recommendations for people of Asian ancestry include genetic testing for an inherited variant of the immune system gene HLA-B* 1502 before they are treated with drugs containing carbazepine to prevent cutaneous adverse drug reactions [3].

### References

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## IMMUNOSUPPRESSION

Prolonged AED intake may lead to changes in the immune system. Most of the aromatic AEDs have been implicated, perhaps because of their widespread use, but other AEDs may also have immunologic side effects. Phenytoin and phenobarbital have been the most noted. Thyroiditis is less common; myasthenia gravis may be aggravated. Hydantoins and barbiturates have been implicated in lymphocytic reactions resembling non-Hodgkin's lymphoma,

lymphosarcoma (within the first 4 months of therapy), reticulum cell sarcoma, and a reversible systemic lupus erythematosus-like syndrome (within weeks) with antibodies against double-stranded DNA. ACTH, when used, for example, in infantile spasms, may suppress the immune system. Similarly, other corticosteroids, which may occasionally be used in infantile seizures, may predispose to infection. During pregnancy the mother is thought to be slightly more susceptible to infection because of functional endogenous immunosuppression. Cell-mediated immunity and humoral immunity are decreased by changes (usually decreases) in immunoglobulin levels. This affects IgA levels (17-23% of patients with PHT, 11% with CBZ) and, to a lesser extent, IgG and IgM levels. There may be decreased T-lymphocyte function and rarely periarteritis nodosa.

## INCIDENCE

Information validity is essential if effective treatment is to be rendered. The approach to epidemiology has become more comprehensive and has imparted a greater breadth of understanding of epilepsy. Incidence is an epidemiologic measure that reflects the number of new cases of a particular disease in a given population over a given time. Incidence is calculated most often as an annual rate per population (e.g., the number of cases/100,000 inhabitants/year). The numbers of cases included in studies depends on the rigor and reliability of the information collected and the accuracy and homogeneity of the disease under study. Total population, age-specific, and cumulative incidence values may be derived [1].

Estimates of incidence vary across studies because of differences in classification, ascertainment, inclusion criteria, and diagnosis. Figures vary widely according to whether febrile seizures, isolated seizures, active epilepsy, or lifetime values are considered and whether hospital or community data are included. Total population annual incidence for epilepsy in the United States for the 181,000 people diagnosed yearly (CDC) is about 1/1,500 or 0.07%. Worldwide total population incidence of a first seizure (representing both single and recurrent seizures) has been estimated to be between 26 and 70/100,000 patient-years, with a mean annual incidence of a first unprovoked seizure of 56.8 per 100,000 person-years [1,2]. The worldwide incidence of epilepsy and unprovoked seizures varies between 17.3 and 73/100,000, but typically is between 30 and 50/100,000 per year, depending on the inclusion criteria [2]. The median annual incidence rate of *active* epilepsy (at least two seizures) is 47.4 per 100,000, with higher incidence rates reported in developing countries compared with industrialized nations [3,4]. This may be due to several acquired conditions, among them poor perinatal care, malnutrition of child and mother, infectious diseases (especially brain parasites), and head trauma. Trends over time reveal a decrease in incidence in children and an increase in the elderly. The age-specific incidence of epilepsy is high in childhood and in patients over

65 years, resulting in a bimodal distribution of the incidence rate (*see* table) [1]. Males have a slightly higher incidence than females. The distribution of seizure type and epilepsy syndrome varies among the different studies, giving variable and frequently conflicting results. However, focal seizures seem to occur more often than do generalized seizures, and compared with symptomatic localization-related epilepsy (approximately 60-70%), the incidence of IGE and West syndrome is much less.

**Age-Specific Incidence Rates of Epilepsy in Rochester, Minnesota 1935-1967**

| | Cases/l00,000/year | |
|---|---|---|
| **Age group (years)** | **Cause not identified** | **Cause identified** |
| 0–1 | 43.6 | 29.1 |
| 1–9 | 65.8 | 3.5 |
| 10–19 | 36.6 | — |
| 20–39 | 28.4 | 10.3 |
| 40–59 | 8.5 | 4.0 |
| 60+ | 56.8 | 25.2 |
| Total | 37.8 | 8.6 |

*Source*: From Ref. 1.

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## INCONTINENCE (URINARY)

Urinary incontinence is a frequent feature of generalized tonic-clonic seizures but is not a constant finding. Incontinence may also occur less regularly with partial seizures and infrequently with some absence seizures. When urinary incontinence occurs, it is not synonymous with the occurrence of a seizure. Incontinence occurs in the setting of a nonspecific loss of consciousness since it may be seen during syncope or encephalopathy of various etiologies and reflects only a full bladder and muscular relaxation that occur together. Some children have both enuresis and seizures that exist as coincidental conditions, and prolonged EEG may be necessary when the episodes are frequent to ex-

clude a primary epileptogenic mechanism. However, when seizures occur during sleep, other signs of seizures are usually apparent.

## INCONTINENTIA PIGMENTI

Incontinentia pigmenti is a neurocutaneous condition that occurs almost exclusively in females and is diagnosed in the neonatal period. Initially, cutaneous lesions appear over the body as erythmetaous lesions with bullae that form. The bullae subsequently become crusted and then pigment. Seizures occur in about 10-15% of patients in association with mental retardation and spasticity. Incontinentia pigmenti achromians (*see* Hypomelanosis of Ito) is another neurocutaneous syndrome associated with seizures, but with hypopigmented lesions.

## INDUCED SEIZURES

Both extrinsic and intrinsic factors can induce, precipitate, trigger, or provoke seizures. The induction of seizures may be immediate, such as during intermittent photic stimulation in patients with IGE. Factors important for generating seizures in PWE include alteration in the level of consciousness with activation by sleep transitions and sleep deprivation, nocturnal sleep, daytime naps, relaxation, or inactivity. Physical activity that induces fatigue or strenuous physical activity (*see* Sports) may provoke seizures. Emotional stress generating emotional stimulation, conflict, anxiety-depression, and other psychological triggers as well as hormonal influences such as menses and pregnancy may evoke seizures. In patients with and without epilepsy, metabolic and systemic derangements such as acid-base imbalance, hypoxia, fever, and electrolyte imbalances such as hypoglycemia, hyponatremia, or hypocalcemia, and renal or hepatic insufficiencey (altering AED metabolism) may trigger seizures. Drugs may act to alter the seizure threshold as well. Many classes of pharmacologic agents have been implicated, including antidepressants, neuroleptics, hypoglycemic agents, antibiotics, sympathomimetics, and a host of other agents. Additionally, abrupt withdrawal of AEDs or toxic concentrations of some AEDs may provoke seizures. Barbiturates and benzodiazepines are particularly problematic when treatment is stopped abruptly and may induce either breakthrough seizures or status epilepticus. Additionally, substance abuse, including alcohol and illicit drugs, may be particularly ictogenic.

Induction (or activation) has also been utilized as an extremely useful technique in the diagnosis of PNES. While a normal EEG during a habitual spell with loss of consciousness suggests a nonepileptic basis, it is the induction of a spell when provoked that qualifies the event as psychogenic with near 100% specificity [1]. Provocative techniques to demonstrate suggestibility in concert

with EEG have been used successfully both during hospital-based video-EEG monitoring as well as in the short-term outpatient setting [2].

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## INHIBITORY SEIZURES

Inhibitory seizures are seizures that cause a clinical loss of function such as aphasia, blindness, amnesia, deafness, neglect, atonia, and numbness. "Negative" motor responses or other localized phenomena may mimic other neurologic disorders such as a transient ischemic attack (TIA) when the corresponding cortex is involved during inhibitory seizures [1-3]. A focal motor "negative seizure" is also referred to as a focal atonic seizure, nonconvulsive seizure paralysis, hemiparetic seizure, epileptic hemiplegia, and ictal hemiparesis [3]. Clear negative motor responses may interfere with the ability to perform a voluntary function (e.g., the initiation of movement) or result in a deficit of an ongoing movement (e.g., paralysis). The mechanism of inhibition of motor function by a seizure in the somatomotor, primary, or supplementary sensorimotor areas, or in negative motor areas have been reproduced during electrical stimulation studies of the brain [2]. Bilateral negative motor responses have been noted on subdural electrical with primary negative motor areas and supplementary negative motor areas referenced to reflect these regions [2]. Surface EEGs have shown rhythmic delta activity or focal spikes over the motor strip. The differential diagnosis of ictal hemiparesis includes a postictal deficit (i.e., Todd's phenomenon), TIA, in addition to focal inhibitory seizures, particularly in elderly patients.

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## INTERICTAL EPILEPTIFORM DISCHARGES

Interictal epileptiform discharges (IED) represent a distinctive group of waveforms that are characteristically seen in persons with epilepsy. Normal back-

ground rhythms (e.g., runs of vertex waves), a variety of artifacts, and variants of uncertain significance (e.g., wicket waves) may mimic abnormal IEDs and lead to over-interpretation of the EEG [1]. In epilepsy, the interictal EEG may reveal paroxysmal bursts or phase-reversals that are paroxysmal occurring as single events or in bursts and mimic abnormal IEDs. IEDs may be single, rhythmic, or periodic over time with a spatial distribution that is similarly variable, ranging from focal to bilateral, multifocal, or diffuse. These IEDs may be divided into several categories and include a spike, sharp wave, and/or polyspikes with or without aftergoing slow waves. By definition, spikes are discharges with the major negative component of the complex lasting > 20 ms but < 70 ms, while sharp waves last > 70 ms and < 200 msec, often followed by an aftergoing slow wave that is notably different from the ongoing background [2]. Spike morphologies can also be monophasic, diphasic, or triphasic and an after-going slow wave may be present. Spikes are predominantly surface-negative potentials, though brain surgery may alter the recorded dipole and result in the appearance of surface-positive IEDs. The amplitudes of IEDs vary from approximately 20 μV up to several mVs. IEDs have been reliably associated with epilepsy at rates sufficient to be clinically useful, though prominent intra- and inter-patient variability in morphology may occur and those with the most pronounced spikes on EEG are not necessarily associated with a greater severity of epilepsy [3]. Scalp detection of IEDs is based upon dipole localization and the surrounding field, but may be different from the site of seizure genesis. In most cases, an IED will reflect radially oriented dipoles detected on the scalp, but in other situations, tangential dipoles from individual epilepsy syndromes (BCECTS) or developmentally or surgically altered cortex may create unusual dipoles and produce patterns challenging to the EEG reader. Rarely, normal individuals may possess IEDs on EEG without the phenotypic expression of seizures. The photoparoxysmal response, generalized spike-and-wave, or centro-temporal IEDs are most frequently encountered, and may represent idiopathic, genetically acquired traits represented on EEG without the expression of seizures [3]. The spatial distribution of a focal IED provides the variable association with the clinical expression of epilepsy depending upon location. For example, in the absence of a structural lesion, central, parietal, and occipital spikes, in general, are more benign regions with a reduced potential for epileptogenicity.

The interictal EEG has a pivotal role in providing ancillary support for a clinical diagnosis of epilepsy [1-3]. In EEG, IEDs may help classify the epilepsy or epilepsy syndrome by identifying IEDs in conjunction with the clinical semiology. Classification of the epilepsies is based upon distinguishing seizures that are localization-related from those that are generalized by the type and distribution of IEDs noted on the EEG. Focal IEDs may be focal, regional, lateralized, or secondarily generalized discharges in their field of involvement. They may help provide information useful in localizing the epileptogenic zone for the purposes of surgical treatment. Frontal, anterior temporal, and midline IEDs have the highest correlation with seizures. The frequency of repetitive

generalized discharges may help to classify generalized epilepsies with < 3 Hz spike-and-slow waves (aka slow-spike-waves or atypical generalized spike-waves) seen in the encephalopathic generalized epilepsies while 3 Hz or greater is characteristic of the idiopathic generalized epilepsies. Furthermore, treatment information can be clinically relevant following therapy (as in the case of absence seizures) in addition to predicting when a trial of antiepileptic drug taper is planned by providing information about persistent IEDs on EEG. In the absence of IEDs, epilepsy is not excluded because of the deep cortex, fissures, gryi, and sulcal neuroanatomy, which may not readily be represented at the scalp during routine recording. The EEG, while ideally suited for evaluating patients with epilepsy, is also not specific for etiology when demonstrating IEDs. The scalp EEG may demonstrate interictal and ictal discharges in the same or different regions of the brain [3].

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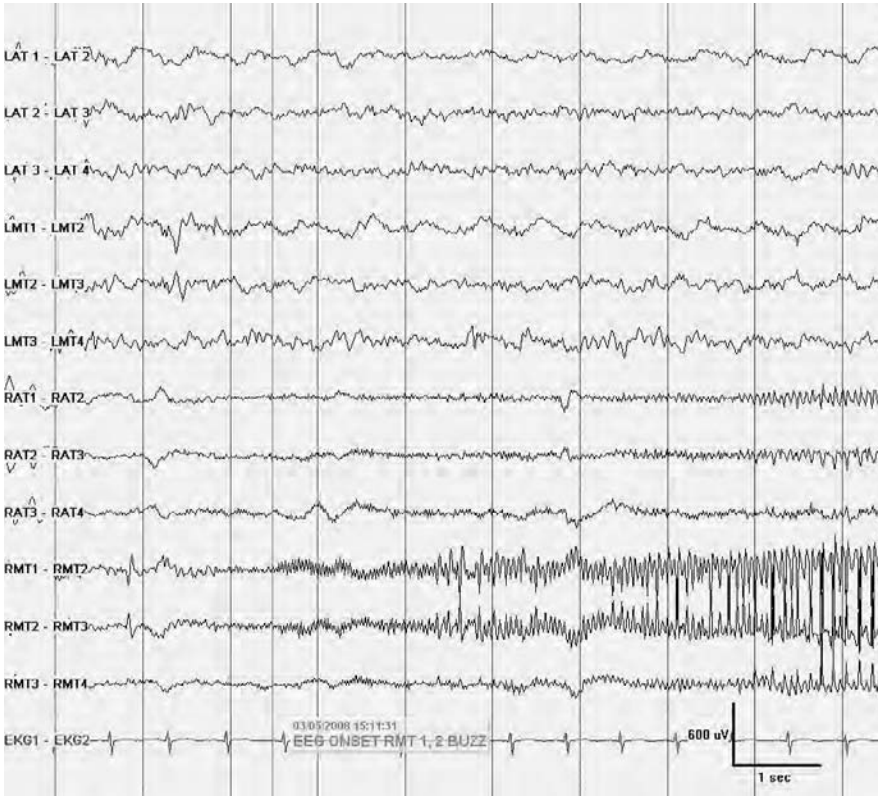
## INTRACRANIAL EEG

Recording the EEG directly from the brain (electrocorticography) has some distinct advantages over scalp-recorded EEG [1-3]. Intracranial EEG or *invasive EEG* is used primarily for epilepsy surgical planning and for functional cortical mapping. Intracranial EEG, unlike scalp EEG, is not adulterated by the dampening effects of the skull, and therefore the same waveforms appear differently and more prominently on intracranial EEG [1]. Normal waveforms appear "spikier," volume conduction does not occur, myogenic artifact is absent, and mixtures of different waveforms, including fast (i.e., beta rhythms) and very fast frequencies (i.e., gamma rhythms, ripples, and very fast ripples), are evident on intracranial recordings. Intracranial EEG is used in the surgical evaluation of patients with intractable LRE only after noninvasive evaluations with scalp EEG yield discordant or nonlocalizable information. The reasons for pursuing intracranial EEG monitoring include hemispheric lateralization, lobar or intralobar localization, and demonstration of a single resectable epileptogenic zone. Subdural, depth (intracortical), as well as less utilized epidural and foramen ovale electrodes are different electrode types employed for phase II monitoring. Hemorrhage (intraparenchymal with depth and subdural with strips and grid electrodes) is the most common complication, although infection and brain edema (especially with grids) may also rarely occur. When IEDs appear (*see* Interictal Epileptiform Discharges) on invasive recordings, they have a different morphology than scalp EEG recordings, with




Intracranial EEG demonstrating right temporal seizure onset in a patient with temporal lobe epilepsy. Note the high frequency regionally that begins with an RMT2 spike and remains maximal at the same electrode derivation. (Two bitemporal subdural strips R/L AT and R/L MT = right/left anterior (middle) temporal.)

briefer, higher amplitude, mixed morphologies and polarities, and appearing with greater prominence, though intracranial electrodes are primarily placed for capturing seizures. Hippocampal seizures often occur with rhythmic ictal theta discharge, but they may begin with different patterns and waveform frequencies.

Depth recordings illustrate the variability of spread of the seizure discharge from seizure to seizure (*see* Stereostatic Depth Electroencephalography). There is no simple correlation between seizures and the surface EEG. Seizures that arise from deep-seated generators in the mesial or inferior aspects of the hemispheres (e.g., mesial frontal lobe epilepsy) may not be detectable on scalp recording due to low amplitude of the ictal discharge (e.g., in mesial frontal lobe epilepsy)—hence the need for invasive electrodes implanted at or near the generator. Other seizures may have such a rapid and widespread field of involvement that scalp EEG recordings demonstrate only a nonlocalized propagated field to represent the seizure onset.

Intracranial EEG is warranted with less regularity with the evolution of improved neuroimaging and noninvasive techniques. When invasive EEG is warranted, it may not only allow localization of the epileptogenic zone for resection, but also clarify situations where resection would be unlikely to be of benefit and spare a PWE the risks of an unnecessary procedure. When seizures are multifocal or nonlocalized, surgery is frequently not beneficial, but when bitemporal seizures are captured on intracranial EEG, some patients may still benefit from resection of one temporal lobe, especially when a structural lesion is present [3].

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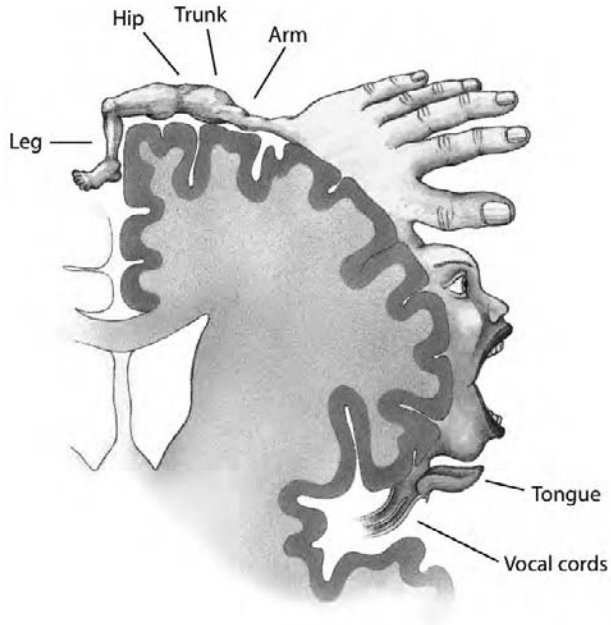
# J

## JACKSONIAN SEIZURES

Jacksonian seizures are partial seizures characterized by a progressive spread (or jacksonian march) from one part of the body to another without alteration of consciousness. Subsequent secondary generalization may occur in partial-onset seizures. Jacksonian seizures may be purely motor with tonic contraction of the thumb or big toe followed by the hand or the foot, then clonic involvement of the hand, forearm, arm or foot, leg, and thigh, purely sensory with ascending paresthesias, or both sensory and motor symptomatology. Jacksonian seizures result from a progressive spread of electrical excitation in the rolandic cortical region when a sensorimotor area is involved. Propensity to affect certain body parts parallels the region of cortical representation for that body part as represented by the human homunculus (*see* figure). Perioral and hand involvement are therefore most common. Jacksonian seizures are rare, especially in children and their causes are multifactorial.




The human homunculus depicting representation of cortical function relative to location. Used with permission from Devinsky O. Epilepsy: Patient and Family Guide, Third Edition, Demos Medical Publishing, 2008.

# JACTATIO CAPITIS NOCTURNA (HEAD-BANGING)

Also known as rhythmic movement disorder, or "head-banging," jactatio capitis nocturna is a nonepileptic disorder involving repetitive movements that occur at sleep onset, during stage 1 sleep, or during brief arousals from sleep [1]. The disorder is quite common in young children, particularly in males (at a ratio of 4:1), and is present in approximately 60% of infants at 9 months [1,2]. As children grow up, the incidence drops sharply to only 5% at 5 years old [1]. Because the condition is largely confined to childhood, it is frequently misdiagnosed as epilepsy when symptoms persist into adolescence or adulthood [1].

Children are commonly seen to exhibit one of several stereotyped patterns, most commonly involving the head and neck. Lateral "head-rolling" is the most commonly witnessed motion, and anterior-posterior "head-banging" may also occur [1]. However, full-body involvement may be noted in some children in a "body-rocking" type of movement. The duration of head-banging episodes is widely variable, ranging between a few seconds and half an hour [1].

This nonepileptic rhythmic movement disorder does not have a clearly identifiable etiology, but the symptoms are believed to result from a habitual movement pattern. While these rhythmic, repetitive movements are often mistaken for seizures, organic pathology can be ruled out due to the voluntary reproducibility, suppressibility, and distractibility characteristic of jactatio capitis nocturna. The specific minimal diagnostic criteria for rhythmic movement disorder include the patient exhibiting rhythmic body movements during drowsiness or sleep and at least one of the four types of disorder being present (head-banging, head-rolling, body-rocking, or body-rolling) [2]. Additionally, the presence of another medical diagnosis or parasomnia that may explain the symptoms precludes the diagnosis of head-banging [2]. Most children will never require more than supportive treatment, using behavior modification tools and injury prevention, and few studies exist to examine the clinical efficacy of available interventions for persistent rhythmic movement disorders.

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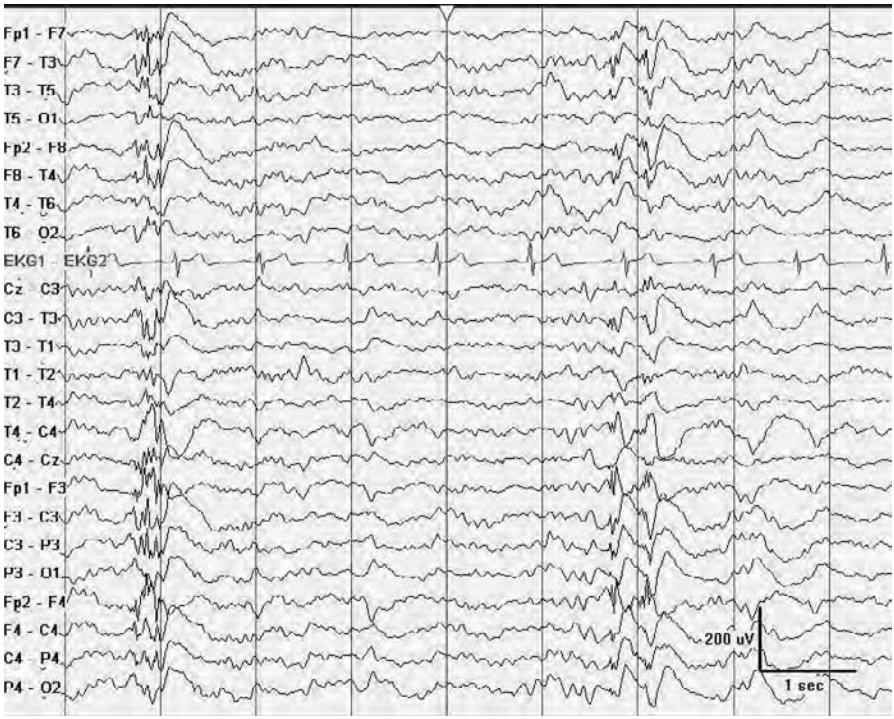
# JANSKY-BIELCHOWSKI DISEASE

Jansky-Bielchowski disease (neuronal ceroid lipofuscinosis type II) is the late infantile form of neuronal ceroid-lipofuscinoses (NCL), seen prominently in

patients from Finland. The disease is associated with autosomal recessive transmission. The onset occurs at age 2-4 years, and seizures are usually composed of massive myoclonic jerks triggered by sensory stimuli. Generalized tonic-clonic seizures, atonic seizures, atypical absences, or combinations of these seizure types may also occur. Patients with Jansky-Bielchowski disease suffer rapid and progressive neurocognitive retardation, ataxia due to involvement of the cerebellum, blindness, and spasticity. Death usually occurs within 5 years of onset. The EEG demonstrates multiple abnormalities, including diffuse slowing of the background rhythms, multifocal independent spike discharges, occipital IEDs that occur in bursts or prolonged runs, in addition to the characteristic appearance of polyphasic complexes with photic stimulation at low flash frequency. The histologic features are consistent with the neuronal ceroid lipofuscinoses (*see also* Ceroid Lipofuscinoses).

## JUVENILE MYOCLONIC EPILEPSY

Juvenile myoclonic epilepsy (JME) is a common but underrecognized IGE syndrome accounting for 10% of all epilepsy cases [1]. JME is an IGE syndrome with a polygenetic basis caused not by a single but by multiple genes and other factors and is characterized by myoclonic jerks, generalized GTC seizures, and sometimes absence seizures. The syndrome has previously been termed "myoclonic epilepsy of Janz" based upon the initial descriptions of the syndrome as "impulsive petit mal." Myoclonic seizures are the defining characteristic of the syndrome and occur in all patients with JME. In addition, generalized (clonic)-tonic-clonic seizures occur in up to 95% and absence seizures in up to one third of patients with JME [1]. Seizures usually begin in adolescence, typically between 8 and 18 years of age, with absence beginning earlier than myoclonic or GTC seizures. JME occurs more frequently in females. A family history of epilepsy is often present, and JME is familial in approximately 40-50% of cases with a pattern of genetics that suggests a polygenetic mode of inheritance with heterogeneity [2]. Patients with JME have a normal neurologic examination. Neuroimaging is also normal. Seizures classically occur in the early morning on awakening, but may also be noted just prior to sleep with notable sleep-related precipitation, though sporadic seizures may also occur. JME is characterized by brief, irregular clusters of upper trunk and limb myoclonus often with clinical and EEG asymmetries that can lead to misdiagnosis. Consciousness is not disturbed with a single myoclonic seizure, though it may be impaired with myoclonic seizures occurring in rapid repetition. Myoclonus usually occurs soon after morning awakening and may also be increased following sleep deprivation, fatigue, photic stimulation, emotional stress, and alcohol consumption. Seizures may sometimes be perceived as "shocks" or "shakies" that occur internally without overt manifestations of myoclonus.




Bursts of generalized polyspike-and-wave discharges during sleep during seconds 2 and 7 in a patient with JME.

Neuroimaging of the brain does not reveal any etiologic abnormalities. However, the interictal EEG in JME characteristically demonstrates "fast" 4-6 Hz generalized, fronto-centrally predominant, polyspike-and-waves, though fast and classic 3 Hz spike-and-waves may also be seen. The generalized polyspike-and-waves are diagnostic when they occur as an ictal manifestation of a corresponding myoclonic jerk. The discharge consists of a bilateral, more or less synchronous discharge of 5-20 negative spikes with a frequency of 12-15 Hz and with increasing amplitude, sometimes reaching 150-300 μV. The spikes are followed by slow waves of changing frequency, but are at about 3.5 Hz. The duration of the discharge ranges from 3 to 5 seconds. Interictal discharges are shorter, with fewer spikes. Irregular spike-and-wave IEDs and lateralized features may occur both clinically and on EEG and may be misleading and suggest an LRE instead of IGE [3,4]. Even unilateral myoclonic jerks and figure-of-4 signs have been described in JME [4]. The background electrocerebral activity is normal. Generalized IEDs on the EEG are increased by hyperventilation, sleep deprivation, and intermittent photic stimulation (*see* Photosensitivity). JME is a heterogeneous entity with several genetic mutations. Autosomal dominant features have been described with gene mutations on chromosomes 2, 3, and 5. Several loci termed EJM 1, 2, and 3 have been re-

ported, producing with other gene mutations in other loci the polygenetic variations and respective phenotypic expressions. The EJM 1 locus caused by the EFHC1 gene mutation on chromosome 6 was first described in the JME phenotype [2], although EMJ 2 characterizing the gene mutation of the neuronal nicotinic acetylcholine receptor on chromosome 15 and EJM 3 reflecting a transcription regulator gene mutation on chromosome 6, in addition to other gene mutations, have also been described. Seizures and myoclonus associated with JME usually respond well to sodium valproate, with (clonic) tonic clonic, myoclonic, and absence seizures ceasing in > 85% of patients. Lamotrigine, as well as topiramate, levetiracetam, and zonisamide, may also prove efficacious. Monotherapy is usually effective, though failure may respond to valproate and lamotrigine in combination. Vagus nerve stimulation and the ketogenic diet may be tried when AED resistance has been firmly established as broad-spectrum therapy. However, JME carries a favorable response to AED therapy in 80-85% of cases, which controls most of the seizures in most patients. Recognizing JME is critical as there is an extremely high recurrence rate if treatment is discontinued. Lifelong therapy is recommended at this time, and selection of an appropriate antiepileptic treatment should reflect this long-term use.

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# K

## KETOGENIC DIET

The ketogenic diet (KD) was introduced in 1921 by Wilder based on observations that fasting decreased seizure frequency. It has been used to treat childhood epilepsy that is refractory to AED therapy and is broad spectrum in terms of its efficacy being successful for absence, drop attacks, myoclonic seizures, infantile spasms, and mixed seizure types associated with the Lennox-Gastaut syndrome. The diet is high in fat, low in carbohydrates, and adequate in regard to protein content [1]. The KD acts to mimic the metabolism of prolonged fasting, resulting in ketosis, the factor believed to be partly responsible for an elevated seizure threshold. Larger prospective studies of more than 50 patients have yielded seizure reductions at 3 months between 38 and 81% [1]. The first randomized controlled trial, which had an intent-to-treat prospective design and no blinding, studied 145 children. Half started the ketogenic diet immediately and half after a 3-month delay. Of the children in the diet group, 38% had at least a 50% reduction in seizure frequency, 7% had at least a 90% reduction, and one child became seizure-free [2]. The precise mechanism is unknown, with changes in pH or fluid-electrolyte balance, direct inhibitory action of fatty acids, neurotransmitter alteration, and altered mitochondrial biogenesis leading to enhanced alternative energy stores having been proposed [3]. Neurotransmission accentuating GABA has been a leading theory in the efficacy induced by the KD. Using transcranial magnetic stimulation, a change in cortical excitability with a lower level of neural excitation within the cortex has been shown with neurophysiologic changes that further implicate accentuation of GABAA inhibition in the cortex.

A typical "4-1" KD consists of 4 calories from fats for every 1 from proteins and carbohydrates, with a total caloric intake of 75 calories/kg of body weight. Medium-chain triglycerides or vegetable oils may also be used. While short-term benefit has been shown, patients may pose difficulty with compliance. Additionally, the diet becomes less effective around the time of puberty, though it has been shown to be efficacious in adults as well.

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# KINDLING

Repeated low-intensity electrical stimulation of specific cerebral structures (amygdala, hippocampus, entorhinal cortex, and neocortex) in animal models using subthreshold/subconvulsive stimulation creates autonomously epileptogenic discharges capable of producing focal and secondarily generalized seizures. The electrical kindling of an epileptogenic zone takes place after a variable period of time depending on the stimulus, the animal species (different in rats, cats, primates), and the specific brain region analyzed. A single stimulus may cause a single seizure, but with kindling the effect persists long after repeated stimulation ceases. This phenomenon is thought to be similar to the occurrence of human focal seizures, but there is as yet no convincing evidence that secondary epileptogenesis from kindling exists in humans. The efficacy of an AED may be measured by the graded response of AED dose and the ability to inhibit kindling in an animal model. During kindling, several stages are described. First, the entraining of an afterdischarge at the site of stimulation is seen. Second, repeated daily stimulation leads to a behavioral response that can be graded and quantified. Third, there appear autonomous focal clonic seizures, followed by rearing of the animal (mice/rats) with loss of balance. The EEG reflects a classic three-stage paradigm that has been characterized as: (a) a *dependent stage* with the appearance of an abnormal epileptogenic focus, which does not induce clinical seizures and disappears with excision of the primary focus; (b) an *intermediate stage* in which independent discharges in an immediate and remote focus are present with the possibility of seizures arising from the secondary focus, albeit with disappearance of clinical seizures after excision of the primary focus; and (c) an *independent stage* in which seizures arise from the secondary focus and persist after excision of the primary focus.

Since early descriptions first appeared in 1967, the kindling phenomenon has provided a valuable experimental model in epilepsy, allowing studies of electrophysiologic and neurochemical changes arising from seizures and the testing of possible AEDs.

There is some evidence in humans that epileptogenic foci in the mesial temporal regions may arise from epileptogenic neocortex surrounding distant primary structural lesions, suggesting the potential for secondary epileptogenesis in humans. Others believe that the concept of secondary epileptogenesis in himans has not been adequately demonstrated. FDA-approved AEDs such as levetiracetam have been tested using the kindling model, demonstrating efficacy in this particular model without demonstrating efficacy in other more conventional models such as maximal electroshock and phenylenetetrazol models [1]. Corneal stimulation has also been used to successfully induce kindling beyond direct stimulation of cerebral cortical structures.

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## KOJEWNIKOW'S SYNDROME

*See* Epilepsia Partialis Continua.

## KUFS DISEASE

Kufs disease (aka ceroid liposfuscinois, neuronal type 4)is the rare adult-onset form of ceroid-lipofuscinoses (*see also* Ceroid Liposfuscinois) characterized by progressive neurocognitve decline, generalized muscular rigidity, ataxia, tremor, myoclonic jerks, and seizures. Kufs disease usually exhibits autosomal recessive transmission with onset around 20-30 years of age. Kufs disease has two clinical phenotypes: type A with progressive myoclonus epilepsy with dementia, and type B with behavioral abnormalities and dementia, associated with pyramidal and extrapyramidal signs. The EEG reveals generalized spike-and-wave discharges with photosensitivity to low frequencies. Giant cortical potentials with somatosensory evoked potentials are typical [1]. Death usually occurs within 10 years of the onset of the disease. Dolichols are found in urinary sediments. Specific granular storage abnormalities may be confirmed histologically on electron microscopy in skin biopsy with fingerprint or curvilinear bodies [1].

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# L

## LACOSAMIDE (VIMPAT®)

Lacosamide is a recently approved AED developed for use as adjunctive treatment in adults with partial-onset seizures. It is available as an oral and intravenous formulation [1]. In animal models locosamide has been shown to demonstrate efficacy in partial seizures as well as in status epilepticus. In human randomized controlled clinical trials, lacosamide was shown to be effective in demonstrating significant reduction for patients with partial-onset seizures. Lacosamide is completely absorbed from the GI tract with an elimination half-life of 13 hours, <15% protein binding, and linear pharmacokinetics. No AED drug interactions are expected with lacosamide. Side effects were only mild to moderate in intensity, even in the intravenous human studies, with dizziness, headache, back pain, and somnolence reported [1]. Doses of 100-800 mg/d in twice-daily doses have been evaluated.

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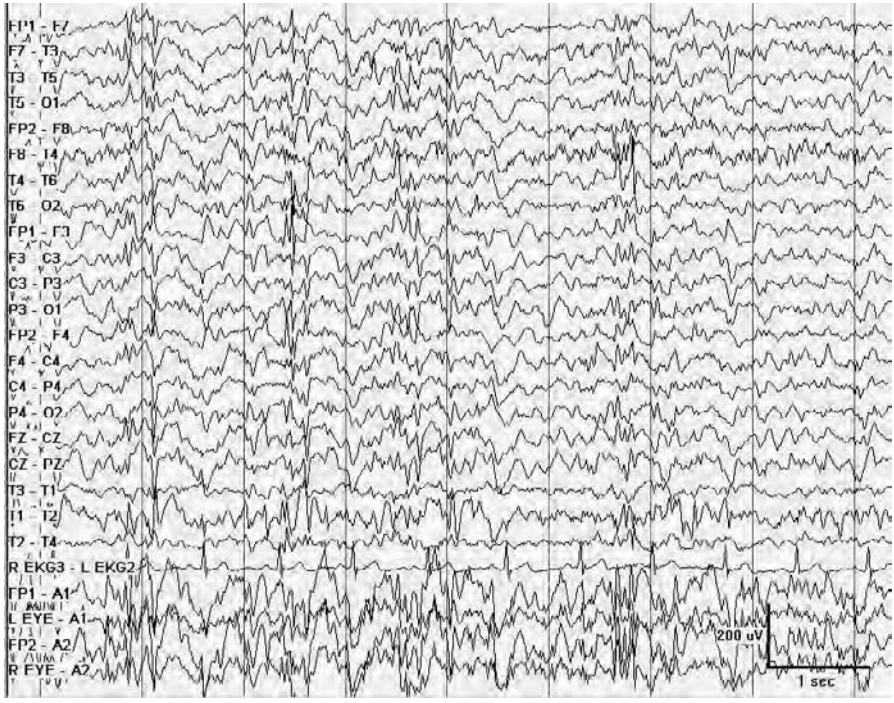
## LAFORA DISEASE

Lafora disease (LD), is a fatal form of one of the five progressive myoclonus epilepsies, and a genetic condition with autosomal recessive transmission. It may be distinguished from the Unverricht-Lundborg syndrome by mental deterioration and more rapid decline. Onset of seizures in Lafora disease begins between the ages of 6 and 19 years and typically present with tonic-clonic and focal seizures with visual manifestations. Later, low-amplitude myoclonus increased with stimulation (e.g., startle, touch, and movement) appears with a rapidly progressive dementia. Myoclonus becomes nearly continuous and may become massive as the disease progresses to death in 5-10 years from initial symptomatology.

The EEG shows focal epileptiform discharges, frequently in the occipital region, occasionally multifocal or generalized, and activated by photic stimulation. The early EEG has normal or mild diffusely slow background frequencies with single complexes and brief bursts of posterior-predominant generalized polyspikes and spike-and-wave discharges. Ultimately nearly con-




Frequent bursts of polyspikes on the EEG of a patient with Lafora body disease.

tinuous generalized polyspikes, polyspike-and-waves, with a marked response to intermittent photic stimulation appear with progression of the disease (*see* figure). The EEG abnormality then progresses with a greater degree of background slowing, frequent generalized polyspikes, and spike-and-wave discharges, in addition to and multifocal spikes.

The presence of Lafora bodies in the tissues of target organs is diagnostic for LD. Intracytoplasmic inclusion bodies containing polyglucosans are found in the brain, skin, liver, and skeletal muscle. Round or oval periodic acid Schiff-positive glycogen B particles (Lafora bodies) are evident in the sweat glands on skin biopsy. Laforin is tyrosine phosphatase, which is a protein involved with neuronal growth and development [1]. Mutations of the EPM2A and EPM2B genes on chromosome 6, which codes for laforin, have been isolated and cause the progressive decline in cognition and refractory epilepsy [1]. Additionally, malin, which is an E3 ubiquitin ligase, may be inherited in a recessive fashion to prevent degradation of laforin and contribute to LD [2].

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# LAMOTRIGINE (LAMICTAL®)

Lamotrigine (3,5-diamino-6-[2,3 dichlorophenyl]-1,2,4 triazine) is a phenyltriazine that is structurally unrelated to any other AED in current use; it is available in 5, 25, 100, 150, and 200 mg tablets. In animal models it has shown an AED profile similar to that of phenytoin and carbamazepine, stabilizing the inactive state of the sodium channel. Its antiepileptic action is probably related to its inhibitory effect on glutamate release and stabilization of neuronal membrane voltage-sensitive sodium channels. The pharmacokinetics in normal human subjects includes a near-complete bioavailability of 98%, 55% protein binding, a long plasma half-life of approximately 24 hours, and linear kinetics. Enzyme-inducing AEDs reduce its half-life to approximately 12-15 hours, and VPA increases it to about 60 hours. Lamotrigine undergoes hepatic glucuronidation and renal excretion. Lamotrigine has demonstrated efficacy and has received approved by FDA for use as adjunctive therapy in children 2 years and older for partial seizures, generalized seizures associated with LGS, and primary GTC seizures, and for conversion to monotherapy in patients at least 16 years of age with partial seizures [1-3]. Lamotrigine is also approved for use in bipolar disorder. In the initial RCTs of patients with intractable focal seizures already on other AEDs, lamotrigine reduced seizures by 50% in approximately one quarter to one third of patients, with a median seizure frequency decreased by 20-36% [1].

The drug is well tolerated and has not demonstrated evidence of significant adverse effects on memory, attention, concentration, motor speed, language, or cognition. Skin rash has received a lot of attention, but monotherapy studies demonstrated no significant differences when compared with carbamazepine [4]. Stevens-Johnson syndrome and serious hypersensitivity rash occurred in 0.3% of adults and 1% of children and were increased by rapid titration and concurrent use with VPA. Dosing recommendations are dependent upon the co-mediation used and usually indicate titration of optimal doses over 1-2 months.

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# LANDAU-KLEFFNER SYNDROME

Landau-Kleffner syndrome (LKS) is an acquired epileptic encephalopathy. characterized by an acquired aphasia, epileptiform discharges on the EEG, epileptic seizures in most cases, and behavioral problems. The onset of LKS occurs between age 3 and 8 years but may occur as early as 2 years or as late as 14. Most affected individuals are males. In LKS, deterioration of language function with IEDs on EEG occurs commonly with seizures and behavioral disturbances.

Normal development occurs with a loss of language function after 2 years of age. A progressive loss of language supervenes in previously normal children. Initial presentation is with comprehension difficulties, verbal agnosia, followed by expressive problems and intact hearing. Resolution is age-dependent and improves with early language therapy. Mutism may develop with an inability to recognize familiar sounds (auditory agnosia). The language dysfunction may have different manifestations, fluctuate, or change forms during the course of LKS, though later expressive aphasia becomes notable. No relationship between the EEG abnormality and type of aphasia has been shown to be reproducible.

Seizures usually are infrequent, and the treatment of epilepsy patients with LKS has shown little impact of successful seizure control on the aphasia. Less often, repeated seizures occur, especially at night. The clinical phenomenonology of the seizures is varied, with partial motor seizures with and without impaired consciousness appearing most conisistently. GTC seizures may also be encountered during sleep. Todd's phenomenon is particularly common. Seizures are usually well controlled with AEDs and remit by 15 years of age, though most patients are left with residual language and cognitive deficits.

The Landau-Kleffner syndrome may present with attention deficit disorder, hyperactive behavior, personality disturbances, affective problems, and cognitive regression separate from the frustration associated with the aphasia. Up to 50% of patients with LKS have some behavioral difficulties. Hyperactivity is common, though apathy may also occur, in addition to impulsivity and aggressiveness. Organizational difficulty, impaired writing, loss of social functioning, repetitive behaviors, and global cognitive regression may also occur.

The EEG is abnormal with IEDs despite the fact that clinical seizures are absent in 30% of patients [1]. Initially, the background rhythm is normal. Repetitive high-amplitude spikes and spike-waves (sometimes focal) supervene and are maximal in the centrotemporal regions, reflecting a perisylvian substrate. The IEDs are often bilateral and independent, and they may have a left- or right-sided predominance. The primary auditory cortex has been implicated despite the presence of extrasylvian or multifocal IEDs [2]. During slow-wave sleep, continuous spike-wave discharges are commonly seen [1-3], raising the possibility of a relationship to the syndrome of epilepsy with continuous spikes and waves during slow sleep. A trial of high-dose steroids for 6-12 weeks has been recommended for patients with LKS. Benzodiazepines, ethosuximide, valproic acid, and immunoglobulins have been effective in treating seizures. There is a complex

relationship between the aphasia, seizures, and EEG correlates. Multiple subpial transaction has been used; patients with epilepsy, language regression, treatment intractability, and evidence of focality are candidates for operation [3].

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## LANGUAGE

The hemispheric location of language function is dependent upon cerebral dominance. Language function is processed by reception of written or spoken words through cortex located at the supramarginal and angular gyrus of the anterior parietal lobe in Wenicke's area. The temporal lobe serves to integrate language within the dominant hemisphere, while expression of language is effected through the posterior-inferior frontal lobe at Broca's area. More posterior temporal-occipital lobe connections serve visual functions mediated by primary visual cortex involved in the visual interpretation of language.

The theory of language organization in the brain is largely based upon observational data from patients with traumatic brain injury, cerebrovascular disease, tumor involvement, and functions determined during epilepsy surgery evaluations [1]. Sites associated with expression of language through generation of speech function are variably located along the cortex and can go several centimeters beyond the sylvian fissure outside the classic anatomic boundaries of Broca's area in the face-motor cortex [1]. Functional recovery has been noted using functional neuroimaging and intraoperative stimulation in patients who experience deficits from structural lesions due to redistribution of intact neural networks [1].

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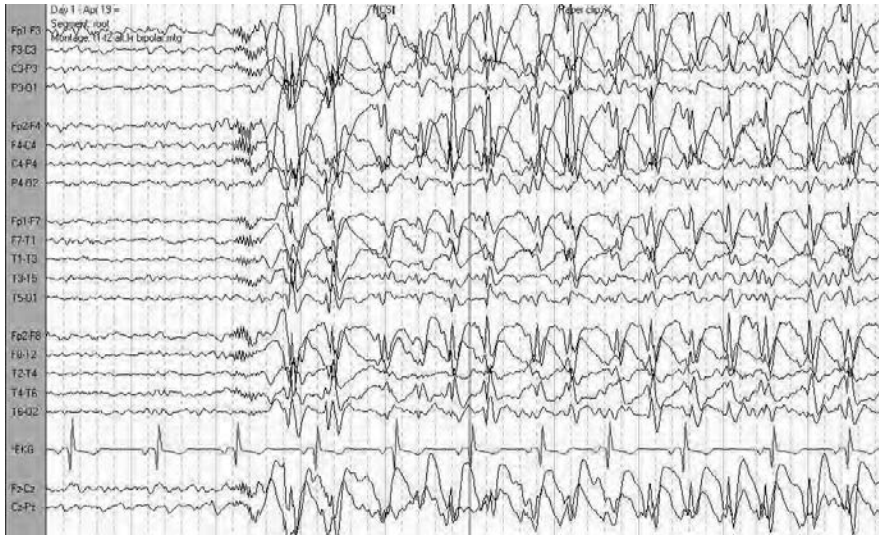
## LENNOX-GASTAUT SYNDROME

Lennox-Gastaut syndrome (LGS), also called Lennox syndrome, is one of the encephalopathic (symptomatic) generalized epilepsies with characteristic EEG abnormalities. LGS is a severe epileptic encephalopathy of childhood that describes a group of PWE characterized by the clinical triad of multiple mixed

generalized seizure types, including tonic seizures, atonic seizures, and atypical absences; interictal EEG abnormalities with slow spike-and-wave discharges during wakefulness, abnormal background rhythm, and paroxysmal runs of rapid fast activity during non-REM sleep; and cognitive dysfunction that occurs in nearly all patients. The Lennox-Gastaut syndrome accounts for approximately 3-5% of childhood epilepsies, although higher percentages are seen in referral centers. Onset usually occurs before 8 years of age, and the syndrome is most common at age 2-6 years. Lennox-Gastaut syndrome may appear in previously normal children (25-30%) or may appear secondarily in the context of a preexisting insult, such as West syndrome (30-40%) [1]. Other predisposing factors include head trauma, malformations, CNS infections, tumors, cerebral dysgenesis, and vascular injuries.

*Tonic seizures*, the characteristic seizure type in LGS, are present in up to 90% of patients when sleep recordings are obtained. These seizures involve the trunk, typically symmetrically, though sometimes with lateralization. Seizures may be brief, with abrupt upward tonic eye deviation (*sursum vergens*) and respiratory disturbance. Seizures may be mild and are common during sleep, and clinical manifestations may often be missed without continuous EEG recording. While tonic seizures may involve the neck flexors and facial muscles, when the extremities are involved, falls may occur and result in injury. Clinically, difficulty distinguishing tonic seizures from atonic seizures may occur, resulting in a *drop attack*. When tonic seizures are brief, difficulty distinguishing them from myoclonic seizures may exist. When they are prolonged, they may result in a vibratory component leading to a mischaracterization as a GTC seizure. Ictal EEG shows rapid bilateral rhythmic spike or sharp activity predominantly over the vertex and anterior head regions (generalized paroxysmal fast activity) preceded by a flattening (electrodecremental) phase, or with slow spike-and-waves. Postictal EEG suppression is minimal or absent. *Atypical absence* seizures last between 5 and 25 seconds with an incomplete loss of consciousness. These seizures are associated with progressive loss of tone beginning in the face or neck muscles, often with eyelid flutter. The EEG shows irregular 2-2.5 Hertz bilaterally symmetric, spike-and-slow wave discharges. Seizures are not induced by hyperventilation or photic stimulation. *Atonic seizures* present as drop attacks or falls in association with a brief myoclonic movement (*see also* Drop Attacks). Other seizure types, including generalized tonic-clonic seizures, partial complex seizures, or unilateral clonic seizures, may be seen in Lennox-Gastaut syndrome. Nonconvulsive status epilepticus with tonic seizures and obtundation are seen with reports of up to 95% of patients with LGS [1].

The waking EEG shows diffusely slow posterior dominant rhythm and frequently intermixed slowing. Poor sleep architecture is seen with alteration in sleep cycling. The interictal EEG in LGS is characterized by 2-2.5 Hz slow spike-and-wave activity (*see* figure) associated with multifocal temporal or frontal spikes, polyspikes, and slow-wave discharges in three quarters of patients. Although nonspecific, the slow spike-and-wave EEG pattern is funda-



EEG in a patient with LGS. Note the slow spike-and-wave burst, diffusely slow background, and preceding burst of GPFA.5

mental to the diagnosis of LGS. During slow-wave sleep, slow-spike and slow-wave discharges are seen diffusely and synchronously. Generalized paroxysmal fast activity with runs of ≥10 Hz spikes are considered an integral feature of LGS on EEG and is most prominent with sleep recording and an electrographic association of clinical and subclinical tonic seizures. Ictal EEG has various manifestations.

In children with LGS, diffuse cognitive dysfunction may not be evident at onset but become apparent with time, occurring in over 75% of patients with initially normal mental status [1]. Severe cognitive deficits are recognized more often with seizures that begin before 3 years of age, those with frequent intractable seizures, or those with symptomatic causes. Psychiatric and behavioral disturbances are frequent and often severe, with early progressive intellectual decline, learning difficulties, aggressive behavior, and personality disturbances such as aggressivity and attention deficits common.

Nonspecific abnormalities are noted on neuroimaging, with atrophy a common finding on CT brain scans. Similarly, pathologic analysis has revealed nonspecific neuronal loss without consistent congenital brain abormalities unless a specific symptomatic etiology is present. The differential diagnosis of LGS includes myoclonic-astatic epilepsy, neuronal ceroid-lipofuscinoses, continuous spike waves during slow sleep, and other encephalopathic generalized epilepsies.

Seizures associated with LGS are notoriously resistant to treatment, with a satisfactory response occurring in < 20% of cases. Benzodiazepines have been frequently used, but tolerance and side effects (primarily sedation) have presented problems. A paradoxical precipitation of tonic seizures has been re-

ported to occur with benzodiazepines in LGS. Sodium valproate has been more effective in cryptogenic LGS with a broad spectrum of activity in controlling myoclonic, atypical absence, and atonic seizures. Other effective agents include lamotrigine, topiramate, and felbamate, though felbamate may have serious side effects (*see* Felbamate [Felbatol®]). Older AEDs including phenobarbital and ethosuximide may have a role in the treatment of seizures with LGS. Carbamazepine and gabapentin may exacerbate seizures. The ketogenic diet has been shown to be effective in LGS and other encephalopathic generalized epilepsies. Early use of corticosteroids occasionally provides surprisingly beneficial results, though a high rate of relapse usual limits their use to acute repetitive seizures and status epilepticus. Surgery is designed to be palliative, with vagus nerve stimulation demonstrating utility. Corpus callosotomy has been effective in reducing drop attacks and may be more useful for the cryptogenic form of LGS than those with previous West syndrome, resulting in more than two thirds of patients with LGS being seizure-free when completion of the corpus callosal section is performed.

The overall prognosis for LGS is poor. Progressive deterioration of mental development, behavior, and seizure occurrence is unfortunately the rule, and few patients with LGS lead independent adult lives. Seizures occur daily in most patients and may be interspersed with episodes of status epilepticus, with a greater risk of morbidity and mortality. There is progressive decline in intellect with psychiatric and personality problems, occasionally with psychosis. The clinical features may remain constant in adulthood or give way to other seizure types, most frequently partial-onset seizures. Remission is unusual, and poor prognostic signs include a preceding West syndrome, early onset before 3 years of age, an underlying symptomatic etiology, greater frequency and multiplicity of seizure types, and repeated status epilepticus.

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## LEPTIN

Leptin is a hormone associated with human eating behavior. Leptin is involved in the critical role of balancing energy expenditures of the body, and the primary physiologic role is in defense of body fat. Obese people have high blood levels of leptin. When leptin is reduced either by weight loss or genetically, this triggers hypothalamic and cortical effects of regulating food-seeking behavior and a reduction of energy expenditure and hence serves to provide information to the brain about energy stores. In epilepsy, leptin has been evaluated as a function of weight gain and found to be associated with a differential effect among AEDs (e.g., VPA).

## LEUKOENCEPHALOPATHY

Leukoencephalopathy refers to a pathologic condition that affects the white matter of the brain. Subacute sclerosing panencephalitis (Van Bogaert disease) is a chronic viral infection (leukoencephalitis) affecting children and adolescents following measles infection that is characteristically associated with seizures (*see* Subacute Sclerosing Panencephalitis). Acute hemorrhagic leukoencephalopathy of Weston-Hurst is an acute, fulminating, demyelinating disorder of unclear etiology related to postinfectious encephalomyelitis. Progressive multifocal leukoencephalopathy is a widespread demyelinating disorder of brain and spinal cord. It has been associated with previous papovavirus infection, systemic neoplasia, or acquired immunodeficiency. Seizures may occur and are usually of partial onset similar to other leukoencephalopathies.

Leukoencephalopathies may also reflect heredodegenerative disorders of the central nervous system, predominantly involving white matter, that are due to an inborn error of metabolism. Metachromatic leukodystrophy, globoid leukodystrophy due to cerebral galactosidase deficiency (Krabbe's disease), Pelizaeus-Merzbacher disease (sudanophilic leukodystrophy), adrenoleukodystrophy, Canavan's disease, and Alexander's disease are leukoencephalopathies with various ages of onset that are associated with an encephalopathy that is often severe and frequently may be associated with seizures.

## LEUKOPENIA

Leukopenia refers to a reduction in the serum white blood cell (WBC) concentration and may occur in response to AED use. Transient leukopenia occurs in approximately 12% of patients treated with carbamazepine, with a lesser number associated with a persistent effect. Leukopenia has been defined as a WBC count of <4,000/mm3, while moderate leukopenia occurs between 3,000 and 3,500/mm3, and severe leukopenia between 2,000 and 3,000/mm3.

## LEVITIRACETAM (KEPPRA®)

Levitiracetam (LEV), the S-enantiomer of alpha-ethyl-2-oxo-1-pyrrolidine acetamide, is currently used as adjunctive therapy for partial-onset seizures in adults and children 4 years of age and older [1]. However, LEV is also effective in monotherapy, with efficacy that compares to extended-release carbamazepine in addition to being well tolerated [2]. In addition, LEV appears to posess a broad spectrum of activity for multiple seizure types, including partial-onset as well as generalized seizures including myoclonic seizures [3]. It has a fast and sustained efficacy upon initiation and demonstrates good tolerability in both children and

adults. It has a unique mechanism of action and binds to the synaptic vesicle protein 2A. The pharmacokinetic profile is favorable, with a lack of enzyme-inducing properties and a low potential for drug-drug interactions, making it a promising AED for treatment of epilepsy in the elderly. It is not hepatically metabolized but rather is hydrolyzed within the blood and subsequently excreted at a rate that is dependent upon renal elimination; lower doses are required with renal insufficiency. The adverse events include headache, fatigue, somnolence or insomnia, dizziness, and neuropsychiatric abnormalities including depression and rarely psychosis. Doses range from 500 to 3,000 mg/d.

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## LIDOCAINE (XYLOCAINE®)

Lidocaine is a local anesthetic agent that may act as a convulsant drug to precipitate seizures when administered intravenously. Seizure induction is most commonly seen in the setting of cardiac conditions for its antiarrhythmic properties and has been a common mode of therapy during advance cardiac life support. Lidocaine has also been used therapeutically in the past as a treatment for status epilepticus resistant to other medications [1]. The principal adverse events observed in these cases have been cardiovascular in origin, with blood pressure, EKG, and continuous EEG monitoring required.

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## LIPIDOSES

Lipidoses are hereditary disorders of autosomal recessive inheritance leading to lipid deposition in neurons. Lipidoses previously were called amaurotic familial idiocies, but successive classifications have been based on analysis of abnormal storage and deposition substances and subsequent identification of the relevant enzymatic deficiency. Lipidoses now include the sphingolipidoses (*see* Sphingolipidoses), the ceroid lipofuscinoses (*see* Ceroid Lipofuscinoses), the mucolipidoses, and disorders due to the accumulation of simple lipids, includ-

ing phytanic acid (Refsum disease), triglycerides, and cholesterol esters. Sphingolipidoses and ceroid lipofuscinoses may present with seizures during the course of the disease state.

## LISSENCEPHALY

Lissencephaly is a diffuse cortical malformation caused by an incomplete neuronal migrational disorder that occurs during early brain development. This abnormality of cerebral cellular migration results in an absent or reduced gyration and a broadened but poorly organized cortex with a reduced total surface area. Lissencephaly is one of the most common neuronal migrational disorders. Isolated lissencephaly is referred to as "classic" or type 1 lissencephaly (Miller-Dieker syndrome) and is the result of defective neurogenesis and nucleokinesis that results in abnormal layering and gyration of the cortex. A spectrum of structural aberration occurs from a variable combination of agyria and pachygyria to complete agyria and a smooth cortex without gyration. The clinical manifestations with the more severe phenotypes include profound mental retardation, fixed motor deficits, and a reduced life expectancy [1]. Seizures are seen in the majority of patients and are often intractable to AEDs. They are usually manifest as infantile spasms in the first year of life and evolve to symptomatic generalized epilepsy with mixed seizure types, or they may manifest as partial seizures. A majority of patients with clinical manifestations of lissencephaly possess a gene mutation of LIS1 or the XLIS (DCX) doublecortin gene [2]. Patients with deletions of the entire LIS1 gene on chromosome 17p13.3 predict a more severe reduction of gyration in the posterior regions, while those with DCX-associated lissencephaly are more pronounced anteriorly, though the association does not appear to predict phenotypic severity [2]. Neuroimaging is optimal with brain MRI scans, which are usually diagnostic of lissencephaly. Type 2 lissencephaly is also known as "cobblestone lissencephaly" due to the shallow groves in the cortex resembling a cobblestone street. Many syndromes of lissencephaly type 2 (i.e., Walker-Warburg syndrome, Fukuyama muscular dystrophy) are associated with muscular dystrophy and weakness rather than seizures.

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## LIVER DISEASE

The liver is the primary site of drug metabolism in humans. Therefore, liver disease (LD) can significantly alter the pharmacokinetics of all drugs, includ-

ing AEDs, and changes in drug metabolism vary according to the disease process and degree of involvement. LD may arise as a complication of AED treatment in PWE, or can limit individual AED selection in patients with advanced liver disease.

Acute hepatopathies, drug-induced (idiosyncratic) hepatotoxicities, and chronic liver disease are different categories of liver disease that may involve PWE. The effect of LD upon drug-binding capacity, biotransformation, and potential for toxicity is dependent upon the individual AED [1]. Acute AED-related hepatotoxicity has included hypersensitivity syndromes with skin rashes, lymphadenopathy, hepatosplenomegaly, arthralgias, renal insufficiency, and fever (*see* Barbiturates; Phenytoin). Specific drug toxicity found in particularly predisposed patients or the elaboration of metabolites because of rarely used degradation pathways (e.g., valproate) may be responsible for hepatotoxicity. Acute or subacute hepatitis is rare, with an estimated overall incidence of 0.1% for valproic acid and phenytoin and even less for phenobarbital and carbamazepine. The course of acute AED-related hepatitis is variable. If it occurs, immediate discontinuation of the offending AED is recommended, which may prevent subsequent morbidity and mortality. Other causes of hepatitis (e.g., virally mediated hepatitis) must first be excluded. Hepatotoxicity due to VPA is idiosyncratic and fortunately rare. It has been most associated with children under the age of 10 years, developmental delay, and the use of polypharmacy (*see* Polypharmacy), often during the first 6 months of treatment. The microscopic picture of AED-related hepatotoxicity is one of acute hepatocellular or mixed hepatitis with cholestasis and centrolobular necrosis. Symptoms such as nausea, vomiting, anorexia, malaise, fatigue, and abdominal pain may develop. Of the newer AEDs, idiosyncratic fatal hepatotoxicity has been associated with felbamate (*see* Felbamate). Liver transplantation is considered when irreversible or progressive liver dysfunction occurs. Selection of AEDs with low protein binding and minimal drug-drug interactions (e.g., LEV) are most useful to limit interactions with immunosuppressants or antibiotics often utilized in posttransplant recipients. The effect of steroids may be blunted by EIAEDs. Furthermore, immunosuppressants (e.g., cyclosporine) may result in neurotoxicity and produce seizures, but the use of EIAEDs may increase renal elimination of the immunosuppressant and lead to transplant rejection through reduction of circulating drug concentrations.

In some patients, chronic AED therapy might be the cause of delayed hepatocellular damage. Valproate should be avoided due to the potential for further hepatotoxicity (*see* Valproate). Reduced protein binding of highly protein-bound AEDs such as phenytoin may lead to toxicity in patients with advanced liver disease (*see* Phenytoin). In addition, sedating AEDs such as the benzodiazepines or barbiturates may precipitate hepatic encephalopathy in patients with compensated liver disease. Newer AEDs such as gabapentin, pregabalin, and levetiracetam (*see* Gabapentin; Levetiracetam; Pregabalin) may be useful AEDs of choice with liver disease given the lack of appreciable hepatic metabolism. The effect of the newer AEDs that are classified as either

weak enzyme inducers or glucuronidated during hepatic metabolism (LTG, TPM, and ZNS) remains to be elucidated. In evaluating hepatic function in a patient on AEDs, the physician should distinguish between mild changes in hepatic function, reflected by increase in gammaglutamyltransferase, alkaline phosphatase, lactate dehydrogenase, and a slight, frequently transient, increase in AST and ALT, indicating hepatic enzyme induction. These changes are usually without specific pathologic significance [1].

Chronic liver disease rarely is the principal cause of seizures. When acute liver disease occurs, seizures are usually the result of associated hypoglycemia (*see* Hypoglycemia). Reports of patients with increased seizures during liver disease have stemmed from the association of those suffering from alcoholic liver disease. Many of these patients had epilepsy associated with traumatic brain injuries or alcohol-related seizures. Seizures are also common in patients with liver disease associated with Reye's syndrome.

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## LOADING DOSE (ORAL)

There is frequently a time delay between the initiation of treatment and the achievement of a therapeutic dose or serum concentration that is dependent upon the pharmacokinetics, safety, and tolerability of the individual AED. AEDs with shorter half-lives, such as leviteracetam, may be initiated on an outpatient basis to achieve an effective steady-state concentration within 3 days. Such effects may not be achieved for up to 3 weeks with AEDs with longer half-lives such as phenobarbital. To avoid the problem of lengthy time intervals to reach a steady-state drug concentration, a loading dose of some AEDs may be given (e.g., double the daily dose for 2-3 days). The AEDs that may be successfully loaded orally include phenytoin; AEDs that can be initated rapidly orally on either an inpatient or outpatient basis include valproate, gabapentin, and levetiracetam. AEDs that can be started rapidly orally (inpatient only is recommended, otherwise titration as an outpatient) include felbamate, gabapentin, topiratmate, oxcarbazepine, and pregabalin. For some drugs such as carbamazepine and lamotrigine, attaining an immediate therapeutic dose is impossible either due to intolerable side effects, as in the case of carbamazepine, or due to safety issues, as in the case of lamotrigine [1]. AEDs that can be initiated intravenously include phenytoin, phenobarbital, valproate, and levetiracetam. Although poorer tolerability with brief symptoms of toxicity may be seen with loading doses, therapeutic AED levels may be reached in a briefer period of time, often within about 3 days, with the use of oral loading techniques [2].

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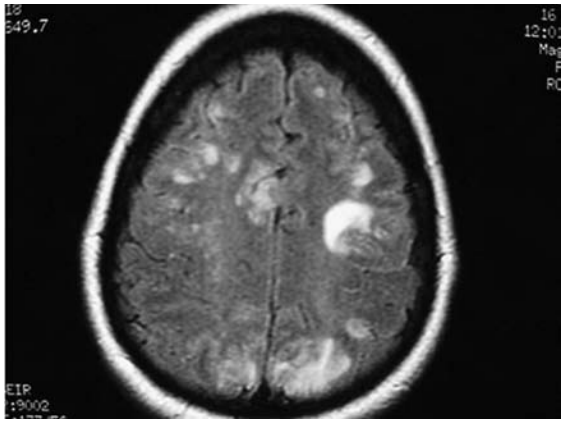
## LORAZEPAM (ATIVAN®)

Lorazepam (LRZ) is a benzodiazepine used as a first-line drug in the treatment of generalized convulsive status epilepticus (*see* Status Epilepticus), though it is approved as an anxiolytic and preanesthetic agent by the FDA. LRZ is effective in approximately 80% of a variety of types of status epilepticus, and has also been used as a chronic maintenance AED; however, tolerance usually limits its applicability. Lorazepam has also been used successfully in neonatal status epilepticus and sublingually in children with acute repetitive seizures. Limited reports of postanoxic myoclonus have also been described. Pharmacokinetic characteristics indicate that LRZ is rapidly absorbed orally (similar to diazepam), is approximately 90% protein bound, and has plasma levels in 90-120 minutes, with peak brain concentrations occurring 30 minutes after use. Sublingual administration leads to higher peak levels more rapidly (within 60 minutes) but without significant differences seen after 2-3 hours. LRZ has a longer half-life than diazepam (about 15 hours in healthy individuals) despite a first-pass effect that results in an absolute systemic absorption of only 29% compared with intravenous use. LRZ binds to the high and low-affinity benzodiazepine receptors to produce its effect and undergoes glucuronidation as the primary means of clearance prior to renal excretion. It is more effective and has a longer duration of action than diazepam and less respiratory depression, with fewer than 4% of cases resulting in respiratory depression, indicating its relative safety. Side effects have included sedation, dysarthria, amnesia, mental slowing, in addition to hallucinations and delirium. In children, doses of 0.05 mg/kg in children under 12 years of age to adult doses of up to 0.5 mg/kg (total 1-8 mg) have been used at rates of 2 mg/min to treat status epilepticus. Initial doses of 4 mg i.v. may be repeated in 10 minutes if there is no response to treatment.

## LUPUS

Systemic lupus erythematosus (SLE) is a multiorgan system autoimmune disease that often involves neuropsychiatric sequelae during the course of illness. SLE is common, with an overall prevalence of approximately 50/100,000, with



Axial images on a brain MRI of a 40-year-old female with subacute headache, confusion, and new onset of acute repetitive seizures.

an incidence that has more than tripled over the last 40 years [1]. SLE is characterized by circulating autoantibodies and immune complexes and affects primarily young non-white women. Widely accepted diagnostic criteria include neurologic involvement including seizures. Neurologic involvement usually portends a poor prognosis and involvement is a harbinger for a poor prognostic sign that is second only to renal disease [1]. Of the major neuropsychiatric symptoms that may occur, seizures are one of the most commonly reported features, occurring only second to headache when comparing neurologic symptoms either early in the course or at any time during the course of the disease. In a large study, the mean latency from time of diagnosis to intitial involvement was 5.75 years, affecting patients (mostly women) at a mean of 41 years of age [1]. The true incidence of seizures is difficult to determine in SLE. Overall, seizures have been reported in 14-25% of patients [1,2], though CNS involvement up to 42% has been noted [1]. Seizures may be generalized or focal and typically occur with other CNS manifestations. Seizures may occur as an early presenting sign in 8-27% of patients [1] or as the intial presentation in 10% of those with CNS involvement [1], presenting as an isolated seizure (*see* Single Seizure). EEG abnormalities are not uncommon though they tend to be non-specific.

AEDs can cause falsely positive serologic testing for SLE and create drug-induced SLE. Lupus-like reactions may occur as a rare side effect of AEDs, including phenytoin, barbiturates, ethosuximide, carbamazepine, and valproate. AED-induced SLE resembles idiopathic lupus erythematosus but rarely is associated with CNS involvement. Although idiopathic and drug-induced lupus may coexist, disappearance of lupus after stopping AEDs confirms a drug-induced etiology, and antihistone antibody presence may indicate drug-induced lupus as the likely culprit.

In drug-induced lupus, antibodies to the histone complex of DNA are found, but antibodies to the double-stranded DNS are absent and complement levels are normal. Seizures that occur during a flare of SLE may not require chronic AEDs and primary treatment of the inflammatory response with steroids and cytotoxic agents as well as correction of electrolyte imbalances may be adequate. The presence of CNS involvement may reflect a more severe condition and a poorer prognosis.

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## LYRICA®

*See* Pregabalin.

# M

## MAGNESIUM

Magnesium is involved at the cellular level in the mechanisms of neuronal excitation by its effect in blocking calcium entry into the cells. Low extracellular magnesium may increase membrane excitability. Part of the *N*-methyl-D-aspartic acid (NMDA) receptor-cation channel subtype of the glutamate receptor affecting neuronal excitation is regulated by Mg2+, thus having theoretical antiepileptic properties. Magnesium sulfate has been widely used by obstetricians in the United States for the treatment of eclampsia (*see* Eclampsia) [1]. Mechanistically, magnesium has the potential to reverse cerebral arterial vasoconstriction, which is operational in maternal vasospasm associated with eclampsia. Benzodiazepines and phenytoin have been advocated by others when epilepsy or impaired consciousness is present during eclampsia.

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## MAGNETIC RESONANCE IMAGING (MRI)

An important role of high-resolution brain MRI is to define the presence of a structural abnormality responsible for epilepsy. However, brain MRI may be normal in up to one third of patients undergoing anterior temporal lobectomy (ATL) for LRE [1].

A variety of pathologic etiologies are able to be detected using a dedicated epilepsy protocol, with characteristic appearances that may be present, including mesial temporal sclerosis, cortical dysplasia, primary tumors of the brain, vascular malformations, and encephalomalacia [1,2]. The most successful outcome after resective epilepsy surgery is found when high-resolution MRI is concordant with other aspects of the presurgical evaluation. Dedicated protocols for imaging in epilepsy patients have been developed to focus the suspected regions of interest [2]. MRI has several advantages over head CT scanning. Higher-resolution studies are capable of demonstrating small lesions using MRI, particularly in the mesial and inferior aspects of the temporal lobe where CT is limited by bone artifact. MRI may more clearly define lesions revealed on CT scan such as cavernous angiomas, with surrounding hemosiderin,

cortical dysplasias, and mesial temporal sclerosis. MRI is very sensitive, and overinterpretation of findings must be approached with caution. With interhemispheric asymmetry, the pathologic significance may be difficult to interpret. Increased T2 signal intensity may be seen with histologic lesions as well as with edema. Reversible abnormalities can occur after recurrent seizures and status epilepticus. Guidelines for neuroimaging in epilepsy suggest obtaining T1, T2, three-dimensional volumetrics, fluid attenuated inversion recovery (FLAIR), and fast-spin echo inversion recovery sequences in transverse, axial, and sagittal planes [3]. MRI spectroscopy and functional MRI are techniques that may complement anatomic MRI.

**Example of Dedicated Brain MRI Epilepsy Protocol Performed on GE 1.5T LX HORIZON Version 9.1**

| | TR | TE | TI | flip | Thickness | Matrix | Nex |
|---|---|---|---|---|---|---|---|
| T1 Flair sag | 2000 | 7.5 | 750 | 90 | 5 skip 2 | 256x256 | 2 |
| DWI ax | routine | | | | | | |
| GRE ax | 500 | 20 | | 20 | 5 skip 2 | 256x128 | 1 |
| Flair ax | 8000 | 120 | 2200 | 90 | 5 skip 2 | 256x 224 | 1 |
| T2 ax FSE | 5000 | 85 | | 90 | 5 skip 2 | 512x256 | 2 |
| Flair cor | 8000 | 120 | 2200 | 90 | 4 skip 1 | 256x224 | 1 |
| T2 cor FSE | 5000 | 85 | | 90 | 4 skip 1 | 512x256 | 2 |
| T2 cor IR | 5500 | 20 | 200 | 90 | 4 skip 0 | 256x256 | 2 |
| 3D fspgr-IR preped cor | 14 | 6 | 600 | 15 | 1.6mm zipx2 | 256x192 | 1 |

Source: Tatum WO, Benbadis SR, Hussain S, et al. Ictal EEG remains the prominent predictor of seizure-free outcome after temporal lobectomy in epileptic patients with normal brain MRI. Seizure 2008;17:631-636.

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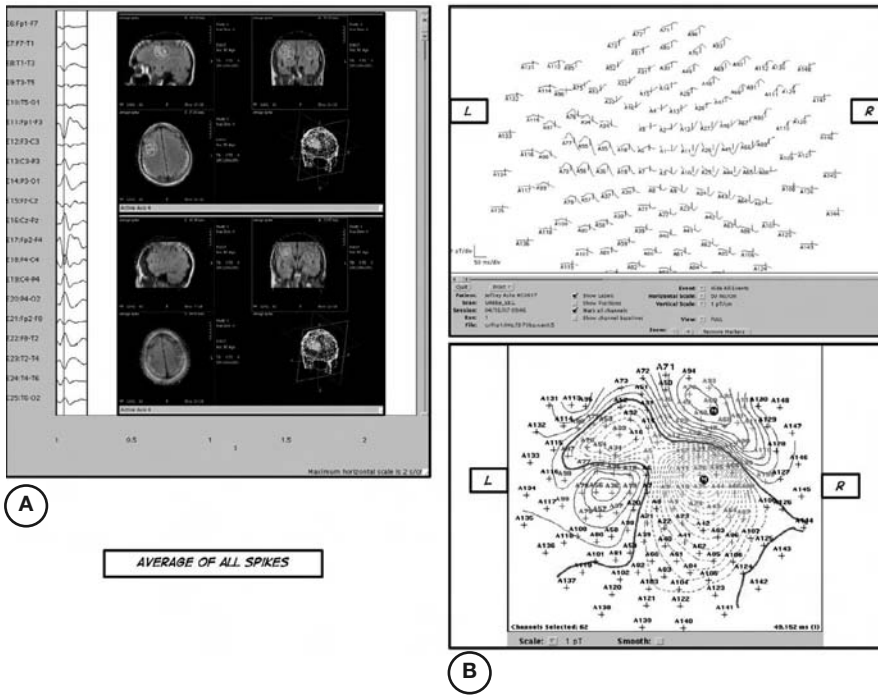
## MAGNETOENCEPHALOGRAPHY (MEG)

MEG is a noninvasive direct measure of the brain's normally inherent electrophysiologic capability of neurons to produce magnetic fields [1]. Transmembrane ion movements in active neurons generate magnetic fields that may be recorded by external devices [2]. Since the magnetic fields produced by the brain are extremely weak, sensitive superconducting quantum interference devices (SQUIDs) and magnetically shielded rooms are used to record the MEG




MEG demonstrating magnetic sources (A) combined with MRI and contour maps (B).

from neuronal sources within the brain [1,2]. Early systems used a single probe, resulting in a long laborious testing period; more recent multiprobe machines use up to 248 channels assembled with SQUIDs arranged radially around a central probe. Epileptiform discharges that have been identified on EEG can be measured by averaging techniques and localized to provide information regarding the direction of current flow. The functional information is often combined with structural information from brain MRI to provide three-dimensional information used in the selection process of patients for resective epilepsy surgery. MEG has a high temporal (in milliseconds) and spatial resolution (in millimeters), in contrast to scalp-based EEG. The depth of the generator can be more easily determined, and the sources are recorded extracranially and do not carry the risk that invasive electrodes present. MEG is unaffected by the skull in contrast to scalp-based EEG. Modeling (single equivalent dipole analysis) of the spatial distribution of magnetic fields allows intracranial calculation of the intracranial source localization for dipole "fitting". Time series waveforms that contain an interictal spike are projected into a two-dimensional format and, via mathematical models, demonstrate the source of the IED. MEG measures current flow tangentially at the surface of the brain, while EEG measures radial flow preferentially, though the two techniques are complementary, permitting information regarding activity along the banks of the sulci or the tops of the gyri.

A number of studies have reported that MEG is superior to EEG with respect to spike-detection sensitivity and localization relative to extratemporal epilepsy [1-3]. The inverse problem of source localization is less problematic with MEG than EEG due to the lack of distortion of the magnetic properties with MEG as opposed to the electrical properties with EEG. Therefore, IEDs are in general more abundant in MEG than EEG, the spikes are of briefer duration, and in many patients subpopulations of IEDs are found with different topographic maps, indicating better localizing properties with MEG for interictal IEDs than with EEG [2]. In addition, there has been clinical value noted in patients with recurrent seizures after epilepsy surgery through resection of clusters of MEG source spikes adjacent to the margins of prior resection.

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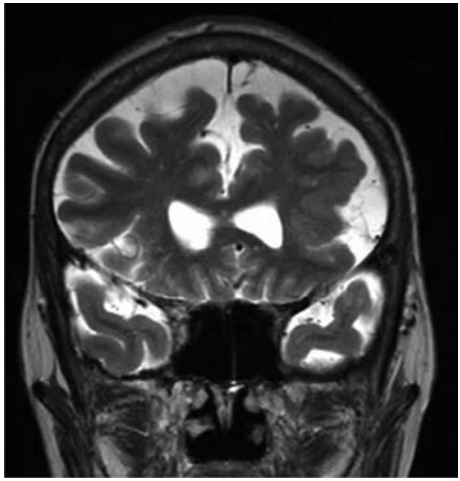
## MALFORMATIONS

Cerebral malformations include *malformations caused by epilepsy*, with major or minor malformations in newborns of mothers with epilepsy having been indirectly attributed to AEDs taken during pregnancy, genetic factors, and environmental factors (*see* Pregnancy). In addition, *malformations causing epilepsy* are also common with epilepsy beginning in the newborn or infant, presenting with neonatal seizures or West syndrome. Some effects of cerebral malformations may also appear in childhood or even in adulthood. There exist a wide variety of malformations with different pathophysiologic origins, morphologies, clinical significances, and symptomatic presentations. The diagnosis of a brain malformation is confirmed postmortem, though with the advent of high-resolution, high-field-strength MRI of the brain, in vivo diagnosis of malformations is possible [1]. Some malformations are associated with a characteristic clinical presentation. For example, chromosomal abnormalities such as Aicardi's syndrome present in females with infantile spasms but also have retinal lacunae and an absent corpus callosum. Similarly, brain malformations may be seen with inborn errors of metabolism, such as pyruvate dehydrogenase deificiency (associated with infantile spasms or myoclonic seizures in infancy) that is also usually associated with agenesis of the corpus callosum. Other malformations may present with seizures and cognitive or somatic abnormalities, including hydrancephaly, porencephaly, schizencephaly, holoprosencephaly, agenesis of the corpus callosum, or those associated with multiple brain



Cortical dysplasia of the left frontal lobe depicting a malformation of cortical development on MRI in a patient with localization-related epilepsy and focal seizures.

malformations. Microcephaly is associated with epilepsy in approximately 40% of cases, though rarely are seizures the only presenting clinical feature. There may also be disorders that occur with neuronal migration, including lissencephaly, pachy gyria or polymicrogyria, and hemimegalencephaly. In addition, agenesis or hypoplasia of all or part of the corpus callosum may be noted in patients with cerebral dysgeneses and be associated with genetic defects [2]. Focal cortical dysplasia is a common cause of refractory localization-related epilepsy, though in this case, a genetic basis is not found. The "balloon cells" that may be seen on histologic examination with large swollen neurons are a characteristic feature of these malformations. Nodular heterotopia is one of the more common (15-20%) forms of cortical malformation, responsible for 2% of patients with epilepsy. Subcortical band heterotopias also cause medically refractory seizures, developmental delay and motor disability, and multiple seizure types, but few improve with seizure surgery. In all migrational malformation disorders with epilepsy, medically refractory seizures are common; seizures may begin within the first year of life, with most seizures being partial, although hypsarrythmia and burst suppression patterns occur. With lissencephaly, more than 90% will have seizures. Traditionally, classifications of the malformations of cortical development have been based upon anatomic morphologies, though the discovery of gene mutations underlying the malformations have begun to subclassify types based upon information related to genetic transmission [1-3].

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## MALINGERING

Malingering is infrequent in patients with nonepileptic seizures (*see* Psychogenic Nonepileptic Seizures) when compared to those that manifest con-

version disorder with seizures [1]. Patients who malinger actually "fake" symptoms for some secondary gain-usually having monetary, position, or legal implications. As such, malingering is a conscious falsification of symptoms that create benefit for the patient feigning the symptoms. While many patients with PNES are felt to be malingering, in fact, this is rare, except for those involved with litigation or incarceration. Malingering is confirmed if the individual is confronted and admits to a conscious knowledge of the symptoms for a tangible benefit.

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## MARRIAGE

Marriage may provide a stabilizing influence for PWE, but social factors affecting marriage in patients with epilepsy vary among cultures [1]. Men and women with epilepsy have lower marriage and fertility rates overall. This is likely multifactorial, associated with psychosocial consequences of epilepsy, the effects from seizures, and potentially adverse effects of AEDs inducing sexual dysfunction (*see* Sexuality). In addition, there is also a stigma associated with the genetic risks for the offspring (*see* Genetics) if PWE marry with perceived risk of malformation. Marriage between two people with an IGE may result in a higher risk of having a child with epilepsy. Social and legal barriers to PWE pursuing marriage were present as recently as 25 years ago. According to a recent 19 state questionaire study, while a significantly smaller percentage of persons with active epilepsy were married or part of an unmarried couple than those without the disorder, a greater percentage of those with active epilepsy were previously married compared with those without the disorder [2].

### References

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## MELAS SYNDROME

MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) is a progressive neurodegenerative disorder most commonly caused by the mitochondrial A3243 mutation passed only by women

to their children [1]. The onset occurs in childhood, between 2-10 years of age, and begins with muscle weakness and pain, headaches, vomiting, anorexia, and seizures. The seizures are often associated with stroke-like episodes of transitory hemiparesis, blindness, or altered mental status [1,2]. The stroke-like episodes are not ischemic but instead are symptoms associated with a metabolic blood supply mismatch. A build-up of lactic acid leads to vomiting, abdominal pain, fatigue, weakness, and exercise intolerance. There may be associated memory problems and psychiatric symptoms and hearing loss. Short stature, underweight status, migraine, diabetes, and lipomas may be more commonly seen, in addition to a progressive dementia. The diagnosis is made on clinical grounds in combination with an elevated serum lactate and muscle biopsy demonstrating "ragged red fibers" with special staining techniques. Carriers of the MELAS mutation also are prone to symptoms, and because some are treatable, early detection and proactive management may reduce the burden of disease. MELAS is one of a family of disorders of the mitochondrial respiratory transport chain, including MERRF, chronic external ophthalmoplegia, Kearns-Sayre syndrome, and Leber's optic atrophy [2].

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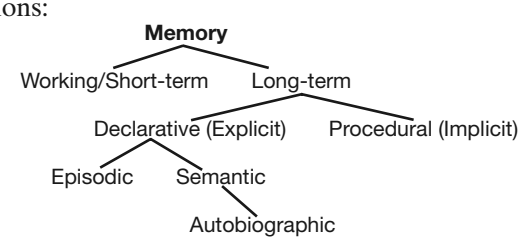
## MEMORY

Disturbances of memory are among the most common complaints of people with epilepsy. In TLE, memory impairments are well documented, which is not surprising given the associated neuroanatomy including the hippocampus and mesial structures of the temporal lobe [1]. Terms used to describe memory, including episodic, semantic, declarative, and procedural, in addition to explicit and implicit memory function, have dominated the field of neuropsychological description of memory dysfunction. Collectively, these areas control memory function pertaining to data acquisition, retention, and retrieval of recent memories. Distant memories, controlled by multiple areas throughout the brain, are usually spared, and as such, patients typically report preservation of distant memories. The following schematic and definitions may be applied to memory and its variations:



Declarative memory: Information in memory that can be retrieved explicitly.
Episodic information: Information in memory that is tied to the time and/or place of occurrence (i.e., being tied to one's past).
Long-term memory: System of storage for information stored for very long periods of time.
Procedural memory: Information in memory that facilitates a type of skill, such as motor and cognitive performance.
Semantic information: Information in memory that is generic in form without being tied to some time or place of occurrence (i.e., the fund of knowledge such as world facts).
Working memory: System of memory storage responsible for small amounts of information for short periods of time.
Verbal memory: Memory that includes the ability to generate and understand speech.
Visual memory: Memory that includes the ability to remember what is seen.
Autobiographic memory: Memory of one's personal history and identity.
Procedural (implicit) memory: Preferences, skills, and activities that can be acted upon or performed without conscious thought (e.g., driving a car).
Declarative (explicit) memory: Memory that includes the ability to store facts.

Interictal memory disorders in PWE affecting the temporal lobe often show evidence of memory-acquisition problems. Furthermore, electrical stimulation of the temporal lobes affects the laying down of memory and recall. Frontal lobe foci occasionally may produce memory disturbances as well. Possible mechanisms include (a) underlying damage to neocortex and mesial temporal areas known to be involved in memory, (b) the possibility that frequent interictal discharges may transiently disrupt cognitive processing and (c) impairment of memory by AEDs (*see* Antiepileptic Drugs). Ictal and postictal memory disturbances may be difficult to distinguish from each other. Furthermore, intermittent memory deficits may, in part, be ictal and due to intermittent subclinical seizures that affect the hippocampus and mesial structures. Seizures characterized primarily by distortion of memory are referred to as *dysmnestic seizures*. Seizure control via medications or surgery may be effective in slowing cognitive decline when seizure control occurs. During the postictal state, patients exhibit variable impairment of memory. Postictal memory disturbance may be difficult to distinguish from postictal global confusion, aphasia, or other cognitive deficits. However, some patients do appear to show a degree of anterograde or retrograde amnesia disproportionate to global cognitive disturbances in the postictal state. Verbal material is preferentially affected with left hemisphere hippocampal damage and visuospatial material with right hemisphere foci. Some of the apparent memory disturbance in people with epilepsy may be a result of their inability to register information ap-

pearing in rapid succession during standard memory tests. A variety of factors have reliably predicted the degree of memory impairment for PWE. Those with a higher IQ and greater baseline memory ability tend to display slightly fewer deficits. However, those who have suffered longer from seizures or those who have had more severe (e.g., tonic-clonic) and more frequent seizures are likely to have greater memory impairments. Other factors include localization pathology (hippocampal sclerosis vs. other) and the side of the surgery (worse for left-sided surgery).

Though surgery may be a curative option for patients with medically intractable epilepsy, it may compromise memory function. Overall memory function is most impaired in people with bilateral lesions. The single most famous case in history of memory impairment following resective surgery for epilepsy was that of a man referred to as H.M. H.M. underwent a bilateral temporal lobectomy in which 8 cm of hippocampal, amygdala, and cortical tissue was removed, resulting in severe anterograde and some retrograde amnesia. This operation has provided much of the information we know today about the effects of surgery on postoperative memory. For patients who qualify for epileptic surgery, prediction of postoperative memory functioning has long been assessed via preoperative invasive Wada testing. More recently, however, functional magnetic resonance imaging (fMRI) has started to replace Wada testing due to its high reliability and less invasive measures [2]. Activation fMRIs are useful in comparing the severity of memory impairment to the extent and location of pathologic lesions in particular areas. Unlike normal subjects, who demonstrate bilateral symmetric activation of the mesial temporal lobes, epileptic patients may show a reduced or asymmetric activation in the temporal lobe ipsilateral to the epileptogenic zone.

The risk of memory decline is also site-specific relative to the side resected. The left temporal lobe is highly associated with language and verbal memory, and resection of this area is potentially likely to result in verbal memory deficits. Resections of the right temporal lobe, on the other hand, may also show visual memory deficits but, if so, to a lesser degree and occasionally associated with improved function [3]. Data also suggest that personal semantic memory is preserved in both left and right temporal lobe epilepsy (LTLE) (RTLE) patients; it also supports the idea that the laterality of the seizure focus contributes to differences in impairment of remote memory (which encompasses both episodic and semantic memory) among TLE patients. Overall, patients with LTLE tend to show more deficits in remote memory than those with RTLE (autobiographic only), while bilateral TLE patients display the worst memory functioning of all. Preliminary evidence suggests that memory deficits are also capable of being stopped or even reversed postsurgery by postsurgical cognitive training (rehabilitation) [4].

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## MENINGITIS

Meningitis refers to an inflammation of the meninges surrounding the brain due to an infectious, chemical, or neoplastic cause. Infections of the central nervous system (CNS) are a common cause of symptomatic epilepsy [1]. Seizures result when meningitis progresses to involve the cortical surface of the brain in the form of meningoencephalitis or involve the parenchyma directly from brain abscess, both of which are associated with a greater incidence and prevalence of seizures and epilepsy. In survivors of CNS infections, the risk of epilepsy is between 6.8-8.3%, though in developed countries only 1-5% of incident cases of epilepsy are presumed to be due to prior CNS infections [2]. Worldwide, about 890,000 cases of bacterial meningitis occur each year, hence an estimated 37,000 people are at risk of developing epilepsy following bacterial meningitis [2]. Seizures are a common complication of acute bacterial meningitis and may affect approximately one third of patients early on during the illness [1]. Meningitis may result from either direct extention (trauma or surgery) or as a result of systemic "seeding" from a non-CNS infectious source. Bacterial meningitis is more likely to progress to seizures than is aseptic meningitis. The probability of developing epilepsy varies according to the etiologic agent responsible and is highest with *Streptococcus pneumonia* [3]. Neisseria meningitides, *Haemophilus influenza*, and *Streprotcoccus pneumonia* account for 80% of cases [2]. Most seizures occur within 5 years of meningitis. The risks for epilepsy include early seizures during the acute illness and a persistent neurological deficit (other than hearing loss). A high incidence and prevalence of epilepsy in developing countries is presumed to be due to a higher rate of prior CNS infections. With meningoencephalitis, the meningeal veins may thrombose and result in focal seizures in the surrounding inflammatory tissue. Unexpectedly, antibiotics can occasionally act as proconvulsants in the setting of a febrile illness and may necessitate a lumbar puncture to exclude meningitis as the etiology for seizures. Furthermore, seizures often cause a peripheral pleocytosis, and when a complete blood count demonstrates an elevated white blood cell count, a primary as opposed to a secondary response may be suggested, prompting concern for meningitis. Unusual causes for meningitis includes *Listeria*, with seizures in one fourth of patients and a high mortality, and Rocky Mountain spotted fever (a nonbacterial, rickettsial infection), which may present with seizures in approximately 10% of patients. Patients who are

immunosuppressed are at greater risk for meningitis with organisms not usually seen in an immunocompetent host (*see* AIDS). Patients who develop meningitis early in life may develop encephalopathic generalized epilepsy or LRE, and treatment is directed toward the individual epilepsy classification (*see* Classification of Seizures and Epilepsies). When medically refractory LRE occurs with a prior history of meningitis, underlying mesial temporal sclerosis (*see* this topic) often occurs and can be successfully treated with anterior temporal lobectomy [3].

Fortunately, bacterial meningitis is preventable and the incidence of bacterial meningitis has declined with the accomplishment of successful vaccination programs (*see* vacines). Early diagnosis and institution of appropriate antibiotic therapy are of the utmost importance to optimize therapy for meningitis, though the question of early corticosteroid therapy to limit seizures is yet to be answered.

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## MERRF

This mitochondrial encephalomyopathy is one of the progressive myoclonus epilepsies and is related to several other conditions involving abnormalities of mitochondrial enzymes (*see* MELAS Syndrome). Myoclonus epilepsy with ragged red fibers (MERRF) is a myoclonic epilepsy syndrome with action and intention myoclonus, generalized seizures, ataxia of variable onset, and rapidly progressive mental deterioration. MERRF and related mitochondrial disorders may be associated with deafness, optic atrophy, peripheral neuropathy, or upper motor neuron signs. The inheritance pattern is most consistent with maternal transmission. The clinical onset occurs in the second decade of life, with seizures that are predominantly myoclonic. Physical characteristics include encephalopathy, gait ataxia, myopathy, short stature, and deficits of hearing and vision with optic atrophy. The interictal EEG often demonstrates diffuse slowing of the posterior dominant rhythm in addition to epiletpiform discharges that have a variable relationship to the myoclonus. Giant SSEPs may be seen. The diagnosis is made by a finding of increased blood pyruvate and lactate, the presence of the characteristic "ragged red fibers" on muscle biopsy that are the hallmark of the condition, as well as abnormalities of the mitochondrial respiratory chain. MERRF occurs as a result of a point mutation of the mitochondrial gene responsible for transfer of RNA. Levetiracetam has been reported to have an antimyoclonic effect in MERRF syndrome [1].

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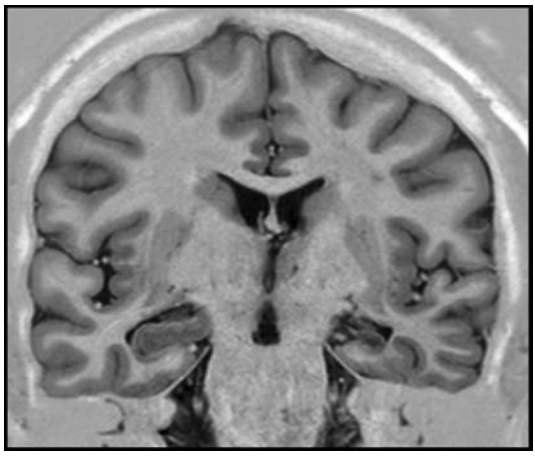
# MESIAL TEMPORAL SCLEROSIS (HIPPOCAMPAL SCLEROSIS)

Mesial temporal lobe epilepsy is the most common target for PWE that requires surgical treatment for refractory complex partial seizures in adulthood. A significant percentage of patients who have mesial temporal lobe epilepsy have a clinical, radiographic, or pathologic pattern of mesial temporal slcerosis (MTS) (i.e.,hippocampal sclerosis) [1,2]. In surgical series of TLE, 43-72% of patients with the histopathologic features of MTS can be shown [3]. Hippocampal slcerosis is demonstrated by cell loss in the hippocampal pyramidal cell layer and hilus, with associated volume loss and gliosis found in the mesial temporal area or Ammon's horn [3]. The seizure-free rate for adults with hippocampal sclerosis and TLE is approximately 70-80%, though short-term studies have reported higher rates of success. There has been much debate as to whether MTS is a lesional cause for or effect of recurrent seizures. Precipitating factors may occur, such as febrile seizures or status epilepticus, hypoxia, trauma, or infection/inflammation of the CNS, though idiopathic as well as familial cases have also been noted. Excessive intracellular calcium or excitatory neurotransmitters may be the means by which MTS is unltimately expressed. Dual pathology (*see* Dual Pathology) exists in a substantial number of patients who harbor both MTS as well as a second lesion that may also be epileptogenic. TLE due to MTS usually starts during childhood or adolescence, though adult-onset is not uncommon [3]. TLE associated with MTS has been most commonly associated with early injury patterns in childhood remote from the precipitating event. In one retrospective review of 38 adult-onset MTS patients with TLE, >50% of patients with adult-onset TLE due to MTS showed features of an autoimmune pathophysiology, with apparent in-



A 42-year-old male with severe left hippocampal formation atrophy in a pre-operative inversion-recovery coronal brain MRI with intractable complex partial seizures due to mesial temporal sclerosis.

flammation to suggest limbic encephalitis [3]. In adult-onset MTS, the inflammatory lesions evolved to hippocampal atrophy with a process that was often bilateral, in contrast to the unilateral process seen with patients with secondary MTS due to early injury or those with dual pathology. Human and animal studies indicate that MTS may be the consequence or the cause of chronic epilepsy and, in some cases, probably both.

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## METABOLIC ERRORS (INBORN)

Seizures are a frequently recognized part of the clinical presentation for an inborn error of metabolism, especially when onset occurs in the neonatal or early infantile period. The importance of recognizing these important disorders lies in the fundamental treatment of seizures as a symptom so that optimal medical treatment, family counseling, and overall prognosis may be carried out. When the presentation of an inherited inborn error of metabolism initially presents to the clinician as seizures, the seizures are often associated with other neurologic abnormalities. The ultimate diagnosis may require time to demonstrate evolution of the disease that reflects the progressive course until specific testing and gene detection results in a definitive diagnosis. Some disorders result in severe refractory epilepsy and may be categorized according to age of onset. In newborns, inborn errors of amino acid metabolism include organic acidurias (e.g., ketotic hyperglycinemia, maple syrup urine disease), pyridoxine dependency, peroxisomal disorders (e.g., Zellweger syndrome, neonatal adrenoleukodystrophy), and urea cycle disorders. In early infancy, lysosomal disorders (e.g., Tay-Sachs disease, Krabbe disease, GM I & II gangliosidosis), disorders of vitamin metabolism (e.g., biotinidase deficiency), aminoacidurias (e.g., phenylketonuria), urea cycle disorders, and other inborn errors of metabolism (e.g., Menkes kinky hair disease) may be associated with seizures. In late infancy, the neuronal ceroid lipofuscinoses, mucopolysaccharidoses, enzymatic deficiencies (e.g., metachromatic leukodystrophy), and other syndromes without identifiable etiologies (e.g., Alpers' disease) become apparent and may be associated with seizures. In childhood and adolescence, lysosomal disorders (e.g., Gaucher's disease and sialidosis, or cherry red spot myoclonus syndrome), neuroaxonal dystrophy, juvenile forms of ceroid lipofuscinosis, and the progressive myoclonus epilepsies (e.g., Lafora body disease and Unverricht-

Lundborg disease), and the mitochondrial disorders (e.g., MERRF and MELAS) become manifest with seizures. By organizing the pattern of the individual clinical presentation, stratifying the associated neurologic features with the epilepsy syndrome relative to age and progression will help to facilitate recognition of the more common diagnoses. Treatment of seizures in patients with inborn errors of metabolism should focus first and foremost on the underlying metabolic disturbance. Treatment of an underlying electrolyte disturbance or dietary (e.g., hypocalcemia), vitamin (e.g., pyridoxine), or enzymatic deficiency (e.g., Gaucher's disease) may lead to improvement. Even bone marrow or liver transplantation (e.g., urea cycle disorders) has been beneficial for patients with inborn errors of metabolism and seizures. AEDs are often necessary as adjunctive treatment specific for the individual seizure type (e.g., myoclonus) (*see* Myoclonus).

## METACHROMATIC LEUKODYSTROPHY

*See* Sphingolipidoses; Inborn Errors of Metabolism.

## MENSTRUAL CYCLE

A complex neuroendocrinologic feedback system, the hypothalamic-pituitary-ovarian axis, regulates the menstrual cycle and is intimately connected with women and epilepsy [1]. The menstrual cycle may be altered in women with epilepsy, and the hormones responsible for the cycle may interact with AEDs and manifest seizure breakthrough around the menstrual cycle. The principal ovarian steroid hormones are estrogens (estradiol, estrone, and estriol) and progesterone. Estradiol is the most potent of the estrogens [1]. The hormonal secretion is controlled by the hypothalamus and pituitary. Gonadotropin-releasing hormone (GnRH) is secreted by the hypothalamus and stimulates the release of follicle-stimulating hormone (FSH) by the pituitary. The release of FSH stimulates formation of the ovarian follicles, which subsequently excrete estradiol during maturation of the follicle. Estrogen released by the follicle has a feedback effect upon the brain, and FSH is reflexively inhibited while GnRH is stimulated [1]. The result of a rapid rise in estrogen that is released by the follicle is the surge of luteinizing hormone (LH), which induces oocyte maturation, subsequent ovulation, with postovulation conversion of the follicle into a corpus luteum. The end of the follicular phase of the cycle precedes ovulation by about 36 hours. Following ovulation, the luteal phase begins with athe secretion of progesterone by the corpus luteum. The progesterone also has a complex feedback system on the hypothalamic-pituitary-ovarian axis and inhibits secretion of GnRH, FSH, and LH [1]. If there is no pregnancy, the corpus luteum regresses and production of progesterone and estradiol decline.

When the progesterone secretion tapers off and GnRH inhibition decreases, menses occurs and the process repeats in a cycle [1,2].

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## MIGRAINE

Migraine and epilepsy are both common disorders as well as common comorbidities [1], and a genetic link between migraine and epilepsy has recently been suggested [2]. Up to 50% of PWE have various forms of headache temporally related or unrelated to seizures (*see also* Headache). In most studies, the type of headache was not associated with type of seizure or epilepsy syndrome with 8-14% of patients manifesting migraine [3]. Some variants of migraine such as those that occur with abdominal pain, cyclic vomiting, or confusion may include complex partial seizures within the differential diagnosis of migraine. Postictal migraine-like headaches are a common feature following GTC seizures (*see also* Headache). Complicated migraine can result in ischemic lesions that then lead to seizures (migraine-related stroke and epilepsy). There is also description of migraine attack that leads directly to a seizure (migralepsy), and numerous patients have reported this experience [2]. Migraine and epilepsy are each on the differential diagnosis of episodes affecting consciousness, sensorimotor function, and behavior. Several epilepsy syndromes report a high incidence of migraine, including benign epilepsy of childhood with centro-temporal spikes, benign epilepsy of childhood with occipital spike waves, and occasionally childhood absence epilepsy [1].

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## MITOCHONDRIAL ENCEPHALOMYOPATHIES

A group of syndromes associated with mitochondrial dysfunction in which abnormalities of the mitochondria of muscle fibers and abnormalities of the oxidation-phosphorylation coupling are implicated. These now include chronic progressive external ophthalmoplegia, Kearns-Sayre syndrome, Leigh's dis-

ease, Alpers' disease, MERRF, and MELAS syndrome. The diagnosis is based on increased serum lactate and CSF lactate. Definitive diagnosis is made by muscle biopsy and tests of the respiratory mitochondrial chain. The EEG is abnormal in most patients, showing focal and diffuse epileptiform discharges and focal and diffuse slowing in different patients.

## MOGADON®

*See* Nitrazepam.

## MONOTHERAPY

The treatment of epilepsy with a single AED is advantageous and has been the favored approach to therapy in adults and children (*see* Treatment). The potential benefits of monotherapy include better tolerability, fewer side effects, including teratogenicity, fewer drug-drug interactions, the same or better efficacy, better adherence, and less expense when compared with polytherapy. For initial monotherapy, treatment is consistently undertaken following a second seizure (and in some cases after the first seizure) given the higher risk of recurrence following a single event. The vast majority of patients can achieve adequate seizure control with monotherapry, and patients converted to one AED from polytherapy frequently show improvement in both seizure control and side effects [1]. In the United States, FDA approval of an AED for monotherapy requires the demonstration of superiority over another treatment or over placebo. In the European Union, regulation of AEDs may occur with equivalent efficacy, though similar inefficacy for the population studied have been a concern for accepting comparative study designs in the United States. For monotherapy trials designs, placebo-controlled trials raise ethical possibilities, and superiority has never been shown for a newer AED compared to an older standard AED; consequently few AEDs have received initial monotherapy approval in the United States. Two large VA cooperative, comparative trials played a pivotal role for developing guidelines for older AEDs highlighting CBZ monothreapy as an initial AED of first choice for treating LRE when compared to barbiturate AEDs. Since 2004, recommendations for patients with newly or recently diagnosed LRE can be iniated on newer AED monotherapy including lamotrigine, gabapentin, oxcarbazepine, and topiramate (though levitiracetam has also demonstrated efficacy), as well as older AEDs including carbamazepine, valproate, phenytoin, and phenobarbital. Guideline-based recommendations for the selection of AEDs can assist physicians in initiating an appropriate, safe, and effective treatment. A landmark study comparing the newer and older AEDs recently identified lamotrigine as a clinically better and more cost-effective alternative standard over carbamazepine for patients di-

agnosed with partial-onset seizures [2] and valproate as the drug of first choice for many patients with generalized or unclassified epilepsy when compared to topiramate and lamotrigine. However, in selecting a monotherapy, assessment of the patient profile must be included in regard to the need for rapid introduction, pharmacokinetics, tolerability, and comorbidity involved.

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## MORTALITY

Death in people with epilepsy may be related to seizures or the cause of the seizures or be independent and unrelated to epilepsy. The mortality in epilepsy is increased as much as threefold compared to an age-matched general population. However, an association between epilepsy and higher mortality rates has been heterogeneous, and the higher risk of dying with epilepsy is not uniform. Precise identification of mortality with and from epilepsy has been elusive because of the varying sources of data examined (such as death certificates or insurance statistics) and is difficult to compare because epilepsy is often associated with other factors affecting mortality (trauma, stroke, brain tumor, encephalitis, etc). Several risk factors affect mortality, with the chief factors being cause, seizure type and associated mental handicap, seizure control, and perhaps duration of epilepsy. The coexistence of epilepsy with mental retardation makedly raises the risk of death. In addition, the lack of seizure control also leads to an increased risk of death associated with epilepsy. There appears to be a greater risk with remote symptomatic epilepsy than in those with the idiopathic partial or generalized epilepsy, most pronounced in the first year following diagnosis [1]. The standardized mortality ratio (observed deaths over expected deaths) ranges from 1.6 (Iceland) to 4.1 (France), with the United States reporting 2.1-2.3 for epilepsy [1]. The highest SMR are found in children, though the highest mortality is found in persons >75 years of age. Seizure-related deaths appear to be uncommon in the general population, although these account for between 24 and 62% of mortality figures in hospital-based populations [2]. The cause of epilepsy is related to mortality. The most common causes of death in community-based studies are usually pneumonia, cerebrovascular disease, and primary and secondary neoplasia [2]. Additional causes directly related to the seizures include status epilepticus that cannot be controlled and cardiac arrhythmia during a seizure (*see* Arrhythmia). Causes related to the circumstances of the seizure include suffocation, aspiration, and trauma received during the seizure, accidental death or drowning. In contrast,

while sudden unexplained death in epilepsy is infrequent in community-based settings, it is common in hospital-based studies. SUDEP is probably the most common direct epilepsy-related cause of death. SUDEP represents a sudden unexplained death that occurs without evidence of trauma, drowning, or status epilepticus in a person with epilepsy (with/without evidence of a seizure, usually generalized tonic-clonic) and no anatomic or toxicologic cause. Estimates of the frequency of SUDEP are heavily influenced by the population studied, with a community study from Rochester reporting 0.35-2.7/1,000 person-years in a prospective medical examiner-based study [2]. Purported causes include cardiac dysrhythmia during a seizure, cardiac ischemia, and neurogenic pulmonary edema. About 1-16% of deaths may result from accidents that usually occur by drowning from swimming or bathing [3]. Causes of mortality that occur due to epilepsy include depression that leads to suicide (*see* Suicide) that is high in patients with temporal lobe epilepsy. The highest SUDEP rates have been reported in candidates for epilepsy surgery, though successful surgery appeared to reduce the risk of dying in patients with uncontrolled seizures postoperatively [4]. Status epilepticus (*see* Status Epilepticus) is a seizure emergency and carries a mortality of 7-46%, which is highest in the first 30 days and in those with acute symptomatic seizures. The most common causes of mortality after status epilepticus are from anoxic encephalopathy and cerebrovascular disease (*see also* Cerebrovascular Disease).

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## MOVEMENT (SEIZURES INDUCED BY)

Certain seizures can be induced by passive or active movement of an extremity or by a startle reaction (*see* Startle Syndromes) [1]. The inciting stimulus may in some cases be generated by proprioceptive feedback resulting from a movement that arises via thalamocortical activation due to alerting combined with a hyperexcitable cortex[RJ3]. Movement-sensitive epilepsy may be associtated with *startle-induced* seizures in patients with lesions of the motor cortex and infantile hemiplegia who have tonic seizures involving the paralyzed side or children with diffuse cortical lesions who have tonic bilateral seizures. Other types include *touch-induced epilepsy*, where certain seizures can be induced by somesthetic stimulation without startle. Patients may thus auto-

induced somatomotor seizures or sensorimotor seizures (*see* Auto-Induced Seizures). *Movement-induced* epilepsy consists of unilateral or bilateral tonic seizures, seen in some patients with focal cortical lesions. Hyperglycemic seizures have a predisposition to focal seizures that may be induced by active or passive movements and are often seen in elderly patients with nonketotic hyperglycemia. An underlying ischemic basis has been proposed. In this case, seizures usually remit following normalization of blood glucose. *Paroxysmal kinesigenic choreoathetosis* and familial paroxysmal dystonic choreoathetosis overlap with an epileptic mechanism and movement-induced initiation of the recurrent events (*see also* Reflex Seizures).

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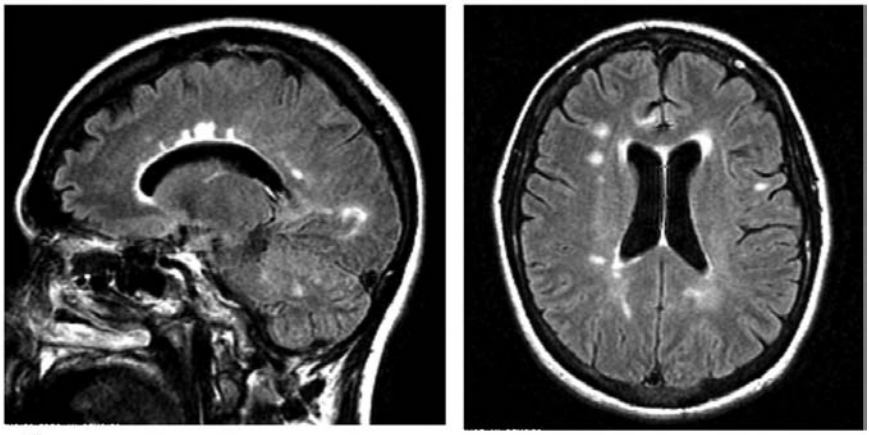
## MOYAMOYA DISEASE

Moyamoya disease is a chronic progressive condition characterized by bilateral occlusion of the distal carotid artery associated with telangiectatic vessels at the base of the brain that appears as a "puff of smoke" on angiography. In Japan, an estimate of 3/100,000 persons have moyamoya disease, though it is uncommon in non-Asian populations. The most frequent manifestations in childhood are TIA, ischemic stroke, and partial seizures. In those patients affected that are older than 30 years of age, intracranial hemorrhage may lead to diagnosis.

## MULTIPLE SCLEROSIS

The relative risk of seizures is higher in MS than in the general population [1]. In multiple sclerosis, association with seizures has been noted to occur with an incidence of 1-4% [1]. The peak expression of epilepsy is noted around 30 years of age, and patients with MS are threefold more likely to develop epilepsy than the general population [2]. Partial seizures are usually seen and appear during the course of the illness, though secondarily generalized seizures and even status epilepticus may occur [1]. Seizures may also occur at onset, but are rarely seen as the presenting clinical feature of MS [2]. The functional relationship between visible demyelination and identification of the epileptogenic zone may be ill-defined, though evoked potentials may help identify clinically "silent" areas of involvement. Larger, demylinating, unresolved plaques may be delineated on gadolinium-enhanced brain MRI with DWI and FLAIR sequences and directly involve the immediate cortical or subcortical regions. These are most likely to be associated with ongoing seizures. Epileptic seizures may also rarely occur as a consequence of drug treatment in MS, including interferons, abrupt decreases in baclofen, or 4-aminopyridine [1]. However, the prognosis




(A) Sagittal and (B) coronal brain MRI in a 38-year-old with remitting and relapsing multiple sclerosis and localization-related epilepsy. Note the ovoid plaques oriented perpendicular to the corpus callosum as well as other diffuse subcortical white matter demyelinating lesions adjacent to the cortex.

of epilepsy in MS patients has been favorable for control [1]. Other physiologic nonepileptic "seizures" (e.g., painful tonic spasms, paroxysmal dystonias, akinesia, and dysesthsias) may occur in MS and be responsive to carbamazepine or gabapentin independent of an antiepileptic mechanism.

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## MULTIPLE SUBPIAL TRANSECTION

Multiple subpial transection (MST) is a nonresective epilepsy surgical technique that was developed to permit treatment of refractory focal seizures that emanate or encroach upon eloquent cortex. MST selectively interrupts rather than excises the horizontal propagation of epileptogenic cortex rendering the epileptogenic generator incapable of establishing cellular synchrony but preserving the columnar organization or the neocortex. The procedure essentially disconnects the horizontally oriented intracortical fibers while preserving radially oriented afferent and efferent cortical axons associated with arterial and venous supply. The technical aspect involves perforation of the pia and instrumentation using an instrument specially designed to make 5-mm parallel transections of the cortical gyri through the hole. The linear transections are 0.3 mm wide (per specifications of instrument design) at the target and are guided by intraoperative electrocorticography. Focal lesions adjacent to the central

sylcus (i.e., primary motor or sensory regions) as well as those eloquent areas that may be important for language function (as in Landau-Kleffner syndrome) are common targets for MST given the consequences of resection in those areas. Common clinical conditions that may serve as substrate for MST include incomplete lesionectomies, resections in eloquent cortex, focal dysplastic cortex, Rasmussen's encephalitis, epilepsia partialis continua, and the Landau-Kleffner syndrome. MST is a viable alternative to resection in extratemporal epilepsy, and the efficacy has been noted [1]. In 99 patients treated with the "Morrell procedure" who underwent MST applying the Engel classification, 52% reported seizure-free outcome with follow-up after more than 1 year [2]. Approximatley two thirds had associated resective surgery, though those with MST had only similar outcome. Morbidity in this series was permanent in 7%. Activities of daily living are not adversely impacted by MST. The precise role of MST relative to timing and relationship to respective surgery as well as long-term follow-up remains to be established.

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## MUSICAL AUTOMATISMS

Musical automatisms have been described during partial seizures. Singing and humming with a melodious quality represent complex automatisms during complex partial seizures. Musical automatisms are rare and were reported in 1.4% of patients in a large series [1]. Nonwordless humming was observed in patients with partial seizures of temporal lobe origin, while singing was more suggestive of frontal lobe origin. Singing was more often lateralized to the right hemisphere.

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## MYOCLONIC ENCEPHALOPATHY (EARLY MYOCLONIC ENCEPHALOPATHY)

Myoclonic encephalopathy (also called early myoclonic encephalopathy) is a rare syndrome with a variety of causes. The onset is in the neonatal period, with fragmentary myoclonic jerks interspersed with occasional massive myoclonus, partial seizures, or infantile spasms. Death usually occurs before the

age of 1 year. Initially, the EEG shows high-voltage runs of spikes, irregular spike-and-slow waves separated by periods of voltage suppression. The EEG pattern may deteriorate over time to hypsarrythmia. Myoclonic encephalopathy resembles the syndrome of early infantile epileptic encephalopathy with suppression-burst, but the latter syndrome includes cerebral malformations, and focal myoclonus is absent.

## MYOCLONIC EPILEPSIES

Myoclonic epilepsies are epileptic syndromes in which myoclonus occurs either at onset or as a prominent feature during the course of the disease. The International Classification of the Epilepsies distinguishes between *idiopathic generalized epilepsies* including benign myoclonic epilepsy of infancy and the juvenile myoclonic epilepsy syndrome, and *cryptogenic* or *symptomatic generalized epilepsies*, including early myoclonic epilepsy with encephalopathy, infantile epileptic encephalopathy, severe myoclonic epilepsy of infancy, epilepsy with myoclonic absence, Lennox-Gastaut syndrome with myoclonus, myoclonic-astatic epilepsy, and progressive myoclonus epilepsies (*see* Myoclonus Epilepsies, Progressive).

## MYOCLONIC EPILEPSY IN INFANCY (BENIGN)

Myoclonic epilepsy in infancy (also called benign myoclonic epilepsy) is a rare epileptic syndrome. It begins between the fourth month and the first year of life in a previously normal infant and in the absence of a family history of epilepsy. Myoclonic jerks are brief, mild, spontaneous, and frequent, especially during light sleep. Myoclonic epilepsy is not associated with other seizure types. The EEG demonstrates a normal posterior background rhythm, but generalized spike, polyspike, and slow waves occur synchronously with myoclonic jerks. Myoclonus can be induced by intermittent photic stimulation. Myoclonic epilepsy of infancy usually responds to the early use of AEDs, for example, valproic acid. Long-lasting sequelae are unusual.

## MYOCLONIC EPILEPSY IN INFANCY, SEVERE

Severe myoclonic epilepsy of infancy (SMEI), or Dravet syndrome, is a rare early childhood epileptic encephalopathy characterized by early prolonged febrile and afebrile seizures followed by intractable epilepsy manifested by varying seizure types and subsequent neurocognitive delays. The estimated incidence is 1/40,000 children of < 7 years of age. Mutations in the voltage-gated sodium channel (Nav 1.1) alpha-subunit gene (SCN1A) have been reported

in up to 70% of patients with SMEI. The onset of this disorder begins in the first year in previously normal infants and is characterized by unilateral or generalized clonic, tonic-clonic, myoclonic, or partial seizures. Tonic seizures are not a feature that suggests SMEI. Convulsions may initially be precipitated by fever and soon become frequent and prolonged. Approximately 25% of patients have a history of febrile convulsions or a family history of epilepsy. Neuroradiologic studies are normal in most patients, but structural abnormalities such as cerebral or cerebellar atrophy of various degree and focal arachnoid cysts have been anecdotally reported [2]. Despite febrile seizures, hippocampal sclerosis has been infrequent [2]. The EEG is usually normal at onset and comes to show generalized spikes, polyspikes, and slow waves, focal abnormalities, and photic sensitivity.

Severe myoclonic epilepsy of infancy in childhood is frequently associated with progressive ataxia, dementia, pyramidal signs, as well as worsening myoclonus. Treatment is generally ineffective, with ongoing seizures and myoclonus.

### References

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## MYOCLONIC EPILEPSIES, PROGRESSIVE

Progressive myoclonic epilepsies (PME), originally delineated by Unverricht and Lundborg, reflect a classification of a family of myoclonic syndromes [1]. Characteristic findings in PME include massive myoclonus, focal and segmental myoclonus, tonic-clonic seizures, progressive dementia, and cerebellar or pyramidal signs. Inheritance is usually by autosomal recessive transmission, though an autosomal dominant transmission may be seen when other neurologic signs are present. Unverricht-Lundborg disease (*see* Unverricht-Lundborg Disease) is degenerative, with a genetic defect that codes for cystatin B. Other varieties of PME have identified biochemical abnormalities; Lafora body disease, the ceroid ipofuscinoses, sialidoses type I and type II, the mitochondrial encephalopathies (MERRF, MELAS), and the gangliosidoses (GM1, GM2). Other forms of PME are associated with particular neurologic manifestations: mitochondria myopathies and dentato-rubro-thalamic atrophy. Ramsay Hunt syndrome (*see* Ramsay Hunt Syndrome) includes a heterogeneous group of disorders.

Clinical features of PME may include a cherry-red spot in the optic fundus (lipidoses and mucolipidoses), early blindness (ceroid-lipofuscinoses), intracytoplasmic inclusion bodies (ceroid lipofuscinoses), abnormalities of lipid meta-

bolic enzymes in serum, leukocytes, and cutaneous fibroblasts (lipidoses), and amyloid inclusions in skin, muscle, liver (Lafora disease).

### Reference

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## MYOCLONIC-ASTATIC EPILEPSY (DOOSE SYNDROME)

Myoclonic-astatic epilepsy of Doose (MAE) is a generalized epilepsy syndrome of young children charactereized by multiple seizure types. Myoclonic seizures, astatic seizures, myoclonic astatic seizures, as well as generalized tonic-clonic, absence, myolconic absence, and tonic seizures may occur [1]. Status epilepticus is common. Onset occurs between the ages of 7 months and 6 years, usually in children with previously normal development. The syndrome is more frequent in males. A family history of epilepsy is present in approximately one third of cases.

The EEG may be normal initially but later develop a characteristic biparietal theta background rhythm composed of a 4-7 Hz rhythm, with irregularly generalized spike wave and polyspike wave discharges. Paroxysmal EEG patterns are increased by intermittent photic stimulation. The course of this epileptic syndrome is variable, with long-term prognosis varying from termination of seizures with normal development to intractable epilepsy with mental retardation, with a relationship of poor control of seizures and cognitive deterioration suggested. Seizures are often difficult to treat but may remit spontaneously in 50-66% of patients [2]. However, clinical deterioration similar to that seen in Lennox-Gastaut syndrome can be seen. In fact, Doose syndrome may overlap with the Lennox-Gastaut syndrome and early myoclonic epilepsy.

Treatment recommendations have largely be based upon treatments rendered for other generalized epilepsies. Valproate has been recommended as the first-line treatment, though lamotrigine, levetiracetam, and topiramate have also been used in small series with the newer-generation AEDs including LTG, TPM, and LEV, which appear to offer significant benefit to children with MAE [2]. However, the ketogenic diet may be effective and perhaps should be considered early in the course of treatment.

### References

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## MYOCLONIC-ASTATIC SEIZURES

The term "astatic" (loss of stasis) has been replaced by "atonic" (loss of tone) seizures or "drop attacks," though the term "astatic" has remained in use as a modifier for certain types of seizures and epilepsy syndromes. Myoclonic-astatic seizures begin with symmetric myoclonus involving the upper limbs, followed by a diffuse loss of muscle tone. Injurious falls may result. Myoclonic-astatic seizures are seen in the Lennox-Gastaut syndrome, myoclonic-astatic epilepsy of Doose, and other myoclonic epilepsies of childhood. The EEG of children with myoclonic-astatic seizures shows polyspike corresponding to the myoclonus and slow wave discharges with the loss of tone.

## MYOCLONIC SEIZURES

Myoclonic seizures consist of brief and violent muscular contractions that are usually bilateral and do not produce clinically apparent impairment of consciousness unless occurring in frequent repetitive clusters. Myoclonic contractions may be single or multiple, lasting for seconds to hours, with contractions that may be rhythmic or irregular [1]. When the upper limbs are involved, patients may drop or throw objects, and when the legs or trunk are involved, sudden falls with injury may occur. Myoclonic seizures may be spontaneous or induced by flashes of light, more rarely by other types of triggering stimuli (*see* Reflex Seizures).

The usual EEG correlate of myoclonic seizures is generalized polyspike-and-slow waves. Epileptiform discharges recorded on the scalp EEG may be visible in the case of cortical myoclonus or invisible in the case of subcortical myoclonus. Certain cortical discharges with myoclonus are detectable only with use of signal back-averaging techniques.

Myoclonic seizures are seen in the IGEs such as benign myoclonic epilepsy of childhood, juvenile myoclonic epilepsy, as well as encephalopathic generalized epilepies such as Lennox-Gastaut syndrome, progressive myoclonus epilepsies, in addition to a wide variety of seizures associated with systemic, toxic, and metabolic causes. Some AEDs such as phenytoin, carbamazepine, and lamotrigine have been reported to be less effective or even to aggravate myoclonic seizures.

### Reference

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## MYOCLONUS

Myoclonus is a brief, involuntary, lightning-like contraction of one or more muscle groups. Myoclonus may be epileptic or nonepileptic in PWE. Epileptic

myoclonus arises from paroxysmal epileptiform discharges in the central nervous system and may be seen with myoclonic epilepsies associated with idiopathic generalized epilepsy (e.g., JME) or encephalopathic generalized epilepsy (progressive myoclonus epilepsy).

## MYSOLINE® (PRIMIDONE)

This is a barbiturate used in the treatment of generalized, partial and myoclonic seizures (*see* Primidone). Most of the drug is metabolized via the CYP 450 enzyme system to phenobarbital, with a small amount existing as phenylethyl malonic acid (PEMA). The efficacy of mysoline in epilepsy was established in 1985 in a large comparative VA cooperative trial [1]. Though similar to phenobarbital, its application has been limited by sedation. Formulations of primidone are available in tablets of 50 and 250 mg and as a suspension of 250 mg/5 mL.

### Reference

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# N

## NARCOLEPSY

Narcolepsy is a sleep disorder, not a type of epilepsy. It is characterized by excessive daytime somnolence causing a rapid onset of sleep, often in inappropriate settings (during recreation, conversation, vigorous activities). Narcolepsy also includes symptoms of cataplexy (emotional triggers of sleep attacks), sleep paralysis (temporary inability to move on awakening), and vivid hallucinations on waking and going to sleep, but the complete tetrad of symptoms may not be seen. More prolonged periods of automatic behavior may occur for which the patient is amnestic. Like other sleep disorders (*see* Sleep), it may be confused with epileptic seizures because of its paroxysmal nature, sudden falls, and unresponsiveness during sleep attacks. It may be distinguished from seizures by the more prolonged periods of sleep-like flaccid unresponsiveness, the absence of convulsions, and postictal confusion.

Diagnosis of narcolepsy is based on its clinical features and sleep studies that include analysis of sleep latency and overnight polysomnography to ensure adequate nighttime sleep. The EEG measures the latency of sleep onset with naps during multiple sleep latency testing demonstrating sleep onset rapid-eye-movement (REM) sleep in narcoleptic patients. Treatment includes modification of sleep habit, the use of short daytime naps, and stimulant medication.

## NEONATAL SEIZURES

Neonatal seizures occur during the first 4 weeks of life. Neonates are very prone to seizures, and this period represents the time when the seizure threshold is at its lowest. Any insult to the brain from hypoxia, ischemia, hemorrhage, or metabolic or infectious causes during this time is capable of inducing a hypersynchronous neuronal firing that may generate a seizure [1]. Neonatal seizures include *clonic seizures*, with focal clonic jerking of the face, limbs, and axial muscles. Less often seizures will be hemiconvulsive, axial, or multifocal. *Myoclonic* seizures often occur with generalized or focal (particularly flexor muscles) myoclonic jerks. *Tonic seizures* are also common and may occur with focal flexion of the trunk, symmetric or asymmetric. Rarely, neonatal tonic seizures present as tonic deviation of the eyes with nystagmus in association with an occipital EEG discharge. *Other seizure types* not well categorized by standard seizure classification schemes also occur in the neonatal period.

Neonate seizures may manifest with eye movements such as repetitive opening and closure, eyelid fluttering, or oscillatory and rotatory movement of the eyes. In addition, poorly coordinated movements of the limbs, chewing, sucking, apneic episodes, and seizures with autonomic signs such as intermittent cardiac dysrhythmias (e.g., tachycardia) or fluctuations in blood pressure may be manifestations of neonatal seizures. These seizures may be difficult to distinguish from normal neonatal behavior and conditions such as "fidgetiness." Any form of neonatal seizure can progress to neonatal status epilepticus. Brain maturation significantly influences the evolution of some important aspects of seizures [3]. The mechanisms of seizure initiation, propagation, and termination may be somewhat different in the neonatal period, though the differences in age-related mechanisms have not yet been fully clarified [1].

Seizure onset in the neonatal period necessitates a search for the underlying cause or causes, which determine the ultimate prognosis. Neonatal seizures may be symptomatic or cryptogenic. Important etiologies include *anoxic-ischemic encephalopathy* (*see also* Anoxia/Hypoxia; Hypoxia). Anoxia-ischemia is probably responsible for 50-75% of neonatal convulsions. Initially seizures are infrequent, but they become more severe 12-24 hours after birth. *Intracranial hemorrhages* account for about 15% of all neonatal convulsions. Intraventricular hemorrhages predominate in the premature neonate. EEGs of premature neonates that have had periventricular hemorrhage characteristically show positive sharp waves in the rolandic area. *Metabolic disturbances* are common causes of neonatal convulsions. Seizures with hypocalcemia of early onset usually respond poorly to AEDs unless the underlying problem is corrected. Late-onset hypocalcemia (developing after the first week) carries a better prognosis. Hypocalcemia is not infrequently associated with hypomagnesemia. Hypoglycemia is a potentially serious cause of neonatal seizures if it remains uncorrected. Toxic causes of seizures from maternal alcohol or drugs are rare, but important to recognize. Other metabolic causes of seizures in the first month of life include hypernatremia, hyponatremia, pyridoxine deficiency (rare with modern feeding formulas), and inborn errors of metabolism (*see also* Metabolic Errors). *Central nervous system infections* account for about 15% of cases of neonatal convulsions. Bacterial infections predominate, but herpes simplex encephalitis rarely may be encountered at this age. *Cerebral malformations* may also lead to neonatal seizures.

Ten to 25% of neonatal convulsions or neonatal status epilepticus remain idiopathic. A few of the neonatal syndromes have been highlighted by the International Classification of Epileptic Syndromes. *Idiopathic neonatal convulsions* ("fifth-day fits") are focal or multifocal tonic seizures seen between days 3 and 6 of life in previously normal children. Prognosis is guarded, with a risk of further seizures or psychomotor retardation. *Benign familial neonatal convulsions* are an inheritable epilepsy that occurs in neonates, but not in adults, caused by hypofunctional mutations in genes codifying for the M-type K+ current. Clonic, apneic, or, more rarely, tonic seizures are seen in previously normal newborns around the second to third day of life. Seizures are frequently

repetitive. The EEG is normal. Diagnosis is based on a family history of a similar presentation. Inheritance is by autosomal dominant transmission with normal penetrance but variable expression. Two genetic loci (CMM6 and RMR6) on the long arm of chromosome 20 have been linked to the syndrome. The risk of developing epilepsy after benign familial neonatal convulsions is higher than the general population. *Early myoclonic encephalopathy* is a rare epileptic syndrome presenting with several seizure types. Occasional myoclonic jerks may be partial or fragmented, massive myoclonic jerks, partial motor seizures, or tonic spasms. Seizures present in the first month of life and may be associated with major metabolic problems. The EEG shows bursts of spikes and sharply contoured spike waves, irregular and arrhythmic slow-wave bursts separated by periods of relative voltage suppression lasting 3-10 seconds. The bursts of epileptiform EEG activity are not synchronous with the myoclonic jerks. The EEG pattern deteriorates over time to hypsarrythmia or a multifocal epileptiform pattern. Neurologic examination is always abnormal, and prognosis is grim (*see also* Myoclonic Encephalopathy). *Early epileptic encephalopathy with burst suppression* is a syndrome characterized by Ohtahara in 1978. Clinical characteristics are similar to those of early myoclonic encephalopathy, except that neonates with Ohtahara syndrome are less likely to show myoclonic and partial seizures. Diagnosis is made by identification of severe cerebral malformations believed to be responsible for the condition.

The treatment of neonatal seizures consists of supportive care for the child, correction wherever possible of the underlying cause, and judicious use of AEDs. The enhanced seizure susceptibility has been suspected to be due to a depolarizing action of GABA in the developing brain. A well-established characteristic of some neonatal neurons is a tendency to exhibit burst-firing. Therefore, phenobarbital and pheytoin have been the mainstays of treatment, though fewer than half of neonatal seizures respond to these agents even at high doses [3]. Parenteral or rectal benzodiazepines may therefore be required. Long-term AED therapy may be useful, but is not necessary in all cases, and video-EEG may reveal electrographic seizures that have an adverse impact on normal developing brain function [4].

The prognosis of neonatal seizures depends on the gestational age, the frequency and characteristics of the seizures, the severity of EEG abnormality, and most importantly the underlying cause. Mortality ranges from 10 to 35%, mental retardation ensues in 10-25% of cases, infantile cerebral hemiplegia occurs in 13-25% of cases, and 10-25% of cases later develop epilepsy. Despite the potential for serious sequella, two thirds survive without residual deficits.

## References

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4. McBride MC, Laroia N, Guillet R. Electrographic seizures in neonates correlates with poor neurodevelopmental outcome. Neurology 2000;55:506-513.

## NEUROFIBROMATOSIS

*See* Von Recklinghausen's Disease.

## NEUROPATHY

Neuropathies may surface during the treatment of PWE. A peripheral polyneuropathy may be associated with the underlying condition (i.e., infantile neuroaxonal dystrophy or Seitelberger's disease), epilepsy [1], comorbidity (e.g., diabetes), or a potential side effect of chronic use of AEDs. Electrophysiologic abnormality characterized predominantly by slow nerve conduction velocities may be detected in a significant number of patients on chronic AED therapy with clinical features that including paresthesias or hyporeflexia. Histologic examination reveals axonopathy with secondary demyelinization. Phenytoin has been primarily implicated, although the barbiturates and carbamazepine may also induce neuropathy. Less is known about the newer AEDs at this time relative to causing neuropathy, though a role of folate deficiency has been debated. Some of the AEDs (carbamazepine, gabapentin, pregabalin) may be helpful for the treatment of neuropathic pain, while others such as phenytoin may either produce neuropathy or assist with its painful consequences.

### Reference

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## NIEMANN-PICK DISEASE

Niemann-Pick disease is a sphingolipidosis characterized by accumulation of sphingomyelin in the reticulo-endothelial system [1]. Inheritance is by autosomal recessive transmission, with Ashkenazy Jews at higher risk. Four clinical forms of Niemann-Pick disease have been described. The most common form has an onset in the first year of life. Patients have hepatosplenomegaly, severe and rapidly progressive cognitive decline, cherry-red spots on funduscopic examination, myoclonic seizures, and a variety of other neurologic abnormalities, with death occurring usually by the age of 5 years. The other forms of Niemann-Pick disease have less marked hepatosplenomegaly, onset later in life, and a more gradual progression [1]. The diagnosis depends upon the clinical profile and a deficiency of sphingomyelinase activity in a biopsy specimen

(i.e., rectal or splenic tissue). In the infantile form, IEDs may be absent on EEG, with generalized seizures, and action myoclonus referred to as rhythmic cortical myoclonus [1].

### Reference

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## NIGHT TERRORS

Night terrors are a nonepileptic, intermittent, paroxysmal phenomenon occurring early in the night during slow-wave sleep. Night terrors occur typically between 18 months and 5 years of age. Children characteristically arouse their parents with an alarming scream and appear as though they are terrified, but recall nothing unusual when they are awakened. The interictal EEG is normal. Night terrors are best considered age-dependent normal benign sleep behaviors and as parasomnias need to be distinguished from nocturnal seizures of childhood, panic attacks, and nightmares [1].

### Reference

1. Zucconi M, Oldani A, Ferini-Strambi Ll, Dizzozero D, Smirne S. Noctutrnal paroxysmal arousals with motor behaviors during sleep: frontal lobe epilepsy or parasomnia? J Clin Neurophysiol 1997;14:513-522.

## NITRAZEPAM (MOGADON®)

Nitrazepam is a benzodiazepine derivative that has been used adjunctively as an AED mostly for the treatment of encephalopathic generalized epilepsies incuding West Syndrome/infantile spasms, Lennox-Gastaut syndomre, febrile seizures, and atypical absence seizures; it may be especially effective for myoclonic seizures. Bioavailability of nitrazepam is 78%, a Cmax of 1.4 hours, 85-88% protein bound with hepatic metabolism that occurs without autoinduction. It possesses sedative and hypnotic properties that are similar to the benzodizapine family of drugs, with drowsiness, tolerance, withdrawal effect encountered with chronic use and sedation, disorientation, confusion, incoordination, and gait difficulties acutely. The usual daily dose is 0.5-1.0 mg/kg given as twice-daily dosing. Nitrazepam is not yet available in the United States.

## NOCTURNAL FRONTAL LOBE EPILEPSY

Seizures that originate within the frontal lobes often occur during sleep and in many patients are entirely restricted to sleep [1]. Nocturnal frontal lobe epilepsy

(NFLE) may occur sporadically or as an inherited form. The inherited form occurs with an autosomal dominant inheritance (autosomal dominant NFLE, or ADFLE) [2]. Two subunits, the alpha 4 and beta 2 subunits of the neuronal nicotinic acetylcholine recptor, have been associated with ADNFLE. NFLE is often misdiagnosed as a sleep disorder and vice versa. The seizures may appear bizarre to observers and be labeled as psychogenic nonepileptic seizures. Complex and brief bimanual-bipedal automatisms, vocalization, ambulation, with minimal impairment of consciousness evident complicate the fact that many patients have no abnormal finding on interictal or even ictal EEG. Additionally, brain MRI often shows no abnormality. Video-EEG is the statndard for comfirming the diagnosis, and AEDs to treat partial seizures are utilized.

### References

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2. Scheffer IE, Bhatia KP, Lopes-Cendes I, et al. The dominant nocturnal frontal lobe epilepsy: a distinctive clinical disorder. Brain 1995;118:61-73.

## NYQUIST THEOREM

The Nyquist theorem specifies that the highest measurable frequency is half the sampling rate. During analog-to-digital conversion, for example, the highest frequency that can adequately be resolved for a 200 Hz signal is 100 Hz. Signals that are higher than the Nyquist frequency are subject to "aliasing" and appear as poorly characterized lower frequencies leading to a misrepresentation of the signal. To avoid aliasing, it is necessary to eliminate the frequency components of the signal that are higher than the Nyquist frequency. This applies as well to topographic maps, source localization, and other spatial analyses that may allow aliasing for higher spatial frequencies if the sampling rate is inadequate.

## NYSTAGMUS

Bidirectional nystagmus most commonly results from interictal elevations of AEDs and represents an observable neurologic sign of AED toxicity (*see* Toxicity). It may also be seen with unilateral predominance as a manifestation of seizure mimics (e.g., benign paroxysmal positional vertigo). In addition, nystagmus may occur as an ictal manifestation in patients with seizures including an overt or persistent and subtle feature of status epilepticus. During seizures there may be tonic deviation of the eyes to a position of extreme lateral gaze with an additional clonic component (oculoclonic movement) that may rhythmically interrupt maintaining full excursion with rapid jerky movements that produces epileptic nystagmus. However, nystagmus is rarely the only sign of a

seizure, but may include horizontal, vertical or unilateral, disconjugate, or see-saw directional movements. Conjugate horizontal eye movements are the rule. The mechanism of epileptic nystagmus is presumed to be activation of frontal eye fields that controlling saccades and pursuit movements. Eye movements can be electrically induced from large areas of the human contralateral dorsolateral frontal cortex as well as the precentral gyrus. The electrically defined frontal eye fields are anterior to the face region and posterior to the middle frontal gyrus [1]. In obtunded patients, the localizing value of epileptic nystagmus is limited. Video-EEG correlative studies have identified epileptic foci in the hemisphere contralateral to the fast phase of the nystagmus, predominantly in parieto-temporal regions, but also in ipsilateral and contralateral frontal and occipital regions [2]. During awake PWE and simple partial seizures, epileptic nystagmus usually localizes to the contralateral hemisphere with the epileptic discharge frequency usually above 10 Hz [2].

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# O

## OBESITY

There is a steady increase in the prevalence of obesity in the United States [1]. Obesity constitutes a significant health risk, with hypertension, diabetes, and hyperlipidemia producing cardiovascular and cerebrovascular disease, as well as increasing the risk of some cancers (uterine, colon, and breast) [1]. Weight gain in PWE may be multifaceted with a reduced participation in physical exercise (*see* Sports), unchecked appetite stimulation or altered mood from AEDs, and potential metabolic alterations in genetic syndromes associated with weight increase [1]. Drugs that promote weight gain include carbamazepine, gabapentin, pregabalin, and valproate. Those that result in weight loss are felbamate, topiramate, and zonisamide. Lamotrigine, levetiracetam, and phenytoin are considered weight-neutral.

### Reference

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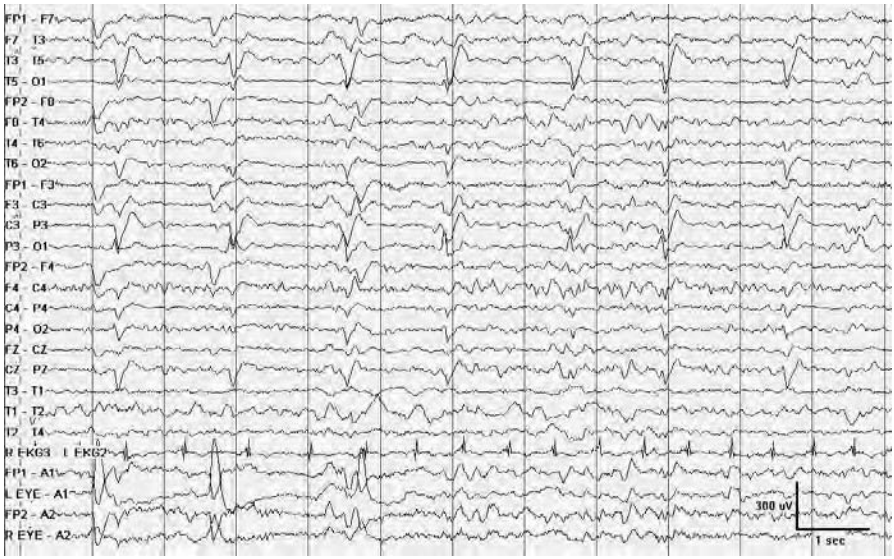
## OCCIPITAL LOBE EPILEPSY

Occipital lobe epilepsy with partial seizures begins with a sudden change in visual function (*see* Visual Manifestations) and may present as simple partial, complex partial, or secondarily generalized seizures. They may present as visual symptoms or notable visual movement. When seizures begin in the primary visual cortex, unformed colors or lights (phosphenes) may occur. Simple, unformed visual hallucinations in the contralateral visual fields may be described by the patient as spherical, multiple, or colored lights appearing in 50-60%, though auras more typical of temporal lobe epilepsy may also be reported [1]. In contrast, seizures that begin in the temporo-occipital supplementary visual cortex result in complex figures or detailed scenes or other stereotypic hallucinations [1]. Ipsilateral forced eye blinking, forced eye closure, eye flutter, contralateral nystagmus (*see* Nystagmus) and contralatreal tonic version of the eyes or the head (*see* Versive Seizures) may be observed by witnesses as the motor manifestations of occipital lobe seizures. In addition, spread to the contralateral occipital lobe may be rapid and, rather than "positive" phenomena of visual hallucinations, result in "negative" phenomena of scotomata, visual field deficits, or ictal blindness [1]. The clinical manifestations of occipital lobe

epilepsy reflect the different patterns of propagation. Infrasylvian propagation to the temporal lobe is most common and may result in a semiology more characteristic of temporal lobe origin when the patient experiences complex partial seizures [1]. On the other hand, when the onset is in the supracalcarine area, the spread may involve the supra-sylvian convexity, resulting in more robust motor manifestation that are more typical of supplementary motor seizures when mesial, and focal sensory or motor if lateral propagation occur to the parietal-frontal dorsolateral cortex. Motor signs were most common, seen in nearly 75% of children [2].

Occipital lobe seizures may have syndromic association:

- *Benign occipital epilepsy of childhood* (*see* Benign Epilepsy): An early-onset (about 5 years), or Panayiotopoulos type, and late-onset (about 8 years), or Gastaut type of benign occipital epilepsy (BOE) may occur. Confusion with basilar migraine may occur. With the early-onset form, visual symptoms are never the predominant ictal manifestation, as with the late-onset form, most are nocturnal, many occur as a single event, and have prominent autonomic features of vomiting, eye and head deviation, and are partial motor, hemi-clonic, or generalized seizures [3]. Daytime seizures present with elementary visual phenomena (amaurosis, scotomas, phosphenes) or elaborate phenomena (hallucinations, illusions), though prominent elementary visual hallucinations, intact consciousness, daily occurrence, and more guarded prognosis are more characteristically seen with late-onset BOE. One third of patients suffer diffuse headache with nausea and vomiting, suggesting migraine.
- *Migraine*: Occipital lobe epilepsy (OLE) with simple partial or subtle complex partial seizures may be difficult to distinguish from migraine with prominent visual auras, and overlap syndromes do exist. Additionally, postictal migraine-like headaches are indistinguishable from migraine and are a common phenomenon of occipital lobe epilepsy, furthering the difficulty in distinguishing migraine from seizures of occipital origin, though the greater complexity with fortification specter and kaleidoscopic effect of the visual auras is helpful.
- *Symptomatic occipital lobe epilepsy*: This type of epilepsy, such as Sturge-Weber syndrome, is due to the resultant posterior quadrant leptomeningeal angiomatosis with calcification that commonly occurs, leading to associated occipital lobe epilepsy. A syndrome of bilateral occipital calcifications with epilepsy has also been noted, with seizures that begin in early childhood with visual symptoms that may predominate prior to complex partial seizures. Posterior cerebral artery infarction with hemianopsia and viable hemi-sensory-motor deficits may occur from stroke, trauma, or complicated migraine or other structural lesion and result in partial seizures. Mitochondrial encephalomyopathies and progressive myoclonus epilepsy may also occur with occipital lobe seizures.
- *Cryptogenic occipital lobe epilepsy*: This form may also occur without a known structural basis or syndromic association (*see* figure).




Occipital PLEDs in a patient with cryptogenic occipital lobe epilepsy and recurrent focal seizures.

The EEG demonstrates IEDs that are restricted occipital lobe abnormalities in <20% of patients [1]. The IEDs are usually posterior temporal but widely distributed and bitemporal or generalized and bifrontal or bioccipital in up to 50% of cases [1]. In chidren IEDs may be high-amplitude, bilateral, in prolonged runs of spikes and sharp wave waves. Like adult patients with OLE, the early-onset BOE demonstrates a greater predisposition to extratemporal IEDs, and "fixation-off" sensitivity may be observed when IEDs are activated by eye closure. In BOE, a superifical dipole has been used to differentiate the benign from the symptomatic form. Ictal recordings typically show bilateral ictal rhythmic frequencies that may be lateralized or maximal over the temporal-occipital derivations [1]. Similar to the location of IEDs, focal occipital onset occurs in <20% of patients, though posterior quadrant localization was noted to occur in up to 57%, though false lateralization may occur.

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## OLFACTORY SEIZURES

Olfactory manifestations of partial seizures represent a special sensory symptom that may present as an illusion of an increase in the sense of smell, a hallucination, or with a distortion of smells [1]. Olfactory hallucinations are usually of an unpleasant nature such as the smell of organic decomposition, chemical smells, burning rubber, or other unidentifiable undesireable smells. These seizures are also referred to as "uncinate" seizures because of their frequent involvement of the uncus in the mesial temporal lobe or orbitofrontal cortex [1]. Uncinate seizures should raise the suspicion of symptomatic partial epilepsy and may warrant evaluation for underlying frontal or temporal lesions. Nevertheless, many such cases are benign.

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## OPERCULAR EPILEPSY

Epilepsy that eminates from the opercular region is associated with seizures that display prominent oropharyngeal symptoms. Increased salivation, lip smacking and chewing, swallowing, speech arrest, laryngeal symptoms, gustatory hallucinations, occasionally epigastric discomfort, fear, autonomic signs, or hemifacial spasms may occur. Opercular or supra-insular IEDs have been identified on EEG. Seizures are seen with symptomatic or cryptogenic partial epilepsies, though the term "oropharyngeal seizure" has also used for benign epilepsy of childhood with centro-temporal spikes. Seizures in this setting include increased salivation, difficulty speaking, swallowing or gargling, chewing movements or clonic movements of the jaw, inability to move the tongue, forced contraction of the tongue, inability to open the mouth, swallowing of saliva, pharyngeal constriction, and gum or tongue tingling.

## OPTICAL IMAGING

Hemodynamic changes are associated with focal seizures with an increase in cerebral metabolic rates, and increase in regional cerebral blood flow has been demonstrated with fMRI, PET, SPECT, and autoradiography [1]. Optical recording of intrinsic signals provides the highest combined spatial and temoral resolution of any brain mapping technique [2]. It measures cerebral blood volume and hemoglobin oxygenation of cerebral cortex and is utilized during neurosurgical procedures for patients with refractory seizures [1,2]. Recording seizures in the operating suite is rare and, therfore, interictal discharges are the

electrophysiologic marker typically recorded during electrocorticography (*see* Electrocorticography). A hypoxic-hypoperfusion hypothesis has been developed that may be relevant to intraoperative seizure recordings. When electrographic epileptiform abnoramlities occur, there may be focal changes in perfusion and oxygenation that precede the onset of a spontaneous seizure thereby permiting an opportunity for seizure prediction and treatment [1].

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## ORBITOFRONTAL EPILEPSY

Orbitofrontal seizures may be confused with temporal lobe seizures due to the connections with the limbic system. Olfactory hallucinations may occur prior to a stare, impaired consciousness, oral and limb automatisms, and autonomic features with ictal fear or anguish, tachycardia, diaphoresis, and papillary dilatation. Ipsilateral head turning has been observed in temporal lobe epilepsy but can also occur in orbitofrontal epilepsy [1]. More bizarre automatisms such as screaming, laughing, coughing, and pelvic thrusting may occur. Interictal epileptiform discharges on EEG may occur in the orbitofrontal area, spread to the temporal or frontal areas, or appear bifrontally. Ictal discharges may start and remain in the orbital cortex for longer periods of time (>1 minute) prior to the occurrence of clinical symptoms [2] (*see also* Versive Seizures).

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## OXCARBAZEPINE (TRILEPTAL®)

Oxcarbazepine (OXC; 10,11-dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide) is the 10- keto analog of carbamazepine (CBZ) and is indicated for use as monotherapy or adjunctive therapy for partial seizures with or without generalization as well as GTC in both adults and children age 4 and older [1]. Randomized controlled trials have shown OXC to have similar efficacy to

CBZ, VPA, and PHT, but fewer adverse events when compared to CBZ, possibly because it is not metabolized to the 10,11-epoxide. Additionally, while OXC was developed in an attempt to improve the tolerability of CBZ without affecting its anticonvulsant potency, the two compounds have different chemical structures, active metabolites, and mechanisms of action. When compared to the older and newer AEDs, OXC was similar to LTG for time-to-treatment failure but was better than CBZ in one large unblinded, randomized, controlled trial [2]. OXC is metabolized to an active 10-monohydroxy derivative (MHD), is 40% protein bound, and does not undergo autoinduction. Fewer drug-drug interactions are encountered relative to CBZ. MHD is largely responsible for the efficacy of OXC and is a weak inducer of hepatic enzymes. However, it may inhibit the CYP450 enzyme family CYP2C19, and an interaction from co-administration with high-dose OXC and PHT (or PB) may result. Compared with CBZ, the discontinuation rate due to adverse events was significantly higher among patients on CBZ (26%) as opposed to OXC (14%). Most of the adverse events are mild to moderate. Somnolence, dizziness, diplopia, nausea, vomiting, insomnia, rash, and hyponatremia have been problems when compared with placebo. Serious dermatologic reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in both children and adults. Severe hyponatremia (<125 mEq/L) has been reported in 2.5% of PWE with an age-dependent prevalence (substantially higher in the elderly). Therapeutic effects are noted between 600 and 2,400 mg/d [3,4].

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# P

## PANAYIOTOPOULOS SYNDROME

Panayiotopoulos syndrome (PS) is a common childhood epilepsy syndrome included within the idiopathic focal epilepsies of childhood. PS serves as an eponym for the physician who initially described it, seeking to distinguish occipital lobe epilepsy from migraine [1]. Normal children with infreuquent lengthy nocturnal seizures associated with vomiting, eye deviation, and overall excellent prognosis reflect PS. Autonomic seizures are the hallmark of PS, though other ictal patterns may occur. In contrast, childhood epilepsy with occipital paroxysms described by Gastaut is characterized by brief seizures with visual symptoms. Visual symptoms include such elementary visual hallucinations, or amaurosis, followed by hemiclonic seizures and postictal migraine-like headache in 50% of patients. Seizures may consist of purely or almost purely autonomic phenomenon in >90% followed by more conventional ictal manifestations such as impaired consciousness with staring or eye deviation to one side [2]. Other less frequent nonautonomic ictal features include speech arrest, hemifacial spasm, oropharyngolaryngeal movements, visual hallucinations suggesting a maturation-related continuum with rolandic and idiopathic occipital epilepsies [2]. Seizures last from more than 30 minutes to hours, essentially reflecting autonomic status epilepticus, though there has been no clinical evidence of resultant damage to the brain.

The typical findings on interictal EEG in PS include focal, multifocal, and irregular generalized spikes that increase or appear for the first time during sleep. In contrast to the localized occipital spikes that attenuate with eye opening seen in childhood epilepsy with occipital paroxysms, PS may demonstrate multifocal extraoccipital spikes on interictal EEG that predominate over the occipital lobes. In about 10-15% of children, focal spikes may occur with brief irregular generalized spikes [2]. In addition, spikes may not infrequently appear over the centrotemporal regions in keeping with an idiopathic epilepsy. Hence, PS is less regionalized, with the typical clinical and electrographic features that involve autonomic networks within multiple bihemispheric cortical and subcortical regions rather than the occipital lobe alone. Background interictal EEG is normal as is neuroimaging. Ictal recording have been reported to occur, demonstrating occipital, fronto-temporal, and frontal onsets [2].

The combination of prolonged seizures with prominent autonomic features and multifocal spikes on interictal EEG in children that are developmentally normal is almost diagnostic of PS [2], though the differential diagnosis

includes a wide range of common childhood conditions (*see* Abdominal Aura). As a rule, seizures are infrequent and spontaneous remission occurs within 2 years of onset in keeping with a benign idiopathic focal epilepsy. Many patients have only a single seizure, and seizures rarely continue over a longer period of time. As in rolandic epilepsy, treatment should be reserved for children with frequent or distressing seizures and should be an individualized decision [1]. Carbamzepine has been a preferred treatment by some, with <10% requiring two AEDs or becoming refractory to treatment [2].

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## PANIC DISORDERS

Panic and anxiety disorders are common in epilepsy, occurring in 19-45% of PWE compared to an estimated 2.5-6.5% occurrence in general population-based studies [1]. In addition, seizures may manifest as panic disorders or acute anxieties due to the underlying limibic neuroanatomy common to both conditions [2]. In panic disorder, situational "spells" peak in 10 minutes and are associated with at least four other symptoms of palpitations, sweating, tremor, shortness of breath, chest pain, nausea, fear of dying, dizziness, loosing control, paresthesia, chills, or hot flashes. In partial seizures, ictal fear occurs with an unprovoked intense fear reaction for seconds to minutes that may be associated with impaired consciousness or postictal state. Other seizure types may be present to highlight the potential epileptic nature of the panic or anxiety, and history is crucial to ensure proper treatment.

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## PARALDEHYDE

Paraldehyde has been used primarily in the past as an AED in the treatment of status epilepticus or serial seizures. Because of its sedating effect, it was also used as a hypnotic in association with alcohol withdrawal and seizures. Although it could be administered either orally or rectally, it is irritating when given parenterally and may result in dissolution of the plastic tubing. Paraldehyde metabolism requires excretion through pulmonary expiration and should

be used with caution to minimize the complications in patients with significant pulmonary disease states. Paraldehyde is little used in Europe and is no longer available in the United States.

## PARASITOSES

Parasites are relatively unusual causes for seizures in developed nations, but they are the most common cause of seizures in certain regions of the world. Among all helminthic parasistes involving the human CNS, *Taenia solium* cysticercosis is by far the most common cause of seizures as well as other neurological conditions. Cysticercosis is the primary cause of recurrent seizures in Central America, South America, and sub-Saharan Africa. The pork tapeworm *Taenia solium* is endemic in most developing countries. Parasitic infections that lead to seizures are seen in a child or young adult in almost half of cases and may cause adult-onset epilepsy in almost 30% of a rural population [1]. Most cases of neurocysticercosis associated with epilepsy occur in rural settings where the number of patients never treated with AEDs may exceed 80% [3].

Parasite-induced seizures may be associated with acute, subacute, or chronic encephalopathies secondary to migration of parasite eggs, larvae, or adults to the cerebral parenchyma. Migrating organisms cause conditions like cysticercosis, filariasis (bancroftii), distomatoses, bilharziasis, loaiasis, and numerous others. Alternatively, seizures can result from an allergic reaction or antigenic response following therapy with sudden death of a parasite in cases of distomatosis, cysticercosis, and loaiasis. Toxoplasmosis and amebiasis due to *Acanthamoeba* can produce acute meningitis with seizures. Seizures can result from focal cerebral parasitic disease with abscess (amebiasis histolitica), cysts (hydatidosis, paragominiasis, cysticercosis), or calcifications (toxoplasmosis, cysticercosis, paragominiasis).

The clinical characteristics of parasitic seizures are not specific. About half of parasitic seizures are partial seizures. Seizure incidence varies with the degree of infestation, number of cysts, localization, size, and evolution. Seizures are the presenting manifestation of parasitic disease in 30% of cases, though status epilepticus is infrequent. Treatment is usually advocated for acute infections for the parasitosis (and the resulting epilepsy), but there has been controversy regarding the effectiveness of the medical treatment for cysticercosis [1]. Residual calcifications, recurrent seizures, and multiple cysts before albendazole therapy carry the highest relapse rate in neurocysticercosis after AED withdrawal. Diagnosis of parasite-related seizures is made by head CT scan or MRI showing multiple, disseminated cysts of different ages with variable degrees of calcification. Outside the CNS, parasitic cysts are destroyed by the host immune response. Malaria due to *Plasmodium falciparum* is the main cause of childhood seizures in Africa and in malaria, it may be the antimalarial drugs themselves that cause seizures [2].

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## PARIETAL EPILEPSY

Parietal lobe seizure foci are less common than are foci in the temporal or frontal lobes, but they are not rare, comprising about 5-6% of the localization-related epilepsies [1]. Parietal seizures may present as simple partial seizures or as secondarily generalized seizures. Somatosensory seizures (*see* Somatosensory and Other Sensory Seizures) may induce symptoms in any body part, but face, tongue, or hand symptoms are most frequent in accordance with the large representation of these regions in the somatosensory homunculus. Paracentral lobule ictal discharges may cause focal sensory symptoms in the genital area and sometimes postural rotatory features (possibly from anterior spread of seizure activity). Infero-lateral parietal foci may cause vertigo (*see* Vertigo), spatial disorientation, a falling sensation, or nausea. Visual symptoms of posterior parietal seizure discharges include bright lights, metamorphopsia, or hallucinations [1]. These symptoms may be difficult to distinguish from migraine (*see* Migraine). Nondominant parietal foci can cause an illusion of partial body displacement (asomatognosia). Dominant hemisphere disturbances affect language.

In diagnosing parietal lobe epilepsy, scalp EEG is frequently unhelpful and may even be misleading [1]. Intracranial EEG may be nonlocalizing [2]. Neuroimaging and ictal SPECT may help demonstrate altered parietal neuroanatomy and regional cerebral hyperperfusion that helps with localization. Functional mapping can enable safe resection of epileptogenic lesions with excellent surgical results [2].


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## PAROXYSMAL NOCTURNAL DYSTONIA

The syndrome of paroxysmal nocturnal dystonia (PND) has received attention due to the difficulty in delineating the clinical features as a movement disorder as opposed to epilepsy (*see* Frontal Lobe Epilepsy) [1]. The confusion or

lack of distinction between NFLE and PND arises from the lack of IEDs on interictal and a significant number on ictal EEG recording. Clinically, the events may appear at any age in previously normal patients with dystonic or ballistic movements that occur repeatedly and last for 15-50 seconds arising from slow-wave sleep. The episodes occur frequently—2-20 times per night. The interictal and ictal EEG recordings are often normal, yet the events remit with carbamazepine. The pathogenesis is unclear; like kinesigenic paroxysmal choreoathetosis, the phenomenon may be nonepileptic in nature [1]. Nonetheless, ablation of cerebral frontal cortex has eliminated the clinical events in some patients with seizures manifest as PND. Within the group of sleep-related, paroxysmal disturbances, seizures can be seen in three subtypes of patients with NFLE, a distinct partial epilepsy, nocturnal motor seizures with dystonic features, paroxysmal arousals, and wandering episodes. These events occur as recurrent, abrupt arousals from NREM sleep with occasional stereotyped motor behaviors (lasting <20 seconds). Nocturnal paroxysmal events are dystonic or dyskinetic movements of the head, trunk, or limbs with vocalization (20 seconds to 2 minutes), while episodic nocturnal wanderings (in <40% of patients with NFLE) last 1-3 minutes and are stereotypic, agitated somnambulisms [1].

PND may be one presenting feature of the group of NFLEs. NFLE subtypes can occur in a given patient. The differential diagnosis includes parasomnias, dystonias, and night terrors. Video polysomnography with added zygomatic and sphenoidal electrodes is required to demonstrate an epileptic frontal-lobe onset. Carbamazepine is effective in some patients, but a third are resistant, and in one small series of eight children with nocturnal frontal lobe epilepsy oxcarbazepine demonstrated a seizure-free outcome.

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## PARTIAL (FOCAL) SEIZURES

Partial seizures have a focal onset. They are associated with localization-related epilepsy and reflect seizures arising from neuroanatomic or functional neuronal activation restricted to part of one hemisphere. When a symptomatic anatomic basis for the partial seizures is identified on neuroimaging, this has ramifications not only for diagnosis and localization, but also in predicting intractability to AEDs and a favorable outcome with epilepsy surgery [1,2]. There are numerous etiologies for partial seizures, including mesial temporal sclerosis, tumors, cortical dysplasia, vascular malformations, and encephalomalacia, though mesial temporal sclerosis is the most common cause in the surgical series [2] (*see* Etiology). Partial seizures may remain focal and propagate to one or more adjacent regions, remain restricted to one hemisphere, have asyn-

chronous involvement of the contralateral hemisphere, or involve both hemispheres synchronously with subsequent secondary generalization. The first clinical sign (*see* Aura) during the course of a partial seizure may have localizing value in the evaluation of epilepsy surgery. Auras have been reported in 46-70% of patients with partial seizures, though a wide range has been reported with variability of aura recall. The signs or symptoms that develop are specific to the region of brain first activated and not necessarily the site of onset. If the epileptic focus is in a clinically silent area, spread to an area that induces a recognizable clinical correlation may result in detection of a propagated and false localization.

Partial seizures are divided into three groups: simple partial seizures without impairment of consciousness (*see* Consciousness), complex partial seizures with impaired consciousness, and partial-onset seizures that secondarily generalize. Partial seizures may evolve in a number of ways. Simple partial seizures may remain simple partial or progress to complex partial; complex partial seizures may appear as an isolated seizure type; simple partial and complex partial seizures may secondarily generalize; or simple partial seizures may evolve to complex partial seizures that subsequently secondarily generalize. Complex partial seizures may be mistaken for absence seizures and are frequently referred to as "petit mal" seizures by patients. However, they are very different entities. Complex partial seizures usually have onset in adults and often have an aura lasting 30-60 seconds, automatisms that may be very complex, gradual termination, and a focal pathology and epileptiform abnormalities on EEG. Absence seizures are most common in children or adolescents and have an abrupt onset of brief impairment of consciousness lasting 10-20 seconds multiple times throughout the day, with abrupt termination and an idiopathic etiology and generalized epiletpiform discharges on EEG. Etiologies, treatment, and prognoses differ with respect to the epilepsy classification (*see* Epilepsy and Classification of Seizures and Epilepsies). Furthermore, some seizures may appear so bizarre (e.g., frontal lobe seizures and some temporal lobe seizures with prominent affective symptomatology) that psychogenic seizures are mistaken for epileptic partial seizures [3].

The EEG during simple partial seizures may show rhythmic spike or sharp wave discharges, with or without slow waves, maximal in the region of the seizure focus, or more commonly no correlate on scalp recording. Complex partial seizures usually demonstrate rhythmic theta or delta frequencies, especially in TLE, though a generalized EEG voltage attenuation (electrodecremental pattern) may occur more commonly in extratemporal complex partial seizures at the start of an ictal event. However, even well-localized partial seizures if they are deep-seated (e.g., mesial frontal lobe) may have no detectable change noted on scalp EEG. Partial seizures most commonly originate in the temporal lobes, with frontal lobe epilepsy being the next most common site of partial seizure origin. In the United States and other industrialized countries, 30-40% of patients with partial seizures remain uncontrolled with respect to AED therapy, accounting for most of the healthcare utilization for patients

with epilepsy [2]. Recent advances in diagnostic neuroimaging has greatly increased interest in surgical therapy for patients with partial seizures.

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## PETIT MAL

As "grand mal" has become a common euphemism for convulsive seizures in the general population, so has "petit mal" come to represent "less bad" seizures. Petit mal and pyknolepsy are older terms that were used synonymously with absence seizures. Rather than absence seizures (*see* Absence Epilepsy), "petit mal" seizures have become a commonly misused term to represent complex partial seizures among the nonneurologic community. However, even though both may appear as "staring spells," they are diametrically opposed relative to diagnostic and treatment implications; the electroclinical features are outlined in the table.

**Petit Mal Seizure and the Clinical Features of Complex Partial and Absence Seizures**

| Features | Absence seizure (petit mal) | Complex partial seizure |
|---|---|---|
| Onset | Abrupt | May have aura |
| Duration | Usually < 30 s | Usually >30 s |
| Automatisms | Duration dependent | Present |
| Awareness | No | No |
| Termination | Abrupt | Gradual |
| EEG | Generalized epileptiform | Focal epileptiform |
| Pathology | Idiopathic | Focal cortical lesion |

Petit mal or absence seizures are the prototypic generalized seizure type. True petit mal seizures are absence seizures and represent generalized seizures with bilateral cerebral onset, seizure semiologies, and EEG onset [1]. The clinical features may be heterogeneous even within the same seizure type, and considerable variability is seen among the epilepsy syndromes [2]. Petit mal seizures with a normal mental status suggest IGE, and syndromes of the generalized epilepsies involve a constellation of more than one dissimilar generalized seizure type including absence. Proper classification of petit mal seizures is crucial so that iatrogenic exacerbation of generalized seizures does not occur.

The concept of an "intermediate petit mal" has been noted to reflect the continuum of seizure types between typical petit mal of IGE and atypical petit mal of SGE.

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## PHENOBARBITAL

With the exception of bromides (*see* Bromides), phenobarbital was the first major anticonvulsant, introduced in 1912. Proprietary names for medications containing phenobarbital include Luminal®, Aparoxal®, Epanal®, Gardenal®, Kaneuron®, and Ortenal®. Phenobarbital is the most prescribed AED in the world because of its low cost and long record of safe use. Sedative properties do limit its use when other AEDs are available. It is effective in all forms of epilepsy with the exception of typical absence. Formulations include tablets of 15, 30, 60, and 100 mg, with an elixir in 20 mg/5 mL and 30 mg/7.5 mL concentrations. Ampules containing 65 or 130 mg/mL intended for intravenous use are available.

The general properties of phenobarbital include it as a weak acid, with pKa = 7.3. The drug ionization and diffusion depend on the pH of the internal milieu. The pharmacokinetics of phenobarbital is linear. Oral bioavailability is excellent, with 80-90% absorption, except in the newborn. The speed of absorption after oral intake depends on the formulation of the tablet, gastric acidity, stomach contents, and gastric emptying. Peak plasma levels are seen 1-18 hours after ingestion. The volume of distribution is 0.54-0.75 L/kg in adults and 0.41-1.31 in young children. Phenobarbital is bound to serum proteins with a binding fraction of 45-54% for adults, 49-67% for children, and 36-43% for newborns. Salivary levels (reflecting unbound drug) of phenobarbital are about 35% of serum levels, but salivary measurements may be unreliable since they depend on salivary pH. The serum half-life of phenobarbital is 46-136 hours in adults, 21-78 hours in 5- to 10-year-old children, and 59-182 hours in newborns. Steady-state serum levels are achieved 15-21 days after starting the medication without a loading dose. Phenobarbital induces hepatic enzymes, resulting in accelerated biotransformation of other drugs and endogenous and exogenous steroids. Elimination of phenobarbital is decreased by a number of enzyme inhibitors. Valproic acid produces a consistent increase of barbiturate levels due to the inhibitory properties on hepatic metabolism of phenobarbital. Optimal plasma concentrations of phenobarbital are 15-30 mg/L, or 64-130 μmol/L.

Benign side effects of phenobarbital are frequent, and, fortunately, severe side effects are rare. Sedation is seen in up to two thirds of patients. There is

often a paradoxical excitation in children, the elderly, or those with cognitive deficits, even with small doses. Phenobarbital commonly inteferes with learning in children, with irritability, aggressiveness, and depression being relatively common. Abrupt stopping of medication may lead to withdrawal symptoms or signs that include seizures. Dyskinesias are rare. Barbiturate-related connective tissue disorders including barbiturate-induced rheumatism, Dupuytren's contractures, plantar fibromas, lederhosen syndrome, Peyronie's disease, and thickening of facial features may occur. As an enzyme inducing AED, there is an increase in hepatic enzyme functions with reduction of serum calcium, phosphate, 25-hydroxycalciferol, and folate levels. Peripheral neuropathies are rare, though hemorraghic disease of the newborn and passage of PB into maternal milk may lead to sedation of the infant. Idiosyncratic reactions, including rash (less than 3% of cases) or hypersensitivity syndromes, are rare.

## PHENYLKETONURIA

Phenylketonuria (PKU) is a rare genetic inborn error of metabolism that occurs in infants, children, and adults. One in 12,000-15,000 infants is born with PKU in the United States. PWE and PKU are deficient in the enzyme phenylalanine hydroxylase and are unable to metabolize phenylalanine, an amino acid found in foods high in protein such as meat, milk, and cheese. In patients with PKU, high levels of phenylalanine may cause mental retardation, hypotonia, speech delay, and seizures. Seizures start later in the first year of life as myoclonus, generalized seizures, or infantile spasms (West syndrome). A diet restricted in phenylalanine is recommended as the primary treatment. However, sapropterin dihydrochloride, a synthetic form of tetrahydrobiopterin, has been modestly effective in stimulating the enzymatic activity of pheylalanine hydroxylase to decrease phenylalanine in conjunction with dietary control [1].

### Reference

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## PHENYTOIN (PHT, DIPHENYLHYDANTOIN, DILANTIN®)

Phenytoin (PHT, diphenylhydantoin, Dilantin) is an efficacious drug for partial-onset and generalized tonic-clonic seizures. It is ineffective in absence and myoclonic seizures and may lead to exacerbation of these seizure types. PHT is the most widely used AED drug in the United States.

For lower serum concentrations, phenytoin possesses linear kinetics, with serum levels and rate of excretion being proportional to administered dose. At higher concentrations, however, PHT saturates the hepatic excretion capacity, and the AED is excreted at a constant rate independent of dose (zero-order kinetics), giving an expotential increase in serum concentrations. The practical consequence of this is that PHT serum levels may rise precipitously after a small increase in dose. PHT is well absorbed orally, with bioavailability in the 20-90% range. Peak plasma levels after oral intake are dose-dependent, peaking in 3-12 hours. Protein binding is significant, with 87-93% of PHT bound to albumin. Phenytoin free fractional concentrations are correlated with biologic activity and may therefore change with alterations in serum proteins or other drugs that bind to serum proteins. The recognized "therapeutic range" for PHT is 10-20 mg/L (40-80 μmol/L), but higher levels may be needed to control seizures without causing toxicity. Free serum levels may be measured by special techniques, and therapeutic free levels are 1-2 mg/L. Salivary levels reflect the free fraction and are approximately 10% of serum total levels. Serum half-life of phenytoin ranges from 8 to 60 (usually 24) hours for adults and from 12 to 22 (usually 16) hours for children. Steady-state serum levels are achieved without a loading dose in approximately 5-10 days. The volume of distribution for PHT is 0.5-0.8 L/kg. Enzyme induction (*see* Phenobarbital; Antiepileptic Drugs) occurs to a significant extent with PHT. Phenytoin is metabolized by the cytochrome P450 enzyme CYP2C9. The rate of metabolism is genetically determined and varies according to race. Caucasians possess three alleles, of which CYP2C9*1 accounts for three quarters of the enzymatic acitivity, though with mutant alleles CYP2C9*2 and 3, a 30-40% reduction of enzymatic activity may lead to clinical toxicity [1]. Interactions between the EIAEDs may have catastrophic effects, with compromise of concomitant exogenous therapy with cardiac drugs (especially anticoagulants), psychotropics, and chemotherapy, among others, as well as endogenous substrates (e.g., hormones, vitamins). Free serum fraction of PHT is increased via displacement on the carrier protein albumin by aspirin, certain sulfa drugs, heparin, and valproate.

Side effects of PHT occur typically with serum levels in excess of 20 mg/L, but some individuals cannot tolerate even much lower levels. As with all AEDs, ideal serum ranges are specified under an assumption of monotherapy. Typical PHT side effects include anorexia, nausea, dysarthria, dizziness, diplopia, nystagmus, ataxia, confusion, and obtundation. Sedation and change in cognitive function and psychomotor slowing is usually insidious. There may occasionally be progressive cognitive deterioration, referred to as phenytoin encephalopathy [2]. A paradoxical effect may be seen at higher serum concentrations with exacerbation of seizures. Gingival hyperplasia occurs in 30-60% of patients and is believed to be related to a salivary deficit of IgA. Cerebellar syndrome occurs more often in patients with preexisting cerebellar lesions. Chronic peripheral neuropathy often occurs, though usually subclinical. Enzyme induction may lead to abnormalities in phosphorus and calcium metabolism and lead to osteopenia and osteoporosis as well as decreased effectiveness of oral contraceptives. In

addition, endocrine/metabolic changes may occur, with effects on endogenous hormonal function (i.e., thyroid dysfunction). Abnormalities in immunologic function may occur and even in rare cases be associated with lymphoma (not to be confused with lymphadenopathy, referred to as pseudolympoma). Dyskinesias, asterixis (especially at higher doses), myoclonus, oro-facial dyskinesias/dystonias, and choreathetosis may be prominent and be confused with seizures. While phenytoin has remained a first-line AED for the treatment of status epilepticus, its use as an initial AED for both localization-related and generalized epilepsy is waning with the advent of newer AEDs with more favorable pharmacokinetics and adverse events (especially cosmetic and teratogenic effects in females). Ampules of 250 mg/5 mL are available in hospital pharmacies for parenteral use. A loading dose of 16-20 mg/kg is given by slow intravenous infusion at 25-50 mg/min while monitoring blood pressure and EKG.

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## PHONATORY SEIZURES

Phonatory seizures are seizures that involve *speech*. Phonatory seizures may be manifested by verbalization, vocalization, or speech arrest. In phonatory seizures, unlike aphasic seizures, the internal language is intact. Speech arrest (aphemic or anarthric) is common in TLE and occurs in up to 75% of patients with recurrent CPS, though it is not consistently localizing to the dominant hemisphere and is more nonspecific than the presence of *ictal speech* or dysarthric seizures (difficulty with enunciation) that occur with nondominant focal seizures [1]. The vocalization of an epileptic "cry" may occur during a GTC in IGE, though verbalization can occur with focal seizures in LRE with intact speech when the nondominant hemisphere is involved and occur as a localizing semiologic characterisistic [1]. Speech is inhibited despite the voluntary attempt to speak with involvement of the primary motor cortex in the dominant posterior-inferior frontal lobe or the anterior portion of the medial frontal lobe in the SSMA with the negative speech responses encountered as a result of electrical brain stimulation. Phonatory seizures may also comprise positive symptoms, with uncontrolled vocalization, palilalia, grunts, whines, or cries. Bizarre colorful vocalizations may occur with seizures that involve the SSMA or frontal lobe.

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# PHOTOSENSITIVE SEIZURES (PHOTIC-INDUCED SEIZURES)

Intermittent light stimulation, whether by the interruption of a steady light source or the intermittent appearance of flashing light, may induce a seizure. The estimated prevalence of seizures from light stimuli is approxmimately 1/1,000-1/4,000 people aged 5-24 years [1]. Photoconvulsive seizures are not to be confused with a photomyoclonic EEG response. Photoconvulsive stimuli in the environment include changing light sources—for example, moving from relative darkness to a brightly lit region, when traveling down tree-lined avenues on a sunny day, when watching a revolving wheel, helicopter blades, or stroboscopic lights in a discotheque or EEG laboratory. Photosensitive seizures can be observed in generalized (usually generalized tonic-clonic, myoclonic, or absence) as well as partial seizures. They can be observed in idiopathic or symptomatic epilepsies, in those that are chronic and degenerative, or in those that are acute [2]. Children, adolescents, and young adults are most susceptible to photoconvulsive seizures, and photosensitivity usually disappears by the third decade of life [1]. Alcohol withdrawal is a risk factor for photoconvulsive or photomyoclonic responses. Television epilepsy is a type of photic-induced reflex epilepsy in response to watching certain TV images. These seizures usually develop in late childhood and are generalized or rarely partial. Factors responsible include flickering images, screen brightness, geometric figures, and rarely actual content of the picture [1]. A photoparoxysmal response on the interictal EEG is common but not invariable with TV epilepsy. In some patients, visual patterns rather than simple light may induce seizures [1]. Visual scanning of pictures or objects with geometric and contrasting contours, for example, vertical bands on wallpaper, venetian blinds, or radiators, may induce seizures. The EEG often demonstrates regular 3 Hz or faster, bilateral, synchronous, generalized spike-and-slow wave discharges.

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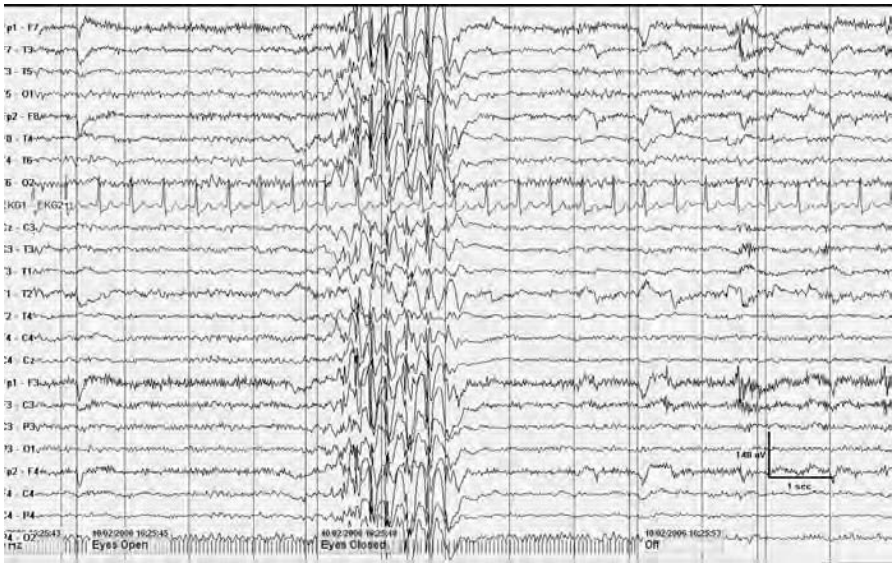
# PHOTOSENSITIVITY

Photosensitivity refers to the triggering of clinical seizures or the demonstration of bursts of spontaneous IEDs on the EEG by light. Intermittent photic stimulation has been widespread as a routine activation technique throughout the world. Photosensitivity is not synonymous with epilepsy, and photosensi-

tivity may occur independent of clinical seizures [1]. Overall, approximately 4% of PWE have a photoparoxysmal response (PPR), but only 70-77% of those with a PPR (*see* figure) have epilepsy [1]. Though subject to debate, a PPR that outlasts the duration of the stimulus appears to be more likely in PWE than with a *self-limited* repsonse. Frequencies that are most likely to trigger photosensitivity lie between 15 and 18 Hz [2], and most patterns consist of bursts of generalized spike-and-waves or polyspike-and-waves.




Self-limited photoparoxysmal response at 15 Hz frequency in a patient with JME.

Photosensitivity and the PPR on the EEG may be associated with three types of seizures: absence, myoclonic, and the majority with GTC seizures. Photosensitivity is frequently familial, more frequent in women, and generally appears at puberty. In PPR patients, photosensitivity disappears in approximately one third in the third decade of life or diminishes with the use of valproate. There is no single photosensitive epilepsy, rather there are photosensitivity components in a number of epileptic syndromes. Pure photosensitive epilepsy is the most common form of reflex epilepsy where seizures occur only in response to photosensitivity under cetain circumstances of daily living (*see* Reflex Seizures), accounting for over one third of photosensitive people with seizures. Of the IGEs with photosensitivity, juvenile myoclonic epilepsy hasphotosensitivity demonstrable in up to 30-40% of patients, while absence epilepsy and epilepsy with GTC seizures are less likely to demonstrate a response. Other epilepsies such as epilepsy with eyelid myoclonia with absence, pattern-sensitive epilepsy (seizures provoked by light), seizures with auto-induced flicker (*see* Auto-Induced Seizures), pure photosensitive epilepsy and reflex epilepsies with photosensitivity causing spontaneous or provoked seizures, epilepsy with tonic-clonic

seizures on wakening, and childhood absence epilepsy demonstrate photosensitivity. Photosensitivity may less frequently be associated with some of the encephalopathic generalized epilepsies such as progressive myoclonus epilepsies or epilepsy with myoclonic absences. In addition, localization-related epilepsies, especially when partial seizures originate in the occipital lobe, may be provoked by intermittent photic stimulation. Valproate, lamotrigine, and levetiracetam may be effective in treating persons with photosensitivity, as can polarized darkened glasses to limit photogenic stimulation.

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## POLYCYSTIC OVARY SYNDROME

Polycystic ovary syndrome (PCOS) is characterized by the presence of chronic anovulation and androgen excess, often with polycystic ovaries, though polycystic ovaries are not required for the diagnosis. PCOS is the leading cause of chronic anovulatory infertility, with resultant menstrual irregularities and dysfunctional uterine bleeding. Increased gonadotrophic-releasing hormone increases luteinizing hormone, with reduced follicle-stimulating hormone that results in increased production and decreased clearance of androgens accounting for hyperandrogenization. It is the most common endocrine disorder in women of reproductive age, affecting 4.0-6.8% of premenopausal women [1]. PCOS causes clinical manifestations including menstrual irregularities, and signs of hyperandrogenism with truncal obesity in 60-70% of patients in the United States, with subsequent clinical signs of acne, alopecia, and male-pattern hirusitism involving the body and face. More importantly, it is associated with long-term serious health consequences such as diabetes mellitus in addition to reproductive symptoms. Metabolic derangements including the metabolic syndrome are two to three times higher in women with PCOS [2]. Previous studies have described an association between epilepsy and features of PCOS in women treated with AEDs. Epilepsy [1] and valproate [3] have both been implicated as causing PCOS, and though the impact of VPA upon reproductive endocrine disorders has been controversial, attention to the potential of causing hormonal and metabolic disturbances when prescribing long-term AED therapy should be observed [3]. For some women, infertility is the issue for PCOS, and in these patients clomiphene to induce ovulation may be used. When fertility is not the issue, metformin may improve insulin sensitivity in PCOS, decrease circulating androgens, and improve ovulation and menstrual cycle function [2]. Though metformin is not approved by the FDA for the treatment of PCOS, the drug is commonly used for this purpose.

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## POLYPHARMACY

While monotherapy is the preferred approach to newly diagnosed epilepsy, almost one third of individuals will have insufficient seizure control with a single AED (*see* Refractory Epilepsy). The AED cumulative load is higher in polytherapy, and therefore the risks of adverse events increase. Still, with failure of repeat monotherapy trials, multiple seizure types or frequent and prolonged seizures including status epilepticus are encountered, and polytherapy may become necessary. The clinical usefulness of using two AEDs together lies in its potential to produce additive and supra-additive (synergistic) effects on controlling seizures. The desired intention of potentiating the effect of each individual AED, with the hope of utilizing lower doses in concert, must be balanced with the potential for interactions between the different AEDs and non-AEDs. In practice, a small number of patients may benefit from using two AEDs together (about 10%), and while their efficacy may be supra-additive, their toxicity is also frequently additive. Synergism in polytherapy has been shown both experimentally and in human studies [1]. A "rational" polytherapy has been suggested based upon unique combinations of individual mechanisms of action to promote a greater likelihood of synergy [2]. However, decreasing polypharmacy may also demonstrate a decrease in side effects and even a decrease in seizure frequency. Still, reduction of polypharmacy to monotherapy is not always possible, and the withdrawal course of an AED may be difficult (especially with withdrawal effects from certain AEDs), and as such, patients should be warned of the potential for breakthrough seizures and the long-term therapeutic goal should be reemphasized. Nevertheless, even in a difficult-to-treat group of mentally retarded, institutionalized PWE, a reduction in polytherapy has been shown in 19% without loss of seizure control [3]. Strategies to reduce polytherapy have included avoidance of precipitating events (e.g., photic stimulation in JME), recognition of PNES with video-EEG monitoring, selection of appropriate patients for resective epilepsy surgery, and avoiding excessive overtreatment [4].


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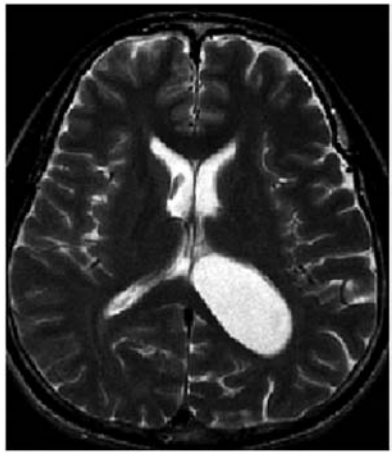
## PORENCEPHALY

Porencephaly is a chronic condition in which the brain has cavitation that results from direct communication between the ventricular system and subarachnoid space to form a cystic dilation of one of the lateral ventricles. Porencephaly is not specific for an etiology. Most cysts are caused by vascular occlusions associated with large intracranial vessel thrombosis and may be caused by a perinatal cerebral infarct or hemorrhage, malformation such as hemimegencephaly, or Sturge-Weber syndrome, often translating clinically to the manifestations of a hemiparesis or cerebral palsy. Acquired lesions such as trauma or Rasmussen syndrome may result in porencephaly as well. Seizures are a frequent consequence of porencephaly. EEG may reveal focal voltage attenuation and polymorphic delta, with focal or regional interictal epileptiform discharges. Patients with prenatal and perinatal insults associated with large porencephalic cysts are good candidates for functional hemispherectomy when seizures remain uncontrolled.



Axial images of a high-resolution brain MRI demonstrating left porencephalic cystic dilation in a patient with HHE syndrome successfully treated with left anterior temporal lobectomy.

## PORPHYRIA

Porphyria is a group of disorders of heme biosynthesis that may be subcategorized as hepatic and erythropoietic. Seizures (and other neurologic problems) occur only in the hepatic group. Acute intermittent porphyria, porphyria cutanea tarda, hereditrary coproporphyria, and variegate porphyria may be associated with seizures. Seizures occur in 15% of cases of patients, may be precipitated by AEDs, and begin up to 28 days after drug exposure. Most AEDs are problematic because of their porphyrogenic potential, which has been demonstrated both in vitro and in vivo. Bromides have long been used more safely than most AEDs, though tolerability issues have given rise to more use of newer AEDs without significant hepatic metabolism, such as gabapentin [1]

and, theorectically, levetiracetam, though lists of drugs that exacerbate porphyria are available [2].

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## POSITRON EMISSION TOMOGRAPHY (PET)

Positron emission tomography scanning (PET) and single photon emission computed tomography (SPECT) are *functional* neuroimaging techniques that provide complementary information to anatomic imaging techniques to image the *anatomic* characteristics of the brain. EEG and fMRI are similar to PET, and dissimilar to anatomic MRI in that PET identifies functional and not structural properties of the brain. The most common radioisotope employed for PET is 2-deoxy-2-[18F]fluoro-D-glucose (FDG), or 18F-fluorodeoxyglucose (FDG). FDG is transported into neurons in proportion to glucose consumption of neurons and is trapped rapidly in the cells. PET with FDG, therefore, produces a representation of cerebral energy metabolism. The other energy substrate for brain is oxygen, and 15O2 PET images can also reflect energy metabolism in brain. This radioactive tag allows heterogeneous rates of regional cerebral glucose utilization to be estimated. In addition to [18F]FDG to image the regional cerebral metabolic rate, and [15O] water to measure regional cerebral blood flow, radiolabeled ligands coupled with dopamine and serotonin permit assessment of neurotransmitter synthesis. Furthermore, benzodiazepine anagonists, NMDA, opiates, tryptophan, and serotonin ligands have been used to evaluate receptors in targeted areas of the brain.

PET scanning has proven useful in the localization of seizure foci and in exploration of the underlying in vivo assessment of physiologic functions of epilepsy in humans [1]. FDG-PET studies have demonstrated that brain regions near partial seizure foci are hypometabolic during the interictal period and hypermetabolic during seizures. Though the region of interictal hypometabolism almost always correctly lateralizes to the epileptogenic zone and is most pronounced in the temporal lobes, localization is less consistent with extension beyond the ictal onset zone into the frontal or parietal lobe [2]. PET may rarely falsely lateralize the seizure focus. Interictal regional hypometabolism with PET is seen in 60-90% of patients with TLE. Interictal hypometabolism with PET can be used in the decision process for selecting patients for surgery [1], invasive EEG planning, as well as predicting a more favorable postoperative outcome when localized hypometabolism is present [2], while bilateral temporal hypometabolism portends a poorer postoperative surgical outcome. Patterns of mesial temporal lobe hypometabolism vary (mesial > lat-

eral and vice versa), though neocortical TLE often has lateral > mesial hypometabolism. However, intralobar localization is not reliable across patient selection in TLE. PET with FDG may be less likely to demonstrate an abnormality early in the course of LRE or extratemporal LRE, and in those with normal MRI brain. PET will be abnormal in the presence of a structural lesion, especially when higher field strength magnetic fields and newer generation scanners performed with a dedicated epilepsy protocol are utilized (*see* Magnetic Resonance Imaging). Volumetric anatomic brain MRI has shown a correlation between decreased FDG-PET and hippocampal and temporal lobe volumes.

PET studies with 15O water are less reliable for identification of the epileptogenic zone and have not been consistent in predicting postoperative seizure outcome [3]. Still, decreased perfusion (similar to SPECT) is able to identify 50% of patients with epilepsy that reveal an alteration between metabolism and perfusion [4]. PET studies with neurotransmitter receptor markers give clues to neurochemical mechanisms of epilepsy. Opiate receptors, for example, may increase in the region of the epileptogenic zone, possibly as an inhibitory control mechanism, while benzodiazepine receptors decrease.

The method of PET scanning typically involves interictal injection of a radioactive isotope tagged to a physiologic probe (e.g., glucose), which is taken up in a particular part of brain following preparation of the radioactive isotope by a cyclotron. Regional hypometabolism reflects a localized reduction in glucose transport across the blood-brain barrier. Next, the isotope is injected intravenously into a patient (commonly interictally in PET and ictally in SPECT). Then, the isotope localizes to a certain region of brain or targeted cellular structure or neuroreceptors in accordance with the binding affinity of the receptor, cerebral blood flow, or physiologic measure. The radioactive decay of the isotope releases high-energy particles (positrons), which travel a short distance to impart paired gamma rays traveling in opposite directions. The scintillation counters detect the gamma rays in the scanner, and the computerized tomographic techniques generate an image of the isotope localization in brain with the interpretation of the images performed in accordance with various models of tracer distribution, binding, decay, and an understanding of the underlying biology.

PET studies suffer from some limitations. They require specialized equipment and personnel and are expensive to obtain. PET studies average metabolic activity over minutes, so rapid events such as seizures are uncommonly analyzed, and briefer events are not able to be detected. Spatial resolution is in theory about 2-3 mm under ideal conditions (superior to SPECT), but in practical application the resolution may be less. Changes in cerebral blood flow and in the concentration of endogenous compounds that may compete with the radioactive label may greatly affect the results. Finally, PET gives little information on cause and effect. Still, despite these limitations, PET remains an indispensable tool in the presurgical localization of the epileptogenic zone in patients with intractable LRE.

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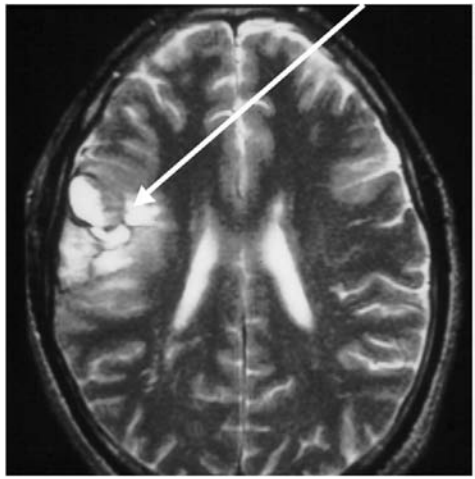
## POSTTRAUMATIC EPILEPSY

Head injury constitutes a significant morbidity and mortality and is a well-recognized preventable cause of seizures [1]. The number of patients with serious head injuries has risen with time. Posttraumatic seizures are spontaneous seizures that occur after penetrating or nonpenetrating head injury not attributable to an alternative cause. Posttraumatic epilepsy reflects spontaneous, recurrent unprovoked seizures that follow head trauma. Approximately 70-80% of seizures following head injury occur within the first 2 years, though they may occur years later; this becomes less likely when no seizures occur during the first 3 years. Posttraumatic seizures are classified as *early* or *late* seizures. *Early seizures* occur within the first week after the injury, and *immediate seizures* occur within the first day. Approximately 50% of early seizures occur within the first 24 hours and are more likely to occur with young children less than 5 years of age. Early seizures are a risk factor for late seizures and PTE, although this risk may be different for children and adults, with the elderly highly vulnerable to late PTE from any type of head injury. They reflect the initial trauma to the brain, have been described as concussive convulsions, and usually do not recur or require AEDs. Early seizures that occur within the first week are usually GTC seizures and reflect the severity of a focal or multifocal brain injury, increasing the risk to >25% that the individual will develop PTE when they occur. Late seizures usually have a focal onset and occur after the first week corresponding to a fixed injury to the brain reflecting posttraumatic epilepsy (PTE). Early seizures develop into status epilepticus in about 10-20% of cases, are more common in children, and increase the risk of late PTE.

The incidence of posttraumatic epilepsy is relative to the situation, is responsible for >20% of the symptomatic cases of epilepsy, and may occur years after the initial trauma [1]. Head trauma during *military* conflicts produces an incidence of posttraumatic epilepsy with severe injury (i.e., penetrating injury) appearing in nearly 50% of survivors, while head trauma sustained in civilian life produces a much lower incidence of epilepsy [2]. Several risk factors pre-



MRI of brain demonstrating posttraumatic hemorrhagic contusion of the right central head region in a patient with posttraumatic epilepsy.

dict development of posttraumatic epilepsy after injury, though mild to moderate *civilian* head injuries usually reflect only a <5.0% risk of PTE, increasing to 30% with more severe injuries such as intracranial hemorrhage [2]. Reports of a graded risk in civilian head injury with respect to severity has been demonstrated: 1.5% with mild (<30 minutes), 2.9% with moderate (30 minutes to 24 hours), and 17.2% with severe (>24 hours) head injury, with severity a reflection of the duration of the loss of consciousness or amnesia. Seizure incidence also depends on the extent of injury, especially in the setting of a military injury, such as depressed skull fracture, intracranial hemorrhage, dural penetration injury, prolonged posttraumatic coma >24 hours, and brain abscess associated with the highest risks for PTE [2]. The site of injury (especially centro-parietal > temporal > occipital or frontal lobe involvement) has also been found in prior series to reflect relative risks [1].

Closed head injuries must be severe to significantly increase the incidence of epilepsy [2]. Almost every patient with epilepsy relates a history of some minor head trauma—for example, a fall from a swing, a hard blow from a soccer ball, or a tumble from the crib—and even 5 years following a mild civilian closed head injury with or without transitory loss of consciousness, the risks for PTE have been noted to be similar to the general population.

Neuroimaging predicts a greater risk for both early and late posttraumatic seizures when a focal brain lesion with intracranial blood is seen, but when seizures have not occurred, the significance of abnormal findings on the likelihood of developing seizures is less predictable. EEG initially reveals nonspecific findings, but are useful for detecting nonconvulsive status epilepticus in comatose patients when video-EEG monitoring has been pursued. Routine EEG is less reliable in predicting the risk of posttraumatic seizures, though late focal abnormalities appear more consistent than early findings.

Treatment of early seizures may not be required, and the possibility of psychogenic nonepileptic seizures, especially in the case of mild civilian closed head injury, should be kept in mind [3]. When severe head injury and brain edema is present, treatment of early seizures may minimize increasing intracranial pressure and status epilepticus and should be considered. Prophylaxis has been previously proposed empirically, though randomized controlled trials [4] have consistently failed to show a preventative effect from

AED prophylaxis with many different drugs, including phenytoin, phenobarbital, carbamazepine, and valproate [5]. Late posttraumatic seizures do require treatment with AEDs like any seizures associated with a symptomatic cause with individualized treatment (*see* Treatment) that is appropriate for the individual. Seizures that become intractable to AEDs may respond to surgical therapy, though outcome may be guarded as the severity and association with diffuse structural injury increases.

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## PREGABALIN® (LYRICA)

Pregabalin (PRB) is an AED that, like gabapentin, binds with high affinity to the alpha2-delta subunit of voltage-gated calcium channels in the central nervous system. Similar to gabapentin, there is an association with animal evidence of carcinogenicity with a high incidence of hemangiosarcoma identified in two different strains of mice, but the clinical significance of this finding is unknown. Pregabalin is indicated as adjunctive therapy for adults with partial-onset seizures and has shown a dose-related response [1]. Similar to GBP, PRB has shown utility in nonepileptic conditions that involve neuropathic pain associated with diabetic neuropathy and postherpetic neuralgia. It is well absorbed after oral administration and is eliminated largely by renal excretion with a T1/2 of about 6 hours, though patients with renal insufficiency require modification of dose administration [2]. PRB is predominantly excreted unchanged in the urine, undergoes negligible metabolism, and does not bind to plasma proteins; drug interactions are not expected to occur. Adverse effect in the pivotal trials included dizziness, somnolence, ataxia, and weight gain similar to GBP. Weight gain of 7% or more over baseline was observed in 8% of patients, and higher frequencies of weight gain and peripheral edema were observed in patients taking both PRB and thiazolidinedione antidiabetic agents. Laboratory abnormalities included increased CPK and reduced platelet counts. PRB is a Schedule V controlled substance with euphoria and withdrawal symptoms reported in some patients on abrupt discontinuation. Doses of up to 600 mg/d are available. On a mg/kg basis, PRB has about four to six times greater potency than GBP.

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## PREGNANCY

There are over 1.1 million women of childbearing age in the United States with epilepsy [1], with 3-5 births per 1,000 occurring in women with epilepsy (WWE) [2]. Women with epilepsy are conceiving with increasing frequency. Furthermore, 40% of pregnancies are unplanned, affecting approximately 8,000 children born annually in the United States [1]. Epilepsy as an individual risk factor for birth defects in the offspring of WWE does not appear to be associated with greater teratogenicity beyond that associated with the AED [3]. Attempts at comparing healthy women and WWE unexposed to AEDs have not revealed a higher risk of birth defects, though the severity and frequency of seizures in untreated WWE may well be < in those receiving AEDs. Most WWE maintain seizure control during pregnancy. Worsening of baseline seizure frequency occurs in 15-37% of WWE and may be the result of nonadherence, low AED serum concentrations, or increased metabolism. Conversely, 13-25% experience improvement during pregnancy [4]. Convulsive seizures during pregnancy appear to be more troublesome than nonconvulsive seizures. Even one GTC seizure may result in deceleration of fetal heart rate, fetal periventricular hemorrhage, premature delivery, and/or fetal demise [4]. The impact of a nonconvulsive seizure on the fetus is less clear. Seizure emergencies including serial seizures or status epilepticus may occur during pregnancy and lead to maternal and fetal mortality in 31% and 48%, respectively [4]. The risk of increased seizure frequency during pregnancy appears higher among women with localization-related epilepsy, AED polytherapy users, and for monotherapy with oxcarbazepine (OXC). Seizures during pregnancy may result in cognitive dysfunction, with more than five generalized seizures during pregnancy conferring a risk of lower verbal IQ for children exposed in utero. The risk of maternal death during pregnancy for WWE is 10 times greater than that in the general population. This risk appears to be due to the effect of seizures, often associated with nonadherence to AED recommendation. Seizures occurred during delivery in 3.5% of patients in the EURAP study and were most likely in WWE who had seizures during pregnancy [5].

While uncontrolled seizures are more hazardous than pharmacologic therapies, pharmacotherapy during pregnancy is a principal concern for the clinician treating WWE, especially when utilizing polytherapy or valproate. Being a WWE is not the same as being a man with epilepsy, since no risk of birth defects is conferred by a father with epilepsy. Pregnancy is never a physiologi-

cally passive condition and may result in anatomic major congenital malformation (MCM), behavioral neurodevelopment compromise, or even fetal demise whether AEDs are utilized or not. The medical treatment of women during pregnancy involves the care of two lives—the female patient and her unborn infant. The risk of developing a MCM varies depending upon the criteria applied. Most consider a MCM as an abnormality identified at birth or within the first 12 weeks of life. These MCMs involve an essential embryonic structure and require some form of intervention, commonly surgical correction. Reports have now been released from pregnancy registries in North America, the United Kingdom, Australia, Finland, Sweden, Italy, The Netherlands, and international, multicenter study groups in Canada, Japan, Italy, the United Kingdom, and the United States [3,5]. The risk of MCM in infants born to mothers with epilepsy exposed to AEDs in utero is approximately 4-8% compared with a 2-4% risk in the general population [1,3,5]. The risks of teratogenicity have been regarded as multifactorial, including genetic predisposition, although most prospective studies show that AED-related factors are the primary risk factors for an increase in congenital malformations rather than the epilepsy itself. The most common MCMs seen are found in the general population, including cardiac defects, cleft lip/palate, hypospadias, and club foot [3]. Thus far, no individual AED-specific MCM has been found with the exception of spina bifida, more commonly associated with valproate (1-2%) and carbamazepine (0.5-1%) [3]. The frequency of suboptimal outcome is increased for WWE compared with that of the general population. The risk of birth defects is increased with polytherapy, reported with higher frequency in the first-generation AEDs and with higher-dose AEDs. Exposure to AEDs in the first trimester of pregnancy has been associated with an increased risk of MCMs [3,5]. Specific AEDs have been associated with higher risks of certain MCMs such as congenital heart disease and cleft palate with phenytoin and the barbiturates and neural tube defects with valproate and carbamazepine [5].

Available lists of "drugs that pregnant women should avoid" may result in well-meaning but hazardous medical advice to discontinue AEDs at the expense of disastrous results of seizure breakthrough, acidosis, and hypoxia to the fetus. Most WWE must continue AEDs during pregnancy to prevent the potential harmful effects imposed by seizures to the fetus via direct drug exposure or indirectly through seizure-related maternal injury. Most information on teratogenesis available has been drawn from studies having methodologic limitations, small numbers of patients evaluated, and heterogeneity in populations studied, which have made comparating risks for individual AEDs difficult [3]. Anticonvulsant embryopathy reflects the higher frequency of MCMs, growth retardation, and hypoplasia of the midface and fingers seen in the offspring of WWE exposed to AEDs. The mechanisms for drug-induced birth defects are unknown. Several theories for MCMs or neurodevelopment birth defects include folate insufficiency, AED-reactive intermediates (epoxides and free radicals), AED-triggered apoptotic-related mechanisms, neuronal suppression, and ischemia/hypoxia.

Vitamin supplements including folate are recommended during pregnancy. Supplementation with folic acid dosed between 1 and 4 mg/d are used. During the last 4 weeks of pregnancy, PWE on enzyme-inducing AEDs should be given vitamin K1 (Mephyton(c)) to minimize the potential for hemorrhagic disease of the newborn secondary to depletion of coagulation factors by AEDs.

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## PRENATAL SCREENING

Prenatal screening is important to attempt detection of major and minor fetal congenital malformations. It will permit preparation for adequate care for the neonate, particularly for neural tube defects and cardiac defects [1]. Prenatal testing is recommended to determine whether any anomolies in the developing fetus are evident for the purposes of intervention [2].

- An initial first trimester level-2 (anatomic screening) ultrasound at 11-13 weeks is recommended to address whether major malformations such as neural tube defects are present.
- Serum alpha-fetoprotein at 16 weeks is obtained to screen for neural tube defects.
- A second trimester ultrasound is obtained between 18 and 22 weeks to ensure proper development of the cardiac structures and head and spine development and to detect minor malformation of the face including cleft lip or cleft palate. Fetal cleft lip detection is best determined at a fetal age of 20 weeks or more.

Surgical correction of a congenital malformation immediately after birth may be required when the malformation is severe. Some prenatal interventions such as in utero correction of neural tube defects are possible. Studies have found that a majority of parents with knowledge of facial anomolies are better prepared following prenatal counseling. On the other hand, some patients are best made aware of malformations before term so that they may consider therapeutic abortion if a major malformation is detected.

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## PREVALENCE

Epidemiology has furthered our understanding of the frequency of epilepsy in the general population. There are aproximately 50 million PWE in the world, 80% of whom live in resource-poor countries [1]. Studies of frequency and distribution of the epilepsies use incidence (*see* Incidence); prevalence rates vary as a function of a given population and also show variation dependent upon defined demographics (e.g., age and etiology). *Incidence* reflects the number of new cases (usually per 100,000 population) per time (usually per year). *Prevalence* measures the total number of people (per 1,000 population) at a specified time. Prevalence figures may be biased depending on the stability of the study population. *Active prevalence* refers to those PWE identified (either with respect to treatment or seizures) within a specified period of time (usually <5 years). Active prevalence estimates typically exist over a range and depend upon the population studied, though figures of approximately 7.1/1,000 population make epilepsy one of the most common serious neurologic conditions encountered [2]. When mortality is comparatively low, prevalence may appear to overestimate the frequency of the disorder (e.g., PWE who do not tend to remit, such as those with JME). When mortality is high (e.g., status epilepticus), prevalence may be underestimated because of bias that accounts for the survivors only. Studies in different countries give a broader range of prevalence figures for inhabitants with epilepsy. Prevalence variations may be ascribed to the different study methodologies, collection, and case ascertainment of epilepsy (age, sex, seizure type), as well as true prevalence differences due to local factors such as etiology (e.g., neurocysticercosis). The Rochester, Minnesota, epidemiologic study found a rising incidence and prevalence in the elderly (*see* Incidence). Etiology may play a role in prevalence rates, possibly because many cases are termed "cryptogenic" [3]. In Mexico, Ecuador, and Peru the prevalence of epilepsy is higher because of neurocysticercosis (*see* Parasitoses), while in developing nations health interventions have been used to successfully treat conditions in PWE and thus change with time.


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# PRIMIDONE (MYSOLINE®)

Primidone (PRM) has a chemical structure that is similar to phenobarbital (PB), though with a pyrimidine ring that has two instead of three carbonyl moieties. Its clinical use is therapeutically identical to PB as most of the compound is metabolized to PB. PRM is used for the treatment of patients whose seizures do not respond to the many of the first-line or second-line AEDs. It may be a useful adjunct in treatment of partial, generalized tonic-clonic, and myoclonic seizures. PRM is metabolized and undergoes biotransformation primarily to PB, though phenylethylmalonamide (PEMA) accounts for a much smaller active metabolite that also possesses antiepileptic activity, and as such, the major action of PRM is exerted via PB instead of PRM or PEMA. The mechanisms of PRM and PB overlap, though PRM had no effect upon postsynaptic GABA and glutamate responses in lower doses in contrast to PB, though both limited high-frequency neuronal repetitive firing at relatively high concentrations. PRM has near complete bioavailability, protein binding of <10% (both PRM and PEMA, *see* Phenobarbital), and an elimination half-life that is dependent upon the presence of enzyme induction that may be produced by co-administered medication. PRM itself has a 3- to 12-hour half-life and thus should be taken at least three times daily. PRM has efficacy in partial and secondarily generalized seizures, but may also have activity in IGEs such as JME. Sedation can be extreme with PRM, especially in the early stages after initiation of therapy, and dose-related side effects are evidenced. Symptoms include those of neurotoxicity; somnolence, ataxia, incoordination, and depression, in addition to longer-term effects of connective tissue disease, adverse effects upon bone health, and hypersensitivity reactions. A large multicenter controlled comparison of 622 patients as part of the VA cooperative study in PWE and partial seizures found no significant advantage in efficacy of PRM over phenobarbital, carbamazepine, or phenytoin [1]. While PRM controlled focal seizures in fewer patients, there was a greater likelihood to discontinue therapy because of sedation. In treatment of naïve children barbiturate AEDs in the form of PB were found to result in an unacceptably high discontinuation rate due to sedation [2]. PRM is available as 50 and 250 mg tablets and as a syrup formulation.

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## PROGABIDE (GABRENE®)

Progabide (PGB) is a synthetic molecule produced with the express intent of increasing cerebral GABA concentrations. Its principal metabolite (PGA) also has been demonstrated to possesss antiepileptic properties. PGB has been used in Europe but is not available in the United States. This AED has some documented efficacy, but there is a high incidence of adverse events, including hepatotoxicity, which have limited its utility.

## PROGNOSIS

Comparison of prevalence and incidence ratios have suggested that the mean duration of epilepsy is approximately 12-13 years, although this theoretical value does not take into consideration either the age of onset, the clinical type, or the response to treatment. Remission rates for epilepsy with treatment vary according to when the study was done, the retrospective versus prospective methodology, and the length of follow-up. Overall, approximately 70% of PWE enter long-term remission [1], and more than one half of those who do so enter remission within the first year after diagnosis. Patients with many recurrent unprovoked seizures have a substantial risk for continued seizures [2], but RCTs have demonstrated that "therapeutic" concentrations of an AED employed after an intial seizure reduces the percentage of patients with recurrent seizures. Favorable prognostic factors for remission include a young age of onset, early age at diagnosis, GTC seizure type, idiopathic or cryptogenic etiology, and normal neurologic examination and neuroimaging. Conversely, a known cause, focal or multiple seizure types, perinatal neurologic deficit, use of more than one AED to control the seizures, greater number and duration of seizures prior to diagnosis, and abnormal EEG were poor prognostic signs for remission. Frequent GTC seizures portend a reduced likelihood of remission [3]. The duration of active epilepsy prior to control has been an important predictor of remission, and if seizures are not controlled, fewer patients are expected to achieve remission. Uncontrolled epilepsy after 1 year of treatment represents a significant risk for long-term epilepsy, and if seizures continue for more than 4 years only 10% achieve remission. Early use of AEDs does not influence the prognosis for seizure control (*see* First Seizure). An abnormal EEG when treatment is stopped increases the chance of relapse, especially when generalized spike-and-waves are seen [3], but a normal interictal EEG does not exclude a relapse.

After being free from seizures for several years, 10-60% of patients will relapse after tapering AEDs [3]. Relapses occur predominantly in the first year, particularly in the first 6 months. Predictors of a successful trial of taper have included rapid seizure control, few seizures, AED monotherapy, and low serum AED concentrations. The presence of neurologic or psychiatric deficits wors-

ens the prognosis. Even seizure freedom longer than 4 years carries risks of breakthrough seizures, both on and off AEDs, though with continued AEDs the risks were halved in a large study performed by the Medical Research Council [4]. Most children deserve a trial of taper of AEDs after 1-2 years of being seizure-free. The longer adults remain seizure-free (2-5 years), the greater the chance of successful taper, with higher relapse rates seen with complex partial seizures and PWE and an older age at diagnosis [4]. Some patients will experience delayed breakthrough after seemingly successful taper, but it is rare that reinstitution of treatment does not again render them seizure-free.

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## PROLACTIN

Biochemical markers have been suggested to be useful in separating epileptic seizures from nonepileptic seizures. Elevated postictal serum levels of different enzymes and hormones have been demonstrated after epileptic seizure, though prolactin has been cited most frequently. Prolactin is a lactogenic polypeptide hormone secreted by the anterior pituitary under dopaminergic control from the hypothalamus. Serum prolactin levels can be considered a peripheral marker of hypothalamic neurotransmitter activity and may rise briefly after epileptic seizures involving the hypothalamic region. Raised serum levels are found after approximately 80-90% of generalized tonic-clonic seizures, though less consistently after complex partial seizures, and do not occur after simple partial seizures, brief focal seizures such as frontal lobe seizures, myoclonic seizures, or drop attacks. Similarly, prolactin levels do not rise after absence, mylconic seizures, drop attacks, and status epilepticus [1], but may rise after repetitive seizures. Measurement of serum prolactin has been used to help distinguish psychogenic nonepileptic from epileptic seizures. However, serum prolactin elevations have been rarely reported to occur after syncope, compromising specificity for epileptic seizures. Hence, both false-positive and false-negative results make this technique less reliable [1].

Specificity of the prolactin test for epilepsy can be shown after a two- or threefold rise within 20 minutes after a seizure compared to baseline [2]. The baseline sample for comparison should ideally be taken at the same time on a different (seizure-free) day, but a sample obtained an hour after an episode is

probably a reasonable approximation. Capillary blood prolactin assays have also been measured and accurately reflect serum concentrations. Hence, an elevated serum prolactin level after an event is suggestive of an epileptic seizure, but a normal or nonsignificant elevation does not necessarily reflect a nonepileptic seizure or event.

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## PROPHYLAXIS

Seizure prophylaxis involves the institution of AED therapy in patients at risk for seizures following injury to the brain from many different etiologies, including head injury, neurosurgical intervention, intracranial hemorrhage, infection, and other causes [1-3]. One complication of severe injury to the brain is new-onset seizures. No guidelines exist to guide seizure prophylaxis immediately after patient stabilization, and consequently, the choice as to whether or not to administer AEDs for seizure prevention and for what duration has been at the discretion of the providing physician. Because there is some potential toxicity from AED therapy, the decision to treat prophylactically involves an evaluation of the risk-benefit ratio. With subarachnoid hemorrhage, prophylaxis is frequently advised due to the theoretical risk of a seizure to facilitate recurrent aneursymal hemorrhage. Following intracranial hemorrhage or head trauma without depressed skull fracture, prophylaxis does not appear beneficial beyond the first week of treatment. Overall, seizures occuring within a few weeks of craniotomy occur in approximately 5% of cases, although the incidence varies widely by type of preoperative lesion and the population studied. It is difficult to distinguish seizures due to surgery from those due to the underlying brain disorder that necessitated surgery. Among postoperative seizures, almost half occurred in the first week (particularly the first 48 hours) [2]. Risk factors for postoperative seizures include arteriovenous malformations, aneurysm, meningiomata, trauma, lesions situated in the centroparietal region, and preoperative seizures.

Brain injury-specific seizure prophylaxis has been addressed. Patients with traumatic brain injury had a 12% likelihood of developing posttraumatic seizures, while those with penetrating brain injuries had a more than 50% likelihood [1]. Because of these high incidence values, current recommendations are for prophylaxis initially, but to then discontinue after the first week as it has no influence on long-term prevention [2]. For patients with brain tumors, early prophylaxis decreases the incidence of developing seizures after surgery by 40-

50% but has no effect on minimizing the incidence of late-onset seizures (seizures occurring after the first week) when compared with placebo or no treatment. Furthermore, AEDs are not effective in preventing first seizures in patients who are newly diagnosed with brain tumors and should therefore be avoided. Similar findings were found for patients undergoing a craniotomy for brain abscesses, vascular malformations, etc. [2]. Early prophylaxis for patients with viral encephalitis is also an indication for treatment, as both focal and generalized seizures are a common manifestation of infection in these patients. New-onset seizures were also found in one of five (18%) patients with brain hemorrhage, and the likelihood increased if the person's bleed worsened in the first 24 hours. Thus, early prophylaxis was found to be beneficial in these patients especially when consciousness is altered and the risk for nonconvulsive seizures is high. This evidence points to a widely agreed-upon recommendation to prescribe AEDs on a short-term basis to prevent early-onset (provoked) seizures within the first week after insult and to avoid using thereafter because AEDs are ineffective in avoiding true postlesional/unprovoked epilepsy.

Research has also focused on studying the effectiveness of particular AEDs used for seizure prophylaxis. A meta-analysis of 13 studies and 15 AEDs found both PHT and CBZ to be effective in preventing seizures within the first week after head trauma. However, some classic AEDs—phenytoin, carbamazapine, valproic acid, and phenobarbital—were not found to be effective in protecting against the onset of late, unprovoked seizures [3]. This evidence suggests that prophylactic use of AEDs, particularly PHT and CBZ, is effective in preventing immediate and early-onset seizures (within the first week) but should be avoided thereafter unless the patient receives a diagnosis of posttraumatic epilepsy (seizures that occur beyond the first week).

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## PSYCHOGENIC NONEPILEPTIC SEIZURES

Psychogenic nonepileptic seizures (PNES) account for the vast majority of nonepileptic seizures. PNES are as prevalent as trigeminal neuralgia and multiple sclerosis and occur in all ages, though typically around 18-30 years of age. Such persons account for 5-20% of the more than 2.5 million patients with seizure disorders, of whom up to 40% may be seen in general neurology clinics [1]. They account for 20-30% of admissions to epilepsy-monitoring units in patients with intractable seizures, and 20-33% may develop "pseudo-status

epilepticus" [2]. They are seen throughout the world in various countries with remarkable consistency. Prolonged delays in diagnosing PNES are common, and time and expense can be enormous with diagnostic evaluations, treatments, and physician follow-up assessments inside and outside the hospital setting to make PNES an important concern for both patient and society.

Historical information yields a high seizure frequency without any response to AEDs; psychiatric comorbidity, unusual triggers such as arguments or anxiety, posttraumatic physical-mental-sexual abuse, fibromyalgia or chronic pain syndromes, and a "positive" review of systems may all suggest PNES. A number of characteristics have been described to suggest PNES (*see* table).

**Clinical Features Differentiating PNES and ES /TTTCH**

| Clinical features | Pscyhogenic seizures | Epileptic seizures |
|---|---|---|
| Onset | Gradual, discontinuous | Sudden |
| Out of sleep | Rare (pseudo-sleep) | Yes |
| Semiology | Eyes closed | Eyes open |
| Duration | Usually >2 minutes | Usually <2 minutes |
| Postictal | Rare (variable) | Common |
| Injury | Infrequent (mild); tongue tip | Frequent (mild); tongue postero-laterally |
| Suggestable | Yes | No |
| EEG | Normal/obscured | Abnormal |

The appearance of gradual onset or cessation, discontinuous pattern, asynchronous or alternating head or extremity movement, continuous eye closure, intact awareness with bilateral tonic or clonic motor movement, or opisthotonic posturing are all strongly suggestive of PNES. The single behavioral feature of eye opening was found to have an extremely high sensitivity and specificity, and in one study of 156 patients with ES, 97% had their eyes open in the beginning of their seizure (sensitivity 98.1%; specificity 96.2%; PPV 0.987), while 96% had their eyes closed during PNES (sensitivity 96.2%; specificity 98.1%; PPV 0.943) [3]. Video-EEG remains the technique of choice for a definitive diagnosis by the capture of a typical episode with impaired consciousness unassociated with a change from the baseline EEG during the ictus. Short-term outpatient EEG with video and activation may also be successful in achieving a definitive diagnosis of PNES. Psychiatric comorbidities are common, with somatoform disorders, dissociative disorders, personality disorders, affective disorders, and posttraumatic stress disorders found commonly [4]. While malingering or "faking" seizures reflects a conscious decision and purpose for the event, this is infrequently the case and appears more common in the incarcerated and those involved in litigation. Similarly, a factitious disorder implies awareness of the event, but with a need to obtain attention of the illness as the "gain" (vs. money or position). However, the vast majority of PNES patients have "conversion disorder with seizure," a subcategory of somatoform disorder in which the individual has no awareness and no gain. Neurologic abnormalities may also occur in the context of NES, but concomitant epilepsy is atypical in the community setting, occurring in approximately 10-18% of patients [5].

Ideally, spontaneous PNES captured without provocation are desirable as well as reproducing the habitual events in question, though suggestion should always be verified with family and/or friends. While provocation ("induction") has been unethical, proving the diagnosis with this technique has been shown to improve healthcare utilization by PNES patients. Specificity approaches 100%, and the presence of suggestibility is strongly suggestive of a psychogenic origin when the event in question results in loss of consciousness and a normal EEG. Indirect markers have been utilized to provide supportive information for a diagnosis of PNES. Prolactin concentrations recovered 10-20 minutes after a possible seizure may prove useful to help differentiate an epileptic generalized tonic-clonic or complex partial seizure from a PNES. In older children and adults, prolactin levels more than twice the baseline concentration (baseline obtained 6 hours later) were a useful adjunctive measure for helping to distinguish patients suspected to have had epileptic seizures (*see* Prolactin). However, prolactin may be elevated in other conditions including syncope produced during head-up tilt table testing, and has not been found to be specific.

Outcomes of PNES are generally poor and are nearly always discussed in terms of seizure reduction. Approximately half of patients will experience a substantial reduction or cessation of symptoms over 6-12 months, though 71% of PNES patients continue to have seizures 4 years after the diagnosis and 56% are dependent on Social Security assistance [6]. Outcome is often better in patients with younger ages, earlier diagnosis, shorter duration, less psychopathology, and fewer convulsive features. Continued co-management with psychiatric evaluation and treatment is crucial.

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## PSYCHOSIS

Psychosis encompasses a broad and elusive mental expanse reflecting a fundamental disintegration of self and its connection to nonself with common fea-

tures that include impaired content and coherence of thought, reduced connection to reality, hallucinations, delusions, disorganized speech and behavior, and extremes of affect and motivation [1]. Psychosis is more common in PWE than in the general population. The incidence of psychosis among people with epilepsy in the community is 5-7%, though apparently less in patients with IGE and higher in patients in the hospital than in those in the community [1]. Those with epilepsy of long duration and with frequent seizures appear most at risk. Modulation of dopaminergic pathways within the limbic structures has been postulated to play a primary role in psychosis, and neuroradiographic studies have identified subtle differences such as small hippocampi in the brains of monozygotic twins discordant for schizophrenia marking the biologic basis. The likelihood of developing psychosis is directly related to localization, seizure control, and seizure intensity. Psychosis is most commonly an *interictal* phenomenon, but may less frequently also appear as a postictal or rarely an ictal event. Some patients with TLE develop a schizophreniform psychosis after years of recurrent seizures. In PWE, a schizophreniform psychosis has denoted the absence of schizoid personality traits, a preserved warmth of affect, and the ability to continue social interactions that have differentiated the features from schizophrenia in patients without epilepsy [1,2]. A complex relationship exists between interictal psychosis and seizure frequency, in that some patients deteriorate after a flurry of seizures and some deteriorate after a long seizure-free interval. The latter phenomenon may relate to the value of electroconvulsive therapy to adjunctively treat psychoses. A reciprocal relationship between psychosis and epilepsy was described by Landolt as paradoxical or "forced normalization" characterized by the appearance of psychosis with subsequent normalization of the EEG with improvement of the seizures. Psychosis may be precipitated by improvement in seizures either from medications or following successful epilepsy surgery [3,4]. *Postictal* psychosis occurs in 2-7.5% of PWE and may be very dramatic, occurring after an initially uncomplicated postictal state. Within hours or days but lass than 1 week, acute or subacute delusions, hallucinations, and paranoia lasting more than 15 hours but <3 months become evident without AED toxicity, evidence of status epilepticus, prior primary psychosis, or head injury and may demonstrate a response to antipsychotic agents [1,2]. The postictal paranoid states with confusion may last hours to weeks. Affective psychoses may also occur after complex partial seizures. In a practical sense it is often difficult to distinguish ictal from postictal psychoses, especially since subtle complex partial seizures may occur during sleep. Seizures may rarely result in an *ictal* confusional state with psychotic elements, though this is rare [1]. More commonly, ictal visual, auditory hallucinations, autoscopy, derealization, or depersonalization may combine with affective changes such as fear or paranoia [1]. Nonconvulsive status epilepticus or "subclinical" IEDs, especially involving the temporal lobe, have been suggested to create psychosis [1]. In this case, examination reveals delirium, as well as more cardinal symptoms of psychosis. Epilepsy-associated psychosis may respond best to a combination of AED and neuroleptic medication.

Patients with epilepsy-associated psychosis require treatment or careful observation, even for brief postictal psychosis, since psychosis is distressing and potentially dangerous. Joint management by a neurologist and psychiatrist is useful [1-4]. Individual psychotropic medications (*see* Psychotropic Medications) may carry a high risk of seizures in patients without epilepsy and should be avoided or merit caution with their use. Phenothiazines—chlorpromazine, loxapine, clozapine, and the butyrophenones less so—may be proconvulsant. Antidepresssants such as the tricyclics, buproprion, maprotiline, clomipramine, and amoxipine may lower the seizure threshold, but this is not an absolute contraindication to their use.

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## PSYCHOSOCIAL PROBLEMS (*see also* BEHAVIOR; EMPLOYMENT)

At the time of diagnosis of childhood epilepsy, psychosocial problems are common that continue into adulthood despite the patient being neurologically and intellectually normal [1]. Learning disabilities, mental illness, attention deficit disorder, and mental retardation are common comorbidities that have obvious psychosocial effects within the family unit. For those with normal intelligence, the social, emotional, and psychiatric problems associated with epilepsy are worse than in either the community or control groups with chronic illness. Psychosocial difficulties impinge on aspects of daily living in obvious ways, but characterization for study can be difficult. Measurement tools have included the Minnesota Multiphasic Personality Inventory (MMPI) and the Washington Psychosocial Seizure Inventory (WPSI).

People with epilepsy find it more difficult to drive, work, marry, and obtain education [1,2]. Poor social outcomes have been demonstrated in population studies in North America [1] and in many regions around the world evaluating PWE [2]. Contributors to these difficulties include seizures, medication side effects, underlying neurologic conditions, and, perhaps most important, ongoing social stigma attached to epilepsy (*see* Stigma). One study in Finland of noninstitutionalized children found greater immaturity and psychiatric comorbidity with childhood-onset epilepsy [3]. Education, employment, and marriage rates were less in these children [3]. In patients with LRE, 35% repeated

a grade in school, 23% required mental health assessment, and 5% were prescribed psychotropic medication [1]. For those patients followed into adulthood, 2% had a criminal conviction, 13% had unplanned pregnancies, 16% were socially isolated, and 30% were financially dependent or unemployed, reflecting a worse outcome for PWE than the general population [1]. For patients with IGE manifest as absence seizures, a study comparing epilepsy to a nonneurologic chronic illness (juvenile rheumatoid arthritis) demonstrated that the PWE had lower educational levels, lower work status, and markedly higher rates of behavioral and psychiatric difficulty [4]. Psychosocial difficulties are usually more marked in patients seeking specialized consultation for frequent seizures or learning disabilities [1], with improvement possible after surgery has resulted in a seizure-free outcome.

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## PSYCHOTROPIC MEDICATIONS

Psychotropic medications are among the most commonly prescribed medications. Concern arises because phenothiazines, butyrophenones, tricyclic antidepressants, and lithium can cause seizures [1,2]. The risk for seizures depending on dosage has been estimated at 0-0.6% for amitriptyline, 0.1-0.6% for imipramine, 0.5-12.2% for clomipramine, 0.1% for doxepin, 0.2% for fluoxetine and fluvoxamine, 0.1% for paroxitine, and 0.4% for maprotiline (*see* table). The incidence rate of a first unprovoked seizure is about 0.07% to just under 0.1%. Selective serotonin reuptake inhibitors (SSRIs) have less effect on seizure threshold. Their effect in patients with epilepsy has not been well studied, but an increase in seizures and possibly increases in seizure duration can occur at higher or toxic doses. In higher doses, bupropion increasingly causes seizures-approximately 4 in 1,000 patients at dosages of 300-450 mg/d; seizures were responsible for its initial withdrawal from the market. At 450 mg/d, the incidence was 0.35-0.44% with a cumulative 2-year risk of 0.48%, rising to over 2% at 600 mg/d. SSRIs such as Citalopram may not significantly affect seizure frequency in patients with epilepsy [3]. New atypical antipsychotic medications such as clozapine may exhibit a proconvulsant effect, which may occur at low doses of 300 mg/d during initiation. Animal experiments in mice suggest that seizure sus-

ceptibility may be due to chronic norepinephrine inhibitors such as reboxetine, desipramine, and imipramine. In toxic doses, psychotropic medications can precipitate seizures in normal individuals. Psychotropic medications are often beneficial for psychiatric conditions in people with epilepsy, and properly monitored use is generally safe. Most patients show an improvement in psychiatric status, with seizure worsening only in a minority (<10%). Some AEDs, such as carbamazepine, valproate, and lamotrigine—and less consistently gabapentin and topiramate—may directly benefit psychiatric symptoms.

**Antidepressant Medications and the Risk of Seizure Provocation**

***TCAs and Tetracyclic Antidepressants***

| Antidepressants | Seizure Incidence (%) | Antidepressants | Seizure Incidence (%) | Antidepressants | Seizure Incidence (%) |
|---|---|---|---|---|---|
| Amitriptyline | <0.1–0.3 | Amoxapine | 24.5–36.4 | Clomipramine | 0.7-3.0 |
| Desipramine | <0.1 | Doxepin | <0.1 | Imipramine | <0.1–0.9 |
| Maprotiline | 0.4–15.6 | Nortriptyline | <0.1 | Protriptyline | <0.1 |

**SSRIs and SNRIs**

| Antidepressants | Seizure Incidence (%) | Antidepressants | Seizure Incidence (%) | Antidepressants | Seizure Incidence (%) |
|---|---|---|---|---|---|
| Citalopram | <0.1 | Fluoxetine | <0.1–0.2 | Fluvoxamine | <0.2 |
| Paroxetine | <0.1 | Sertraline | <0.1 | Venlafaxine | <0.26 |

**Other Antidepressants**

| Antidepressants | Seizure Incidence (%) | Antidepressants | Seizure Incidence (%) | Antidepressants | Seizure Incidence (%) |
|---|---|---|---|---|---|
| Bupropion | 0.6–1.0 | >450 mg/day | 0.6–2.19 | SR 400 mg/day | 0.4 |
| SR 300 mg/day | 0.1 | | | | |
| Mirtazapine | <0.1 | Nefazodone | NA | Trazodone | <0.1 |

TCA = tricyclic antidepressant; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; SR = sustained-release formula; NA = limited information.

*Source*: Adapted from Barry JJ, Huynh N. Psychotropic drug use in patients with epilepsy and developmental disabilities. In: Devinsky O, Westbrook LE, eds. Epilepsy and Developmental Disabilities. Boston: Butterworth-Heinemann, 2001:205-217. With permission from Elsevier.

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# PYRIDOXINE

Two types of pyridoxine-related seizures occur in the neonatal period: pyridoxine dependency and pyridoxine deficiency (pyridoxine is vitamin B6). Both

are rare but important conditions that result in neurocognitive damage and deterioration without prompt recognition.

Pyridoxine dependency is an inborn error of metabolism that typically develops in utero but appears within the first week of life, typically within the first several days. The condition results from a defect on the binding site of the enzyme glutamic acid decarboxylase (GAD). Linkage studies have helped identify the genetic basis for the enzymatic defect [1]. Pyridoxine is a cofactor for GAD. As a result, inadequate GABA is present to allow for primary inhibitory neurotransmission of brain function. Seizures may be characterized by partial seizures, infantile spasms, or myclonic and atonic seizures. The interictal EEG is characterized by bursts of high-voltage delta and generalized IEDs interspersed with periods of asynchronous attenuation. High doses of pyridoxine are critical to administer in the early period because administering 100 mg of pyridoxine intravenously is likely to result in complete cessation of seizures. With continuation of replacement therapy, even normalization of the EEG is expected to occur. Pyridoxine dependency is an autosomal recessive disorder that typically occurs in neonates but may occur up to 19 months of age. Therefore, a trial of pyridoxine is recommended for infants up to 18 months of age who have refractory seizures of unclear etiology. If left untreated, most patients develop intractable seizures and die within a few months. Daily doses of pyridoxine usually approximate <100 mg/d and are adjusted based upon seizure control and normalization of CSF glutamate levels.

Pyridoxine deficiency also causes seizures in neonates and infants [2]. Pyridoxal phosphate is the active metabolite of pyridoxine used to function as the cofactor for both enzymes GAD and GABA transaminase, which serve to regulate production and elimination of CNS GABA. In both pyrixodine dependency and deficiency, CSF GABA is reduced. However, in pyridoxine deficiency serum concentrations are reduced, while they are normal in pyrixodine dependency. Single dosing is required for pyridoxine deficiency to affect a result, while life-long administration of vitamin B6 is necessary for pyridoxine dependency.

Pyridoxine-responsive epilepsy has described a group of patients involving neonates, infants, and children who respond to treatment with pyridoxine. Infantile spasms and acute recurrent seizures have responded in monotherapy and with pyridoxine and in adjunctive therapy in conjunction with conventional AEDs [3].

## References

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# R

## RAMSAY HUNT SYNDROME (DYSSYNERGIA CEREBELLARIS MYOCLONICA)

Ramsay Hunt syndrome type 1 (RHS type 1—there are three different syndromes with the same name) is a rare and somewhat confusing neurologic condition, also known as dyssynergia serebellaris myoclonica, named after James Ramsay Hunt. RHS type 1 encompasses several rare neurologic disorders, many of which are autosomal dominant and characterized by epilepsy, tremor, action myoclonus, incoordination, progressive gait disturbance, and cognitive impairment. The tremor can begin asymmetrically, typically between the age of 10 and 30 years, more often in the arms than legs, and progressing over 10 or more years. A degenerative disorder, some cases arise from genetic mitochondrial dysfunction, but other studies have failed to corroborate this. A PRKCG mutation (SCA-14) has been reported as causing a Ramsay Hunt phenotype [1].

In this heterogeneous syndrome, two groups have been identified [2]: one associated with epilepsy and one associated with ataxia and progressive myoclonus where seizures are infrequent and cognitive abnormalities are mild. Some patients with Ramsay Hunt syndrome have a phenotype that resembles progressive myoclonus epilepsy (*see* Baltic Myoclonus) [2]. When seizures are associated with Ramsay Hunt syndrome, they may be myoclonic, tonic-clonic, or focal in origin and are less common during sleep. As suggested by its alternate title, dyssynergia cerebellaris myoclonica, cerebellar findings may be prominent (*see also* Ataxia). The typical EEG shows bursts of spike-and-slow wave activity overlying an otherwise normal background with marked photosensitivity. Progression of the clinical picture is usually slow. Valproate has been successful in treating the seizures.

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## RASMUSSEN'S ENCEPHALITIS

Rasmussen encephalitis is a rare childhood disorder of progressive hemispheric atrophy of the brain associated with cognitive dysfunction, hemiparesis, and

epilepsy. Histopathology has demonstrated evidence of chronic inflammatory changes characteristic of encephalitis, including perivascular inflammation and glial nodules. Patients are resistant to AEDs, and hemispherectomy was first used by Dr. Theodore Rasmussen in 1958 to treat this chronic focal encephalitis. Rasmussen encephalitis starts about 7 years of age in previously normal children who develop focal motor seizures with increasing frequency and resistance to AED treatment [1]. In 80% of patients with Rasmussen encephalitis, seizures develop as the presenting clinical feature before the age of 10 years. Seizures are usually focal motor seizures, secondarily GTC seizures, and in 20% of cases present as status epilepticus. Epilepsia partialis continua and focal motor seizures are characteristic during the course of the illness and rapidly increase in frequency and severity as the condition progresses. There is concomitant progressive cognitive deterioration and a unilateral paresis that is encountered. Late-onset adolescent and adult variants have been noted with a milder, more protracted course noted with a later onset [2]. The potential for multifocal independent sites of inflammation to spread have been proposed in Rasmussen encephalitis. Brain MRI is normal early in the course. With progression, neuroimaging studies typically demonstrate progressive hemispheric hyperintensity on T2 images, with atrophy often associated with lateralized deficits using functional neuroimaging using PET or SPECT. EEG findings may show bilateral abnormalities that often include lateralized or regional slowing, with progressive alpha asymmetry, voltage attenuation, and multifocal IEDs often lateralized to the affected hemisphere. The etiology for the unilateral progressive disease is unknown. A viral etiology has been hypothesized, but no virus has been identified. Autoantibodies to GluR3 have been demonstrated in the blood of patients with RE and suggested to act as the responsible mechanism to initiate the excitotoxicity that results in the progressive brain injury and resultant epilepsy. A T-cell-generated immune response that produces cytoxic inflammation and apoptosis may be another means of developing and then perpetuating RE, though the antigenic trigger is yet unknown.

Surgical or autopsy specimens demonstrate perivascular lymphocytic cuffing, microglial nodules, and nonspecific gliosis. Pathologic examination of operated brain tissue shows the active and remote multifocal inflammatory lesions in the cortex and subcortical white matter with neuronal degeneration. AED treatments are often ineffective, though levetiracetam and topiramate may have a role. The precise role of antiviral agents, IVIG, and immunosuppressants is ill-defined. Epilepsy surgery disconnecting and resecting the abnormal hemisphere has proven efficacy in the treatment of seizures associated with RE. Hemispherectomy, hemicorticectomy, and functional hemispherectomy have had a high yield for seizure freedom or nondisabling seizure outcome [3].

## References

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## READING EPILEPSY

Reading epilepsy is a form of reflex epilepsy that consists of seizures that reflexively occur with the act of reading printed text. Most reading epilepsies are localization related with focal seizures that may be due to a cryptogenic or symptomatic form. *Primary reading epilepsy* is usually triggered by reading out loud. After a variable period of reading time, jerking of the jaw occurs, followed by generalized tonic-clonic seizures. Seizures arise only during reading, and patients are otherwise normal. The interictal EEG is unremarkable, but the ictal EEG shows an epileptiform correlate. The etiology is complex, with an apparent influence of proprioceptive stimulation arising from oculomotor, pharyngeal, and laryngeal musculature. In addition, there is also a possible contribution for comprehension and cognition to be created by the mental effort of reading. *Secondary reading epilepsy* is denoted when a cortical lesion is apparent. These are typically focal seizures associated with temporo-parieto-occipital IEDs, especially on the dominant side.

## REFLEX SEIZURES

Reflex seizures (RS) may manifest as partial seizures or generalized seizures and represent approximately 4-7% of patients with epilepsy [1]. Reflex epilepsies consist of recurrent seizures that are triggered consistently by an environmental stimulus. Reflex seizures are precipitated by unique sensory, proprioceptive, motor, or cognitive stimuli. Stimuli are varied and may be generated via extrinsic or intrinsic mechisms. RS are seizures that may be triggered (provoked or induced) by a specific stimulus. The situation in which the seizure occurs is usually referred to as the trigger. However, this situation does not imply that a unique mechanism is responsible in all patients. The terms "reflex seizures" and "reflex epilepsy" are misleading, since simple reflex loops are not involved in initiating epilepsy. Seizures may be triggered by light, eye closure or eye blinking, auditory stimuli (music), reading, speech (spontaneous or during reading), movement, eating, gastric distention or abdominal pain, sensory stimulation, immersion in hot water, dressing, physical exercise or activities (e.g., toothbrushing), thinking or cognition, arithmetic, situational decision making (card playing, checkers, chess, etc.), and others.

Many RS are manifest as partial seizures, though generalized seizures may also occur. The uniqueness of the stimulus that acts as a specific trigger for a particular patient to cause epileptic seizures defines the type of reflex epilepsy for that patient. RS may be related to cognitive efforts (e.g., reading epilepsy),

associated with a special sensory stimulus (e.g., musicogenic epilepsy), or caused by an environmental exposure (e.g., hot water epilepsy). Some seizures are more likely to occur with generalized epilepsy (e.g., photic stimulation), others with localization-related epilepsy (e.g., eating). Still others may be more likely to occur with individual seizure types such as thinking triggering generalized seizure types: myoclonic, absence, and GTC seizures. Though RS are capable of provoking generalized seizures and focal seizures, some RS may occur occur with both IGE and LRE (e.g., reading epilepsy). Generalized RS may occur with a simple trigger (light) or a complex trigger (intellectual activity). A focal seizure may occur by triggering afferent stimuli that reach a focal epileptogenic zone (eating), though the mechanisms for RS are often unclear. Multifocal lesions may explain why a particular patient may have seizures triggered by several different stimuli (e.g., light, movement, and hot water).

Photosensitive epilepsy is the most common reflex epilepsy and characteristically is associated with generalized seizures. It typically begins during the age range when the expression of IGEs are seen and may manifest as absence, myoclonic, or generalized tonic-clonic seizures when exposed to photic flash, though photogenicity may infrequently occur with focal seizures [2]. Interruption of visual input and appropriate receptive input has been implicated, causing myoclonic seizures, absence seizures, and palpebral myoclonus with absences (*see* Absence Epilepsy). The phenomenon is well known and a common reflex routinely used in the EEG laboratory in an effort to provoke a diagnostic electroclinical abnormality. Variations on photosensitivity may occur with video games (e.g., Pocket Monsters) or by watching sunlight flicker through trees. Some individuals in a form of self-stimulation may be able to provoke photosensitive seizures (e.g., absence) by moving their fingers rapidly in front of a light (*see* Auto-Induced Seizures). Treatment is at times unavoidable when the stimuli are associated with common environmental exposures, associated with sporadic seizures, or manifest as generalized convulsive seizures that carry the risk of injury. Broad-spectrum AEDs are best when more than one seizure type is encountered.

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## REFRACTORY EPILEPSY

Refractory epilepsies are those in which seizures are not controlled by AEDs. Synonyms include pharmacoresistant, intractable, uncontrolled, and treatment-resistant epilepsy, though definitions vary throughout the literature. When refractory seizures are defined, resistance is usually identified by the number of AED failures at the time of evaluation, though duration of seizures, frequency

of occurrence, and "therapeutic" AED levels may be also taken into consideration. A failed response to AED therapy may occur for a variety of reasons, including pseudo-resistance as well as true refractory epilepsy.

*Pseudo-resistance* may occur when seizures are refractory not because of the nature of the seizures, but because of inadequate or inappropriate therapy. There may be a *misdiagnosis* of epilepsy (most commonly psychogenic nonepileptic seizures) that results in ongoing seizures despite optimized AED concentrations [1]. This etiology is enormous and accounts for 20-25% of admissions for refractory seizures to epilepsy monitoring units. Patients may be *nonadherent*, self-medicate, or have *lifestyle issues* that include abusing illicit drugs and alcohol leading to inadequate treatment despite correct classification and AED prescription. Additionally, seizures may be incorrectly classified, resulting in an *inappropriate AED or dose* for the chosen epilepsy syndrome (e.g., ethosuximide for complex partial seizures or carbamazepine for JME). Further, an underlying *progressive lesion* (e.g., neoplasia) or metabolic condition may be left untreated, resulting in inadequate expectation for AED use (e.g., hyponatremia).

*Refractory epileptic* seizures are present when seizures persist despite adequate treatment [2]. Approximately 20-25% of patients with new-onset epilepsy will have refractory seizures, and response to the initial AED is a powerful predictor, with failed efficacy indicating that the patient will develop refractory epilepsy [2,3]. When two or more AEDs have failed in monotherapy, the likelihood of seizure freedom from ongoing monotherapy trials is low [2]. Infrequently, some patients who are initially believed to have refractory seizures will respond to combination therapy and some to reduction in polypharmacy. Patients who are proven to be refractory to AED therapy with continued seizures or unacceptable medication side effects may be candidates for epilepsy surgery (*see* Surgery for Epilepsy), and referral to a teriary care epilepsy center for video-EEG monitoring and consideration of epilepsy surgery should not be delayed. Lesional cases should merit early surgical attention. Pharmacogenomics in patients with focal seizures have identified individual gene polymorphisms than may influence AED transporter glycoproteins and impair blood-brain barrier transfer of AEDs to provide efficacy. Patients with refractory epilepsy are likely to have impaired health-related quality-of-life measures [4].

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# RELAPSE (WITHDRAWAL OF AEDS)

At least 65% of patients are rendered seizure-free with AEDs after diagnosis, and the overall prognosis is better in IGE and in children [1]. Relapse represents the appearance of a seizure in a patient with previously controlled epilepsy (*see* Cure; Prognosis). Relapse may occur during a period of remission that variably extends from 1 to 2 years to many years of treatment. Many patients experience adverse effects from AEDs, and while serious consequences may occur, subtle cognitive consequences may produce problems during activities of daily living. The findings of the Medical Research Council (MRC) withdrawal study found no net gain in overall quality of life for withdrawal versus continued AED use [2], though a RCT found improved neuropsychological performance and complex motor coordination following withdrawal compared to those continuing therapy [3]. Nevertheless, the risk of relapse should be weighed in the decision to stop treatment, and thus the decision to withdraw AEDs has been controversial [3].

After more than 2 years of successful AED therapy, the overall risk of relapse after medication taper is approximately 30% [2]. However, most withdrawal studies have been open trials or have included a heterogeneous study population of patients treated with one or a combination of AEDs. The MRC AED Withdrawal Study Group reported a 2-year relapse rate of 22% among those PWE who withdrew AEDs as opposed to 41% that continued AED therapy [2]. However, one RCT demonstrated a 2-year relapse rate of 19%, with most relapses occuring within the first 6 months [3]. Still, some PWE may relapse years after stopping treatment. Factors predisposing to relapse include decrease or discontinuation of AEDs, intercurrent disease, sleep deprivation, stress, and substance abuse (use and withdrawal). Approaches to tapering AEDs have varied, though a 20% reduction of the initial dose every 2 weeks has been used with success to avoid overt withdrawal effects that may otherwise occur with rapid taper design over days [3]. Patients on multiple AEDs, a structural lesion of the brain, focal seizures, epilepsy syndromes (e.g., JME), and onset beyond childhood appear to be unfavorable populations in which to attempt a trial of AED taper [3,4]. The value of EEG in predicting outcome after withdrawal in adults is more controversial than the finding of epileptiform discharges in children that portends an increased risk of relapse [3]. In cases of recurring seizures, the decision to resume AED therapy, like that to initiate it in the first place, must be individualized.

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# RELIGION

Historically, epilepsy has long been associated with religion. In patients with epilepsy, hyperreligiosity was initially felt to be an essential interictal behavioral component in patients with temporal lobe epilepsy. Having right-sided temporal lobe epilepsy was previously associated with mystic or religious experiences. However, subsequent analyses have less resolve for EEG lateralizing or localizing seizure capabilities [1]. Approximately half of patients with epilepsy have been reported to harbor interictal experiences of salvation that have furthered an increased interest in religion. Postictal psychosis includes religious experiences, though ictal religious experiences are rare. Religious activity has been suggested to have a biochemical basis evidenced through cerebral flow and neurotransmitter receptor densities that have focused on serotonin and dopamine.

## Reference

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# REMISSION

Remission is a period during which seizures disappear spontaneously or in response to therapy. Remission rate is usually expressed as a ratio of those patients in remission to the total number in a particular population of patients with epilepsy. How long PWE remain on AEDs is individualized. PWE less likely to achieve remission of their seizures and experience relapse include those with a long history of seizures prior to remission, JME or more than one seizure type, a previous failed trial of taper after remission, an abnormal neurologic examination, learning disability, or structural lesion on neuroimaging [1]. Furthermore, treatment of the first seizure does not appear to affect the long-term remission of epilepsy [2].

## References

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## RENAL DISEASE

Renal disease is commonly associated with seizures. Seizures occur in approximately one third of patients with renal failure. Seizures are commonly GTC seizures and may be recurrent or prolonged, appearing as status epilepticus. Myoclonus may also appear prominent with greater degrees of uremia. Focal seizures should prompt a search for an underlying structural lesion. Seizures may be associated with acute uremia, which occurs in the setting of encephalopathy that begins approximately 1 week after acute renal failure appears with oliguria or anuria. Chronic renal failure now has risks for convulsions of 10% or less, with the reduced prevalence probably associated with improvement in the primary disease states precipitating renal failure (e.g., antihypertensive therapy), improved fluid and electrolyte balances through better dialysis techniques, and improved pharmacokinetics of available drugs. Dialysis encephalopathy related to increased aluminum levels has been reduced with improved dialysates, resulting in less frequent seizures.

Therapy with AEDs changes in renal failure. Highly protein-bound AEDs such as phenytoin have reduced protein binding and a shift to increased circulating free fractions. Measuring the free fractions to maintain levels of 1-2 (g/mL usually approximates total serum concentrations of 10-20 (g/mL. In addition, because of the reduction of the serum half-life with uremia, divided doses are recommended into tid or at least bid dosing when phenytoin is utilized. Other highly protein-bound AEDs such as VPA also demonstrate reduced protein binding, and monitoring the free fractions may also be helpful. Carbamazepine levels are not altered by uremia. Some newer AEDs may require replacement following dialysis when lower levels of protein binding are evident, and some (e.g., gabapentin, pregabablin, and levetiracetam) require significant adjustments based upon the creatinine clearance due to the significant renal clearance that occurs. Nomograms are provided in the respective package inserts available from the manufacturers.

## RESOURCES

Local as well as national resources exist for PWE. The following resources can provide information related to seizures and epilepsy and may be helpful to refer patients to:

**Epilepsy Foundation**
8301 Professional Place
Landover, MD 20785
www.epilepsyfoundation.org
Telephone: 301-349-3700; 800-332 (EFA)-1000
Fax: 301-577-2684

**The Epilepsy Institute**
257 Park Avenue South, Suite 302
New York, NY 10010
website@epilepsyinstitute.org; www.epilepsyinstitute.org
Telephone: 212-677-8550
Fax: 212-667-5825

**Citizens United for Research in Epilepsy (CURE)**
730 North Franklin Street, Suite 404
Chicago, IL 60610
info@cureepilepsy.org; www.CUREepilepsy.org
Tel: 312-255-1801
Fax: 312-255-1809

**National Institute of Neurological Disorders and Stroke (NINDS)**
NIH Neurological Institute
P.O. Box 5801
Bethesda, MD 20824
www.ninds.nih.gov
Tel: 800-352-9424; 301-496-5751

## RETIAGABINE

Retiagabine was initially licensed in the United States for development in the late 1990s and has been shown in randomized, double-blind, placebo-controlled trials to be well tolerated and effective in adults with refractory partial-onset seizures [1]. The effect seemed to be dose-related [1], and the utility of retiagabine may extend to other seizure types clinically given its widespread efficacy in multiple animal models of epilepsy tested [2]. The principal mechanism of action is current modulation that alters potassium conductance regulating excitability in neuronal cells, though potentiation of GABA at high concentrations is also found. The effect is to activate KCNQ2 and KCNQ3 channels, channels that have demonstrated mutations in benign familial neonatal convulsions. Side effects have been dose related and are mainly somnolence, dizziness, confusion, speech disorders, vertigo, and tremor [1]. Retiagabine requires tid dosing due to its short half-life. Median changes in monthly seizure frequency occurred in a dose-related fashion with 1200 mg/d producing a 35% seizure reduction. Doses between 600 and 1200 mg/d have been evaluated, though ongoing phase 3 trials are in progress at this time.

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## RETT SYNDROME

Rett syndrome is a progressive encephalopathy of unknown etiology occurring predominantly in young females with an incidence of 1 in 10,000. The syndrome presents with normal development up to 7-18 months, and then evolves to arrest of development and progressive mental deterioration with loss of hand use. Onset occurs between the age of 9 months and 3 years, associated with gait apraxia, axial ataxia, autism, dementia, respiratory problems, and seizures. After the age of 10 years, there is typically a progressive mental and physical deterioration with evidence of microcephaly, spasticity, and hand-wringing movements in addition to cachexia [1].

Seizures appear in up to two thirds of cases, usually relatively late in the course of the syndrome [1]. While seizure types vary, GTC seizures are noted in 50% of patients, though differential diagnostic challenges of nonepileptic behavior may occur that require resolution with video-EEG. The EEG shows a marked change during the sleep-wake cycle, though nonspecific changes of encephalopathic generalized epilepsy may see seen with low-voltage slowing of the background activity and centrally predominant multifocal spikes. Sleep EEG recordings may manifest generalized slow spike-and-wave discharges. Diagnosis may be confirmed by demonstration of the MECP2 deletion, which may be seen in 85% of sporadic cases [2]. The phenotypic consequences of MECP2 mutations may extend beyond Rett syndrome to include patients with a phenotype more typical of Angelman syndrome [3].

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## RIPPLES

Ripples are high-frequency oscillations between 80 and 150 Hz using microelectrode recording [1]. These oscillations have been reported to occur within brain areas where seizures arise, but have been described as “ripples” in normal animal models within the hippocampus and enterorhinal cortex. Fre-

quencies of >150 Hz have been described as "fast ripples" and occur primarily in the hippocampus and ipsilateral to the side of seizure onset. The hypothesis for fast ripples is that small groups of neurons generate hypersynchronous discharges through networks of local recurrent excitatory connections and reflect some of the basic disturbances responsible for epileptogenecity [2].

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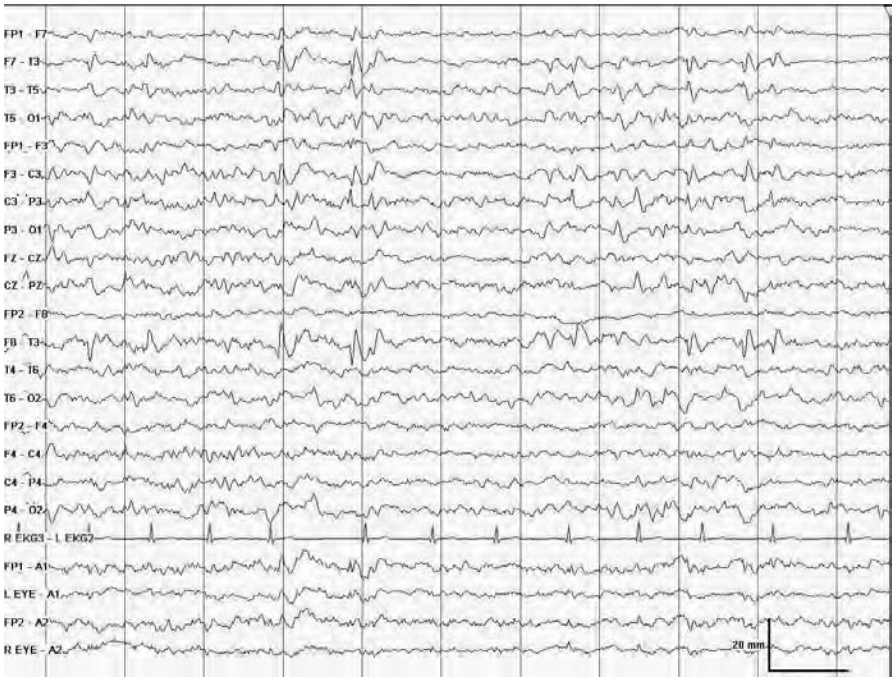
## ROLANDIC EPILEPSY (BENIGN CHILDHOOD EPILEPSY WITH CENTRO-TEMPORAL SPIKES)

Benign rolandic epilepsy (BRE), also called benign childhood epilepsy with centro-temporal spikes (BCECTS), is the most frequent localization-related epilepsy syndrome in childhood. It is classified as benign based upon the prognosis in which the ultimate likelihood of remission before puberty is high, resolving before 14 years of age in the majority [1]. In addition, there is a low seizure frequency and a low frequency of seizure emergencies such as status epilepticus. It is the prototype of the idiopathic (*see* Idiopathic) localization-related epilepsies, and BRE is three to four times more frequent than absence seizures of childhood, accounting for up to 16% of all epileptic seizures before the age of 15.

Age-related onset most frequently begins between 5 and 10 years, with a peak at 9 years. Rolandic epilepsy appears in previously normal children without neurologic or intellectual deficit [1]. Patients perform within the average range on neuropsychological testing, but there may be relatively lower IQ and deficits of language in some [1,2] A similar electroclinical picture may be seen in brain-damaged children, but this latter group should be considered as a distinct subgroup of symptomatic localization-related epilepsy. The seizure characteristics may vary, but frequently are partial seizures with simple partial seizures, with sensori-motor components predominantly involving the face, mouth, and tongue or pharynx noted. Sleep-related seizures (*see* Sleep) are most common and occur in >75% of children with BRE [1]. Nocturnal GTC seizures may have a Todd's paralysis postictally and implicate the focal mechanism in BRE. Seizures remit spontaneously during adolescence. Approximately three fourths of patients have isolated or infrequent seizures, and rarely patients have only one or more isolated seizures during late adolescence or early adulthood [1].

The diagnosis is based on both clinical and EEG characteristics, as the characteristics of the seizures alone are not specific. The interictal EEG shows




Interictal EEG in a patient with BRE. Note the frequent left centro-temporal spike.

frequent spikes and sharp waves in the centro-temporal region increased during sleep, though paradoxically infrequent seizures are encountered clinically. The background is normal without focal or lateralizing features. In some instances, spikes may be maximal temporally rather than centrally. In BRE, a characteristic tangential or horizontal dipole of the IED may demonstrate a negative phase reversal centro-temporally and a contralateral positive phase reversal frontally to belie the benign underpinning of the focal seizures (*see* figure). The sharp waves have a characteristic diphasic morphology with a negative peak followed by a positive rounded component. In addition, centro-temporal spikes may be seen in normal children without reported seizures—and be seen with regularity as an independently inherited trait.

BRE is designated as an idiopathic epilepsy syndrome, and as such, no causative lesions are anticipated on brain MRI despite the focal seizures and EEG abnormalities. Yet, nonetiologic abnormalities may concomitantly be seen in patient with BRE, though they are not more common than in controls and not specific for BRE [3]. An underlying genetic predisposition has been demonstrated for rolandic epilepsy with description in identical twins. Furthermore, overlap may occur between BRE and IGE with cases manifesting coexistent centro-temporal spikes and 3 Hz generalized spike-and-waves in patients with absence seizures.

Seizure frequency is highly variable in rolandic epilepsy, and treatment for focal seizures may be required for frequent seizures (*see* Treatment). The categorization of this syndrome as "benign" refers to the strong tendency to remit over time, not to the minor nature of the seizures, and while remission is almost universally encountered in BRE, the favorable prognosis does not necessarily reflect a "benign" effect.

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## RUFINAMIDE (BANZEL®)

Rufinamide is a structurally unique AED recently approved for use in patients with Lennox-Gastaut syndrome. It has also been evaluated as adjunctive therapy in adults with refractory partial-onset seizures with responder rates of 39% [1]. It appears to have a broad spectrum of activity with a proposed mechanism of action that includes sodium channel blockade. Absorption is facilitated by food and approximates 70% complete absorption, though peak absorption does not occur until 6 hours after ingestion. Rufinamide has low to medium protein binding of 30-40%, an elimination half-life of 7-10 hours, and is primarily renally excreted. No interaction with other AEDs has been shown, and doses of 1600-3200 mg/d appear to be safe and well tolerated [1]. Rufinamide will be available for use in 2009 as an adjunctive treatment for partial-onset seizures with and without secondary generalization in adults and adolescents 12 years of age and older.

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# S

## SABRIL®

*See* Vigabatrin.

## SANTAVUORI-HALTIA DISEASE

Santavuori-Haltia disease is an early infantile form of neuronal ceroid lipofuscinoses (*see* Ceroid Lipofuscinoses) rarely seen outside Finland. This form of NCL presents at 1-1½ years of age with myoclonus, ataxia, visual impairment with optic atrophy, and loss of developmental milestones. The incidence is 1 per 20,000 inhabitants, and the disease is transmitted by an autosomal recessive mode.

Seizures are prominent and include myoclonus, generalized seizures, and drop attacks. A progressive loss of normal background activity is seen with IEDs. Neuroimaging demonstrates cerebral and cerebellar atrophy. The EEG at the beginning of the illness shows generalized slowing and later reveals generalized voltage suppression without ictal activity. Death ensues by approximately 10-13 years of age. Diagnostic features are found on skin biopsy, and microscopic demonstration of granular lysosomal curvilinear bodies in mesenchymal cells has been reported. A chromosomal abnormality has been identified on chromosome 1p32 [1].

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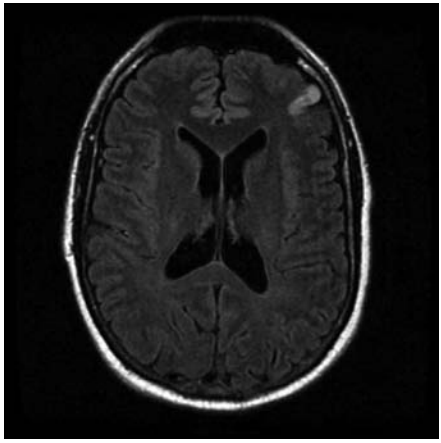
## SCANS OF THE BRAIN (CT, MRI)

Neuroimaging of the nervous system in patients with seizures includes computed tomography (CT) and magnetic resonance imaging (MRI) (*see also* Magnetic Resonance Imaging). An investigation of the cerebral cortex is essential in all patients with a new onset of seizures of unknown cause. Brain CT or MRI is usually not helpful in established, nonprogressive neurologic disorders unless an antecedent head injury or new lesion is suspected. However, neuroimaging is often important with deterioration in a previously stable clinical



Left frontal focal cortical dysplasia identified on brain MRI in a patient with intractable LRE not visualized on CT brain scan.

condition. High-resolution brain MRI is the foundation for patients with medically intractable localization-related epilepsy as an initial part of the presurgical evaluation. However, MRI provides morphologic information only of cerebral anatomy, and thus does not directly reflect function. Therefore, the epileptogenic focus may not always correspond to the anatomic abnormality seen on brain MRI. Cranial CT provides acute information of brain structure, especially highlighting the presence of blood products (e.g., intracranial hemorrhage), but has limited visualization of the temporal regions, with up to one third of intractable epilepsy patients demonstrating normal cranial CT scans but abnormal MRI images (*see* figure). Limitations of neuroimaging include pitfalls of attributing seizures to abnormal CT scan signals with nonspecific pathologic significance (e.g., diffuse cortical atrophy, ventricular dilatation in elderly patients). Focal areas of abnormal high signal lesions may be produced on brain MRI transiently following seizures and may resemble astrocytomas with vasogenic edema [1]. Peri-ictal diffusion-weighted imaging MRI can yield localizing information on the epileptogenic zone in status epilepticus of focal origin [2]. Newer-generation brain MRIs have stronger field strength magnets of 3 T and are now becoming more widespread in availability, offering even higher resolution than the 1.5 T units now widely utilized.

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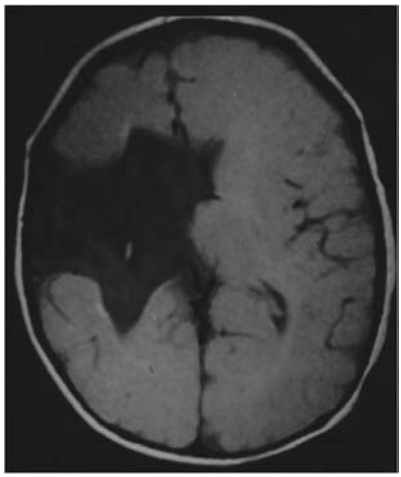
## SCHIZENCEPHALY

Schizencephaly refers to a full-thickness cleft in the cortex extending to the lateral ventricle and lies near the sylvian fissure. Schizencephaly may be unilateral or bilateral and represents a neuronal migrational disorder that affects the telencephalon. The malformation may be sporadic or associated with the gene EMX2 in familial schizencephaly [2]. If the cortical walls are touching the con-



Classic right hemispheric open-lipped schizencephaly. Note the direct communication of the cortex with the lateral ventricle and the relative atrophy of the right hemisphere.

dition is referred to as "closed lip" and, if separated by CSF, then "open lip" schizencephaly. Surgical resection of the cleft may be an effective treatment for those associated with medically intractable localization-related epilepsy [1].

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## SCHOLASTIC ACTIVITIES

Many school children with epilepsy (21-69%) experience scholastic difficulties [1,2]. Epilepsy's most obvious effect on children relating to education is on attendance rate, which may be affected by seizures.

Reasons for difficulty include absenteeism because of seizures, adverse effects of medication, problematic relationships with teachers and schoolmates, and parental fears limiting application. Each of the preceding factors contributes to behavioral problems, inattention, and selective cognitive deficits. Some scholastic problems may be due to an anatomic underpinning leading to neuropsychological handicap or the repeated effects of clinical or subclinical seizures. Children with epilepsy are prone to education underachievement as a result of comorbid learning and behavioral problems. Other factors that may contribute to poor school performance among epilepsy patients include overprotective parental attitudes, a lack of academic motivation, and low self-esteem. Teachers' attitudes toward epilepsy also affect a patient's education as well [3]. Some teachers' automatic labeling of students with known illnesses can give preconceived ideas regarding that student's performance level in the classroom [4]. Children who are stigmatized could feel devalued or discriminated against, feel threatened when interacting with others, or feel they must avoid social situations in which they could potentially be rejected in school [9]. The teacher's attitude to these challenges is paramount.

Most children with epilepsy are normal, but their potential group risk for learning difficulties is increased threefold. About 10% of children with epilepsy

have IQs of <70. Reading skills may be 16% below grade average, while general knowledge may lag 50% [1]. Parents as well as medical and educational personnel should encourage as normal a lifestyle as possible, with active participation in sports (*see* Sports) and peer group activities. Accommodations should be made for children with special learning problems within the system. If this is not feasible, special schools are available to consider on an individual basis.

However, involvement in overspecialized situations may also be problematic. Using a parent-rated behavior questionnaire, children in special institutions were shown to have significantly more problems in hyperactivity/attention deficit and sociability domains. Later age at onset of epilepsy was related to more depression/anxiety [5]. Furthermore, the behavior problems most commonly seen in PWE may be influenced by the type of epilepsy, the type of medication being used, other underlying neurologic disorders, the family environment, and the acknowledgment of other significant preexisting cognitive problems. Though teachers' attitudes regarding epilepsy were generally positive, there were significant deficits in terms of general knowledge about epilepsy, its impact in educational settings, and the appropriate management of epilepsy and seizures in the classroom [6]. Teachers identified the need for more information about seizure classification, classroom seizure management and first-aid, etiology and treatment, impact of epilepsy and its treatment on school performance, talking about epilepsy in the classroom and helping other students understand seizures and epilepsy, and effective parent-teacher communication to facilitate scholastic benefits for PWE.

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## SCOTOSENSITIVE SEIZURES

Scotosensitive seizures are clinical seizures, and EEG discharges, that can be induced by sudden darkness or abolition of central vision (fixation-off). While the combination of fixation-off sensitivity with photosensistivity has rarely been observed, seizures induced by suddenly switching the room light off or on are rare [1]. Typically, they include palpebral myoclonic jerks with absence seizures caused by suppression of central vision, though they may also be seen in pa-

tients with developmental abnoramlities of the brain [1] (*see also* Induced Seizures; Photosensitive Seizures; Reflex Seizures).

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## SEIZURES

A seizure is an electrographic or behavioral change resulting from a sudden excessive, hypersynchronous discharge of cerebral neurons. A seizure is a symptom and not a disease. The behavioral changes of a seizure are stereotyped associated with variable impairment of consciousness, in addition to sensory, motor, cognitive, or autonomic changes. Epileptic seizures are a more common neurologic problem than Parkinson's disease or multiple sclerosis [1]. The importance of understanding seizures in PWE stems from their common occurrence and lack of understanding about those affected by the condition. The two major categories of seizures are localization-related and generalized seizures. Seizures that originate from focal brain regions are associated with localization-related epilepsy, and generalized seizures are associated with generalized epilepsy and characterized by diffuse, bilateral cerebral involvement at onset [2]. The types of seizures are listed in Table 1, though the semiologic spectrum of "focal" and generalized seizures is often appreciated with clinical overlap.

**Table 1 Seizure Types**

| **Localization-related (partial-onset, focal)** | **Generalized** |
|---|---|
| Simple partial, complex partial, and secondarily generalized | Convulsive<br>Generalized tonic-clonic, *tonic,* myoclonic |
| | Nonconvulsive atonic, absence (typical and *atypical*) |

Seizures depicted in bold may be associated with IGE or SGE; those in italics are associated with SGE.

The diagnosis of the appropriate seizure type is crucial so that iatrogenic exacerbation of generalized seizures or incomplete treatment of partial seizures does not occur. Classification systems attempt to categorize seizures for the purpose of defining the epilepsy syndrome (e.g., myoclonic and generalized tonic-clonic seizures of juvenile myoclonic epilepsy syndrome). EEG has been used as an extension of the semiology as an integral part of the classification system. However, separate classification systems based upon semiology alone have also been employed successfully in the clinical management of patients of various age ranges [3]. A proposal to adopt a five-axis classification system (*see* Classification) as well as revised terminology [4] has been put forth. Seizures that reflect an idiopathic (or "primary") origin are associated with a genetic

predisposition and by definition have no structural basis. In adulthood, generalized (clonic) tonic-clonic, absence (typical), and myoclonic seizures are best represented by IGE. Seizures associated with diffuse structural brain injury reflect a SGE that is typically manifested by multiple mixed seizure types, including tonic/atonic ("drop attacks") and atypical absence seizures (absences with <3 Hz spike-and-waves on EEG). Those with symptomatic causes bear a known structural cause, while those with a cryptogenic origin have a suspected symptomatic but unidentified cause. Partial seizures may be idiopathic (e.g., benign partial epilepsies of childhood). Some generalized seizures may manifest "focal" or lateralized features [2]. Some partial-onset seizures may appear with bilateral motor involvement from rapid secondary generalization. The key features of the seizure types are listed in Table 2.

**Table 2 Seizure Types and Key Features of Clinical Expression**

| Seizure type | Key features |
|---|---|
| Simple partial (SPS) | Consciousness is unimpaired ("aura") |
| Complex partial (CPS) | Consciousness is impaired/nonconvulsive |
| Secondarily generalized | Convulsion that may begin first as a SPS or CPS |
| Generalized tonic-clonic | Convulsion of nonfocal origin ("grand mal") |
| Myoclonic | Single lightning-like jerks, often in clusters |
| Typical absence | Very brief staring episodes usually in children ("petit mal") |
| Tonic/atonic | Abrupt generalized rigidity/loss of tone ("drop attacks") |
| Atypical absence | Staring; longer and more "complex" than typical absence |

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## SELF-MEDICATION AND ALTERNATIVE MEDICINE

Self-medication can take the form of the patient altering AEDs (usually dosage) or taking other treatments (e.g., dietary, herbal, botanic, chiropractic, acupuncture, stress management, prayer, magnet therapy, yoga) [1,2]. Typically, a patient may change the AED therapy from that prescribed, such as stopping treatment in the belief that therapy is ineffective or causing side effects. Additionally, the

patient may modify the amount and timing of AED doses (usually a diminution) (*see also* Compliance). The patient may take other drugs in addition to AEDs, for example, those prescribed to another family member or by another doctor who is unaware of ongoing AED therapy. Undesirable drug interactions may arise, which may either increase or decrease AED levels. Some drugs (theophylline, antihistamines, stimulants, tricyclic antidepressants, phenothiazines, atypical antipsychotics, tramadol, certain antibiotics [e.g., metronidiazole]) may decrease seizure threshold (*see* Drug [Non-AED] Poisoning).

About 40% of Americans use complementary and alternative medicine (CAM) for various conditions-44% specifically for seizure control [1]. This has increased largely because of the relaxation in 1994 of the safety standards for herbal and botanic substances as compared with prescription medication. Favored botanicals include ginkgo biloba, soy, garlic, kava kava, and melatonin, with occasional use of cannabis, ephedra, and bee pollen. Respondents noted an increase in seizures on the whole, but they believed they benefited from CAM; most indicated that they would inform their physician. There is no evidenced-based support for the use of herbal or botanic treatments, and some (ephedrine, aspartame, ginkgo seeds, water hemlock) may interact with AEDs or lower seizure threshold. Furthermore, some drugs taken to increase alertness to offset sedation created by AEDs may be detrimental. For example, a dose of >32 mg/d of ephedra may increase the risk of hemorrhagic stroke more than threefold. Some agents such as water hemlock (Cicuta douglasii) are profoundly toxic, with intractable seizures and death reported from even a few bites of the root. Other herbal supplements that have been reported to provoke seizures include the kava kava berry, yohimbe, black cohosh, guarana, pennyroyal, and monkshood [2]. Observational studies suggest that yoga or stress management may help in seizure control (*see* Stress).

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## SEXUALITY

Compared with persons suffering from other chronic disease states, PWE demonstrate a higher incidence of sexual dysfunction. The cause is often felt to be multifactorial, with brain abnormalities, recurrent seizures, AEDs, and psychosocial factors operational. Interictal sexual dysfunction has been demonstrated to have a significantly higher rate in both men and WWE, though men with epilepsy have received less attention. Self-reporting sexual dysfunction may be complicated by the reluctance of PWE to devulge information due to embarrassment, and hence precise quantification of the frequency of sexual

problems is difficult to ascertain. Hypersexuality or sexual deviation appears to be rare, whereas hyposexuality is common. The sexual dysfunction may be variable and include reduced arousal, erectile dysfunction, and anorgasmia in men [1] and reduced libido, vaginal lubrication, vaginimus, and dyspareunia in women [2]. Sexual disturbances in epilepsy depend on several factors. An early age of onset of seizures predisposes to sexual dysfunction, with seizures acting as a negative reinforcement to create low self-esteem and impaired socialization. Seizures arising from the temporal lobe have been implicated to a greater degree than those from other regions given the involvement of the limbic structures affecting mood and behavior. Both interictal IEDs and seizures have been implicated in altering sex hormone levels, and temporal lobectomy has been reported to improve sexual libido when seizures are controlled. Sexuality may also be affected by adverse effects on normally secreted hormones and may be notable when EIAEDs are used, reducing testosterone levels in men and estrogen and progesterone in women [3].

AEDs may indirectly impair sexuality by affecting endocrine function (e.g., decrease in free testosterone levels). Alternatively, AEDs such as barbiturates or benzodiazepines may have a direct cortical effect, reducing libido. Mood and behavioral problems seen in some PWE introduce not only physical and social problems but also psychological problems leading to dysfunctional sexual relationships. Organic searches for medical causes that imply treatment include measuring laboratory studies of thyroid function, glucose, and endocrinologic markers (e.g., testosterone, estrogen, luteinizing hormone, and prolactin levels). Urologic or gynecologic evaluations may disclose a normal examination that prompts symptomatic treatment with lubricants, drugs for erectile dysfunction, psychotherapy, marriage counseling, or a combination of all treatments.

Sexual auras may occur in PWE. They are uncommon but may be associated with genital sensations that may be pleasurable or unpleasurable without sexual content or with symptoms of sexual arousal. Sexual auras most frequently originate in patients with temporal lobe epilepsy, though primary somatosensory cortex, anterior cingulate, and the peri-sylvian areas less frequently engender genital sensations or sexual reactions during seizures. Orgasm has followed sexual auras and suggests right hemispheric lateralization. Sexual automatisms may occur during seizures, with pelvic thrusting, fondling, grabbing, or rubbing the genitals. One study noted that sexual automatisms were more likely to suggest temporal lobe seizures when fondling or grabbing the genitals was seen as opposed to pelvic thrusting or hypermotor sexual automatisms [4].

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## SHUDDERING ATTACKS

Shuddering attacks of infancy are nonepileptic spells (*see* Spells) that may be confused with epileptic seizures. The incidence is low, but may be underrepresented in the literature, with one retrospective study noting that 7% of all nonepileptic events were shuddering attacks [1]. They begin in infancy, are benign events, and are manifest as rapid shivering of the head and upper body, usually lasting a few seconds without loss of consciousness. They may occur up to 100 times daily and with variability both between individual attacks and from patient to patient. Attacks may be precipitated in normal infants by eating, head movement, or more complex tasks felt to represent stimulus overflow as the cause. Shuddering attacks may be confused with other epileptic seizure types, including myoclonic, absence, and other generalized seizure types, though the EEG is normal during video-EEG monitoring and AEDs are unnecessary. Brain MRI is usually normal, and the pathophysiology of shuddering attacks is unknown [1]. Reassurance of the parents and family members is the principal focus, and spontaneous remission is anticipated with development. Propanolol has been used successfully in the treatment of shuddering attacks, and a relationship to essential tremor with an EMG pattern during the attacks that is similar to essential tremor has been found [2].

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## SIALIDOSES

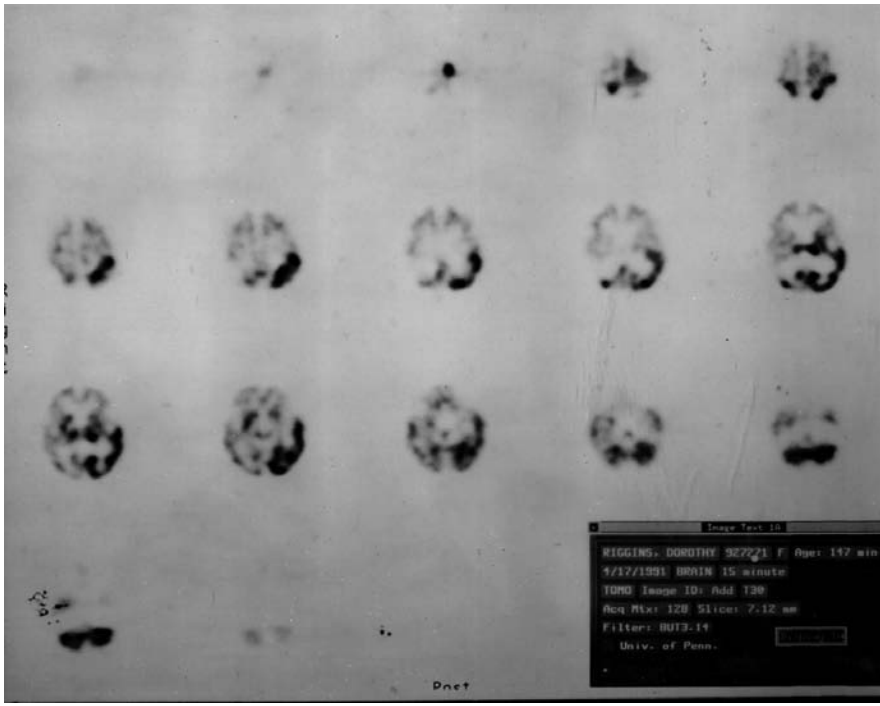
The sialidoses are a group of disorders of lysosomes due to alpha-*N*-acetyl neuraminidase abnormalities. In certain phenotypes, a deficit in betagalactosidase has been reported. Clinical features include a progressive myclonus epilepsy, bilateral cherry-red spots seen on fundoscopic examination, and enzymatic abnormalities in leukocytes and fibroblast cultures. Two phenotypes have been described. Type I (cherry-red spot myoclonus syndrome) is an autosomal recessive disorder of late childhood to adolescence and is characterized by polymyoclonus, progressive blindness with cerebellar signs, tonic-clonic seizures, and peripheral neuropathy. In this form cognitive decline occurs later in the course of the disease. The myoclonus may be disabling with exacerba-

tion/stimulation by movement and is coupled by EEG findings of rhythmic vertex-positive IEDs on a low-voltage background. The genetic defect has been localized to chromosome 10 with a deficiency of alpha-neuraminidase that may be measured. Type II is caused by beta-galactosidase deficiency in addition to a neuraminidase deficiency. Type II is referred to as the juvenile form of sialidosis with onset in the second or third decade. It is predominantly seen in Japan. The clinical presentation is similar to that of Type I sialidosis, but Type II may be associated with facial dysmorphism, corneal clouding, and deafness. Myoclonus is often less prominent.

## SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT)

Single photon emission computed tomography (SPECT) is a cerebral functional neuroimaging technique using a systemically injected or inhaled radiolabeled tracer to measure regional cerebral blood flow. SPECT uses radiotracers labeled with single-photon-emitting isotopes to produce images of cerebral function that measure regional cerebral blood flow (rCBF), cerebral blood volume, and blood-brain barrier permeability. A radiotracer that is commonly employed to measure regional cerebral blood flow is hexamethylpropylene amine oxime (HMPAO) coupled with 99mTc (technetium), though other tracers have been utilized. SPECT is similar to PET (*see* Positron Emission Tomography) in that both are functional neuroimaging techniques that measure similar parameters [1]. In contrast, SPECT is less expensive and does not require an on-site cyclotron to generate the very short half-life isotopes required for PET. SPECT has commercially available isotopes that may be stored for longer periods of time, e.g., hours (vs. minutes with PET), to permit injection during seizures (ictal SPECT scan) as opposed to PET, which is obtained durng the interictal period. PET, in turn, provides greater spatial resolution in addition to the ability to image brain metabolism and neurotransmitter receptors. SPECT also exposes the patient to a higher degree of radiation than PET.

Because SPECT can be prepared at the bedside for more lengthy periods of time, ictal SPECT scanning is more appropriate than PET for study during seizures [2]. Cerebral blood flow may be decreased interictally in the region of the epielptogenic zone, but increases markedly during partial or tonic-clonic seizures. Interictal SPECT scans are unreliable in identifying the epileptogenic zone [1,3]. Focal hyperperfusion reflecting increased rCBF during a seizure is an accurate localizing tool with a sensitivity of ictal SPECT that is similar to interictal PET (*see* figure). The change in rCBF from interictal to ictal scans can be measured and displayed via SISCOM (substraction ictal SPECT coregistered with MRI), which is useful in patients with temporal lobe epilepsy and extratemporal epilepsy during a presurgical evaluation to localize the epileptogenic zone [2,3]. Compared with the traditional qualitative interpretation that




Ictal SPECT scan demonstrating left temporal-occipital regional cerebral hyperperusion.

compares homologous brain regions, SISCOM images demonstrate a significantly higher rate of correct localization (88.2% vs. 39.2%) [3]. In addition, more consistent interrater reliability was seen using SISCOM. SPECT has also been significantly more likely to predict a favorable outcome after epilepsy surgery when SPECT localization is concordant with the site of surgical resection (62.5% vs. 20%). However, the timing of injection is critical to ensure correct identification of the epileptogenic zone associated with the ictal onset zone as opposed to defining a region of propagation. Localization of a seizure focus rapidly diminishes postictally unless the injection is administered <60 seconds after the seizure, when a greater yield may still be found. When the ability to obtain an ictal SPECT scan exists, this may significantly affect the preoperative candidacy or strategy for further pursuit of epilepsy surgery.

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# SINGLE SEIZURE

The first or only seizure that occurs spontaneously without a clear cause is not epilepsy but instead a single (or isolated) seizure. This concept and diagnosis is of great importance because a single isolated seizure does not represent the diagnosis of epilepsy with its attendant medical and psychosocial consequences. Unfortunately, a first seizure in the context of what may ultimately become epilepsy by definition occurs after the second seizure arises. Annually approximately 150,000 adults will present with a first seizure in the United States, and it is estimated that 40-50% of these incident seizures recur to be classified as epilepsy when recurrent unprovoked seizures occur [1]. In prospective studies, the overall risk of recurrence is 30-40% during the first 12 months [2,3]. This underscores the importance of attempting to prognosticate and provide appropriate constraint in therapeutic aggressivity given that most seizures will not recur. Early treatment with AEDs after a single seizure has no impact upon the prognosis of developing epilepsy [4]. Patients have a low risk for recurrence with a single seizure when no symptomatic etiology, no remote symptomatology, nonfocal seizures, and a normal interictal EEG and neurologic examination are found. In these situations, most experts recommend that AED therapy be delayed until a second seizure demonstrates that a reproducible condition (epilepsy) exists [4]. An argument against treatment is the relatively low risk of recurrence and the significant incidence (30%) of AED side effects in those treated, especially if a provocative etiology is implicated [4]. However, AED therapy should be considered after a single unprovoked seizure in PWE and a neurologic deficit (or abnormal neuroimaging study), EEGs with IEDs, or where the risks of a second seizure to an individual are unacceptably high. Therefore, many clinicians will elect not to treat a single seizure when normal individuals without risk factors have normal neuroimaging and EEG unless a symptomatic etiology or risk factors are encountered. Treatment after first seizures with AEDs reduces the risk of recurrence by about 50% [4,5]. Absence and myoclonic seizures are seizure types that do not exist in isolation and therefore do not occur or present as single seizures. Repeated partial seizures may occur before they are recognized as epilepsy, and the diagnosis may be delayed for years when they are subtle or associated with unawareness.

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## SITUATION-RELATED SEIZURES

Situation-related seizures are synonomous with provoked seizures and acute symptomatic seizures. The term is used more commonly in Europe than in the United States, where "reactive seizure" or "acute symptomatic seizures" are terms more commonly employed to reflect the nonepileptic nature of the occcurence. With respect to etiology, three categories have been most commonly found. First, febrile seizures (or convulsions) are very common occurrences in childhood but rarely develop into epilepsy (*see* Febrile Seizures). The second category that may lead to acute seizures includes seizures that arise in association with medical conditions or systemic disorders. Metabolic aberrations including disorders of glucose, calcium, and sodium are common metabolic derangements that may result in seizures, especially dependent upon absolute concentration and rate of rise or fall. Transient hypoxia is a systemic effet that may result in situation-related seizures or epilepsy if associated with more prolonged effect and cortical ischemia. Endogenous fluctuation of seizures may occur during menses, pregnancy, and peri-menopausally to create seizure occurrence or exacerbation. Exogenous hormonal therapies that contain estrogen may be associated with seizure exacerbation, especially in the postmenopausal period. Systemic effects of dehydration, organ failure with uremia, or hypramonemia noted with renal or hepatic failure may arise but not imply a need to treat the problem as epilepsy. Exogenous toxins, including alcohol-related or alcohol-withdrawal seizures as well as stimulant recreational drugs, including cocaine, amphetamines, heroin, and ecstasy, may provoke seizures in a nonepileptic patient or facilitate the onset of a patient with preclinical IGE. Other prescription drugs, including tricyclic antidepressants, neuroleptics, atypical antipsychotics, tramadol, bupropion, lithium, cytotoxic drugs, or contrast media, may act as exogenous toxins to trigger seizures [1-3]. With traditional neuroleptics there is a lowering of seizure threshold in animals, but rarely in humans—largely in poorly controlled studies. Clozapine may have a dose-related induction of seizures occurring in 1-2% of patients taking < 300 mg/d, 3-4% in those taking 300-600 mg/d, and about 5% in those taking more than 600 mg/d of the immediate-release preparation.

Direct structural insults of the brain may occur to provoke seizures during the acute time period of the insult. Seizures may occur contemporaneously with ischemic or hemorrhagic stroke, frequently within the first day or week.

Immediate or early head trauma may induce early seizures due to the initial trauma but not be associated with posttraumatic epilepsy. Hypertensive encephalopathy, including eclampsia, can provoke seizures during the prepartum phase in association with the systemic alterations of eclampsia.

Treatment of a situation-related seizure is directed toward the underlying cause. Brief periods of AED therapy may be warranted (e.g., 1 week following severe head injury or during preop treatment of subarachnoid aneurysm), but long-term treatment should be reserved for cases in which the provoking factors cannot be eliminated.

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## SKIN ERUPTIONS AND TOXIC DERMATOSES

Adverse cutaneous reactions are a common allergic reaction to drugs and are frequently associated with AEDs [1]. Exanthems may present as local or diffuse morbilliform or urticarial eruptions within 2 months of treatment but will usually begin resolving when AEDs are discontinued. They occur with all the AEDs in approximately 3-10% of cases—more frequently upon rapid initiation or increase in AED dose. Of the older antiepileptic drugs, phenobarbital, phenytoin, and carbamazepine have been asssociated with severe rash (e.g., Stevens-Johnson syndrome [SJS]). The newer AEDs, including lamotrigine, topiramate, oxcarbazepine, and zonisamide, have been associated with SJS as well. Leviteracetam and gabapentin have not been associated with SJS, and valproate has rarely been associated. While some adverse reactions are associated with significant morbidity and mortality, fortunately these adverse cutaneous reactions are rare. They may also be the first sign of a more serious systemic hypersensitivity syndrome, and rash-related deaths have occurred. Of the AEDs, the single orally administered agent with the highest risk of rash is carbamazepine. Of the aromatic compounds, phenobarbital has been most associated, and of the new AEDs, lamotrigine, has been most associated with severe adverse cutaneous reactions such as SJS and toxic epidermal necrolysis (TEN). Both acute life-threatening rashes are associated with blisters and epidermal detachment caused by epidermal necrosis, often associated with fever and malaise [2]. The risks among new users of AEDs are listed in the table. SJS or exudative erythema multiforme occurs with cutaneous and mucous membrane maculovesicular eruptions or bullous eruptions that involve detachment

of <10% of the total body surface area. The skin lesions of SJS are initially burning pain with mucous membrane involvement and lesions that appear as three distinct pink rings or small blisters on purpuric macules or aypical target lesions over the face and thorax [1]. Systemic involvement of the viscerae are associated with a poor prognosis. TEN (Lyell's syndrome) manifests as target lesions or morbilliform generalized rash with bullous formation that affects the skin and mucus membranes of the face and upper thorax with >30% detachment. There may be complete loss of the dermis following development of large confluent bullae and a "scalded" appearance. Both SJS and TEN may present as a febrile illness with malaise, anorexia, sore throat, or rhinitis, while TEN may additionally manifest pharyngitis, conjunctivitis, and pruritis [1,3]. Erythema multiforme is a rash that mimics SJS but occurs on the limbs as a response to infection (e.g., herpes), manifests target lesions, but has a benign course. Other skin eruptions and manifestations include nodular erythema, acneiform rashes, pigmented patches (chloasma), and hirsutism, which have been described with the use of phenytoin. About 5% of patients with SJS and 30% of those with TEN will die. Because of the danger of bullous dermatoses, all skin eruptions must be considered when a new drug is started. If a skin eruption occurs, an initially benign-appearing rash may not necessarily be predictive of a benign outcome. The offending drug therefore should be stopped and not restarted. Patients are hospitalized and treated as burn victims in the acute setting with fluid management, parenteral nutrition, and supportive eye and skin care. Immunomodulators have been used but are not validated.

**Risk Estimates of Antiepileptic Drug Therapy**

| AED | New users | SJS or TEN cases | Risk per 10,000 new users |
|---|---|---|---|
| Carbamazepine | 286,360 | 39 | 1.5 |
| Lamotrigine | 55,154 | 14 | 3.8 |
| Phenobarbital | 8,659 | 7 | 8.2 |
| Phenytoin | 36,171 | 30 | 6.9 |
| Valproic Acid | 103,150 | 4 | 0.5 |

Cases occurring within 2 months of initiation of AED therapy.
*Source:* Adapted from Refs. 2 and 4./TSN

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## SLEEP DEPRIVATION

Sleep deprivation has been recognized as an important seizure precipitant. In one study, sleep deprivation was the second most important precipitant after stress, occurring in 18% of patients [1]. Sleep deprivation appears to have its greatest impact in those with idiopathic generalized epilepsies. It is well known that the IGEs such as JME may be precipitated by sleep deprivation in up to three fourths of patients [2]; therefore, recognizing the strong influence of sleep deprivation is important for optimal care. Using transcranial magnetic stimulation (TMS) before and after sleep deprivation in untreated newly diagnosed epilepsy patients, sleep deprivation was shown to increased cortical excitability in epilepsy and was syndrome dependent-most prominently for those with IGE [3]. TMS has been used to demonstrate the activating effect of sleep deprivation in untreated, newly diagnosed epilepsy patients [3]. In one study, sleep deprivation was shown to increase cortical excitability in a syndrome-dependent fashion and was most prominent in patients with IGE. However, patients with LRE also demonstrated ipsilateral increased cortical excitability demonstrated by a shorter interstimulus interval to TMS after sleep deprivation compared to controls [3].

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## SLEEP AND EPILEPSY

Sleep is a well-documented factor influencing the frequency, morphology, and distribution of seizures. Many seizures are activated by sleep or arousal from sleep, have an impact upon sleep integrity, and may be mimicked by sleep disorders [1,2]. Seizures that are activated by sleep or arousal occur commonly in the idiopathic epilepsies. Some IGEs with myoclonus and generalized tonic-clonic seizures (e.g., JME) often present after experiencing a seizure that occurs upon arousal in the morning hours (and less frequently upon retiring at night shortly after initiating sleep). On the other hand, some idiopathic localization-related epilepsies such as BCECTS, present after nocturnal partial-onset seizures are noted. The localization-related epilepsies may also demonstrate selective activation of partial seizures during sleep with frontal lobe epilepsy (*see* Frontal Lobe Epilepsy), often demonstrating multiple

seizures during the sleeping hours [2]. Psychogenic nonepileptic seizures (*see* Psychogenic Nonepileptic Seizures) may occasionally appear to occur out of sleep. However, unlike epileptic seizures, they arise during wakefulness, drowsiness, or soon after arousal or from "pseudo-sleep" and not directly out of sleep. PNES rarely occur between the hours of 12 a.m. and 6 a.m. Therefore, epilepsies that are activated during sleep depend upon the depth of sleep in addition to the clinical characteristics of the epilepsy syndrome.

During EEG recording, normally in the IGEs, IEDs increase during slow-wave sleep and decrease during REM sleep. In the SGEs such as Lennox-Gastaut, there is an increase in IEDs during the initial stages of sleep with a decrease during slow-wave sleep, a tendency of the bursts of IEDs to decrease in duration, the appearance of polyspikes, and multifocal IEDs. In West syndrome, the hypsarrhythmic pattern may disappear during REM sleep. In partial epilepsies, slow-wave sleep predisposes seizures to generalization, but spikes appear to increase during light sleep and decrease during REM. Some epilepsy syndromes such as Landau-Kleffner (*see* Aphasia, Acquired Epileptic; Landau-Kleffner Syndrome) demonstrate profound activation during sleep with electrical status epilepticus (ESES syndrome) and continuous spike-and-slow wave activity occupying 85% or more of the tracing in slow-wave sleep.

Although sleep architecture may be normal interictally on the EEG, disrupted sleep patterns associated with seizures may result in sleep that is disorganized and interrupted by arousals, resulting in sleep deprivation (*see* Sleep Deprivation). An effect of AEDs upon sleep architecture may also be recognized during prolonged EEG recording. In general, AEDs increase stage 1 and 2 sleep and decrease REM sleep. In addition to PWE who have seizures that affect sleep integrity, sleep disorders may adversely affect seizure frequency [1,3]. In PWE, sleep disorders such as sleep apnea affect sleep integrity and can lead to sleep fragmentation and chronic sleep deprivation, which may facilitate seizures in susceptible people [3]. Sleep apnea may trigger seizures in patients with uncontrolled seizures up to eight times more than those with controlled seizures [3]. Improving apnea may improve seizure control in these cases, and addressing sleep patterns therfore appears important for optimizing seizure control in PWE.

Paroxysmal motor disorders of sleep may mimic epileptic seizures, especially when they originate in the frontal lobes [1,2]. Parasomnia may mimic epileptic seizures during sleep. Polysomnambulism or sleepwalking is semipurposeful ambulation that may imitate complex partial seizures with impaired responsiveness, automatisms, and amnesia for the event. Wandering outside of the bedroom is seldom seen, and the episodes occur during normal slow-wave NREM sleep. Night terrors (*see* Night Terrors) may have loud vocalizations similar to nocturnal frontal lobe epilepsy and are common in young children, also occuring during NREM sleep. A disorder of REM sleep in the elderly, REM behavioral disorder, may appear episodic and associated with motor movement that is confused with a seizure, though, like parasomnias, it is readily distinguished with video-EEG monitoring. Nocturnal paroxysmal dystonia

has been described as a movement disorder but has demonstrated a clinical response to treatment with carbamazepine and in many cases probably reflects nocturnal frontal lobe epilepsy. Periodic limb movements of sleep (nocturnal myoclonus) may simulate myoclonus in patients with GTC seizures, raising the possibility of an IGE, though no associated EEG abnormalities are encounted and this may readily be differentiated with polysomnography. To separate sleep-related frontal lobe seizures and parasomnias, a questionnaire scale was developed and found to have a perfect sensitivity of 1.00 (95% CI 0.85-1.00) and high specificity of 0.90 (95% CI 0.73-0.97) with a PPV of 0.91 (95% CI 0.75-0.97) and NPV of 1.00 (95% CI 0.85-1.00). Clinical features such as age of onset (<55 years), event duration (>2 minutes), clustering (more than 5), timing (within <30 minutes of sleep onset), aura presence, stereotypy, absent recall of events, and vocalization were tiered and given a corresponding score of 0 to +2. A total score of +1 would indicate epilepsy, and a score of 0 or less a parasomnia [4].

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## SLEEP STAGES

Seizures are activated during sleep in some patients (*see* Nocturnal Frontal Lobe Epilepsy) and are activated by the lack of it in others (*see* Sleep Deprivation). The diagnostic value of recording an EEG containing sleep increases by one third. The quanitity and quality of sleep are defined by polysomnography used for sleep disorders, but the stages of sleep may also be identified during prolonged EEG recording. Normally, sleep cycles and cycling between NREM and REM sleep remain consistent throughout the life of an individual. Sleep is composed mostly of non-REM (NREM) sleep. NREM sleep is divided into four stages. Stage 1 is the first phase of NREM sleep and corresponds to sleep onset with the appearance of 2-7 Hz mixed frequency activity and vertex sharp waves (5% of total sleep time). Stage 2 demonstrates a decrease in muscle activity, mixed theta and delta activity, and the appearance of sleep spindles (and K complexes) that are the hallmark of this stage (50-55% of total sleep time). Slow-wave sleep makes up stage 3, with diffuse high-amplitude delta activity accounting for < 20% of a 30-second epoch (10% of total sleep time), and stage 4 demonstrates delta activity for more than 50% of the 30-second epoch (10-15% of total sleep time). REM sleep is comprised of low-voltage

mixed-frequency activity on EEG associated with rapid conjugate horizontal eye movements, a relative atonia, and irregular cardiac and respiratory rhythm (25% of total sleep time). Total REM sleep lasts 90-100 minutes and appears in four or five cycles during the night, increasing during the early morning hours. Some medications that have a negligible effect on the EEG (e.g., chloral hydrate) have been used to induce sleep in PWE and increase the yield of recorded IEDs during sedated sleep.

## SLEEPWALKING

Abnormal paroxysmal motor events in sleep can present a unique differential diagnosis that includes partial seizures. Sleepwalking is not an epileptic phenomenon, but a benign nonepileptic parasomnia that occurs during sleep in the transition from non-REM sleep to REM sleep. Epileptic partial seizures that arise from the frontal lobes often occur during sleep and may be characterized by sleepwalking in adults and adolescents. Distinction may be made on clinical and EEG characteristics and in most cases is relatively straightforward (*see also* Sleep).

## SOMATOFORM DISORDERS

It is essential to distinguish epileptic from psychogenic nonepileptic seizures. Somatoform disorders have a high current and lifetime prevalence in patients with PNES. Somatoform disorders exist in patients with physical concerns in whom no medical illness can be found and who don't improve despite treatment. They reflect the most common category of psychiatric conditions seen in patients with PNES and conversion disorder with seizures [1]. Somatoform disorders represent an unconsciouns mental conflict or repressed painful thought converted to a physical symptom. The patient is unaware of the seizures (they are not "faking" them) and do not grasp their significance.

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## SOMATOSENSORY AND OTHER SENSORY SEIZURES

Somatosensory (sensory) seizures are characterized by sensory manifestations. These may involve simple alterations of body sensation, perception, and balance or involve special sensations that include olfaction, taste, hearing, and vi-

sion. Seizures are characterized by somesthetic manifestations such as paresthesias, hyperesthesias, formication, buzzing, electrical sensations, temperature change (including cold or hot), burning, dysesthesias, or pain. Seizures may be unilateral with variable spread eminating from the contralateral sensory strip; bilateral involving the trunk, lower limbs, and face originating from the secondary somatosensory area; associated with proprioceptive problems in the case of parietal foci; or occurring with headache or migraine. They are usually associated with motor phenomena as well. They may remain fixed and the seizures may evolve with a Jacksonian march (*see* Jacksonian seizures).

Auditory seizures may produce the perception of tinnitus, sounds, or vertigo. Visual seizures affect the contralateral visual field producing spots, zigzags, flashes, or lines in Brodmann area 17, or more complex pictures such as shapes, often with color or movement in areas 18 and 19. The greater the involvement of the association cortices, the more the animated quality of the hallucination, which may resemble a dream-like state. Occipital seizures account for about 8% and parietal seizures 1.4% of seizures in epilepsy [1,2].

Specific somatosensory seizure may induce a paresthesia: a sense of ants crawling on the skin (formication), the sensation of pins and needles, buzzing, electric, cold or heat, burning or pain, or loss of limb or distortion of limb shape [3]. The seizure may be associated with motor phenomena, usually with somewhat more complex movements rather than simple jerking of a flexion-extension character. Movements may assume a sinuous "shaking-off-water" pattern. They may remain fixed or localized on a body part or manifest a Jacksonian march over a body part. Typical patterns include a unilateral localization with variable spread from a contralateral sensory strip focus; bilateral involvement of the trunk, lower limbs, or face with a focus in the secondary somatosensory area; seizures that induce alterations in proprioception due to parietal foci; or less frequently the induction of headaches or migraines.

When symptoms are sudden in onset, there may be diagnostic consideration of other causes of similar sensations, such as transient ischemic attacks (TIAs) or migraines.

Features favoring TIAs are the presence of known cerebrovascular risk factors, prominence of negative rather than positive symptoms (e.g., loss of sensations rather than altered perception of limb shape), lack of a "march," or anatomic progression of sensory disturbance. The progression of migrainous sensory disturbance usually takes place over minutes, while seizures do so over seconds. The ictal nature may become apparent if further "positive" ictal motor features supervene. The etiology for somatosensory seizures is not specific for location, and typical causes include tumors, malformations of cortical development, encephalomalacia from traumatic gliosis, cerebral infarction/hemorrhage, vascular malformations, and rarer causes such as celiac disease, mitochondrial disorders, calcification, Kufs and Lafora body disease, and eclampsia. In one series of parietal lobe epilepsy that underwent surgical resection, lesion-based surgery was able to provide information regarding semiology as well as produce a seizure-free outcome in 10 patients [4].

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## SPECTROSCOPY

Magnetic resonance spectroscopy (MRS) is a dynamic test of brain neurochemistry. Minute-to-minute changes in phosphorus permit information that reflects changes in cerebral energy metabolism and pH. MRS has identified alterations that occur in patients with TLE with reduction in the neuronal components (represented by the NAA peak) and increase in the glial elements (creatine and choline) to serve as a noninvasive measure of in vivo function. Areas of interest require large areas of brain to sample, and the resolution of MRS is much lower than PET or SPECT. Still, MRS serves as a means of providing concordance in the presurgical evaluation of patients with intractable epilepsy. In addition, MRS has shown an increase in the level of *N*-acetylaspartic acid (NAA) after status epilepticus, supporting the idea that seizures may cause neuronal damage in the human brain [1].


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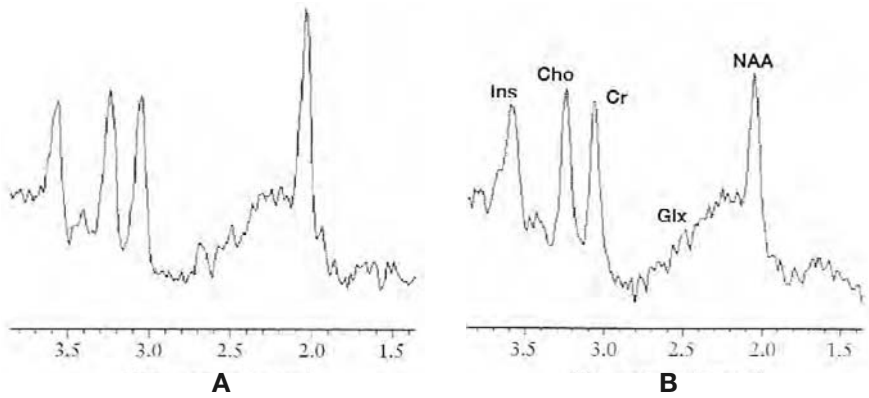


MRS with spectroscopic display of a normal and abnormal display. The normal display (A) demonstrates a normal NAA, Chol and Cr peak while the abnormal display (B) demonstrates a reduction of the NAA (neuronal component) and greater Chol/Cr (glial components).

## SPELLS

A "spell," "event," or "episode" is a nonspecific term used by patients and physicians alike to describe a paroxysmal transitory disturbance in well-being. This may include the sudden onset of sensory, motor, autonomic, psychic, or emotional changes due to a variety of nonepileptic or epileptic causes. In addition to seizures, syncope, panic attacks, or hypoglycemia, for example, may produce sudden malaise that occurs in "spells," prompting a visit to a physician.

The determination of whether these episodes are epileptic or nonepileptic in nature is essential in order to provide appropriate management. A hasty and incorrectly applied diagnosis of epilepsy may have significant social, professional, and medical implications, and great care and a conservative approach to treatment until satisfactory confirmation of the diagnosis appears most appropriate during the evaluation of "spells."

## SPHINGOLIPIDOSES

Sphingolipidoses are disorders of lipid metabolism in which seizures are but one part of a complex involvement of neurologic and nonneurologic features. This group of disorders includes the glucosyl-ceramidoses (gangliosidoses and glucosyl cerebrosidoses) as well as galactosyl ceramidoses including metachromatic leukodystrophy and Fabry's disease.

Metachromatic leukodystrophy (ML) is not uncommonly associated with seizures and represents a rare metabolic disorder of late infancy that includes seizures as a primary clinical manifestation. ML is manifest as weakness and gait disorder with hypotonia on examination. Cognitive decline occurs with a progressive deterioration of motor skills. Focal seizures develop later in the course of the disease and occur in up to 50-60% of patients with juvenile-onset ML—more than twice the frequency than with late-infantile onset [1]. The EEG demonstrates progressive slowing of the background with IEDs that increases in frequency in parallel with the cognitive decline [2]. The diagnosis may be suspected on clinical grounds, but is secured by demonstration of the enzyme deficiency of arylsulfatase A.

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# SPORTS

For individuals with epilepsy, participation in most sports can be encouraged. For a long time, participation in sports or exercise were discouraged in people with epilepsy due to seizure-related injury and the possibility of the intensity of activity inducing a seizure or even worsening one's epilepsy [1]. More recently, restrictions on participation in sports have been reduced, and in fact there have been many situations in which athletics and exercise have been beneficial. Athletics are an important part of development and self-satisfaction for PWE. However, PWE are often excluded or discouraged from becoming involved due to perceived potential for injury from a seizure or loss of seizure control. Involvement in team sports may have a beneficial effect on patients with epilepsy, improving social integration. Sports per se do not worsen epilepsy, and the decision to participate in sporting events must be individualized to ensure optimal effects from participation balanced against the safety issues for the person involved.

Hyperventilation can precipitate some forms of seizures, particularly absence seizures in predisposed individuals. However, the homeostatic effect caused by metabolic acidosis and hypoxia from physical exertion is markedly different from the effect produced from hyperventilation in the resting patient, such that hyperventilation in response to exercise usually does not provoke seizures. Sustained hypoxia or hypoglycemia during sustained, vigorous physical exercise may rarely precipitate seizures. Repeated head injury in certain violent sports, such as rugby, boxing, or martial arts, may lead to epilepsy with substantial head trauma, though even minor head trauma may rarely worsen seizure control [2]. Concussive convulsions may occur with contact sports [3], though there is apparently little increase in frequency of sporting accidents in children with epilepsy compared to normal children. However, there is not much evidence that sports, specifically collision and contact sports, place athletes with epilepsy at an increased risk for any injury compared to athletes without epilepsy. When accidents do occur in children with epilepsy, they are often unrelated to seizures. Special care must be taken with sports in which a seizure could be catastrophic, including aquatic sports and climbing or flying sports [2].

There is growing evidence that limiting adolescent participation in general physical activity could cause potentially harmful psychological consequences. In 1974 the AMA Committee on Medical Aspects of Sports noted that "there is ample evidence to show that PWE will not be affected adversely by indulging in any sport, including football, provided the normal safeguards for sports participation are followed, including adequate head protection" [3]. Furthermore, decreased incidence of seizures while exercising has been documented. The U.S. Commission for the Control of Epilepsy and Its Consequences reported that "physical activity also appears to play a role in seizure prevention."

A few practical suggestions may be helpful to those PWE who wish to participate in sporting events. Individual sporting events are less likely to pose a threat to PWE, depending on the particular activity [1]. Individual or one-on-one sports such as golf, tennis, bowling, or similar events are low-risk sports. Contact sports (e.g., boxing), water sports, sporting events at altitudes (e.g., downhill skiing), and sports ultilizing mechanical equipment (e.g., extreme skateboarding) are higher-risk sports and thus pose greater danger to those with and without seizures. Water sports, off-shore fishing, boating and sailing, and any underwater acitivities (e.g., spear fishing) may be dangerous [2]. Sporting events that involve access to heights such as rock climbing, horseback riding, mountain bicycling, or flying may result in significant injury in case of a breatkthrough seizure. In addition, mechanical sports such as automobile or motorcycle racing all carry potential danger for PWE given the potential for even transient impaired consciousness and the severity of the consequences. Similarly, any activity of "critical timing" such as scuba diving, free-line parachuting, rock climbing, or rappelling should be avoided given the potential for life-threatening consequences in the event of a breakthrough seizure during participation. Prior to any serious involvement in sports, a sports medicine practitioner should become very familiar with the athlete's seizure history. The more information gained by the practitioner, the more prepared all involved will be in the case of any episodes. Taking AEDs regularly is to be recommended, and the effect of exercise on the drug metabolism of a selected group of AEDs showed no significant increase or decrease in drug levels with physical activity [3].

In general, in the event of a seizure during sports activity, normal first aid procedures should apply. No matter what type of seizure is occurring, basic airway, breathing, and circulation should be monitored and treated accordingly. If a convulsive seizure occurs, move potentially harmful objects away from the individual; the head should be cushioned if possible, and any restrictive clothing or equipment should be loosened or removed if necessary. The individual should be moved if the location could pose further danger. If the athlete is having a complex partial seizure, the individual should not be left alone, and the previously mentioned suggestions should be followed (*see* First Aid for Epilepsy). In the event of an absence seizure, the athlete should be carefully guided away from the activity if the situation appears at all dangerous [1]. When dealing with athletes and seizures, some situations call for activation of emergency medical services. In the event the seizure is the athlete's first, if the seizure is prolonged (2-5 minutes), if there is any suspected serious injury, or if there was any respiratory compromise following the event, then EMS should be activated [1,4]. A summary of sporting events and suggested recommendations are included in the table [3]. However, the majority of patients with epilepsy can practice sports normally, and the most serious hazard of epilepsy is often not the seizures per se but the associated emotional aberrations that are prone to develop in PWE.

**Sport-Specific Recommendations for Athletic Participation in Epilepsy**

| Sport | Recommendation |
|---|---|
| Water sports | Generally permitted with precautions—visual supervision of person qualified to rescue and resuscitate, clear water; children supervised by lifeguard or trained adult; no swimming in open water or swimming allowed with flotation device; boating or fishing with flotation device, but avoid if frequent seizures; scuba diving, competitive underwater swimming, or diving prohibited if active epilepsy. |
| Sports at heights | Pilot's license prohibited; sky diving, hang gliding, free climbing discouraged; gymnastics discouraged for parallel bars and acrobatics for some athletes; equestrian sports avoided except as closely supervised therapy for children. |
| Motor sports | Discouraged in active epilepsy. |
| Shooting sports | Dependent upon seizure frequency and type, occurrence pattern, weapon used. |
| Contact sports | No restriction, except possibly in new diagnosis with unclear course. |
| Aerobic sports | No restriction, appropriate headgear and safety for skiing and ice skating. |
| Wheeled sports | No restrictions except if frequent seizures or unclear frequency, appropriate safety equipment. |
| Other sports | Exclusion more likely harmful than a seizure during the activity. |

Adapted from Ref. 3.

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# STARTLE SYNDROMES

Stimulus-sensitive disorders include hyperkeplexia, neuropsychiatric startle, and other stimulus-induced disorders including reflex epilepsy [1]. Hyperkeplexia is an exaggerated startle that may be inherited as an autosomal dominant condition and is manifest as an excessive startle response caused by a mutation of the glycine receptor gene (GLRA1) on chromosome 5. Neruopsychiatric startle syndromes including the "jumping Frenchman of Maine," Tourette's syndrome, and "hysterical jumps" are more common than hyperkeplexia. Anxiety and psychogenic jerks can be differentiated based upon the longer latency of the startle (usually >100 ms) compared with the normal startle latency of <30 ms. The differential diagnosis includes myoclonic seizures, drop attacks, startle epilepsy, and infantile spasms. When a differenetial diagnostic dilemma exists, video-EEG monitoring may be required.

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# STATUS EPILEPTICUS

Status epilepticus (SE) is a common and potentially life-threatening neurologic emergency characterized by prolonged seizures. Traditionally, SE was defined as continuous seizure activity lasting more than 30 minutes or two or more sequential seizures without full neurologic recovery in between. However, because of the high morbidity and mortality associated with continuous seizures, a pragmatic definition of SE has evolved to encompass directions to begin treatment when the seizure duration lasts more than 5 minutes [1,2]. The annual frequency of SE in the United States has been previously estimated to involve up to 195,000 events per year and 42,000 deaths per year [3]. Generalized convulsive SE (GCSE) is the most commonly identified form of SE; though any seizure type may evolve into SE, morbidity and mortality are most critical with GCSE. The manifestations may be overt or subtle. GTC seizures occurring from the outset are seen with the IGEs, as well as with insults due to metabolic, toxic, or infectious agents. Metabolic abnormalities (e.g., hypoglycemia, hepatic encephalopathy, uremia, pyridoxine deficiency, hyponatremia, hyperglycemia, hypocalcemia, hypomagnesemia) and the use of or overdose with drugs that lower the seizure threshold (e.g., theophylline, imipenem, high-dose penicillin G, quinolone antibiotics, metronidazole, isoniazid, tricyclic antidepressants [especially bupropion], lithium, clozapine, flumazenil, cyclosporine, lidocaine, bupivacaine, metrizamide, and, to a lesser extent, phenothiazines) may provoke SE.

GCSE may also commonly occur with seizures of focal onset that are secondarily generalized in patients with LRE and also in patients with a recent focal cerebral lesion (e.g., traumatic or ischemic infarction). Tonic SE may be seen in children with generalized symptomatic epilepsies. Clonic SE may occur in young children with severe febrile convulsions in the absence of emergency treatment or with an acute severe cerebral insult. Myoclonic SE may be seen in IGE such as with JME and manifest as bilateral myoclonus in clusters and intact consciousness. It may also occur in SGE (e.g., PME) or during the course of progressive GCSE, as "electromechanical dissociation" occurs with ongoing SE and continuous convulsions are waning despite ongoing electrographic SE. Status myoclonus may occur in the face of acute encephalopathies such as with a severe anoxic insult that acts as an epiphenomenon of diffuse structural brain injury with stimulus-sensitive multifocal myoclonic jerks of the axial and appendicular musculature.

SE may also be nonconvulsive, and generalized nonconvulsive SE (NCSE) includes typical absence SE that is seen with IGE. Serious morbidity and mortality does not appear to be associated with typical absence SE. The clinical picture varies from brief, intermittent absences to a more continuous alteration in behavior and cognition with mild psychomotor slowing and even catatonia. An acute confusional state is often present, frequently with subtle eye blinking and clonic movements of the face. The EEG may show bilateral, synchro-

nous, continuous or intermittent generalized IEDs that occur irregularly at 3 Hz. The encephalopathic generalized epilepsies, particularly Lennox-Gastaut syndrome, may present with prolonged obtundation lasting from several hours to days, which may be difficult to distinguish from interictal behavior states and reflect atypical absence SE. Atonic SE in young children is extremely rare.

Focal SE may reflect simple partial (somatomotor) SE, with repeated partial motor seizures occurring several times per hour. It occurs with LRE and with an acute insult that involves motor cortex. Ongoing rhythmic jerking movements involving one focal body part (e.g., epilepsia partialis continua), the limb, or half the body (e.g., HHE syndrome) frequently associated with focal or regional epileptiform discharges on the EEG occurs with a multitude of lesions that involve the contralateral somatosensory cortex. Simple partial SE may consist of aphasia or other language problems that may persist postictally and simulate an acute ischemic infarction clarified only by ictal abnoramlities discovered on the EEG. Complex partial SE often presents with confusion, changes in behavior, memory deficits, or changes in the level of consciousness that mimics psychiatric conditions or behavioral disorders. SE with recurrent CPS may originate from the temporal lobes and be underdiagnosed or undertreated with unfortunate results. Clinical correlates may vary, but can include waxing and waning level of consciousness, automatisms, eye deviation (especially with frontal lobe foci), as well as occurring with psychiatric manifestations.

There are many causes of GCSE and NCSE; remote symptomatic, acute symptomatic and idiopathic etiologies are evenly distributed, though a structural basis is more likely to be discovered [1]. Approximately 15% of PWE present with SE, while 15-20% of PWE have a history of SE. Epilepsy is the greatest risk factor for the development of GCSE, and in a prospective population-based study, low AED concentration was the most common etiology [2]. Status epilepticus often occurs following abrupt cessation of AED treatment or with subtherapeutic AED levels, but it may also be seen in patients with low seizure thresholds despite "therapeutic" AED levels. In adults, acute or remote cerebrovascular disease appears in up to 50% of cases, though anoxia, hemorrhage, and tumor are also common causes [1]. Another 50% of cases occur in patients with an acute cerebral insult without a history of epilepsy (with trauma, infections, cerebrovascular events, metabolic disturbances, and drug and toxicity). SE is most common in young children, with 40% developing SE at <2 years [4]. In the pediatric group, fever is the most common concomitant factor, though remote brain insults and low AED levels were also common. Recurrence rates are highest with symptomatic etiologies (either acute or chronic brain injuries) and rare with idiopathic causes or febrile SE [4].

The EEG features of status epilepticus largely center around patterns of waxing and waning epileptiform discharges and rhythmicity, with the discharges appearing focally or regionally (i.e., over the frontal, temporal or other regions) or in a generalized pattern (usually from a focal onset, but also in those that are primarily generalized) [5]. Nonconvulsive status epilepticus can be more diffi-

cult to diagnose because of the spectrum of epileptiform patterns that lie along an ictal-interictal continuum. Some working criteria have been proposed to help distinguish periodic discharges from NCSE utilizing the EEG [5].

SE is potentially a life-threatening emergency and requires rapid and aggressive treatment in most cases. The intensity of treatment should reflect the risk to the patient balanced against the side effects of the treatment (e.g., effects upon cardiorespiratory compromise). Intravenous therapy is the preferred route of administration, though intramuscular and rectal approaches have been utilized [1]. In general, lorazepam (*see* Lorazepam) used up to 0.1 mg/kg has been effective in terinating approximately 65% of SE and was superior to i.v. phenytoin (44%) when used as an initial treatment for GCSE [6]. In the Virgina cooperative study, the aggregate response to the treatment of GCSE with a second-line AED was 7.0%, and the third-line AED 2.3% [6], indicating the importance of initial drug treatment in the cessation of SE. The second AED has been an initial 20 mg/kg phenytoin equivalent (PE) loading dose at 100-150 mg PE/min, and third-line approach to AED management has included phenobarbital (20 mg/kg) and propofol (1-2 mg/kg followed by 1-10 (g/kg/min), midazolam (0.2 mg/kg followed by 0.75-10 (g/kg/min), and high-dose barbiturates (pentobarbital 5-15 mg/kg followed by 1-4 mg/kg/h) for refractory SE given the limited likelihood of response by that time [2]. A duration of SE of more than 1 hour has been a poor predictor of response [7]. Intravenous formulations of valproate or levetiracetam may ultimately define a place in certain types of SE (i.e., VPA for absence SE or leviteracetam for status myoclonus due to hypoxia), and other AEDs such as VPA may be more effective than phenytoin as a second AED in GCSE. Agents for refractory SE such as propofol, midazolam, or high-dose barbiturates should be used in the neurointensive care setting with continuous EEG monitoring to facilitate brain low-energy states reflected by burst suppression. Patients with refractory GCSE may require i.v. fluids and vasopressor support. The search for a reversible primary process should receive attention, and intercurrent problems such as infection, deep vein thrombosis, cerebral edema, and ventilatory support must be addressed and treated immediately.

The morbidity and mortality of SE increases with the duration, though the predominant factor affecting outcome is the underlying etiology [2]. A younger age carries a more favorable outcome than older age. Symptomatic etiologies are more difficult to treat, and mortality is substantially increased in the elderly. In one single-center study, mortality increased from 3% in the pediatric population to 13% in young adults and 38% in the elderly [3]—even more in the critically ill elderly. Newer studies suggest a lower overall in-hospital mortality (3.5%), which more than tripled when mechanical ventilation was received, with other predictors incuding age, hypoxic-ischemic injury, cerebrovascular disease, and patients with greater comorbidities. PWE that have SE occur as a result of low AED levels or substance abuse carry a better response to treatment and the best overall prognosis for survival [1]. Status myoclonus due to hypoxia carries the worst overall prognosis. Morbidity has in-

cluded a persistent encephalopathy with cognitive deficit and memory loss after GCSE with survival. The morbidity of NCSE has been consistently more variable, less predictable, and less reported than GCSE. Absence SE has not demonstrated predictable cognitive deficits, though children typically recover to a significantly greater degree than adults.

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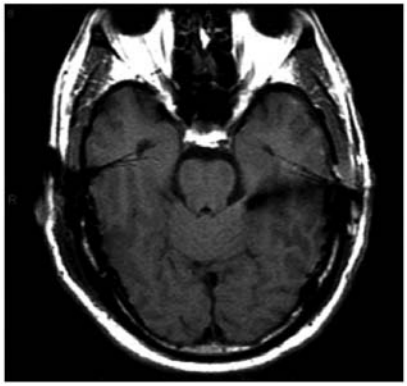
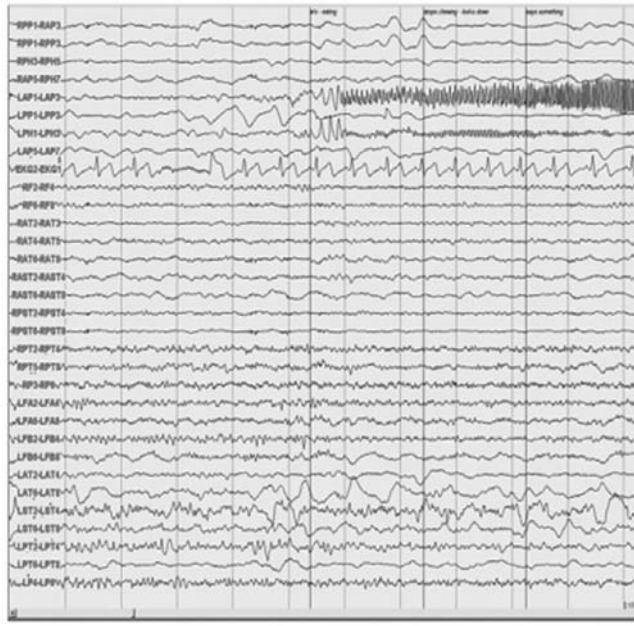
## STEREOSTATIC DEPTH ELECTROENCEPHALOGRAPHY (SDEEG)

Stereostatic depth electroencephalography (SDEEG) is an invasive technique of employing intraparenchymal implantation of individual recording "depth" electrodes composed of a bundle of wires inserted directly into the brain. SDEEG has been used in the preoperative evaluation of focal epilepsy when a noninvasive evaluation has yielded nonlocalized or discordant results. Depth electrodes have been most utilized in temporal lobe epilepsy given the frequency of intractable complex partial seizures. Both rigid and semi-rigid polyurethane electrodes are available, and the choice of trajectory is dependent upon the neurosurgeon's preference. The orthogonal approach (*see* Figure 1) and the occipital temporal approach are two common trajectories utilized and are commonly employed in addition to supplemental subdural electrode strips or grids to record from the neocortex as opposed to deeper structures [1]. IEDs



Axial MRI brain in a patient with intractable temporal lobe epilepsy with depth electrodes implanted bilaterally (placed in the anterior pes hippocampi) inserted through the lateral temporal approach. (Courtesy of D. Sharan Ashwani MD, Jefferson Comprehensive Epilepsy Center.)



Intracranial EEG showing a combined depth and subdural electrode array in a patient with intractable complex partial seizures. Note the onset in the deep contacts of the left anterior hippocampal depth electrode (LAP) with a typical discharge beginning as a burst of mesial temporal sharps followed by low amplitude fast activity in the depth that builds during seizures propagation. (Courtesy of Michael R. Sperling MD, Jefferson Comprehensive Epilepsy Center.)

are frequently seen and are not utilized solely as a means of decision making for respective surgery of the epileptogenic zone as opposed to the greater importance of recording seizures (*see* Figure 2). One of the greatest limitations of SDEEG beyond the risks of intracranial hemorrhage is that of limited sampling of recording sites, which might potentially cause mislocalization of the ictal onset zone. In general with SDEEG, focal onsets in the temporal lobe and those with a long latency of 20 seconds or more for interhemispheric contralateral temporal propagation times are favorable findings on SDEEG for successful surgical outcome.

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## STIGMA

Stigma refers to an identifying characteristic regarded negatively by others not affected by the characteristic of the condition. Stigma can manifest as overt

discrimination against an epileptic individual or be reflected by agoraphobic behavior towards PWE. Compared to the general population, patients with epilepsy have lower employment rates (*see* Employment), incomes, educational levels, and marriage rates [1]. A U.S. study involving nationwide random sampling of 758 adults found that negative stereotypes reflected beliefs that other people hold about PWE, including 27.3% believing that there was a high likelihood of death with every seizure and 66.5% thinking they should put something in the person's mouth during a seizure [2]. In a survey of 19,000 teenagers, 52% had never heard of epilepsy, 46% were not sure if it was contagious, 40% were not sure if people with epilepsy were dangerous, and only 31% reported that they would consider dating someone with epilepsy [3]. A role of epilepsy support must be to challenge the current social construction of epilepsy as disability and as stigma. People with epilepsy deserve well-formulated legislative support such as is embodied in the U.S. Americans with Disabilities Act, the UK Disability Discrimination Act, and recent European Union driving regulations [4].

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## STRESS

Although difficult to quantify, stress during activities of daily living appears to be the most important precipitant to increased seizure frequency [1]. Stress may be important for patients with idiopathic generalized epilepsy but may also act as a trigger in localization-related epilepsy. However, the relationship is derived from clinical experience, and the precise prevalence and degree of activation is difficult to quantify. Stress stems from typical causes, induced by fear, frustration, anger, and worry or a combination of these emotions. The link between stress and epilepsy is, however, largely empiric, with seizures occurring at variable time periods in relationship to the stressor. Animal models suggest a heightened brain excitability underlying the increased synchronization of neuronal activity leading to seizures [2]. Therapies have been directed at relaxation, desensitization, and biofeedback. Other nonmedication or drug precipitants are hyperventilation and sleep deprivation. Consistent precipitation of seizures by stress should raise a suspicion of psychogenic nonepileptic seizures (*see also* Induced Seizures).

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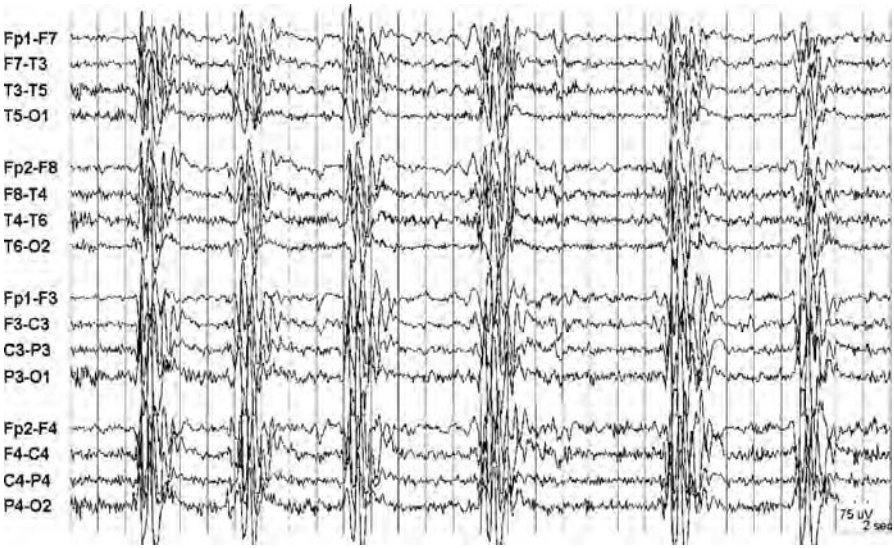
## STURGE-WEBER SYNDROME

Sturge-Weber-Dimitri syndrome is also known as Sturge-Weber syndrome. It is a congenital neurocutaneous syndrome (phakomatosis) characterized by leptomeningeal and cutaneous angiomas associated with calcium deposition in perivascular tissue and blood vessels. The principal clinical features are unilateral cutaneous hemangioma (port wine stain) most frequently involving the first trigeminal dermatome of the upper face that includes the inner canthus, ipsilateral to gyriform intracranial calcifications of the brain. A vascular "steal" phenomenon is created by the overlying leptomeningeal angiomatosis, resulting in underlying hypoxic-induced calcified cortex. The classic "tram-track" appearance on skull X-ray or brain CT may be quite robust. In addition, high associations with mental retardation (50-60%), hemiparesis (30%), glaucoma (50%), and epilepsy often occur. Epilepsy occurs in 70-90% of cases and is seen early in the course. Seizures most commonly begin within the first year of life and may be focal or secondarily generalized. Sometimes seizures are prolonged. Despite occipital cortex involvement, visual seizures are rare clinically, and temporal lobectomy has been used with successful results. In Sturge-Weber syndrome, the EEG is abnormal in the vast majority of patients, with three quarters showing background attenuation or abnormalities. Focal spike-and-wave IEDs may be evident on the EEG.

The symptomatic etiology of PWE and the Sturge-Weber syndrome carries a high risk for medical intractability. In certain severe forms, seizures may contribute to the intellectual deterioration. Early resective surgery appears more beneficial on intellectual outcome than delaying a definitive intervention. Hemispherectomy may lead to improved motor function and and is more common than lobectomy. Pial angiomatosis and occipital calcification without cutaneous angiomas may occur as a forme frustre of Sturge-Weber syndrome.

## SUBACUTE SCLEROSING PANENCEPHALITIS

Postinfectious encephalomyelitis, subacute measles encephalitis, and subacute sclerosing panencephalitis (SSPE) are all distinct entities that can be caused by the measles virus. Subacute sclerosing panencephalitis is encephalitis caused by a mutated wild measles virus. Most individuals affected by SSPE are children and adolescents between 5 and 15 years of age. SSPE presents as a chronic progressive disease. A delayed effect after measles infection is seen




Periodic complexes on EEG in second 3 and second 7 in a patient with SSPE. (From Tatum WO, Husain AM, Benbadis SR, Kaplan PW, eds. Handbook of EEG Interpretation. New York: DemosMedical Publishing, 2008:130.)

up to 10 years later [1]. The presentation is with clinical manifestations of declining school performance, behavioral changes, headache, and sometimes seizures [2]. Characteristically, myoclonic jerks are seen that are time-locked to periodic epileptiform discharges on EEG. The incidence of SSPE has been greatly reduced with vaccination against the measles virus, which has been implemented on a widespread scale, but it may persist in regions where vaccination is not routine [3]. Pregnancy may exacerbate the condition. The diagnosis is facilitated by recovery of measles-specific antibodies from the cerebrospinal fluid. Treatment attempts to arrest the progressive course have utilized intraventricular interferon therapy with or without antiviral immunomodulation without consistent improvement. Seizures are treated symptomatically with AEDs that provide borad-spectrum efficacy for myoclonus and generalized or partial seizures (*see* Myoclonus).

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# SUBSTANTIA NIGRA

Substantia nigra is known to play an important role in seizure generalization [1]. Both excitatory and inhibitory neurotransmitters can modulate this role. Previous studies have shown that GABA as well as aspartate and glutamate participate in seizure regulation through this site. Evidence for such a role comes from studies on the genetically epilepsy-prone rat (GEPR) and other seizure models. In the GEPR, bilateral microinjections of NMDA receptor antagonists in SN block or reduce seizure severity [1].

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# SUICIDE

Individuals with epilepsy have a significantly higher rate of major depressive episodes, and studies on health-related quality of life have shown that depression is a better indicator for quality of life than seizure frequency, severity, or cognitive or memory function [1]. Suicide accounts for one of the highest standardized mortality rates in PWE and is 10 times more common than the general population [2]. The rates of suicide vary in PWE, though an overall average of approximately 11.5% is seen, which is much higher than the rate seen in the general population of 1.1-1.2% [2]. The increased risk appears to affect not only adults, but children and adolescents as well. Risk factors include the presence of an axis 1 diagnosis, youth, physical health problems, family issues, life stressors, and a prior suicide attempt. Suicide attempts during seizures do not occur as a goal-directed behavior, though it may be difficult to distinguish certain peri-ictal moods and behaviors from a suicide attempt. One report noted that 10-20% of individuals who had a suicide attempt will successfully commit suicide within 10 years [2]. Recently, FDA has issued a warning indicating a link between AEDs and a greater risk of suicidal thoughts and behavior. An *Alert* 1/31/08 sent to healthcare providers revealed results from placebo-controlled studies of 11 AEDs including 27,863 treated patients (compared with 16,029 on placebo), which found that 105 versus 35 patients had suicidal thoughts or behaviors [3]. Four treated patients successfully committed suicide. This reflects a twofold rate of suicidality for patients treated with AEDs (0.43% vs. 0.22%) [3]. Recommendations have included realizing that AEDs may facilitate depression, behavior changes, or suicidality and providing informed conset and balancing the risks versus the benefits of the drug.

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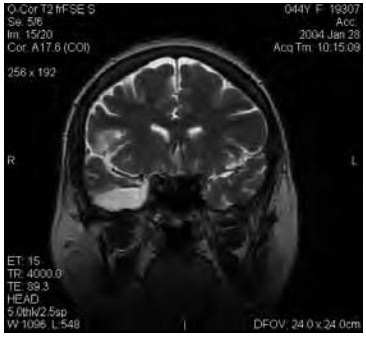
## SURGERY FOR EPILEPSY

Surgical therapy for PWE has been an option for more than 100 years and has been shown to be more beneficial for PWE who are intractable to AEDs than additional trials of medication [1]. In the United States, 30-40% of PWE continue to experience ongoing seizures not controlled by AEDs [2], accounting for most of the healthcare costs. There are potentially 100,000-200,000 surgical candidates in the United States [3], with fewer than 5,000 patients by conservative measure currently undergoing surgery for epilepsy on a yearly basis. Surgical intervention may be indicated if seizures persist and AEDs are ineffective. Treatment-resistant epilepsy is infrequently defined in the literature, and when definitions are used they frequently differ according to the source employed. When a progressive lesion, nonadherence, inappropriate AED or misdiagnosis of epilepsy, and illicit substance abuse have been eliminated as a reason for uncontrolled seizures, after two AEDs have failed as monotherapy, the chance of seizure freedom with additional AED treatment is low [2]. Even after the first well-tolerated AED trial proves to be ineffective, a strong prediction of medial intractability is able to be made. Health policy organizations suggest that patients who continue to have seizures after 3 months of treatment should be referred in order to improve quality of care for those who continue to suffer from seizures after two AED monotherapies. The National Insitute for Health and Clinical Excellence has suggested that if there is diagnostic doubt, a unilateral structural lesion, management unsuccessful after two AED trials, and if the patient is not controlled within 2 years, he or she should be referred to a tertiary care center for futher assessment. Video-EEG should be available not only for differential diagnosis but also for assessment of neurosurgical treatment. There are two approaches to surgical therapy for patients with drug-resistant epilepsy.




Coronal postoperative brain MRI following right antero-mesial temporal lobectomy.

Resective surgery is potentially curative by excision of the seizure focus if it is able to be delineated and safely removed (e.g., temporal lobectomy, extratemporal resections, and hemispherectomy). Temporal lobectomy is the most common epilepsy surgery performed and is a standard of care in the United States, with various surgical approaches involving resection of the mesial structures (e.g., amygdalohippocampectomy) with or without lateral neocorticectomy (*see* figure) [4]. Strategies for surgical treatment of epilepsies in developing countries have been reviewed [5]. Palliative surgery seeks to improve seizure control and quality of life by reducing disabling seizures such as drop attacks that create the potential for recurrent injury (e.g., corpus callosotomy). Initial two-thirds to four-fifths section is peformed to minimize the risks of the disconnection syndrome.

Postoperative outcome from surgery has been proposed by Engel to stratify the effects of the surgical treatment (*see* table).

**Classification of Postoperative Outcome According to Engel (Excluding Early Postoperative Seizures)**

| | |
|---|---|
| Class 1 (seizure-free) | Completely seizure-free, auras only, some seizures but seizure-free for at least 2 years, atypical GTC with AED withdrawal |
| Class 2 (rare seizures) | Initially seizure-free, now rare seizures, rare seizures postoperatively, rare seizures for at least 2 years, nocturnal seizures only—no disability |
| Class 3 (worthwhile improvement) | Worthwhile seizure reduction, prolonged seizure-free intervals for more than half of follow-up period but no < 2 years |
| Class 4 (no worthwhile improvement) | No significant seizure reduction, no appreciable change, seizure worsening |

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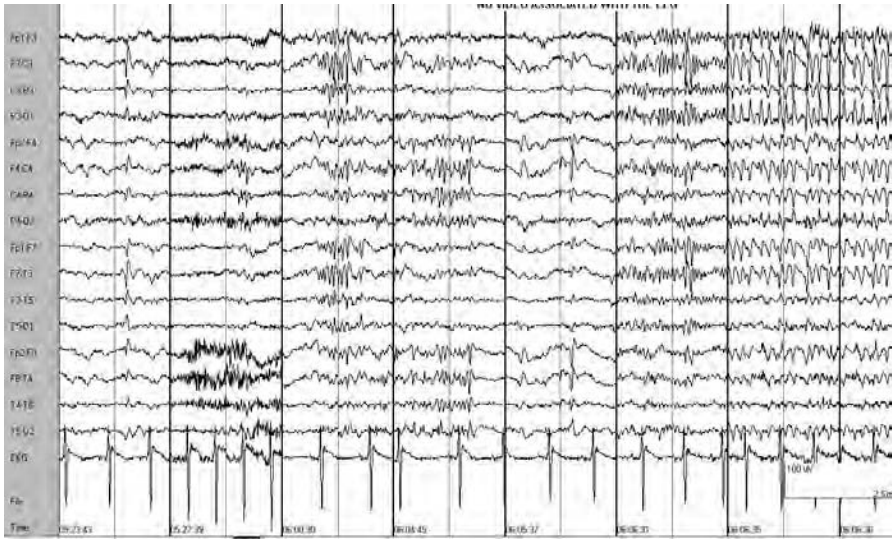
# SYMPTOMATIC EPILEPSY

The symptomatic epilepsies represent an acquired form of epilepsy due to an underlying identifiable etiology. These epilepsies may caused by an acute or



Two-second spike samples using computer-assisted ambulatory EEG in a patient with encephalopathic generalized epilepsy and multifocal spikes, polyspikes, and GPFA. Note the spikes in seconds 1 and 5, polyspikes in 2-4, and GPFA in 7 and 8.

chronic lesion of various etiology and be either localization-related or generalized. Chronic lesions such as perinatal insults that result in a chronic motor deficit (*see* Cerebral Palsy) or chronic static encephalopathy (*see* Encephalopathy) may be seen early in life, while acquired lesions from trauma, brain tumor, stroke, and dementia may occur in the middle and later years. Various seizures types may also be seen and are dependent upon the classification of the symptomatic epilepsy. For example, symptomatic localization-related epilepsy from mesial temporal sclerosis that appears in adolescence may produce characteristic complex partial seizures that suggest a specific location (e.g., mesial temporal lobe). On the other hand, early-childhood-onset mixed seizures that include generalized seizures such as tonic, atonic, atypical absence, and myoclonic seizures are characteristic of a symptomatic generalized epilepsy (encephalopathic generalized epilepsy) with illustrative examples that include West syndrome, early myoclonic encephalopathy, or the Lennox-Gastaut syndrome (*see also* Classification). In contrast, seizures that begin in the elderly may remain so subtle and without awareness that diagnosis may be evaded for years.

## SYMPTOMATOGENIC ZONE

Marked neuronal depolarization in the epileptogenic zone propagates and depolarizes neighboring neurons by synaptic and extrasynaptic mechanisms to

produce symptoms at a site associated with behavioral seizures; the *symptomatogenic zone*. Propagation from the *ictal-onset zone* is spread by axons to distant or nearby cortical structures via intracortical association pathways, commissures, and cortico-thalamo-cortical or cortico-subcortical commissures [1-3]. The behavioral semiology suggests the symptomatogenic zone that may occur at a distance from and not necessarily at the precise location of the epileptogenic zone. If the ictal-onset zone resides in a behaviorally "silent" area, the initial discharge may be asymptomatic, and the first signs or symptoms of a seizure will be those brought about by involvement in areas removed from the epileptogenic zone. Although slow direct spread frequently occurs, more rapid involvement of distant structures via long pathways can occur depending upon the epileptogenic zone in the brain. The propagation of the seizure discharge depends on the starting point. Frontal discharges spread more rapidly to the contralateral hemisphere than temporal lobe seizures [3]. Temporal discharges may spread more rapidly to the ipsilateral frontal lobe prior to contralateral hemispheric spread. A seizure is rarely the result of a single discharge with spread in one direction. Spread along multiple axes is more common. Intracranial recordings illustrate the variability of spread of the seizure discharge from seizure to seizure despite a singular epileptogenic zone. However, in these cases the clinical features of the seizures may remain relatively stereotyped because of spread preferentially along certain pathways [1].

### References

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## SYNCOPE

Syncope is a common event responsible for 3% of cmergency department (ED) visitations and 1-6% of hospital admissions [1]. Syncope is the most common physiologic mimic of a seizure and is often a reason for neurologic consultation in the hospital ("seizure vs. syncope"). Syncope is a sudden brief loss of consciousness resulting from a relative ischemia to the brain usually imposed by a decrease in or cessation of cerebral blood flow. The most frequently encountered types of syncope are vasovagal followed by neurally mediated syncope, orthostatic hypotension, cardiac syncope, and syncope of unknown etiology. In one study, neurally mediated syncope (vasovagal) occurred in 21.2%, cardiac syncope in 9.5%, and syncope of unknown cause in 36% [1]. A higher incidence of structural heart disease is seen in the elderly, while vaso-

vagal syncope is most likely in a younger patient. In neurally mediated syncope, a temporary failure of the autonomic nervous system to maintain adequate heart rate and blood pressure occurs. Within this category are neurocardiogenic syncope that results from triggers such as emotional stress, valsalva from cough, toileting, prolonged heat exposure, exertion, and pain. The fear of medical procedures such as phlebotomy is a well-known cause of vasovagal syncope. In young healthy children and adolescents, a simple "faint" is common, especially between 9 and 14 years of age, and vasovagal syncope may be misdiagnosed as epilepsy for many years until the correct diagnosis is obtained. Nevertheless, even in children a serious underlying cardiovascular disorder such as valvular heart disease, coronary artery malformations, or cardiomyopathies may still occur.

The clinical features of syncope are relative to the severity and duration of ischemia. Presyncopal symptoms of dizziness (lightheadedness), visual compromise (constriction or blurring), nausea, abdominal discomfort, paresthesias, diaphoresis, altered sensations of hot and cold, and observed pallor or cardiorespiratory symptoms may be seen prior to a limp collapse. *Simple syncope* consists of loss of consciousness with a fall, hypotonia, pallor, and upward eye rolling. Consciousness is rapidly regained immediately following the event. *Convulsive syncope* describes the convulsive manifestations that result from syncope and is common form of syncope that leads to generalized hypertonia with tonic posturing and a series of myoclonic jerks predominantly involving the proximal upper extremities. Episodes of multifocal myoclonus, tonic posturing, or clonic jerking are common during syncope and have been reported to occur in normal individuals, with cardiogenic syncope, and with syncope during head-up tilt table tests [2]. While 45-90% [2-4] of syncopal episodes are associated with motor movements, they occur about 20 seconds after the loss of consciousness and last for seconds. These movements are typically briefer, less stereotyped, generalized, and without postictal confusion or lateral tongue laceration in contrast to epileptic seizures. Incontinence can occur with syncope as well as with seizures and represents a nonspecific relaxation of the urinary sphincter musculature and is not a specific sign of epileptic seizures. When syncope remains protracted, a hypoxic seizure may occur that on ictal EEG is in contrast to the background slow-wave prominence and voltage attenuation that occurs during convulsive syncope [4]. It is much more common to diagnose cardiovascular syncope as epilepsy rather than the other way around. Based upon historical information, a point system for scoring has been developed to help separate the two conditions using a standardized format [5]. Usually an adequate history in concert with cardiology evaluation with Holter monitoring, echocardiogram, and tilt-table testing should lead to the correct diagnosis. However, the reproduction of typical symptoms with tilt-table testing may be absent in approximately one third of patients with unexplained syncope, and in 30% of patients the cause is not identified [6]. Video-EEG may become necessary when combined neurologic and cardiac features exist such as PWE who have ictal bradycardia syndrome or when two different semiologies are re-

counted historically.

Distinguishing an epileptic seizure from syncope may be difficult, though history usually permits this distinction (*see* table). However, the patient is often alone during the loss of consciousness, witnesses may misinterpret events (especially with convulsive syncope), and patients may describe a prodromal malaise before seizures, challenging the clinician.

**Clinical Features That Distinguish Syncope from Seizures**

| Syncope | Seizure |
|---|---|
| Triggers present | Triggers rare |
| Sweating, nausea common | Déjà vu or ictal fear common |
| <20 seconds | 1–2 minutes |
| Brief movements (<15 seconds) | Sustained clonic movements |
| Pallor | Cyanosis |
| No postictal state | Postictal |
| Myalgias rare | Myalgias common |

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## SYNDROMES (EPILEPTIC)

Epilepsy does not consist of a single entity; it includes many different seizure types and seizure disorders. An epileptic syndrome consists of epilepsy characterized by a similar constellation of signs and symptoms. An epileptic syndrome is characterized by a cluster of signs and symptoms customarily occurring together, including type of seizure(s), etiology, anatomy, precipitating factors, age of onset, severity, chronicity, diurnal and circadian cycling, and sometimes prognosis (*see* Classification). While specifying epileptic syndromes provides a common scientific basis for diagnosis and treatment as well as research, the disadvantage includes not identifying the underlying mechanisms for the seizures, identifying those with multifactorial causes, and overlapping similar syndromes. In addition, it does not provide for the advances in molecular biologic approach to identify the genomics of the inherited forms of

epilepsy. Nevertheless, syndromic classification appears to identify some well-defined syndromes (e.g., JME) while not clearly distinguishing between others, such as extratemporal LRE (*see* table). For any given patient, identifying the epilepsy syndrome should help guide the selection of an appropriate treatment and assist in the determination of prognosis. More precise classification of syndromes will be possible as more is learned about the pathogenesis of the various forms of epilepsy. Proposals by the ILAE to classify epilepsy syndromes have taken a stepwise approach and included ictal semiology, seizure type (focal vs. generalized; *see* Seizures), epilepsy syndrome (symptomatic vs. idiopathic), etiology, and prognosis (*see* Classification).

**The Localization-Related and Generalized Epilepsy Syndromes**

| | |
|---|---|
| **Symptomatic localization–related** | **Idiopathic localization–related** |
| Temporal lobe epilepsy | Benign rolandic epilepsy |
| Frontal lobe epilepsy | Benign occipital epilepsy of childhood |
| Parietal lobe epilepsy | |
| Occipital lobe epilepsy | |
| **Idiopathic generalized** | **Symptomatic generalized** |
| Childhood absence epilepsy | West's syndrome (infantile spasms) |
| Juvenile absence epilepsy | Lennox-Gastaut syndrome |
| Juvenile myoclonic epilepsy | |
| Epilepsy with GTC seizures on awakening | |

## SYSTEMIC LUPUS ERYTHEMATOSUS

*See* Lupus.

# T

## TALAMPANEL

Talampanel is a potent R(-) stereoisomer that exerts selective noncompetitive AMPA-receptor antagonism. Though chemically in the benzodiazepine class, it does not exert any biologic activity at the GABAA receptor in animal models. Talampanel has been shown to be beneficial as adjunctive therapy in adults with partial-onset seizures [1]. Talampanel is well absorbed from the gut, is 65-85% protein bound, and has a T1/2 of 7 hours that may be affected by acetylation variability. It is metabolized by the cytochrome P450 system (CYP 3A4 pathway) and appears to possess interactions with other AEDs that include CBZ and VPA. Dose-related side effects include drowsiness, dizziness, ataxia, and headache. Doses of up to 75 mg tid have been used in clinical trials [1].

### Reference

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## TAURINE

The precise role of taurine as an amino acid that functions as an inhibitory CNS neurotransmitter in epileptogenesis has been uncertain. Microdialysis studies of both excitatory and inhibitory amino acid release associated with paroxysmal hippocampal activity have found significant increases in the hippocampus of epileptic patients, including increases in glutamate, aspartate, GABA, and taurine during seizures in human hippocampus [1]. Initial evidence for decreased taurine concentrations in the epileptogenic zone was responsible for its use as an adjunctive treatment for seizures. The application of taurine in experimental and human epilepsy started over 40 years ago, and it has been suggested to possess some mild anticonvulsant activity in both humans and experimental animal models. However, supplemental taurine administration has provided variable results in certain human epilepsies, and significant long-term benefit has not yet been validated.

### Reference

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## TAY-SACHS DISEASE

Tay-Sachs disease is an autosomal recessive disorder localized to chromosome 15 (15q23-q24) that causes a genetically mediated deficit of *N*-acetyl-beta-hexosaminidase activity. It has also been referred to as GM2 gangliosidosis due to the deposition of GM2 ganglioside in the neurons. These terms are preferable to the older pejorative term infantile amaurotic familial idiocy. Tay-Sachs disease is a lysosomal disorder or sphingolipidosis (*see also* Sphingolipidoses), which invariably includes seizures as a prominent feature of the disease. Tay-Sachs disease is found with increased incidence in the Ashkenazi Jewish people of Eastern or Central European descent. The onset is usually at age 4-7 months after initially normal development with subsequent loss of motor milestones and progressive cognitive, behavioral, and visual deterioration. A cherry-red macula is noted in >90% of patients, and visual evoked potential amplitude decreases during the course of the illness. From birth, there may be sound-induced clonic movements with a prolonged refractory phase, but without EEG correlate. Seizures supervene at about 1-2 years, become frequent, and are of variable types, including partial-onset seizures and atypical absence. Myoclonic jerks are common and are often startle-induced.

The EEG in patients with Tay-Sachs disease shows progressively abnormal, poorly reactive background activity with subsequent high-voltage delta and fast central spikes. External stimuli may be accompanied by generalized sharp- or spike-and-waves during myoclonic jerks or appear amid multifocal epileptiform discharges. The diagnosis can be made on clinical grounds, family history, and the demonstration of the enzymatic absence or deficiency of hexosaminidase A in cultures of fibroblasts.

## TELEMETRY

*See* Video-EEG.

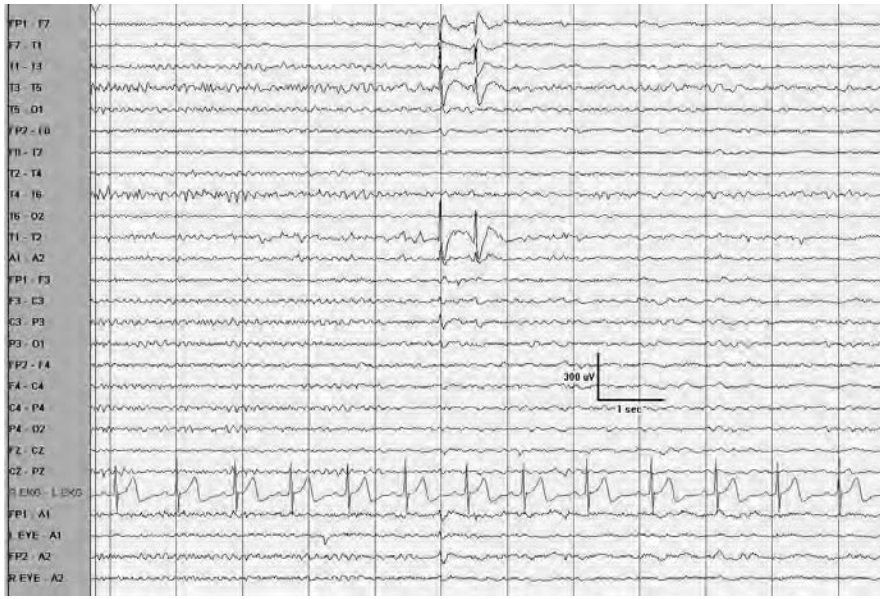
## TEMPORAL LOBE SEIZURES/EPILEPSY

Temporal lobe epilepsy (TLE) is the most common localization-related epilepsy in humans. Complex partial seizures are the most common form of expression and often originate from the mesial temporal structures. Mesial temporal lobe epilepsy is much more common than neocortical TLE. The predominant seizure types often differ, with simple partial and complex partial seizures more often associated with mesial TLE and parial-onset secondarily generalized seizures being prominent in neocortical TLE. Retrospective studies have noted that a large proportion of patients with TLE experienced an early injury in childhood [1]. The onset of mesial temporal lobe epilepsy is usu-

ally during early childhood. While a childhood history of complex febrile seizures often implicates mesial temporal sclerosis (MTS), other insults such as trauma or status epilepticus may act as the substrate for MTS, while the pathologic substrate is more varied in neocortical TLE. Afebrile seizures then reappear around 10-15 years of age and frequently become refractory to AEDs. The semiology of TLE is characterized by common clinical features. Simple partial seizures occur frequently with psychic auras (e.g., déjà vu), nausea or "butterflies," ictal fear, autonomic symptomatology (e.g., borborygmus, pallor, sweating, facial flushing, apnea, pupillary dilation) (*see also* Autonomic Seizures), gustatory, or olfactory auras in mesial TLE. Other symptoms including auditory, vertiginous, or aphasic auras may suggest neocortical origin. The presence of ictal speech often suggests nondominant TLE, while aphasia is seen with neocortical origin or propagation in TLE. A rising indescribable epigastric sensation is a common aura of mesial TLE. Complex partial seizures typically involve an aura and then a fixed stare, impairment of consciousness, and an arrest of ongoing activities (*see also* Complex Partial Seizures). Simple and more complex automatisms such as swallowing, chewing, humming, or limb movements and even complex behaviors may be seen, including ambulation and performing motor tasks without intact consciousness. Seizures typically last about a minute, and postictal confusion with amnesia is usual, but variable. Semiology may have useful localizing or lateralizing value when accurate historical description is provided [3]. Awareness may be impaired, especially in temporal lobe epilepsy, with patients having difficulty identifying their seizures even after they have occurred in their habitual environment [2]. This may be more prominent with left TLE or patients with underlying bitemporal lesions.

The interictal EEG is often normal, with the initial recording in 29-55%. The EEG frequently reveals unilateral temporal IEDs. Spikes or sharp waves appear maximal over the anterior temporal electrodes in up to 90% with mesial TLE. Bilateral IEDs are commonly seen during prolonged recording and do not imply two independent generators that produce clinically distinct seizure semiologies. Ictal EEG during mesial temporal lobe complex partial seizures characteristically demonstrates abrupt regional, rhythmic, ictal sharply contoured theta discharges that regionalize or at least lateralize to the temporal derivations. Simple partial seizures may have no well-defined correlate despite ictal recording, and secondarily generalized seizures may be obscured by myogenic artifact. Neocortical seizures are often more likely to be poorly localized, though they may lateralize with an irregular delta semi-rhythmic pattern that often becomes obscured as generalization supercedes.

Temporal lobe seizures are separated into mesial (limbic) and neocortical onset. Mesial temporal lobe seizures involve the hippocampus, amygdala, parahippocampal gyrus, and related mesial structures. Hippocampal onset accounts for at least 80% of temporal lobe seizures [5]. Mesial temporal sclerosis may be readily visualized on qualitative high-resolution brain MRI. Most frequently, the etiology in mesial TLE is MTS (hippocampal sclerosis), though less frequently gliomas, angiomas, cavernomas, or traumatic or infectious lesions may occur.




EEG in a patient with mesial temporal lobe epilepsy demonstrating a couplet of spike-and-slow waves in the sixth second. (From Tatum WO, Husain AM, Benbadis SR, Kaplan PW. Handbook of EEG Interpretation. New York: Demos Medical Publishing, 2008:76.)

Neocortical temporal lobe seizures result from epileptogenic lesions in the lateral temporal cortex. Auras are less specific in neocortical TLE, and complex partial seizures are less characteristic than are seizures of mesial temporal origin. The age of onset with neocortical TLE is often later in life and rarely with a history of febrile seizures [5]. While the motor component is often more prominent in neocortical TLE, the ratio of motor components in children < 6 years of age may show a greater degree of asymmetric clonic or tonic posturing that progressively declines with age in mesial TLE [6]. Auras may involve language ("aphasic seizures") when seizures originate from the dominant hemisphere. Other auras, including auditory illusions or hallucinations or a disturbance of visual perception, are encountered less frequently. Seizures evolve to complex partial or secondarily generalized seizures when the discharge spreads to and beyond mesial temporal structures.

Temporal lobe seizures are particularly amenable to surgical therapy, provided they originate unilaterally [5]. While most often an acquired form of epilepsy, genetic temporal lobe epilepsies have also been described. Neurocognitive deterioration and progression of disabilities with TLE have been well noted [6].

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## THERMOCOAGULATION

Stereotactic radiofrequency thermocoagulation produces a heat-generated lesion in target areas of the brain in an effort to ablate the structures from generating uncontrolled seizures. Radiofrequency ablation using thermocoagulation has been best studied in the treatment of movement disorders, though patients with gelastic seizures associated with hypothalamic hamartomas have also been reported [1]. To perform the procedure, a themocoagulating probe is inserted into the target sites of the brain via a burr hole that has been placed under local anesthesia. The probe initiates a heat that is operator controlled and typically heated to 80°C (176°F) for 1 minute to create the lesion. Lower seizure-free outcomes have been seen in the limited number of patients that have undergone the procedure, and repeated procedures have been required. Primary problems have resulted in complications as a consequence of failing to restrict the ablation to the targeted sites.

### Reference

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## THETA ACTIVITY

This EEG frequency range of 4-8 Hz is called the theta band (*see* EEG). Frontal, fronto-central, and midline central 5-6 Hz activity is normal in young adults, especially at the onset of drowsiness. High-voltage rhythmic theta activity can also be seen during transition periods between wakefulness and drowsiness in children. Waking predominance of theta activity is abnormal in adults and is indicative of a nonspecific diffuse dysfunction.

## TIAGABINE (GABATRIL®)

Tiagabine is a designer drug that was designed to inhibit the reuptake of GABA into the central nervous system augmenting seizure inhibition. It is in-

dicated as adjunctive therapy in patients with refractory partial-onset seizures [1], though it has been effective in montherapy as well [2]. The bioavailability of tiagabine is 89% and protein binding 96%, with rapid absorption when taken in the fed state. Tiagabine undergoes linear hepatic metabolism by the P450 enzyme system. The half-life is 4-8 hours, which is reduced to 2-3 hours when given with EIAEDs. Tiagabine does not affect the serum concentration of concomitantly administered AEDs. Side effects are dizziness, tremor, abnormal thinking, nervousness, and abdominal pain. Additional side effects include nonconvulsive spike-wave stupor, emotional lability, vomiting, tiredness, headache, and psychosis. The initial starting dose is 4 mg/wk increased by 4-8 mg/wk until reaching 32-64 mg/d tid dosing.

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## TICS

Motor and vocal tics are commonly associated with Gilles de la Tourette syndrome but are nonepileptic in origin and do not confer an increased risk of epilepsy. Single case reports of exacerbation of motor and vocal tics have been reported after temporal lobectomy [1].

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## TOLERANCE

The concept of drug tolerance involves the diminished pharmacologic effectiveness of a drug when used at a constant dose. The clinical manifestations of AED tolerance are decreased effectiveness of a drug with the reappearance or increased frequency of seizures. There may be tolerance to the therapeutic effect of the drug, or to the side effects, or both. Therapeutic tolerance is probably quite rare, affecting only a small number of patients. The phenomenon may take place over a prolonged period of time, varying from several days to months. A transient reappearance of seizures at a particular dose may not necessarily represent tolerance. There may also be a decrease in the undesirable side effects experienced early in the course of treatment.

There are several types of tolerance: tolerance to pharmacokinetic, pharmacodynamic, and clinical features of treatment. Pharmacokinetic tolerance is

seen with some AEDs such as CBZ, which induces its own metabolism by increasing hepatic microsomal enzyme activity leading to a shortened half-life and lower blood levels. This type of tolerance from autoinduction results in a reduction in serum concentrations (and possibly clinical efficacy) but is limited to the first 1-2 months of treatment. Pharmacodynamic tolerance is reflected by a rapid decrease in drug effectiveness and is often seen with maintenance doses of acetazolamide and the benzodiazepines. It occurs in 50-75% of cases during the first 6 months of treatment [1]. Rarely, it may be seen with other types of maintenance AEDs, especially in those with medically intractable epilepsy, and may be referred to as the "honeymoon period" of efficacy. Clinical tolerance to undesirable side effects may occur early in the course of treatment and is much more common, may follow a variable time course, and may occur with some side effects and not others (e.g., sedation with phenobarbital) over time. The metabolic mechanisms involved in functional tolerance are hypothetical and complex and may only be partly applicable to humans.

### Reference

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## TONIC SEIZURES

Tonic seizures are characterized by a sustained muscular contraction and have been noted in conjunction with absence seizures associated with IGE, LRE (*tonic postural* or focal motor seizures), and most commonly SGE (tonic seizures). Tonic seizures are seen predominantly in children in the context of the SGEs, often in addition to absence, myoclonic, and atypical absence seizures. Tonic seizures are characteristic of Lennox-Gastaut syndrome, appearing in 74-90% of patients [1].Tonic seizures may also be seen in adults during generalized (tonic) convulsive status epilepticus. Clinical evolution can be sudden or gradual over several seconds and be manifest as *tonic axial, tonic axorhizomelic*, and *global tonic* seizures in increasing intensity [1]. Tonic seizures involve the face, trunk, and the limbs, with an average duration of 5-20 seconds most common during stages 1 and 2 of NREM sleep. If a tonic seizure ends with a few clonic jerks, it may be difficult to distinguish from a tonic-clonic seizure. Intermediate forms may present with asymmetric distribution, hemitonic seizures, or seizures with subtle motor signs. Falls, often with injuries, are frequent, and tonic seizures are grouped as drop attacks with atonic seizures. However, tonic seizures have a rigid muscular extension, whereas atonic seizures manifest as an abrupt loss of muscle tone-the difference has been referred to as "a falling tree" as opposed to a "shot duck" to separate the two. Tonic (and tonic-clonic) seizures may be predisposed in general to produce scars on the back of the head, while atonic seizures produce them on the front of the head because of the respective patterns of falling.

Tonic seizures may be associated with alteration in the level of consciousness and autonomic disturbances, but unconsciousness may not be obvious with tonic seizures that are very brief. Some tonic seizures may be quite brief and resemble infantile spasm.

The interictal EEG characteristics depend upon the underlying epilepsy syndrome. In most patients with encephalopathic generalized epilepsy, a diffusely slow background with multifocal spikes and sharp waves is seen. Slow spike-and-waves associated with the Lennox-Gastaut syndrome and tonic seizures may not appear until the onset of SGE is well established. The ictal correlates of tonic seizures typically reveal an initial attenuation of the background associated with desynchronization prior to bilateral 10-25 Hz repetitive spikes of increasing amplitude.

Phenytoin has been effective for tonic seizures and tonic status epilepticus. Valproate is an alternative, with an intravenous formulation that is available for rapid loading. Lamotrigine, topiramate, zonisamide, and levetiracetam are evolving as broad-spectrum AEDs for the treatment of patients with mixed seizure types that include tonic seizures. Corpus callostomy is an effective treatment for most patients with drop attacks caused by tonic seizures, though vagus nerve stimulation is a less invasive adjunctive treatment that has been favored as an initial approach when AEDs are ineffective [2].

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## TONIC-CLONIC SEIZURE (GRAND MAL SEIZURE)

The generalized tonic-clonic (GTC) seizure is the most feared of all seizures and often the representative "seizure" type to the lay population adding to stigma (*see* Stigma). The GTC seizure is characterized by an evolution through three different phases. Tonic-clonic seizures may be seen in either IGEs or SGEs. The availability of the new broad-spectrum AEDs has become important in the treatment of patients with GTC when difficulty differentiating seizures that are primarily generalized from those that are secondarily generalized is encountered. In PWE and partial-onset secondarily generalized seizures, increasing use of resective epilepsy surgery makes the distinction paramount as the onset of a GTC seizure may be so rapid that the initial partial phase is not readily detectable [1]. The tonic phase typically lasts 10-20 seconds. Associated with sudden tonic stiffening, there is associated loss of consciousness, and intial flexion and then extension of the torso with forward flexion of the head, elevation of the eyebrows, open eyes roll backwards within

the orbits, the mouth opens, and there is elevation of the shoulders, with axial tonic stiffening and flexion of the forearms, and closure of the mouth (with possible postero-lateral tongue/cheek biting). As the thoracic and abdominal muscles contract, a sustained expiratory ictal cry ("the epileptic cry") from expelling air against a closed glottis during limb extension will result. There may be associated autonomic features including tachycardia, hypertension, mydriasis, flushing, or cyanosis (due to apnea) as well as sweating, sialorrhea, and bronchial hypersecretion. The second phase is the clonic phase, which lasts approximately 30 seconds. The tonic phase gives way to rhythmic one-way contractions of the limbs and facial muscles (again with possible tongue/cheek biting) progressively slowing in a decrescendo fashion to approximately one or two per second before giving rise to the postictal state.

The third and last phase is the postictal phase, which begins after the last jerk. There is a brief tonic phase with trismus, urinary incontinence, and deep, labored breathing. With resolution of the cyanosis, the patient remains immobile and hypotonic with variable durations and intensities of postictal unconsciousness and unresposiveness. There is gradual lightening of the postictal encephalopathy followed by postictal confusion, lethargy, and sleepiness during which the patient may be confused, incoherent, and amnestic. Tongue biting and urinary incontinence do not occur with every seizure.

On ictal EEG recordings, the tonic phase is accompanied by an electrodecremental EEG pattern lasting 1-3 seconds followed by rapid rhythmic activity at approximately 20 Hz slowing down to 10 Hz. This rapid repetitive discharge progressively becomes interspersed with slow waves and the polyspike-and-slow wave discharges of the clonic phase. The end of the seizure is characterized by suppression and slower frequencies in the theta and delta range that increase in frequency and decrease in amplitude. Generalized tonic-clonic seizures may be associated with impaired consciousness, asymmetric motor manifestations, or a prodromal brief malaise or visual blurring at seizure onset. The treatment of GTC seizures is guided by the mechanism of onset (*see* Treatment).

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## TOPIRAMATE (TOPAMAX®)

Topiramate is a sulfamated monosaccharide that is structurally distinct from other AEDs with multiple mechanisms of action, including kainite/AMPA receptor and sodium channel blockade, enhancement of GABAA, and weak carbonic anhydrase inhibition [1]. The compound 2,3:4,5-di-O-isopropylidene-beta-D-fructopyranose sulfamate is approved for adjunctive therapy for partial and generalized seizures in adults and pediatric patients 2 years of age and

older [2]. Topiramate is also effective as adjunctive treatment in patients with the Lennox-Gastaut syndrome and infantile spasms. Initial randomized controlled trials demonstrated efficacy in patients with refractory localization-related epilepsy with and without secondary generalized seizures [1]. Topiramate is 13-17% protein-bound, exhibits linear kinetics, and is not extensively metabolized by hepatic metabolism acting as a weak enzyme-inducer of the cytochrome P450 enzyme system. Primary metabolism mediated by hepatic hydroxylation, hydrolyis, and glucuronidation. No clinically active metabolites have been identified, and drug elimination is via renal excretion with up to 50-80% appearing unchanged in the urine. Clearance is reduced 40-50% in patients with moderate or severe renal impairment. Plasma levels of >9.9 g/mL may provide better seizures control [2]. The more common side effects include somnolence, fatigue, nausea, anorexia and weight loss, paresthesias, psychomotor slowing and confusion, and dizziness [3]. Other side effects have included nephrolithiasis, glaucoma, and metabolic acidosis, but no clinically significant changes in hematologic or hepatic function have been reported during clinical trials [3]. Initial randomized trials suggested that 200-400 mg/d as adjunctive therapy was an effective dose for patients with refractory epilepsy, though subsequent trials have shown that many patients will respond to doses of <200 mg/d.

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## TOXICITY

Toxicity may occur during the course of management with AEDs due to intake of too high a dose, an unusually slow metabolism of the drug, medication interaction, or intercurrent illness. Toxic effects appear during the acute, subacute, or chronic phase of treatment (*see also* Antiepileptic Drugs; Treatment) and may be due to overtreatment that may lead to toxicity from either polytherapy or high-dose monotherapy. In the past, polytherapy was the standard of treatment (i.e., phenytoin and phenobarbital). Many PWE receive higher drug loads and are at high risk of developing side effects during the acute or chronic course of therapy [1]. The effectiveness of the AED (a measure of efficacy and tolerability) has been found to benefit fewer than one third

of patients by the addition of a second AED [2], though some combination such as PB + PHT, CBZ + VPA, and VPA + LTG have been described with synergistic efficacy [3]. The use of three or more AEDs is discouraged given the difficulty of identifying benefits and tolerability consequences that may arise during treatment. Monotherapy is now utilized in 70% of cases in both adults and children [1,3,4], and is recommended by experts as the initial approach to treatment (*see* Treatment). However, even with monotherapy, "toxic" side effects may account for withdrawal from the first AED selected [1,2], and a differential effect may be seen in subpopulatons such as the elderly with a greater tendency to toxicity, especially with the older AEDs.

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## TRANSIENT GLOBAL AMNESIA

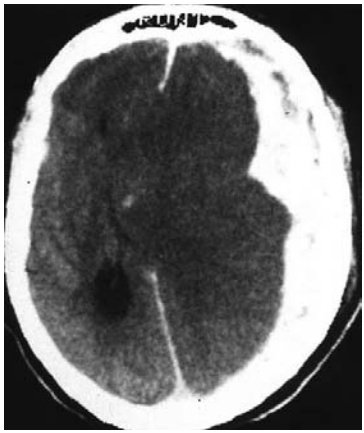
Transient global amnesia is a condition that mimics a complex partial seizure. It is usually seen in patients over the age of 50 and is characterized by confusion and loss of memory for periods ranging from minutes to hours. Attacks usually do not recur, though they may in up to 25%. During the event, the patient appears alert, has normal speech, and may carry out behavioral tasks that resemble complex automatisms such as driving, though they remain amnestic for the activities or conversations during the involved period. Recovery is gradual and usually complete without sequela. Recurrence is not common but may occur. Pathophsyiologies have included purported causes that include TIA, migraine, and complex partial seizures, though no convincing epileptic cause for TGA has proven to be consistently identifiable.

## TRANSIENT PAROXYSMAL DYSTONIA IN INFANCY

This disorder consists of axial contraction and opisthotonos for several minutes without impairment of consciousness. This movment mimics epileptic seizures with a frequency that varies from once a day to once a month, though during the episode the EEG is normal. Seizures appear between the first and fifth month of age, may remit spontaneously or may become progressively worse between the sixth and twenty-second months. The differential diagnosis includes

infantile spasms, tonic seizures, paroxysmal nocturnal dystonia, and "dystonia" due to gastroesophageal spasm.

## TRAUMATIC BRAIN INJURY



Roughly 500,000 traumatic brain injuries (TBIs) occur yearly. Up to 30% of those with severe head injury have posttraumatic epilepsy, while up to 51% of survivors of military-related penetrating head injury develop epilepsy. About half of patients who develop posttraumatic epilepsy continue to have persistent seizures even 15 years postinjury with or without anticonvulsant therapy (*see* Posttraumatic Epilepsy).

Large acute left subdural hematoma in a patient with GTC seizures observed following a motor vehicle accident.

## TREATMENT

The goal of treatment for epilepsy is to decrease seizures and improve the quality of life for the patient. Treatment may take several forms, including AEDs, surgical intervention, vagal nerve stimulation, and rectification of provoking factors for seizures (e.g., alcohol abuse). There are also dietary therapies (*see* Ketogenic Diet) and psychologically based treatments (*see* Biofeedback) for epilepsy. However, therapy with AEDs is the cornerstone to treatment.

The AEDs suppress or decrease the frequency of seizures and treat the seizures as a symptom and not the underlying cause. The use of AEDs leads to remission in about 65% of new-onset epilepsies [1]. Some epilepsy syndromes remit with time; therefore, AED treatment is not implicitly life-long. Moreover, the diagnosis of epilepsy should be clearly established since AEDs may not benefit epilepsy mimics. Consideration should be given to the risk-benefit ratio associated with treating a single seizure in a patient with a normal EEG (*see* Single Seizure). Treatment is usually initiated in patients with more than one spontaneous seizure, though AED treatment is often recommended following a single seizure where the recurrence risk is high (structural lesion on MRI, IEDs on EEG, abnormal neurologic examination, seizure characteristics such as status epilepticus, or those with focal seizures and Todd's phenomenon). Therapy is best initiated with monotherapy unless mitigating circumstances such as ongoing seizures, status epilepticus, multiple seizure types, or very frequent seizures prompt dual therapy early on in the course of treatment.

Valproate for generalized epilepsies and lamotrigine- or carbamazepine-related AEDs for the focal epilepsies may be efficacious therapies with individual selection based upon individual characteristics (e.g., female, elderly) [2-6]. Initial therapy is best effected with monotherapy-for example, ethosuximide for absence seizures, valproate for the generalized epilepsies, and lamotrigine or carbamazepine for localization-related epilepsies [5-7]. Special populations may benefit from particular agents such as women with epilepsy contemplating pregnancy (lamotrigine or carbamazepine) or the elderly (lamotrigine, levetiracetam, or gabapentin). Individual patient characteristics such as comorbid obesity (topiramate or zonisamide) or other neurologic conditions such as migraine (topiramate) or those with peripheral neuropathy (gabapentin or pregabalin) should also be considered in AED selection. Monotherapy provides the most favorable ratio of efficacy to side effects and is recommended to be used for the first and second trial of AED therapy by most experts [7]. A small number may gain additional benefit from AED polytherapy [1].

For AED treatment, the mantra is "start low (dose) and go slow," titrating the dose up gradually to achieve a target dose over a few weeks of treatment. Gradual titration minimizes acute side effects upon initiation of treatment. This is true not only with respect to tolerability but also with respect to safety with some agents such as lamotrigine, which if titrated too rapidly is more likely to produce an allergic skin reaction. With topiramate and zonisamide, there may be improved cognitive and sedative tolerance, requiring gradual implementation over weeks to months. There is occasionally the need to implement an AED treatment over a short time, and AEDs such as phenytoin, oxcarbazepine, gabapentin, and levetiracetam may be introduced at a rapid loading dose when fast AED therapy is required. With extended-release preparations, the ability to minimize dosing frequeny to daily or twice-daily frequencies is possible to maximize adherence (*see* Adherence; Compliance). One can selectively measure serum AED levels to assess compliance, toxicity, and efficacy, though AED levels should be compared at trough levels to ensure proper comparison, especially for AEDs with short half-lives that may fluctuate by more than 50%.

The physician should encourage adherence by regularly scheduled outpatient visits. With continued seizures, verify that the patient is correctly following the prescription, confirm that the diagnosis of epilepsy is correct, and gradually increase the epilepsy-appropriate AED to seizures freedom or clinical toxicity irrespective of serum concentration. With uncontrolled seizures, add a second AED, gradually taper the first aiming for a successive monotherapy trail. Other broad-spectrum AEDs include valproate, lamotrigine, levetiracetam, topiramate, or zonisamide for generalized or unclassified seizures [6]. For focal seizures, lamotrigine, carbamazepine, oxcarbazepine, topiramate, gabapentin or pregabalin may be useful [5,7]. If the second trial of monotherapy fails, after each medication has been pushed to the maximum tolerated dose, the use of two concomitant first-line AEDs may be considered [5]. In the case of myoclonic epilepsies, levetiracetam, lamotrigine, topiramate, zon-

isamide, or a benzodiazepine such as clonazepam may be considered. There are few head-to-head trials to determine the optimal AED for particular seizure types or epilepsy syndromes. AED management must be tailored to the individual. Only 10-20% of patients failing monotherapy can be adequately controlled by polypharmacy [1].

If seizure control has not been reached after at least two to three AEDs or after 6-12 months, patients are considererd to be medically intractable to AED treatment (ensuring adequate adherence), and considering resective epilepsy surgery is a standard of care. For those who are not candidates for resection, vagal nerve stimulation may help provide further seizure reduction as well as avoid side effects associated with AEDs (sedation, allergy).

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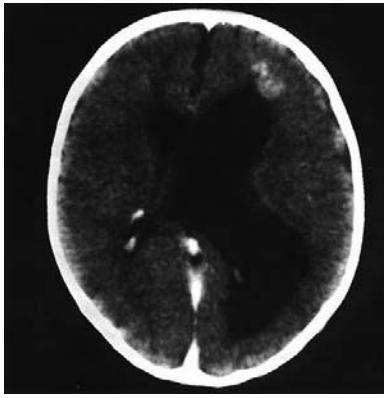
## TUBEROUS SCLEROSIS COMPLEX (BOURNEVILLE'S DISEASE)

Tuberous sclerosis complex (TSC), also known as Bourneville's disease, is one of the common, multisystem, autosomal dominant, neurocutaneous syndromes. TSC presents frequently with infantile spasm or seizures when the congential hamartomas affect the CNS in addition to other organ systems. Seizures may appear before the onset of cutaneous abnormalities and are frequently intractable to AEDs. Variable expression of the clinical features may be seen in



Large left periventricular frontal tuber on CT brain scan (to reveal calcified tubers) in a patient with TS. Note the "trapped" left lateral ventricle from an obstructing tuber below.

TS and include cutaneous manifestations such as adenoma sebaceum that involves the malar distribution on the face, in addition to ash-leaf spots that consist of areas of hypopigmentation on the trunk and the extremities, peri-ungual fibromas, and café-au-lait spots. A variable degree of mental retardation, autism, or both are associated with TSC in more than 50% of patients, though one third may possess normal or borderline mentation.

TSC is usually associated with severe epilepsy, often presenting as infantile spasms within the first year of life, and the clinical picture may evolve in childhood to continue as an encephalopathic generalized epilepsy such as LGS. Slowly developing forms of the disease may present with less severe seizures beginning in late childhood or adolescence, with complex partial and secondarily generalized tonic-clonic seizures predominating the clinical picture. Early onset of seizures and the severity of epilepsy correlate with greater degree of mental retardation.

The EEG in tuberous sclerosis is abnormal in most cases and may show a diffusely slow, poorly organized or asymmetry of background or homologous head regions. Focal or multifocal interictal epileptiform discharges may occur depending upon the distribution of the tubers. Still, even in patients without prominent CNS manifestations the EEG may appear normal. Imaging techniques such as CT head scan and MRI scans are diagnostic in many cases, with calcified tubers being readily identified by CT brain scans (*see* figure). Tuber calcification and cortical atrophy are common findings, though cortical atrophy and ventricular dilation are more frequently seen with severe epilepsy and with mental retardation. There may not be a clear topographic correlation between tubers and the active epileptogenic zone. TSC results from mutations in either TSC1 (hamartin on chromosome 9q34) or TSC2 (tuberin on chromosome 16p13) [1]. AED therapy is seizure-specific (*see* Treatment), though vigabatrin has been found to be particularly effective for focal seizures and infantile spasms associated with TS. Resective epilepsy surgery should be considered when when refractory seizures are encountered, and even bilateral or multilobar resections may be successful [2].

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# TUMORS OF THE BRAIN

Epilepsy is a common occurrence in patients with brain tumors and cancer. Seizures are a major concern in patients with brain tumors, with seizures the likely presenting symptom in the majority of low-grade tumors and a major source of morbidity and reduced quality of life [1]. Pathology plays an important role in determining which patients have seizures. Tumor histology influences seizure frequency, with a seizure incidence of 80-90% for oligodendrogliomas, 60-75% for astrocytomas, 55% for meningiomas, 55% for metastases, and 35-40% for malignant gliomas. Low-grade gliomas, gangliogliomas, and dysembryoplastic neuroepithelial tumors (*see* Figure 1) typically present with seizues, with many continuing to be uncontrolled with AEDs and requiring respective epilepsy surgery. High-grade lesions such as anaplastic astrocytomas, glioblastoma multiforme, or metastatic lesions are associated with seizures as a frequent complication of either the lesion or antineoplastic therapy. High-grade gliomas that arise in the white matter and produce seizures by their influence upon neurons that are infiltrated, compressed, or involved because of their growth are more likely to present with other symptoms such as headache or focal neurologic deficits.

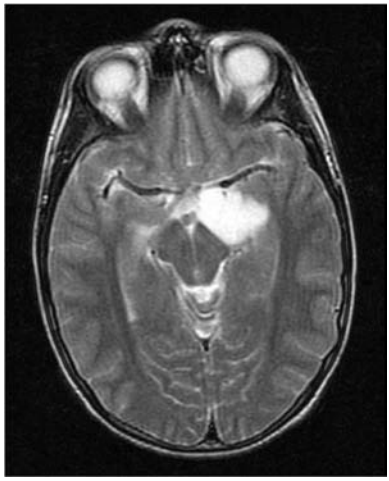

Figure 1 T2 transverse brain MRI demonstrating a dysembryonal neuroepithelial tumor in a 29-year-old male with a 4-year history of medically intractable localization-related epilepsy.

Many seizures recur and represent medically intractable epilepsy that is a remedial epilepsy with lesionectomy. Others may occur within the context of a longstanding medically refractory epilepsy or become evident after resective epilepsy surgery or following treatment with radiation and chemotherapy (*see* Figure 2). Tumors may present in patients with normal neurologic examinations and as a single seizure or as status epilepticus. CT head scan or MRI is readily available for most patients with seizures to facilitate early diagnosis [2]. Although only 10-15% of adult-onset cases of epilepsy are caused by brain tumors, 30-50% of patients with supratentorial tumors have epilepsy. The incidence of an underlying neoplasm varies according to age, and neoplasms are more common with aging. Tumor-associated seizures may be partial seizures or secondarily generalized. The semiology of the seizure may suggest the brain site of involvement. In addition, location is important in determining which patients have seizures. Frequently seizures result from supratentorial tumors in the primary motor cortex or somatosensory cortex, especially in the peri-rolandic areas. Thereafter, seizures arising

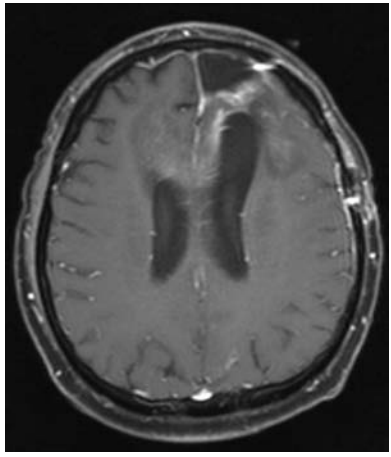

Figure 2 Postradiation, postresection, contrast-enhanced brain MRI of a "butterfly glioma" in a 36-year-old with secondary GTC seizures postoperatively.

from the frontal lobe and temporal lobe are the next most likely regions to be involved [1].

Treatment is indicated with AEDs unless a toxic-metabolic or systemic cause is able to be demonstrated to provoke the seizures. In contrast to those without brain tumors that have a recurrence risk of about 25%, those with brain tumors nearly always recur and imply treatment after a single seizure. So far, seizure prevention has thus far proven ineffective with phenytoin, phenobarbital, and valproate, while creating adverse events in nearly one quarter of patients treated [3]. Questions still remain with regard to the potential for newer AEDs with neuroprotective qualities to be effective, responses from subgroups of patients with tumors, as well as other alternative therapies including antioxidants to prevent the development of a hyperexcitable neuronal circuitry that underlies seizures and epilepsy. At this time "prophylactic" AEDs are not routinely recommended for brain tumor patients, and if used perioperatively, should be tapered off at convalescence following the first postoperative week [3].

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# U

## UNCINATE SEIZURES

Uncinate fits is an old term used to describe partial seizures that begin as an olfactory aura. These seizures have been correlated to involve neocortex in the anteromesial part of the temporal lobe or in the orbitofrontal region [1]. The olfactory bulb within the orbitofrontal cortex and the mesial temporal cortex are linked by the uncinate bundle, giving rise to the name. The character of these olfactory auras is an unpleasant quality often described as rotten smell, burning or electrical smell, solvents , sulfur smells, or decomposing tissue. While olfactory auras have received attention as a common aura, they are in fact relatively rare in isolation.

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## UNRESPONSIVENESS

Unresponsiveness is the inability to respond to an external stimulus. Responsiveness is tested during the seizure. The lack of response to requests to repeat and recall a code word given during a seizure after it has ended demonstrates impaired responsiveness during the seizure as well as impaired consciousness. Often visual, auditory, and tactile abilities or response to verbal command is assessed, though impaired comprehension, consciousness, cognition, or motor initiation may limit one's ability [1]. Preserved responsiveness during complex partial seizures has been demonstrated when the nondominant temporal lobe is involved [2].

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## UNVERRICHT-LUNDBORG DISEASE

Unverricht-Lundborg disease is the prototype of the progressive myoclonus epilepsies and was first described in 1891. The incidence is high around the

Baltic Sea and Mediterranean regions as the disease affects people from Estonia, Finland, and southeast Sweden. Hence, Unverricht-Lundborg has come to be known as Baltic myoclonus. Transmission is by an autosomal recessive inheritance with age of onset between 6 and 14 years. This PME is characterized by spontaneous and stimulus-sensitive myoclonic jerks. The disease ultimately progresses and begins to interfere with speech, swallowing, and gait. Nearly continuous myoclonus and generalized tonic-clonic seizures occur with a myoclonic "cascade" prior to seizures. Slow deterioration occurs with dementia developing after 10-20 years in association with signs of cerebellar dysfunction. A gene mutation involving the cystatic B gene (CSTB or EPM1) on chromosome 21q22.3 has been isolated, though the genotype-phenotype correlation is less well clarified [1]. Nevertheless, a knockout model in mice has demonstrated the potential neuroprotective effect of cystatin B [1]. EEG may reveal a diffusely slow background and generalized spike- and polyspike-and-slow waves that decrease in sleep, unlike the IGEs. Pathologically, widespread degenerative changes are found in the cerebrum and in the cerebellum without storage material as in Lafora body disease.

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## UREMIA

Cellular functions may be disordered in uremia, and seizures may occur in up to one fourth of uremic patients [1]. Focal or generalized seizures may occur in addition to nonepileptic myoclonus, which may be confused with epileptic seizures. The pharmacokinetics of AED therapy are altered by uremia with higher free fractions of protein-bound AEDs, increased volumes of distribution, and hypoproteinemia requiring individualized therapy. In association with renal insufficiency, some AEDs such as gabapentin, levetiracetam, and pregabalin require dose reductions based upon creatinine clearance reduction because of decreased AED elimination. Highly protein-bound AEDs such as PHT may demonstrate a sevenfold difference in free fraction availability in patients with uremia when compared to controls and thus may be a more reliable means of assessing serum concentrations for efficacy or toxicity. During hemodialysis for uremia, AED clearance may be affected, with lower protein-bound AEDs cleared more thoroughly. Replacement with postdialysis supplementation may be required

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# V

## VACCINES

Vaccines, particularly for pertussis, has been implicated as a direct cause of an encephalopathy, refractory epilepsy, and cognitive and intellectual impairment. Smallpox (now eradicated) vaccines may cause encephalitis and epilepsy, and other vaccines have also been incriminated. More recently, public concern has led to a marked decrease in the use of the pertussis vaccine with significant recurrence of the infection. Large-scale studies of this issue have produced conflicting results, although the recent consensus is that the risk of vaccine-induced encephalopathy and/or epilepsy, if it exists at all, is extremely low. There is little scientific evidence supporting a causative role of pertussis vaccines in epilepsy. The risk of encephalopathy after pertussis infection is 0-3 cases per million vaccinations [1]. The risk of a febrile seizure is 1 per 19,496 vaccinations, and risk of an afebrile seizure is 1 per 76,133 vaccinations [1]. A difficulty in interpreting the role of vaccinations in the appearance of certain epilepsies is the age-dependent presentation of predestined epilepsy syndromes (febrile convulsions, West syndrome, etc.), which may coincide with a period of obligatory childhood vaccinations. Additionally, fever stemming from vaccinations may provoke benign febrile seizures. Postinfectious encephalitis and encephalopathy may cause seizures and epilepsy, and therefore vaccinations against these diseases may provide greater protection against these causes of epilepsy. Alleged vaccine encephalopathy could in fact be a genetically determined epileptic encephalopathy that arose de novo and could have mutations in the neuronal sodium channel alpha1 subunit gene (SCN1A) because of a clinical resemblance to severe myoclonic epilepsy of infancy (SMEI), for which such mutations have been identified [2]. Similar to vaccines, the risk of encephalitis following an AED-induced immunosuppression is rare [3]. There are no contraindications for vaccinations against diphtheria, poliomyelitis, tetanus, whooping cough, or tuberculosis. Theoretically, vaccination against mumps is contraindicated in PWE.

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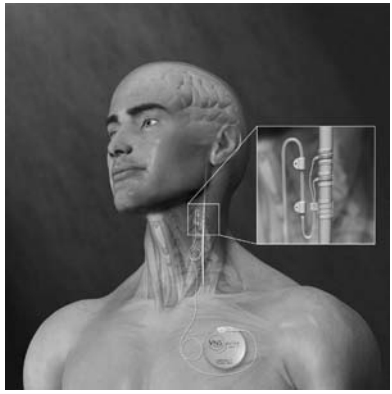
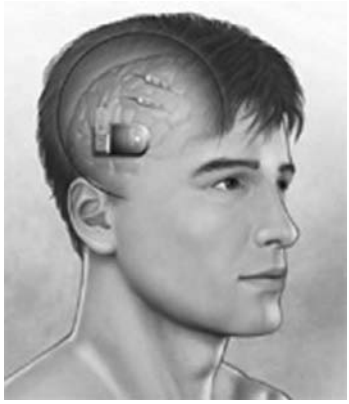
# VAGUS NERVE STIMULATION

Vagus nerve stimulation (VNS) was approved for use in epilepsy in 1997 as the first device for adjunctive treatment of refractory partial-onset seizures in patients over 12 years of age. VNS is comprised of a battery-powered electrical pulse generator ("pacemaker") with a bipolar lead that is subcutaneously implanted in left upper chest with a lead conducting intermittent impulses to the left vagus nerve at programmed settings governed by an external programming wand and a Windows-based proprietary program for adjustment. A hand-held magnet is available for on-demand stimulation as an additional means of device activation. The mechanism has been postulated to involve the central projections of the VNS with fibers terminating in the nucleus of the tractus solitarius with additional brain stem connections in the thalamus, amygdala, hypothalamus, and cortical radiations [1]. Two pivotal trials demonstrated efficacy (EO3 and EO5) over 3-4 months of treatment with responder rates of 31 and 23.4%, respectively [2]. Rarely have patients become seizure-free with VNS. Longer-range studies have demonstrated improved efficacy over the initial years of treatment in contrast to the decline experienced with AEDs [3]. Specific groups of patients including children [4], generalized epilepsy, and the elderly have also demonstrated benefit, suggesting a broad spectrum of activity. The benefits of VNS have included the potential for AED reduction [5], an absence of drug interactions, absence of systemic side effects, and improved quality of life and feeling of empowerment. The disadvantages include negligible likelihood of seizure freedom, the costs of a surgical (outpatient) procedure, the need for repeat generator replacement, and difficulty with body MRI. A variety of parameter settings, including the current intensity, pulse frequency, and duration in concert with duty cycles reflecting time on and off for the stimulation, have been regulated by suggested protocols [6]. VNS has initiated interest in neurostimulation, prompting further research into the potential for deep brain stimulation and direct stimulation techniques (i.e., neuropace). (See figure next page.)



VNS depicted in a model to demonstrate the approximate placement of the VNS. Note the generator in the left subclavicular fossa with electrodes placed around the left vagus nerve via a tunneled lead from chest to neck. (Courtesy of Cyberonics.)



The neuropace system demonstrating intracranial electrodes applied to the dysfunctional cortical surface to detect and deliver direct neurostimulation to the underlying brain. (Courtesy Neuropace.)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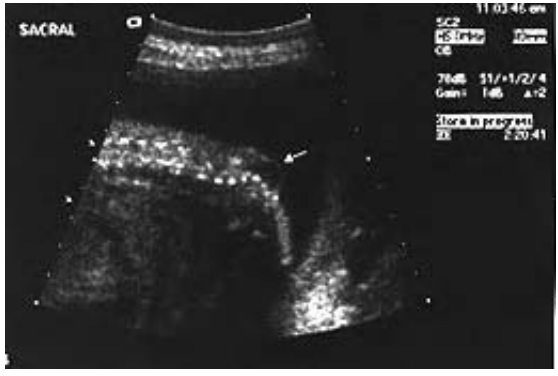
## VALPROATE, SODIUM (DIVALPROEX SODIUM; DEPAKOTE®); (VPA; DEPAKENE®)

Valproic acid was discovered fortuitously when antiepilepsy compounds revealed that the solvent that contained valproic acid was the efficacious chemical during animal testing. Valproate is indicated for epilepsy as well as bipolar disorder and migraine prevention. Valproate is indicated as monotherapy and adjunctive therapy in the treatment of simple and complex absence, the treatment of patients with complex partial seizures with or without other partial seizure types, and in patients with multiple seizure types that include absence seizures. Valproic acid is a carboxylic acid designated as 2-propylpentanoic acid. Depakene® is valproic acid; Depakote® is divalproex sodium and is a more stable compound oligomeric complex composed of sodium valproate and valproic acid in a 1:1 molar relationship. In older comparative AED trials, VPA was shown to demonstrate noninferiority compared with phenytoin, carbamazepine, and phenobarbital in patients with generalized tonic-clonic seizures. Guidelines recommend valproate as the drug treatment of first choice in patients with generalized or unclassified epilepsy [1]. When comparing VPA with LTG and TPM, VPA was found to be better tolerated than TPM, and more efficacious than LTG [1]. VPA has proven to be a broad-spectrum AED with ef-

ficacy shown in the treatment of absence, GTC, and myoclonic seizures particularly in those patients with idiopathic generalized epilepsy, but has also shown efficacy in the treatment of the encephalopathic generalized epilepsies. Efficacy for partial seizures has also been demonstrated in most studies [2].

Valproate is initially metabolized in patients by linear kinetics. Bioavailability is 86-100% of the oral dose. Peak plasma levels depend on the formulation [3]. Plasma levels are maximal 1 hour after ingestion of the solution, 3-8 hours after ingestion of enteric-coated tablets, and occasionally more than 12 hours after meals. Protein binding is 90% for most serum concentrations, but less with serum concentrations above 120 mg/L and in the newborn period. Half-life when used as monotherapy is 8-16 hours but is much prolonged in the newborn (20-50 hours) and in the premature infant (75 hours). A steady state is reached in 2-3 days. The volume of distribution (Vd) is 0.1-0.4 L/kg. Presence of valproate may delay the hydroxylation and the clearance of other drugs, particularly phenobarbital and the carbamazepine epoxide. There is a significant increase in free fraction of valproate in hypoalbuminemia and if taken with acetylsalicylic acid or heparin. There is a marked decrease with other enzyme-inducing medications such as phenobarbital, carbamazepine, or phenytoin, and significant prolongation of the T1/2 of lamotrigine is seen with co-administration of VPA. Suggested blood levels of valproic acid are 50-100 mg/L, or 300-600 (mo1/L, although higher levels have been tolerated with improved seizure control.

The most common side effect of valproic acid is gastrointestinal discomfort, especially if therapy is initiated too rapidly, though this occurs less with divalproex sodium. Nausea, abdominal pain, diarrhea, vomiting, low platelet count, tremor, tiredness, and hair loss are most common. Rare effects include skin rashes, hearing loss, symptomatic hyperammonemia, thrombocytopenia, dose-related thrombocytopenia and platelet dysfunction, and reversible stupor/coma. Concomitant administration of topiramate with valproate has been associcated with hyperammonemia with and without encephalopathy. Fatal hepatoxicity has rarely occurred in patients receiving valproic acid and its derivatives and may occur precipitously [3]. Patients should be monitored for nonspecific signs of fatigue and malaise. It appears most likely during the first 6 months of treatment, in children under the age of 2, with developmental disabilities or inborn errors of metabolism. With polytherapy, valproate should not be administered to




Neural tube defect (spina bifida) on level two-dimensional ultrasound noted in the lumbosacral region of a fetus in a mother with JME treated with VPA.

patients with hepatic disease or compromised hepatic function [4]. Valproate should not be given to patients with known or suspected urea cycle disorders, and hepatotoxicity is believed to be due to abnormal metabolism with the production of markedly toxic metabolites, though since initial observation the incidence of hepatitis has fallen. Pancreatitis is another serious gastrointestinal adverse effect that has been reported in both children and adults and should be suspected in patients noting abdominal pain, malaise, nausea, vomiting, and loss of appetite, which may occur up to several years after exposure. Some cases were described as hemorrhagic with rapid progression from onset to death [3]. Valproate can produce teratogenic effects and is known to produce a 1-2% incidence of spinal dysraphism (*see* figure) in offspring of mothers taking the drug during the first trimester of pregnancy (*see* Pregnancy). Accordingly, the use of valproate in women of childbearing potential requires that the benefits of its use outweigh the risks (*see* Women with Epilepsy).

Valproate is usually taken orally two to three times daily. The extended-release preparation may be taken once daily. Per rectum administration of the syrup has been used in the treatment of status epilepticus. Syrup (1 mL = 250 mg); enteric-coated tablets: 125 (pink), 250 (peach), and 500 (lavender) mg; Depakene® 250 mg capsules; extended-release formulation: 250 (white), 500 mg (gray) Depakote ER®.

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## VALPROATE DERIVATIVES

Valproate derivatives that do not possess the intrinsic hepatoxicity or teratogenicity seen with valproate have been of interest. Three such agents have been pursued in clinical developement. *N*-Valproyl glycinamide (valrocemide) is an amide of valproic acid that appears to be less toxic than its alkyl derivatives [1]. It does not appear to inhibit epoxide hydrolase or cytochrome P450 heaptic enzyme system. Low protein binding, linear pharmacokinetics, and a short T1/2 of 6-10 hours differentiate this compound from valproate. Another agent that functions as a prodrug, SPD 421 (DP16), is a selectively activated during oxidative stress and during seizures and results in a selective delivery of valproate to specific targets, potentially reducing systemic drug loads. A phospholipid

moiety of the prodrug is activated by IEDs or seizures, enhancing selective blood-brain barrier penetration of the drug. Isovaleramide (NPS 1776) is another broad-spectrum derivative that is more potent than VPA in PTZ and MES animal models of epilepsy. It is not protein bound and does not inhibit the CYP 450 hepatic family of enzymes.

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## VASCULITIS

Many forms of vasculitis may involve the CNS including SLE, Behcet's disease, polyarteritis nodosa, among others. The CNS may be affected in approximately one third of patients with systemic vasculitis, resulting in seizures, stroke, intraparencymal or subarachnoid hemorrhage, encephalopathy, or meningoencephalitis [1]. CNS vasculitis may occur as a primary systemic vasculitis (i.e., polyarteritis nododa, Churg-Strauss syndrome, or Wegener's Granulomatosis), or secondary to an underlying disease process such as SLE or other rheumatologic illnesses [2]. Rarely, primary vasculitis of the CNS may occur as in primary angiitis of the CNS. Seizures may occur as the result of a focal abnormalitiy of the brain, a diffuse encephalopathy, or in association with systemic or metabolic complications such as renal failure. In Churg-Strauss syndrome, granulomatous disease may involve the CNS by direct extension eroding through the nasopharynx and subsequently leading to basilar meningitis or dural venous thrombosis with seizures. Though cerebral vasculitis can predispose to seizures, the likelihood of seizures occurring with CNS vasculitis depends upon the underlying type of vasculitis. For example, while seizures are not uncommon with systemic lupus erythematosus, granulomatous vasculitis (i.e., Wegener's granulomatosis) rarely presents with seizures. Both partial and generalized seizures may be seen in systemic lupus erythematosus, and cerebral involvement has been reported in up to 75% of SLE patients [1]. An AED-induced lupus syndrome may occur in patients known to have epilepsy, but drug-induced lupus syndromes infrequently cause CNS problems (*see* Lupus). SLE exerts its effect via an immune mediated mechanism, and deposition of immune complexes in blood vessels may cause a vasculopathy with involvement of the CNS in addition to a multiple end organ effect. In the brain, these mechanisms may result in cerebral edema or ischemia resulting in seizures as well as stroke, dementia, or acute mental status changes.

The incidence of seizures appears to increase with the duration and severity of the underlying vasculitis. For example, CNS lesions may occur 2 to 3 years after the onset of polyarteritis nodosa and may lead to seizures in addition to encephalopathy and other neurological deficits.

Ischemic infarction or intraparenchymal hemorrhage may predispose as an acute or remote phenomenon but are treated with AEDs in the same manner as other symptomatic seizures. Most patients with CNS vasculitis are treated aggressively with a combination of immunosuppressive medications, and the prognosis is better when early recognition and treatment are initiated.

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## VENOUS ANGIOMAS

Venous angiomas are commonly found as incidental findings on neuroimaging in patients with epilepsy. While they are "lesions," they are rarely associated with epilepsy, and a search for overlying dysplastic cortex should be made. Resection is not recommended given the risk of hemorrhagic infarction associated with surgery excision.

## VENOUS THROMBOSIS

Cerebral venous thrombosis (CVT) is a rare condition that represents 0.5% of all strokes (*see* Cerebrovascular Disease). Risk factors have included coagulopathies and thrombocytosis, medication (e.g., hormonal therapies, hypervitaminosis), systemic and CNS infections, cancer, collagen vacular diseases, pregnancy, and the peripartum periods. In addition, severe anemia may also act as a predisposing factor to CVT, with 44% of patients having more than one cause [1]. MR venography remains essential for the diagnosis [2]. Seizures occur as a consequence of hemorrhagic infarction during venous sinus or cerebral vein thrombosis.

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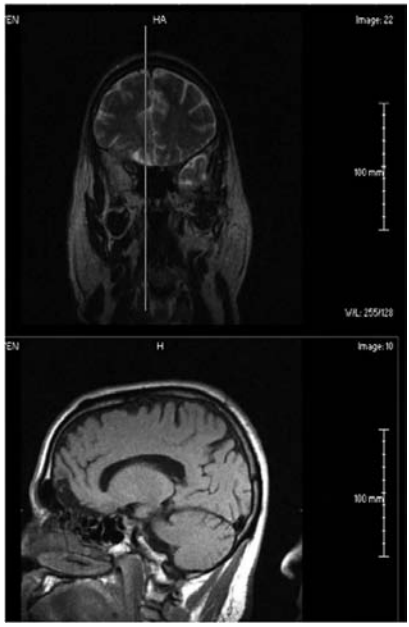
## VERSIVE SEIZURES (*see also* GYRATORY SEIZURES)

Versive seizures are characterized by eye deviation involving the eyes (oculogyric seizures), with or without head involvement, with or without addition truncal rotation (gyratory seizures) typically contralateral to the ictal discharge




A Right anterior orbitofrontal posttraumatic contusion on brain MRI in a patient with intractable epilepsy. The patient underwent successful epilepsy surgery for refractory complex partial seizures characterized by ipsilateral head and eye deviation at seizure onset before contralateral head version, prior to secondary generalization.

when the primary motor cortex is involved. Gyratory seizures are also known as circular, rotator, or volvular seizures and involve adversion of half of the body, emanate from the contralateral frontal lobe, and may involve subcortical spread [1,2]. Seizures are usually partial motor with or without secondary generalization. Some semiologic features suggest a region of onset or propagation:

- Contralateral mesial frontal cortex (involvement of the frontal eye fields) is suggested when seizures occur with rapid tonic deviation of the eyes alone or with head rotation and no loss of consciousness.
- Ipsilateral anterior frontal cortex may manifest with simultaneous eye and head deviation with loss of consciousness.
- Contralateral (less often ipsilateral) supplementary motor area involvement or propagation may produce tonic elevation and abduction of an upper extremity followed by deviation of the head and the eyes to the same side.
- Contralateral primary motor cortex involvement is suggested by sudden truncal gyration to the side opposite the epileptogenic zone, and parietal involvement may be suggested by a sudden curling up of the body.
- Contralateral parastriate occipital cortex involvement may be seen when tonic head and eye deviation occur with rapid eye blinking.

The lateralizing significance of oculocephalic deviation has been variable, and distinguishing between head turning and version is an important point of distinction. Version has become reserved for clear, forced movement of the eyes or head >45 degrees to one side with sustained posturing [3]. Contralateral head and eye version prior to generalization is a reliable lateralizing sign but should be interpreted more cautiously when secondary generalization does not occur [3,4].

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## VERTIGO

Seizures may produce a nonspecific dizziness that is perceived inside one's head (cephalic aura), with or without visual blurring or vertigo. Vertiginous auras can reflect a sense that a PWE is falling or floating, but may also occur as an outright sense of spinning felt in either the vertical or horizontal plane. True vertigo that occurs during focal seizures is associated with involvement of the posterior superior temporal neocortex or antero-inferior parietal cortex and has been reproduced with electrical brain stimulation studies.

## VIDEO-ELECTROENCEPHALOGRAM MONITORING

Video-EEG monitoring is the gold standard for providing a diagnosis when recurrent seizures prompt the need for differential diagnosis, classification, or presurgical characterization [1]. Telemetry is the neurophysiologic technique that allows remote EEG recording at a distance from the patient; it is most commonly performed with cable methods. On-line computer analysis routinely provides automated seizure and spike detection algorhithms in addition to pushbutton event recorders to eliminate problems of failed identification. Digital EEG has provided rapid review of condensed data, montage reformatting, on-site and remote review, and improved storage. Video-EEG long-term monitoring for electroclinical correlation of spells (*see* Spells) is performed for varying durations of time, usually long enough to ensure capture of several of the habitual seizures to ensure reproducibility of the outpatient events. Ancillary testing (i.e., ictal SPECT or provocation) makes inpatient video-EEG flexible with the potential for a higher yield of information, which is especially important during presurgical evaluation, though outpatient computer-assisted ambulatory monitoring with/without video for differential diagnosis may be more cost-effective [2]. Video-EEG is critical for the presurgical evaluation of patients with medically intractable epilepsy given that localization of the epileptogenic zone (*see* Zone) may have diagnostic as well as prognostic implications [3].

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# VIGABRATIN (SABRIL®)

Vigabratin (gamma-vinyl GABA) is a structural analog of GABA and was developed as an AED specifically designed to enhance GABA-mediated inhibition. Brain GABA levels are enhanced by the irreversible inhibition of GABA transaminase, thus preventing GABA breakdown (hence the delay in the onset of AED activity after initiating vigabratin therapy). Animal models have shown an effect for partial and secondary generalized seizures, with no effect, or a possible worsening, in absence seizure models. Vigabatrin is registered in most countries in Europe. In double-blind adjunctive studies in partial-onset seizures, up to 7% were rendered seizure-free on up to 3 g/d while 33-64% had a response of >50% reduction [1]. In the United States, higher doses of up to 6 g/d have been used in randomized controlled trials, though side-effects were greater, and 3 g/d is considered the average effective dose [1]. Most impressive have been the results of patients with infantile spasms. When tuberous sclerosis was associated with symptomatic infantile spasms, uncontrolled studies demonstrated high seizure rates of up to 71% [2].

Initial trials were halted because of the appearance of intramyelinic edema in studies of mice, rats, and dogs, a finding not noted in further studies on monkeys. Side effects most commonly reported include sedation, fatigue, drowsiness, and dizziness in 10-20%. Behavioral abnormalities, including psychosis, are rare but are more commonly seen in patients with a history of mental retardation and psychiatric problems. Dose-related psychiatric problems were identified, and therefore, more gradual institution of lower doses (up to 3 gsd) has been recommended. Irreversible dose-related concentric visual field deficits have been found in patients treated with vigabatrin, though most have been assymptomatic.

More than 60% of the drug is absorbed after an oral dose with a Tmax of 1-2 hours and a Vd of 0.6-0.8 L/kg. Vigabatrin has a T1/2 of 5-7 hours, though it has a pharmacologic effect that can be noted for more than 24 hours, permitting bid dosing. There is no appreciable protein binding, with no significant metabolism occurring. Consequently, AED interactions are not observed with the exception of phenytoin, which may result in a mean decrease in the serum concentration of approximately 20%. Approximately 60-70% of the drug is excreted unchanged by the kidneys with a therapeutic range that is not yet established for clinical use.

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## VIOLENCE

Aggressiveness can be defined as behavior with intent to damage, while violence represents aggressiveness with damage directed toward people or goods. Episodes of aggressive behavior related to epilepsy have gained considerable attention because they respresent an important social and clinical issue for PWE [1]. Aggressiveness and violence may have an interictal, ictal, or postictal component to seizure-related behavior. Patients with temporal lobe epilepsy in the past were felt to exhibit violence as a part of the "interictal personality disorder." However, studies of this issue have been subject to selection bias, and no clear evidence exists that people with epilepsy are more violent than the baseline population. Isolated instances of violence in epilepsy have been noted during complex partial seizures. Such instances of ictal "violence" are extremely rare, occurring in 13 of 5,400 patients in one study [2] and 10 of 699 seizures recorded in 79 patients in another study [3]. In this latter study, 7 of the 10 episodes were due to patient struggling, rather than directed violence, and included spitting, biting, and other "resistive" behaviors as opposed to organized behaviors such as rape or murder [1]. Aggressive behavior often occurs in response to a minimally unpleasant stimulation and particularly in response to being restrained. In a recent study of more than 1,000 video-EEG-monitored cases, only one patient was found to act in a violent fashion against another person [1]. However, patient behavior is dependent upon the interactions between people in the environment.

Violence in people with epilepsy has also been examined as a function of postictal state with delirium, psychosis, or behavior disturbance [4]. Most cases of ictal or postictal aggression have occurred in patients with chronic medically intractable focal epilepsy of frontal or temporal lobe origin [1,2]. Patients with temporal lobe epilepsy and intermittent aggression have demonstrated severe amygdalar atrophy in addition to abnormalities of the frontal cortex. The prevalence of patients with epilepsy in prison is higher than that in the general population, although the proportion of serious crimes is no higher in this group. Therefore, epilepsy itself appears not to be responsible for violent behavior, with aggressive behavior that results in physical violence toward other people being exceptional events [1].


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## VISUAL MANIFESTATIONS

Seizures with visual manifestations may present with elementary unformed hallucinations, complex formed hallucinations, or illusions. Blurring or decreased visual acuity has little specific localizing value. The typical elementary visual seizures of occipital lobe epilepsy are characterized by fleeting visual manifestations [1]. Elementary hallucinations may be either positive or negative phenomena and consist of either simple phosphenes or, more rarely, scotomata or hemianopsia. In one series, 22 of 26 patients with occipital lobe epilepsy had a visual aura though the location of the visual manifestation was not helpful in the lateralization of the seizure focus [1]. Structured hallucinations comprise objects, animals, and people, and more or less complex scenes may occur due to ictal involvement of visual association areas. If seizure propagation spread to the temporal lobe, automatisms and impaired consciousness resulted, whereas if spread to the suprasylvian convexity occurred, seizures mimicking supplementary sensory motor seizures or secondarily generalized seizures would occur.

Illusions (metamorphopsias) represent an alteration in the size or shape of objects. They may appear enlarged (macropsias), diminished (micropsias), or changed in position: vertical or horizontal lines are seen as being oblique, or with undulation of contour, change in color, dulling or heightening of color, the illusion of movement (generally acceleration), an impression of proximity or distance, change in relief, monocular diplopia or polyopia, or perseveration in time of the visual image. Illusions are usually due to parietal or parieto-occipital foci.

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## VITAMINS

Dietary supplements have been recommended in the treatment of PWE and have gained increasing support. Seizures due to pyridoxine deficiency may respond to replacement therapy independent of primary AED therapy. Vitamin

B12 and folate may be depleted in patients taking AEDs and have been proposed to be responsible for both neurologic consequences such as behavioral disorders and peripheral neuropathy in addition to teratogenic effects prompting prepregnancy supplementation (*see* Women with Epilepsy). Guidelines for folate replacement have already been suggested (*see* Folate). Vitamin D has gained increasing popularity. Bone health issues in PWE taking AEDs appear to be related to increased bone turnover. One of the major mechanisms has been through vitamin D metabolism given that hepatically mediated degradation of vitamin D results in reduced calcium absorption with the clinical consequences of osteopenia and osteoporosis. The dose required to achieve normal levels of 25-hydroxyvitamin D levels ranged from 400 to 4000 IU/day.

# VOMITING

Vomiting may occur during a seizure (ictus emeticus) and is seen as a phenomenon that occurs in localization-related epilepsy involving the nondominant hemisphere and especially the right temporal lobe. Intracranial electrodes have demonstrated lateral temporal neocortical propagation to the nondominant temporal lobe at the time of ictal vomiting. It has also been reported in children with idiopathic partial epilepsies [1]. Ictal retching, drooling, and vomiting may be associated with other phenomena, including impairment of consciousness or alimentary or ipsilateral limb automatisms in patients with recurrent complex partial seizures [2]. The mechanism for the asymmetric manifestations is not elucidated, though functional neuroimaging with SPECT has also supported nondominant temporal localization for ictus emeticus [3]. If associated with visual disturbance or headache without impaired consciousness, migraine should be suspected and represents a more common etiology for "ictal" vomiting. Vomiting may follow a seizure but may also be seen after vasovagal syncope (*see also* Abdominal Aura).

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# VON RECKLINGHAUSEN'S DISEASE (NEUROFIBROMATOSIS 1)

First reported by Von Recklinghausen, this inherited condition is characterized by skin pigmentation and firm benign neural tumors involving peripheral nerves and spinal and cranial nerve roots. Neurofibromatosis 1 (NF1) is the most common neurocutaneous disease. Neurologic manifestations are mainly represented by tumors such as optic gliomas, focal areas of high T2-weighted signal known as unidentified bright objects, and mental retardation or learning disabilities. The prevalence of seizures has been reported to range from 3.8 to 6% [1] and an incidence of 30-40 per 100,000. It is transmitted as an autosomal dominant trait or may occur sporadically. Mental retardation, usually mild, is seen in about 10% of patients. Different seizure types that occur with NF1 have included complex partial seizures, generalized seizures, and infantile spasms with early-childhood-onset epilepsy, though partial-onset seizures occur most frequently [2]. Overall, seizures appear to be relatively uncommon in individuals with NF1, and when they occur they have a natural history similar to that of seizures in the general population [2].

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# W

## WADA TEST (INTRACAROTID AMOBARBITAL PROCEDURE)

The Wada test, named after Dr. Juhn Wada, is a procedure that is used preoperatively to evaluate hemispheric lateralization of language and memory function in patients undergoing epilepsy surgery evaluation. The test is performed by interventional radiology, neurology, and neuropsychology with the patient holding arms out in the air counting backwards. Cerebral angiography is initially performed for definition of the cerebral circulation to exclude vascular anomalies and malformations. Selective angiography of the posterior circulation or anterior choroidal artery to isolate the mesial hippocampal structures for memory testing may be used to involve a more restricted area of hemisphere, but is associated with a higher risk that includes stroke. A bolus of amobarbital (or the briefer-acting sodium brevital) is injected via the right transfemoral approach rapidly over 4-5 seconds in two trials of bilateral internal carotid arterial injections. Following injection, the amobarbital is taken up into brain directly from the first pass of circulation and essentially "anesthetizes" a portion of one hemisphere. Typical doses of amytal include 100-150 mg (or 3-9 mg brevital) inducing a unilateral deficit for 5-15 minutes (or 1-5 minutes with brevital). Medication administration is performed until there is resultant contralateral hemiparesis and aphasia when the dominant hemisphere is involved or dysarthria and no language disturbance in cases of nondominant hemisphere involvement. Dynamic EEG may be performed during Wada testing to demonstrate ipsilaterally hemispheric delta slowing as well as the absence of ictal epileptiform discharges, though many differences in Wada protocols exist.

Wada testing has been used to lateralize language representation, and despite the fact that SPECT scans demonstrate hippocampal and posterior cerebral artery perfusion occurring in a minority of Wada studies, cortical stimulation studies have demonstrated good agreement, and functional MRI may demonstrate comparable results [1]. However, the ability to predict memory decline is subject to debate, and the consistency to adequately test mesial temporal structures has been controversial. Nevertheless asymmetries in a discordant direction is cause for concern relative to predicting postoperative memory deficit. Wada testing may also be used to lateralize seizure onset and predict postoperative outcome when a significant asymmetry in memory scores is seen [2,3]. Wada testing has become a neuropsychological extension of the

routine evaluation of patients being evaluated for epilepsy surgery. Whether a surrogate marker such as fMRI ultimately replaces the Wada test or whether the Wada test is eliminated as a routine in the pre-surgical assessment remains to be seen. In pediatric patients functional mapping studies frequently fail to localize language, and Wada testing has also been reported to be less sensitive in children [4]. Propofol may be used to help complete the angiography prior to Wada testing in children younger than 10 years.

### References

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## WEIGHT ISSUES IN EPILEPSY

Obesity carries a risk of serious medical disease states such as hypertension, type 2 diabetes, heart disease, and ischemic stroke. Obesity is a serious public health risk and globally is steadily increasing in prevalence, with 66% of the U.S. population being overweight or obese [1]. People with epilepsy tend to be less physically active than others, and the frequency of seizures appears to be related to activity levels [2]. Epilepsy per se is less consistently associated with weight gain than the effect of the AEDs used for treatment. Iatrogenic weight gain has been most recognized as a consequence of therapy with VPA, though carbamazepine, gabapentin, pregabalin, and vigabatrin may result in weight gain as well. Valproate has been shown in double-blind trials to manifest weight gain compared to other AEDs. Some AEDs have been associated with weight loss, and topiramate, zonisamide, and felbamate have been shown to affect weight in PWE. Phenytoin, lamotrigine and levetiracetam are AEDs that have been shown to be weight neutral.

Because drug-induced weight gain may be reversed by the addition of a "weight loss" AED such as topiramate, given the ramification of being overweight, PWE who require guidance should consider those AEDs that may promote weight loss as a consideration.

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# WEST SYNDROME

Initial descriptions of "bobbings" that "caused complete heaving of the head forward toward the knees subsequently relaxing into the upright position" were aptly noted by Dr. W. J. West in 1841. These initial colorful descriptions unfortunately were due to the fact that he was observing his own son. Previous, less common names have been applied to infantile spasms, the hallmark of West syndrome, including salaam attacks or convulsions, Bitz-Nick-Salaam Krämpfe, flexion spasms, jackknife spasms or convulsion syndrome, massive myoclonia syndrome, nodding spasms, and others. West syndrome is an age-dependent epilepsy of infancy and early childhood with a typical triad of infantile spasms, severe mental retardation, and hypsarrhythmia of the interictal EEG. Age is a key feature, and infantile spasms (IS) typically begin within the first year of life, most often between the age of 4 and 8 months, and rarely after the first year. They rarely persist beyond 3 years of age.

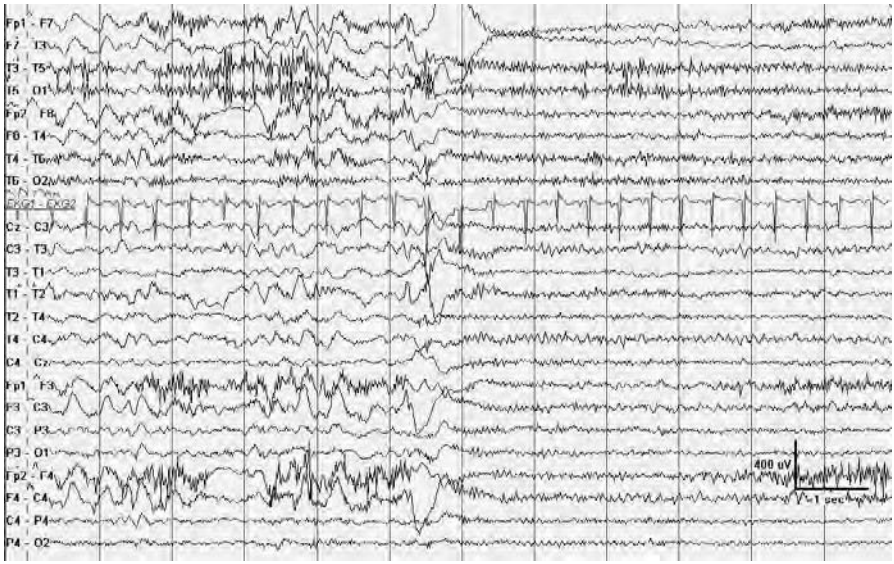
The clinical semiology includes clusters of seizures manifest as IS that present with flexion or extension jerks of the head, neck, trunk, and extremities for 1-2 seconds. Flexor spasms are most frequent, with massive flexion of the head, trunk, and upper and lower extremities, but the diagnosis may be delayed when they appear so subtle as to mimic a normal startle response. Extensor spasms may involve extension of the neck, trunk, and extremities, and mixed spasms alternately involve flexor and extensor muscles. Atypically, IS may show asymmetry or may even be unilateral. In IS, the child may have impairment of consciousness, changes in respiration, crying at the end of the spasm, or, more rarely, smiling or eye deviation. The observation of repeated spasms is what usually leads to the diagnosis of IS and West syndrome. Infantile spasms are usually seen upon awakening in the morning or after a nap. Initially sporadic, their frequency tends to increase over the course of the illness, and occasionally they may resolve spontaneously. In addition to IS, other seizure types may arise concurrently or sequentially [1]. *Psychomotor retardation* may precede the spasms. Early in the course of West syndrome, there is loss of spontaneous smiling, apathy, diminished reactivity to external stimuli, then delay or loss of milestones and stereotyped activities. The EEG characteristically demonstrates *hypsarrhythmia* as the interictal finding. Hypsarrhythmia is a pathognomonic feature of West syndrome with a very high voltage disorganized EEG abnormality, though a modified hypsarrhytmia may actually be more common. Both forms of hypsarrhythmia appear in two thirds of individuals with multifocal independent spike discharges in the remainder. There is an uninterrupted sequence of high amplitude (300 V) spike-and-slow waves of varying amplitude and multiple localizations seen asynchronously and diffusely over the scalp. During sleep there are bursts of more or less synchronous irregular polyspike-and-waves on a highly disorganized background. Continuous videopolygraphic recording has revealed asymmetry, lateralization, suppression bursts, bilateral spike-and-slow wave discharges, and attenuation of activity during interictal

EEG. Ictal recording shows the characteristic electdrodecremental response with an abrupt high-amplitude slow wave in the frontal regions followed by general suppression or rapid bilateral ictal fast activity and, more rarely, slow spike-and-slow wave discharges. If the EEG is normal, reconsider IS and instead consider benign familial infantile convulsions or benign infantile myoclonus.

The differential diagnosis includes benign forms of myoclonus in early infancy, which is critical to distinguish. In benign familial infantile convulsions or benign infantile myoclonus of infancy, similar characteristics appear with sudden lightning-like jerks or "spasms," but psychomotor development and the waking and sleep EEG are normal. Therefore, if the EEG is normal, reconsider the diagnosis of IS. In the latter case, seizures disappear before the age of 2 without sequelae. However, more malignant infantile epilepsies including early-onset myoclonic encephalopathy (*see* Neonatal Seizures), early infantile epileptogenic encephalopathy with burst suppression (Ohtahara syndrome), and severe myoclonic epilepsy of infancy are also present in the differential diagnosis of West syndrome.

Etiology is variable, and genetic counseling is essential when the disorders that produce IS are genetic. Infantile spasms may be cryptogenic or symptomatic. *Symptomatic spasms* comprise approximately 70% of cases [2]. Any cerebral insult occurring in the prenatal, perinatal, or postnatal period may lead to infantile spasms. These include anoxic-ischemic encephalopathy (*see also* Anoxia; Hypoxia), congenital cerebral malformations (Aicardi's syndrome), the neurocutaneous syndromes (i.e., tuberous sclerosis, neurofibromatosis), abnormalities of neuronal migration (i.e., lissencephaly, focal cortical dysplasia, or hemimegalencephaly), chromosomal disorders (i.e., Down syndrome, Miller-Dieker syndrome), porencephaly, or perinatal infections. More rarely, tumors, hemorrhagic syndromes, head trauma, inborn errors of metabolism, severe hypoglycemia, and toxins are implicated. Neonatal onset of IS is associated with cortical dysplasia, whereas late onset after the first year is typically associated with hypoxic-ischemic encephalopathy and genetic abnormalities. If history and physical examination, MRI, and metabolic testing do not reveal an etiology, then *cryptogenic spasms* are able to be discerned.

The diagnosis is based largely on history and physical examination. Detailing historical information about age of onset, evidence of perinatal hypoxia, or infection is essential. Physical examination of the skin for cutaneous lesions characteristic of neurocutaneous syndromes such as ash-leaf spots of tuberous sclerosis, café-au-lait spots of neurofibromatosis, and swirling pigmented skin lesions of incontinentia pigmenti may be identified. Gross physical finding of hemiparesis, mental retardation, and stigmata of Down syndrome are readily distinguished physical abnormalities of note. MRI of the brain is often suggestive of etiology and should be employed when possible for diagnostic and treatment purposes. A metabolic profile is performed when an etiology is not forthcoming from initial evaluation of IS. More than 50 genetic or metabolic disease states have been identified to cause IS [3].




Infantile spasm in a patient with West syndrome. Note the electrodecremental response in second 6. The sensitivity is 400 V/mm. The preictal background demonstrates hypsarrhythmia.

The goal with respect to treatment is complete cessation of IS. Without control, normal neurodevelopment is unlikely. Unfortunately, the underlying diagnosis frequently precludes normal development (e.g., diffuse brain injury from hypoxia). A safe and potentially effective first step is to administer 100 mg of pyridoxine i.v. to identify rare cases of IS associated with pyridoxine dependency. Corticosteroid therapy, particularly ACTH, is effective. There is no concensus as to the formulation (natural ACTH vs. synthetic corticosteroids), administration modality, associated medication, or duration of treatment. A frequent approach is to use 40 IU/d for 1-2 weeks and if there is an incomplete response then to increase to 60-80 IU/d [2]. If ACTH is successful in completely controlling IS, then it is tapered over 1-4 months. If ACTH is ineffective, then it should be rapidly tapered and another drug trial attempted. ACTH may produce side effects such as cushingoid appearance, irritability, and electrolyte imbalances, in addition to hypertension, immunosuppression, growth retardation, and peptic ulcer disease; therefore a proton pump inhibitor should be used concomitantly [2]. In approximately 30% there is relapse when treatment is stopped. Vigabatrin has shown amazing results in the treatment of IS, especially when associated with tuberous sclerosis [4], and has demonstrated similar response rates when compared to ACTH in cryptogenic IS. Adjunctive AED therapy using broad-spectrum AEDs including valproate has been advocated based upon anecdotal data, though no prospective randomized controlled trials have been performed. Several of the new AEDs have evidence of efficacy, including felbamate, lamotrigine, topiramate, and zonisamide. Other

nondrug therapies have included high-dose intravenous immunoglobulin and surgical resection of a localized abnormality after exhausting appropriate drug therapy.

*The prognosis* is typically grave, with death in approximately 30% of patients in one larger study of 214 patients followed for up to 35 years, with many dying within the first 3 years of life. The remaining patients had a high risk of mental retardation (45%), but 24% had a reasonably satisfactory outcome [2], with 17% having IQs of >85. Outcome is dependent primarily upon etiology. However, cryptogenic West syndrome control of the IS is the next most crucial issue for affecting prognosis. Poor prognostic indicators include identifiable fixed or progressive lesions, the onset of spasms before the age of 3 months, or other types of seizures (particularly in symptomatic cases).

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## WHIPPLE'S DISEASE

*Tropheryma whippelii* is the bacillus that has been identified to cause Whipple's disease. Up to 25% of patients have seizures besides the characteristic oculomotor dysfunction in addition to dementia and ataxia [1]. Primary treatment with antibiotics has been recommended due to the high risk of morbidity and mortality in those untreated. Because cerebral manifestations may develop after systemic treatment, AEDs may become necessary in the treatment of partial and secondarily generalized seizures [1,2].

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## WILSON'S DISEASE

Wilson's disease is a disorder of copper metabolism with hepatic and neurologic sequelae. The incidence of epilepsy has been calculated to be about 6% in

patients with Wilson's disease or about 10 times higher than epilepsy in the general population [1]. Seizures may occur at any stage of the disease. However, seizures rarely herald the onset of the disease and appear more often during treatment with the use of chelation treatment such as penicillamine, which produces an abnormal mobilization of copper within the brain. In untreated patients, seizures appear toward the end of the process, some months before death, though seizures do not alter the prognosis.

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## WITHDRAWAL SEIZURES

Withdrawal seizures arise either in the context of acute or chronic intoxication with alcohol abuse (*see* Alcohol, Effects of), or during withdrawal of certain drugs, including AEDs. In the epilepsy-monitoring unit, the reduction of anticonvulsant medication extremely rarely causes the appearance of seizures having an electrical onset or a clinical pattern different from those observed on full medication [1]. Barbiturate and benzodiazepine withdrawal are especially liable to provoke seizures or even status epilepticus. Seizures are a frequent presenting symptom and may commence up to 7 or 8 days following cessation of the sedative-hypnotic. Other withdrawal symptoms typically begin 1-3 days after cessation of drug use and peak at 5-6 days, but may occur later with sedative-hypnotics that have long half-lives. It may be difficult to distinguish withdrawal seizures from a relapse of the epilepsy when AEDs are withdrawn. Withdrawal seizures are usually generalized seizures. Administration of flumazenil may result in abrupt appearance of symptoms, including convulsions, when used to reverse benzodiazepine intoxication. In this case, the withdrawal syndrome resolves rapidly as the effect of flumazenil diminishes. Manifestations include seizures, drug craving, dysphoria, headache, insomnia, anxiety, anorexia, nausea, vomiting, muscle weakness, tachycardia, and tremor. Agitation and confusion may progress to delirium, disorientation, and hallucinations. Rarely, withdrawal seizures emerge in the newborn children of mothers on barbiturate AEDs during the peri-partum period.

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## WOMEN WITH EPILEPSY

More than 1.5 million girls and women with epilepsy face challenges that involve seizures, treatment of seizures, and developing as females in society [1,2].

Problems may arise at different ages and stages of life [2]. Menarche and menopause may either herald or create changes in seizures frequency [2]. Menstruation may be altered by AEDs and reflect hypothalamic-pituitary-ovarian axis disruption during the course of treatment. Fertility and sexual function (*see* Sexuality) may be impaired, and pregnancy (*see* Pregnancy) and development of the fetus before and after birth merits special considerations for treatment course and recommendations for good prenatal care. Bone health and general health issues are important for postmenopausal women but also in those who are premenopausal and require early detection before metabolic and systemic adverse effects become apparent. Changes in hormone balance during maturation from menarche through menopause affect the frequency of seizures and the AEDs used to pursue control of seizures, as well as vice versa [1,2].

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## WORKPLACE ISSUES

Despite evolution since antiquity, epilepsy has continued to bear a stigma and has been subject to discrimination. There is considerable evidence that many individuals with epilepsy experience discrimination or perceive themselves to be discriminated against in the workplace [1]. The Americans with Disabilities Act prohibits discrimination in hiring, promotions, and terminations of qualified people with disabilities. This encompasses subjectivity in the definition of qualified and requires that essential functions of a job be able to be performed with "reasonable" accommodations and disclosure of the disability before the job offer is made (*see* Employment). Although discrimination in the workplace is considered by many to be a significant barrier, validation of discrimination has received little attention [2].

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# Z

## ZELLWEGER SYNDROME

Zellweger syndrome (ZS) is the most common and most severe of the peroxisomal disorders. It appears in early infancy. The clinical manifestations reflect a disorder of peroxisomal biogenesis from mutations that may occur in several different genes, and an abnormality of chromosome 7 is suspected. Dysmorphic features present in the neonatal period with severe encephalopathy, hypotonia, and hyporeflexia on examination. Seizures occur in 80% of patients and include partial-onset seizures as well as GTC, myoclonic, and tonic flexor spasms [1]. Multiorgan system involvement in ZS occurs, and abnormalities involve not only the brain, but the liver, kidneys, eyes, and skeletal musculature. Neuroimaging often demonstrates pachygryia or polymicrogyria regionally in the opercular with heterotopias found within the cerebellum. Partial motor seizures are often readily controlled with AEDs. Multifocal IEDs are commonly seen on the interictal EEG in ZS, and less frequently hypsarrhythmia may occur [1].

### Reference

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## ZONE (EPILEPTOGENIC)

The epileptogenic zone refers to the region of cerebral cortex where localization-related epileptic seizures originate. Specific lesions such as mesial temporal sclerosis or foreign tissue lesions are referred to as anatomic or structural lesions. These focal anatomic lesions produce a surrounding primary epileptogenic zone, which in turn may produce distant epileptogenic zones; a condition referred to as *secondary epileptogenesis* (*see also* Focus). Surrounding irritative zones arise which influence regions immediately adjacent or nearby structures that create the *symptomatic zone* where the clinical semiology of the seizure is represented.

# ZONISAMIDE (ZONEGRAN®)

Zonisamide (ZNS) is a sulfonamide derivative that has been widely used in Japan. ZNS is chemically distinct from other AEDs and has been shown to be effective in refractory partial epilepsies [1,2]. The mechanism of action is severalfold, including blockade of voltage-sensitive sodium channels, blockade of voltage-dependent calcium channels, blockade of potassium-evoked glutamate responses, and reduction of glutamate-mediated synaptic excitation in addition to being a weak carbonic anhydrase inhibitor. In addition, facilitation of dopaminergic and serotinergic neurotransmission, inhibition of excess nitric oxide production, and functioning as a scavenger for hydroxyl and nitric oxide radicals has been shown. Zonisamide is a sulfonamide and may demonstrate cross-hypersensitivity with patients who have sulfa allergies. The most frequent side effects include somnolence, ataxia, loss of apetite, gastrointestinal problems, loss of or reduced spontaneity, and mental slowing [3], but are concentration and co-medication dependent. Several behavioral problems and a dose-dependent impairment of cognition have been noted. Kidney stones have been noted with 1.2% symptomatic and an additional 2.8% identified by sonographic evidence. Doses of 200-600 mg/d are effective and produced serum concentrations between 10-40 (g/mL with titration usually by increments of 100 mg every 2 weeks. Generic substitution is available.

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