2 loại chính
- co giật cục bộ
- co giật lan tỏa

Chapter 593

Seizures in Childhood

Mohamad A. Mikati and Abeer J. Hani

A seizure is a transient occurrence of signs and/or symptoms resulting from abnormal excessive or synchronous neuronal activity in the brain. The International Classification of Epileptic Seizures divides epileptic seizures into 2 large categories: In **focal (formerly known as partial) seizures,** the first clinical and electroencephalographic (EEG) changes suggest initial activation of a system of neurons limited to part of 1 cerebral hemisphere. The term *simple partial seizures* is an outdated classification that refers to focal seizures with no alteration in consciousness whereas complex partial seizures, currently also referred to as focal dyscognitive, denote focal seizures with altered awareness of the surroundings. In **generalized seizures,** the first clinical and EEG changes indicate synchronous involvement of all of both hemispheres (Table 593-1). Approximately 30% of patients who have a first afebrile seizure have later epilepsy; the risk is approximately 20% if neurologic exam, EEG, and neuroimaging are normal. **Febrile seizures** are a separate category. **Acute symptomatic seizures** occur secondary to an acute problem affecting brain excitability such as electrolyte imbalance. Most children with these types of seizures do well. However, sometimes these seizures signify major structural, inflammatory, or metabolic disorders of the brain, such as meningitis, encephalitis, acute stroke, or brain tumor. Consequently, the prognosis depends on the underlying disorder, including its reversibility or treatability and the likelihood of developing epilepsy from it. An **unprovoked seizure** is one that is not an acute symptomatic seizure. **Remote symptomatic seizure** is one that is considered to be secondary to a distant brain injury, such as an old stroke. **Reflex seizures** are usually precipitated by a sensory stimulus such as flashing lights (see Chapter 593.9).

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate seizures and by the neurobiologic, cognitive, psychologic, and social consequences of this condition. The clinical diagnosis of epilepsy usually requires the occurrence of at least 1 unprovoked epileptic seizure with either a second such seizure or enough EEG and clinical information to convincingly demonstrate an enduring predisposition to develop recurrences. For epidemiologic and commonly for clinical purposes, epilepsy is considered to be present when 2 or more unprovoked seizures occur in a time frame of longer than 24 hr. Approximately 4-10% of children experience at least 1 seizure (febrile or afebrile) in the 1st 16 yr of life. The cumulative lifetime incidence of epilepsy is 3%, and more than half of the cases start in childhood. The annual prevalence is 0.5-1.0%. Thus, the occurrence of a single seizure or of febrile seizures does not necessarily imply the diagnosis of epilepsy. **Seizure disorder** is a general term that is usually used to include any 1 of several disorders, including epilepsy, febrile seizures, and possibly single seizures and symptomatic seizures secondary to metabolic, infectious, or other etiologies (e.g., hypocalcemia, meningitis).

An **epileptic syndrome** is a disorder that manifests 1 or more specific seizure types and has a specific age of onset and a specific prognosis. Several types of epileptic syndromes can be distinguished

Table 593-1 Types of Epileptic Seizures

SELF-LIMITED SEIZURE TYPES	CONTINUOUS SEIZURE TYPES
Focal Seizures	***Generalized Status Epilepticus***
Focal sensory seizures	Generalized tonic-clonic status epilepticus
• With elementary sensory symptoms (e.g., occipital and parietal lobe seizures)	Clonic status epilepticus
• With experiential sensory symptoms (e.g., temporoparietooccipital junction seizures)	Absence status epilepticus
Focal motor seizures	Tonic status epilepticus
• With elementary clonic motor signs	Myoclonic status epilepticus
• With asymmetrical tonic motor seizures (e.g., supplementary motor seizures)	***Focal Status Epilepticus***
• With typical (temporal lobe) automatisms (e.g., mesial temporal lobe seizures)	Epilepsia partialis continua of Kojevnikov
• With hyperkinetic automatisms	Aura continua
• With focal negative myoclonus	Limbic status epilepticus (psychomotor status)
• With inhibitory motor seizures	Hemiconvulsive status with hemiparesis
Gelastic seizures	**PRECIPITATING STIMULI FOR REFLEX SEIZURES**
Hemiclonic seizures	Visual stimuli
Secondarily generalized seizures	• Flickering light—color to be specified when possible
Reflex seizures in focal epilepsy syndromes	• Patterns
Generalized Seizures	• Other visual stimuli
Tonic-clonic seizures (includes variations beginning with a clonic or myoclonic phase)	Thinking
Clonic seizures	Music
• Without tonic features	Eating
• With tonic features	Praxis
Typical absence seizures	Somatosensory
Atypical absence seizures	Proprioceptive
Absence with special features:	Reading
• Eyelid myoclonia	Hot water
• Myoclonic absence	Startle
Tonic seizures	
Myoclonic seizures	
Myoclonic atonic seizures	
Negative myoclonus	
Atonic seizures	
Reflex seizures in generalized epilepsy syndromes	
Unknown	
Epileptic Spasms	

Modified from Berg AT, Berkovic SF, Brodie MJ et al: Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia *51(4):676–685, 2010.*

loại co giật => loại thuốc đáp ứng
hội chứng động kinh => tiên lượng

(Tables 593-2 to 593-5). This classification has to be distinguished from the classification of epileptic seizures that refers to single events rather than to clinical syndromes. In general, seizure type is the primary determinant of the type of medications the patient is likely to respond to, and the epilepsy syndrome determines the type of prognosis one could expect. An **epileptic encephalopathy** is an epilepsy syndrome in which there is a severe EEG abnormality which is thought to result in cognitive and other impairments in the patient. **Idiopathic epilepsy** is an older term that refers to an epilepsy syndrome that is genetic or presumed genetic and in which there is no underlying disorder affecting development or other neurologic function (e.g., petit mal epilepsy). In the International League Against Epilepsy (ILAE) classification of etiology of epilepsy, idiopathic epilepsy was replaced by the term **genetic epilepsy**, which implies that the epilepsy syndrome is the direct result of a known or presumed genetic defect(s) in which the genetic defect is not causative of a brain structural or metabolic disorder other than the epilepsy. **Symptomatic epilepsy** is also an older term referring to an epilepsy syndrome caused by an underlying brain disorder that may or may not be genetic (e.g., epilepsy secondary to tuberous sclerosis or to an old stroke); this is referred to as **structural/metabolic epilepsy**, which would be caused by a distinct structural or metabolic entity that increases the risk for seizures and causes the epilepsy. The older terms of **cryptogenic epilepsy** or of presumed **symptomatic epilepsy** refer to an epilepsy syndrome in which there is a presumed underlying brain disorder causing the epilepsy and affecting neurologic function, but the underlying disorder is not known; this is referred to as the **unknown epilepsy**, designating that the underlying cause of the epilepsy is as yet unknown.

EVALUATION OF THE FIRST SEIZURE

Initial evaluation of an infant or child during or shortly after a suspected seizure should include an assessment of the adequacy of the airway, ventilation, and cardiac function, as well as measurement of temperature, blood pressure, and glucose concentration. For acute evaluation of the first seizure, the physician should search for potentially life-threatening causes of seizures such as meningitis, systemic sepsis, unintentional or nonaccidental intentional head trauma, and ingestion of drugs of abuse or accidental ingestion of drugs or of other toxins. The history should attempt to define factors that might have promoted the convulsion and to provide a detailed description of the seizure and the child's postictal state (see Chapter 593.9). Most parents vividly recall their child's initial convulsion and can describe it in detail.

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- nt hệ thống
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- thuốc, độc chất

The subsequent step in an evaluation is to determine whether the seizure has a focal onset or is generalized. **Focal seizures** may be characterized by motor or sensory symptoms, which could include forceful turning of the head and eyes to 1 side, unilateral clonic movements beginning in the face or extremities, or a sensory disturbance, such as paresthesias or pain localized to a specific area. Focal seizures in an adolescent or adult usually indicate a localized lesion, whereas these seizures during childhood are often, but not always, secondary to a

Text continued on p. 2829

Table 593-2 Classification for Epilepsy Syndromes with an Indication of Age of Onset, Duration of Active Epilepsy, Prognosis, and Therapeutic Options

SPECIFIC SYNDROMES	AGE AT ONSET	AGE AT REMISSION	PROGNOSIS	MONOTHERAPY OR ADD-ON*	POSSIBLE ADD-ON†	SURGERY†
EPILEPSIES OF UNKNOWN CAUSE OF INFANCY AND CHILDHOOD						
Benign infantile seizures (nonfamilial)	Infant	Infant	Good	PB	—	No
Benign childhood epilepsy with centrotemporal spikes	3-13 yr	16 yr	Good	CBZ, LEV, OXC, VPA	—	No
Early and late-onset idiopathic occipital epilepsy	2-8 yr; 6-17 yr	12 yr or younger; 18 yr	Good	CBZ, LEV, OXC, VPA	—	No
FAMILIAL (AUTOSOMAL DOMINANT) EPILEPSIES						
Benign familial neonatal convulsions	Newborn to young infant	Newborn to young infant	Good	PB	—	No
Benign familial infantile convulsions	Infant	Infant	Good	CBZ, PB	—	No
Autosomal dominant nocturnal frontal lobe epilepsy	Childhood		Variable	CBZ, GBP, OXC, PHT, TPM	CLB, LEV, PB, PHT	No
Familial lateral temporal lobe epilepsy	Childhood to adolescence		Variable	CBZ, GBP, OXC, PHT, TPM, VPA	CLB, LEV, PB, PHT	No
Generalized epilepsies with febrile seizures plus	Childhood to adolescence		Variable	ESM, LTG, TPM, VPA	CLB, LEV	No
STRUCTURAL–METABOLIC FOCAL EPILEPSIES						
Limbic Epilepsy						
Mesial temporal lobe epilepsy with hippocampal sclerosis	School-age or earlier	Long lasting	Variable	CBZ, LEV, OXC, TPM, VPA	CLB, GBP, LAC, PB, PHT, ZON	Temporal resection
Mesial temporal lobe epilepsy defined by specific causes	Variable	Long lasting	Variable	CBZ, LEV, OXC, TPM, VPA	CLB, GBP, LAC, PB, PHT, ZON	Temporal resection
Other types defined by location and causes	Variable	Long lasting	Variable	CBZ, LEV, OXC, TPM, VPA	CLB, FBM, GBP, LAC, PB, PHT, ZON	Lesionectomy ± temporal resection
Neocortical Epilepsies						
Rasmussen syndrome	6-12 yr	Progressive	Ominous	Plasmapheresis, immunoglobulins	CBZ, LAC, PB, PHT, TPM	Functional hemispherectomy
Hemiconvulsion-hemiplegia syndrome	1-5 yr	Chronic	Severe	CBZ, LEV, OXC, TPM, VPA	CLB, GBP, LAC, PB, PHT, ZON	Functional hemispherectomy
Other types defined by location and cause	Variable	Long lasting	Variable	CBZ, LEV, OXC, TPM, VPA	PHT, PB, CLB, GBP, LAC, ZON	Lesionectomy ± cortical resection
Migrating partial seizures of early infancy	Infant	No remission	Ominous	Bromides, CBZ, LEV, PB, PHT, TPM, VPA	BDZ, LAC, ZON	No
GENERALIZED EPILEPSIES OF UNKNOWN CAUSE						
Benign myoclonic epilepsy in infancy	3 mo-3 yr	3-5 yr	Variable	LEV, TPM, VPA	BDZ, ZON	No
Epilepsy with myoclonic astatic seizures	3-5 yr	Variable	Variable	ESM, TPM, VPA	BDZ, ketogenic diet, LEV, LTG, steroids, ZON	No
Childhood absence epilepsy	5-6 yr	10-12 yr	Good	ESM, LTG, VPA	Acetazolamide, ketogenic diet, ZON	No
Epilepsy with myoclonic absences	1-12 yr	Variable	Guarded	ESM, VPA	BDZ, ZON	No

*Reflects current trends in practice, which may be off-label and may not be FDA approved for that indication. See Table 593-10 for FDA indications.

†May apply to selected cases only. Vagus nerve stimulation has been used for all types of refractory seizures and epilepsy types.

ACTH, adrenocorticotropic hormone; BDZ, benzodiazepine; CBZ, carbamazepine; CLB, clobazam; DZP: diazepam; ESM, ethosuximide; FBM: felbamate; GBP, gabapentin; IVIG, intravenous immunoglobulin; LAC, lacosamide; LEV, levetiracetam; LTG, lamotrigine; n/a, not applicable; OXC: oxcarbazepine; PB, phenobarbital; PHT, phenytoin; PRM, primidone; RFD, rufinamide; TPM, topiramate; VGB: vigabatrin; VPA, valproic acid; ZON, zonisamide.

Continued

Table 593-2 Classification for Epilepsy Syndromes with an Indication of Age of Onset, Duration of Active Epilepsy, Prognosis, and Therapeutic Options—cont'd

SPECIFIC SYNDROMES	AGE AT ONSET	AGE AT REMISSION	PROGNOSIS	MONOTHERAPY OR ADD-ON*	POSSIBLE ADD-ON†	SURGERY†
GENERALIZED EPILEPSIES OF UNKNOWN CAUSE WITH VARIABLE PHENOTYPES						
Juvenile absence epilepsy	10-12 yr	Usually lifelong	Good	ESM, LTG, VPA	BDZ	No
Juvenile myoclonic epilepsy	12-18 yr	Usually lifelong	Good	LEV, TPM, VPA	BDZ, LTG, PB, PRM, ZON	No
Epilepsy with generalized tonic-clonic seizures only	12-18 yr	Usually lifelong	Good	LEV, LTG, TPM, VPA	BDZ, CBZ, ZON	No
REFLEX EPILEPSIES						
Idiopathic photosensitive occipital lobe epilepsy	10-12 yr	Unclear	Variable	VPA	BDZ, LEV, LTG, ZON	No
Other visual sensitive epilepsies	2-5 yr	Unclear	Variable	VPA	BDZ, LEV, LTG, ZON	No
Startle epilepsy	Variable	Long lasting	Guarded	CBZ, GBP, OXC, PHT, TPM, VPA	CLB, LEV, PB, PHT, ZON	Lesionectomy ± cortical resection in some
EPILEPTIC ENCEPHALOPATHIES						
Early myoclonic encephalopathy and Ohtahara syndrome	Newborn-infant	Poor, Ohtahara syndrome evolves into West syndrome	Ominous	PB, steroids, VGB	BDZ, ZON	No
West syndrome	Infant	Variable	Variable	ACTH, steroids, VGB	BDZ, FBM, IVIG, TPM, ZON	Lesionectomy ± cortical resection
Dravet syndrome (severe myoclonic epilepsy in infancy)	Infant	No remission	Severe	CLB, stiripentol, TPM, VPA	BDZ, ZON	No
Lennox-Gastaut syndrome	3-10 yr	No remission	Severe	CLB, LTG, RFD, TPM, VPA	BDZ, FBM, IVIG, steroids, ZON	Callosotomy
Landau-Kleffner syndrome	3-6 yr	8-12 yr	Guarded	LEV, nocturnal DZP, steroids, VPA	BDZ, ESM, IVIG, LTG	Multiple subpial transections, rarely lesionectomy
Epilepsy with continuous spike waves during slow-wave sleep	4-7 yr	8-12 yr	Guarded	LEV, nocturnal DZP, steroids, VPA	BDZ, ESM, IVIG, LTG	No
PROGRESSIVE MYOCLONUS EPILEPSIES						
Unverricht-Lundborg, Lafora, ceroid lipofuscinoses, etc.	Late infant to adolescent	Progressive	Ominous	TPM, VPA, ZON	BDZ, PB	No
OTHER EPILEPSIES AND SEIZURE DISORDERS OF UNKNOWN OR OTHER CAUSES						
Benign neonatal seizures	Newborn	Newborn	Good	LEV, PB	—	No
Febrile seizures	3-5 yr	3-6 yr	Good	PB or VPA if repeated and prolonged	—	No
Reflex seizures	Variable	n/a		LEV, VPA	LTG, ZON	No
Drug or other chemically induced seizures	Variable	n/a		Withdraw offending agent	—	No
Immediate and early posttraumatic seizures	Variable	n/a		LEV, PHT	—	No

Modified from Guerrini R: Epilepsy in children, Lancet *367:499–524, 2006; and Parisi P, Verrotti A, Paolino MC, et al. "Electro-clinical syndromes" with onset in the pediatric age group: the highlights of the clinical-EEG, genetic and therapeutic advances.* Ital J Pediatr *37:58, 2011.*

Table 593-3 Identified Genes for Epilepsy Syndromes*†

EPILEPSY TYPE	GENE	PROTEIN
INFANTILE ONSET		
Benign familial neonatal seizures	*KCNQ2*	Potassium voltage-gated channel
	KCNQ3	Potassium voltage-gated channel
Benign familial neonatal infantile seizures	*SCN2A*	Sodium channel protein type 2α
Early familial neonatal infantile seizures	*SCN2A*	Sodium channel protein type 2α
Early infantile epileptic encephalopathy (EIEE)	*CDKL5 (EIEE2)*	Cyclin-dependent kinase-like 5
	ARX (EIEE1)	Aristaless-related homeobox
	TSC1	Hamartin
	TSC2	Tuberin
	SCN1A (EIEE6)	Sodium channel protein type 1α
	PCDH19(EIEE9)	Protocadherin-19
	KCNQ2 (EIEE7)	Potassium voltage-gated channel
	STXBP1 (EIEE4)	Syntaxin binding protein 1
	SLC2A1	Solute carrier family 2, facilitated glucose transporter member 1
	ALDH7A1	α-Aminoadipic semialdehyde dehydrogenase (antiquitin)
	POLG	DNA polymerase subunit gamma-1
	SCN2A (EIEE11)	Sodium channel protein type 2α
	PLCβ1 (EIEE12)	Phospholipase C β1
	ATP6AP2	Renin receptor
	SPTAN1 (EIEE5)	α_2-Spectrin
	SLC25A22 (EIEE3)	Mitochondrial glutamate carrier 1
	PNPO	Pyridoxine-5′-phosphate oxidase
Generalized epilepsy with febrile seizures plus (early onset)	*SCN1A*	Sodium channel protein type 1α
	SCN1B	Sodium channel protein type 1β
	GABRG2	γ-Aminobutyric acid receptor subunit γ2
	SCN2A	Sodium channel protein type 1α
CHILDHOOD ONSET		
Childhood onset epileptic encephalopathies	*SCN1A*	Sodium channel protein type 1α
	PCDH19	Protocadherin-19
	SLC2A1	Solute carrier family 2, facilitated GTM1
	POLG	DNA polymerase subunit γ1
	SCN2A	Sodium channel protein type 2α
Early onset absence seizures, refractory epilepsy of multiple types at times with movement disorder	*GLUT-1* deficiency syndrome, *SLC2A1*gene	Solute carrier family 2, facilitated GTM1
Generalized epilepsy with febrile seizure plus	*SCN1A*	Sodium channel protein type 1α
	SCN1B	Sodium channel protein type 1β
	GABRG2	γ-Aminobutyric acid receptor subunit γ2
	SCN2A	Sodium channel protein type 1α
Juvenile myoclonic epilepsy (more commonly presents in adolescence)	*EFHC1*	EF-hand domain-containing protein 1
	CACNB4	Voltage-dependent L-type calcium channel
	GABRA1	γ-Aminobutyric acid receptor subunit α1
Progressive myoclonic epilepsy (different forms present from infancy through adulthood)	*EPM2A*	Laforin
	NHLRC1	NHL repeat-containing protein 1 (Malin)
	CSTB	Cystatin-B
	PRICKLE1	Prickle-like protein 1
	PPT1, TPP1,CLN3, CLN5, CLN6, CLN8, CTSD, DNAJC5, MFSD8	Multiple proteins causing neuronal ceroid lipofuscinosis
Autosomal dominant nocturnal frontal lobe epilepsies (presents in childhood through adulthood)	*CHRNA4*	Neuronal acetylcholine receptor α4
	CHRNB2	Neuronal acetylcholine receptor β2
	CHRNA2	Neuronal acetylcholine receptor α2
ADOLESCENT ONSET		
Juvenile myoclonic epilepsy (JME)	See Childhood Onset JME	
Progressive myoclonic epilepsy (PME)	See Childhood Onset PME	
Autosomal dominant nocturnal frontal lobe epilepsies (AD-NFLE)	See Childhood Onset AD-NFLE	
Autosomal dominant lateral temporal lobe epilepsy (AD-LTLE)	See Childhood Onset AD-LTLE	
Autosomal dominant lateral temporal lobe epilepsy (usually presents in adulthood)	*LGI1*	Leucine-rich glioma-inactivated protein 1

*Note that the same gene (different mutations) often appears as causing different epilepsy syndromes.

†Most of these genes can be tested for through commercially available targeted single-gene sequencing or through commercially available gene panels or though exome sequencing (http://www.ncbi.nlm.nih.gov/sites/GeneTests/review?db=genetests).

Table 593-4 Identified Genes for Syndromic Epilepsy Syndromes*

SYNDROME	GENE	PROTEIN
Rett/atypical Rett syndromes	*MECP2* *CDKL5* *FOXG1* *MBD5* *MEF2C*	Methyl CpG binding protein 2 Cyclin-dependent kinase-like 5 Forkhead box protein G1 Methyl-CpG-binding domain protein 5 Myocyte-specific enhancer factor 2C
Angelman/Angelman-like/Pitt-Hopkins syndromes	*UBE3A* *SLC9A6* *MBD5* *TCF4* *NRXN1* *CNTNAP2*	Ubiquitin protein ligase E3A Sodium/hydrogen exchanger 6 Methyl-CpG-binding domain protein 5 Transcription factor 4 Neurexin-1 Contactin-associated protein-like 2
Mowat-Wilson syndrome	*ZEB2*	Zinc finger E-box-binding homeobox 2
Creatine deficiency syndromes	*GAMT* *GATM*	Guanidinoacetate *N*-methyltransferase Glycine amidinotransferase, mitochondrial
Neuronal ceroid lipofuscinosis (NCL)	*PPT1 (CLN1)* *TPP1 (CLN2)* *CLN3* *CLN5* *CLN6* *MFSD8 (CLN7)* *CLN8* *CTSD (CLN10)* *KCTD7 (CLN14)*	Palmitoyl-protein thioesterase 1 Tripeptidyl-peptidase 1 Battenin Ceroid-lipofuscinosis neuronal protein 5 Ceroid-lipofuscinosis neuronal protein 6 Major facilitator superfamily domain-containing protein 8 Ceroid-lipofuscinosis neuronal protein 8 Cathepsin D BTB/POZ domain-containing protein KCTD7
Adenosuccinate lyase deficiency	*ADSL*	Adenylosuccinate lyase
Cerebral folate deficiency	*FOLR1*	Folate receptor alpha
Epilepsy with variable learning and behavioral disorders	*GRIN2A* *SYN1*	Glutamate receptor ionotropic, *N*-methyl-D-aspartate (NMDA) 2A Synapsin-1
17q21.31 microdeletion syndrome	*KANSL1*	KAT8 regulatory nonspecific lethal (NSL) complex subunit 1
Microcephaly with early-onset intractable seizures and developmental delay (MCSZ)	*PNKP*	Bifunctional polynucleotide phosphatase/kinase

*Most of these genes can be tested for through commercially available targeted single-gene sequencing or through commercially available gene panels or though exome sequencing.

Table 593-5 Childhood Epileptic Syndromes with Generally Good Prognosis

SYNDROME	COMMENT
Benign neonatal familial convulsions	Dominant, may be severe and resistant for a few days Febrile or afebrile seizures (benign) occur later in a minority
Infantile familial convulsions	Dominant; seizures often in clusters
Febrile convulsions plus syndromes (see Table 593-2)	Febrile and afebrile generalized convulsions, absence and myoclonic seizures occur in different members. Seizures usually generalized (GEFS+) but in some families may be focal
Benign myoclonic epilepsy of infancy	Often seizures during sleep; 1 rare variety with reflex myoclonic seizures (touch, noise)
Partial idiopathic epilepsy with rolandic spikes (benign epilepsy with centrotemporal spikes)	Seizures with falling asleep or on awakening; focal sharp waves with centrotemporal location on EEG
Idiopathic occipital partial epilepsy	Early childhood form with seizures during sleep and ictal vomiting; can occur as status epilepticus Later form with occipital spikes that block on eye opening; migrainous symptoms and seizures; not always benign
Petit mal absence epilepsy	Cases with absences only; some have generalized seizures In most cases, absences disappear on therapy but there are resistant cases (unpredictable); 60-80% full remission
Juvenile myoclonic epilepsy	Adolescence onset, with early morning myoclonic seizures and generalized seizures during sleep or upon awakening; often history of absences in childhood

EEG, electroencephalogram; GEFS+, generalized epilepsy with febrile seizures plus.

Modified from Deonna T: Management of epilepsy, Arch Dis Child *90:5–9, 2005; and Seneviratne U: The prognosis of idiopathic generalized epilepsy,* Epilepsia *53(12):2079–2090, 2012.*

sơ sinh
- perinatal stroke
- bất thường chuyển hóa như hạ canxi
-

sốt co giật phức tạp
- khu trú
- >15p
-có cơn tái phát trong vòng 24h
trạng thái động kinh có sốt
- sốt co giật kéo dài >30p
....

lesion or the result of a genetic, idiopathic, epilepsy. Focal seizures in a neonate may be seen because of focal lesions like perinatal stroke or because of a metabolic abnormality like hypocalcemia caused by immaturity of the brain connections. Focal and generalized motor seizures may be tonic–clonic, tonic, clonic, myoclonic, or atonic. **Tonic seizures** are characterized by increased tone or rigidity, and **atonic seizures** are characterized by flaccidity or lack of movement during a convulsion. **Clonic seizures** consist of rhythmic fast muscle contractions and slightly longer relaxations; **myoclonus** is a "shock-like" contraction of a muscle of <50 msec that is often repeated. The duration of the seizure and state of consciousness (retained or impaired) should be documented. The history should determine whether an **aura** preceded the convulsion and the behavior of the child immediately preceding the seizure. The most common aura experienced by children consists of epigastric discomfort or pain and a feeling of fear. The posture of the patient, presence or absence and distribution of cyanosis, vocalizations, loss of sphincter control (particularly of the urinary bladder), and postictal state (including sleep, headache, and hemiparesis) should be noted.

In addition to the assessment of cardiorespiratory and metabolic status, examination of a child with a seizure disorder should be geared toward the search for an organic cause. The child's head circumference, length, and weight are plotted on a growth chart and compared with previous measurements. A careful general and neurologic examination should be performed. The **eyegrounds** must be examined for the presence of papilledema, optic neuritis, retinal hemorrhages, uveitis, chorioretinitis, coloboma, or macular changes, as well as retinal phakoma. The finding of unusual facial features or of associated physical findings such as hepatosplenomegaly point to an underlying metabolic or storage disease as the cause of the neurologic disorder. The presence of a **neurocutaneous disorder** may be indicated by the presence of vitiliginous ash leaf–type lesions using an ultraviolet light (Wood lamp), of adenoma sebaceum, shagreen patches, or of retinal phakomas (tuberous sclerosis), of multiple café-au-lait spots (neurofibromatosis), or of V1 or V2 distribution nevus flammeus (Sturge-Weber syndrome).

Localizing neurologic signs, such as a subtle **hemiparesis** with hyperreflexia, an equivocal Babinski sign, and a downward-drifting of an extended arm with eyes closed, might suggest a contralateral hemispheric structural lesion, such as a slow-growing glioma, as the cause of the seizure disorder. Unilateral growth arrest of the thumbnail, hand, or extremity in a child with a focal seizure disorder suggests a chronic condition, such as a porencephalic cyst, arteriovenous malformation, or cortical atrophy of the opposite hemisphere.

After the initial acute investigation, which often includes metabolic and CT scanning, depending on the clinical presentation in emergency room, in a child with a first nonfebrile seizure, it is recommended to obtain an EEG to help predict the risk of seizure recurrence. Subsequent imaging studies with MRI should be seriously considered in any child with a significant cognitive or motor impairment of unknown etiology, unexplained abnormalities on neurologic or psychiatric examination, a seizure of focal onset with or without secondary generalization, an EEG that does not represent a benign partial epilepsy of childhood or primary generalized epilepsy, or in children younger than 1 year of age. Other laboratory tests or lumbar punctures may be pursued depending on the specific clinical settings. Further details regarding the approach to a first seizure are included in Chapter 593.2.

co giật không sốt đầu tiên => EEG để dự đoán nguy cơ có giật tái diễn

593.1 Febrile Seizures

Mohamad A. Mikati and Abeer J. Hani

Febrile seizures are seizures that occur between the age of 6 and 60 mo with a temperature of 38°C (100.4°F) or higher, that are not the result of central nervous system infection or any metabolic imbalance, and that occur in the absence of a history of prior afebrile seizures. A **simple febrile seizure** is a primary generalized, usually tonic–clonic, attack associated with fever, lasting for a maximum of 15 min, and not recurrent within a 24-hr period. A **complex febrile seizure** is more prolonged (>15 min), is focal, and/or reoccurs within 24 hr. **Febrile status epilepticus** is a febrile seizure lasting longer than 30 min. Some use the term **simple febrile seizure plus** for those with recurrent febrile seizures within 24 hr. Most patients with simple febrile seizures have a very short postictal state and usually return to their baseline normal behavior and consciousness within minutes of the seizure.

Between 2% and 5% of neurologically healthy infants and children experience at least 1, usually simple, febrile seizure. Simple febrile seizures do not have an increased risk of mortality even though they are, understandably, concerning to the parents when they first witness them. Complex febrile seizures may have an approximately 2-fold long-term increase in mortality, as compared to the general population, over the subsequent 2 yr, probably secondary to coexisting pathology. There are no long-term adverse effects of having 1 or more simple febrile seizures. Compared with age-matched controls, patients with febrile seizures do not have any increase in the incidence of abnormalities of behavior, scholastic performance, neurocognitive function, or attention. Children who develop later epilepsy, however, might experience such difficulties. Febrile seizures recur in approximately 30% of those experiencing a first episode, in 50% after 2 or more episodes, and in 50% of infants younger than 1 yr old at febrile seizure onset. Several factors affect recurrence risk (Table 593-6). Although approximately 15% of children with epilepsy have had febrile seizures, only 2-7% of children who experience febrile seizures proceed to develop epilepsy later in life. There are several predictors of epilepsy after febrile seizures (Table 593-7).

GENETIC FACTORS

The genetic contribution to the incidence of febrile seizures is manifested by a positive family history for febrile seizures in many patients. In some families, the disorder is inherited as an autosomal dominant

Table 593-6 Risk Factors for Recurrence of Febrile Seizures

MAJOR
Age <1 yr
Duration of fever <24 hr
Fever 38-39°C (100.4-102.2°F)
MINOR
Family history of febrile seizures
Family history of epilepsy
Complex febrile seizure
Daycare
Male gender
Lower serum sodium at time of presentation

Having no risk factors carries a recurrence risk of approximately 12%; 1 risk factor, 25-50%; 2 risk factors, 50-59%; 3 or more risk factors, 73-100%.

Table 593-7 Risk Factors for Occurrence of Subsequent Epilepsy After a Febrile Seizure

RISK FACTOR	RISK FOR SUBSEQUENT EPILEPSY
Simple febrile seizure	1%
Recurrent febrile seizures	4%
Complex febrile seizures (more than 15 min duration or recurrent within 24 hr)	6%
Fever <1 hr before febrile seizure	11%
Family history of epilepsy	18%
Complex febrile seizures (focal)	29%
Neurodevelopmental abnormalities	33%

sốt co giật đơn giản
- co giật cơn toàn thể, thường là co cứng- co giật
- cơ co giật kết hợp với sốt
- kéo dài <= 15p
- k có cơn lặp lại trong vòng 24h

trait, and multiple single genes that cause the disorder have been identified in such families. However, in most cases the disorder appears to be polygenic, and the genes predisposing to it remain to be identified. Identified single genes include *FEB 1, 2, 3, 4, 5, 6, 7, 8, 9,* and *10* genes on chromosomes 8q13-q21, 19p13.3, 2q24, 5q14-q15, 6q22-24, 18p11.2, 21q22, 5q34, 3p24.2-p23, and 3q26.2-q26.33. Only the function of *FEB 2* is known: it is a sodium channel gene, *SCN1A*.

Almost any type of epilepsy can be preceded by febrile seizures, and a few epilepsy syndromes typically start with febrile seizures. These are **generalized epilepsy with febrile seizures plus** (GEFS+), **severe myoclonic epilepsy of infancy** (also called **Dravet syndrome**), and, in many patients, temporal lobe epilepsy secondary to mesial temporal sclerosis.

GEFS+ is an autosomal dominant syndrome with a highly variable phenotype. Onset is usually in early childhood and remission is usually in mid-childhood. It is characterized by multiple febrile seizures and by several subsequent types of afebrile generalized seizures, including generalized tonic–clonic, absence, myoclonic, atonic, or myoclonic astatic seizures with variable degrees of severity. A focal febrile seizures plus epilepsy variant, in which the seizures are focal rather than generalized, has also been described.

Dravet syndrome is the most severe of the phenotypic spectrum of febrile seizure-associated epilepsies. It constitutes a distinct entity in the onset of which is in infancy. Its onset is characterized by febrile and afebrile unilateral clonic seizures recurring every 1 or 2 mo. These early seizures are typically induced by fever, but they differ from the usual febrile convulsions in that they are more prolonged, are more frequent, are focal and come in clusters. Seizures subsequently start to occur with lower fevers and then without fever. During the 2nd yr of life, myoclonus, atypical absences, and partial seizures occur frequently and developmental delay usually follows. This syndrome is usually caused by a de novo mutation, although rarely it is inherited in an autosomal dominant manner. The mutated gene is located on 2q24-31 and encodes for *SCN1A*, the same gene mutated in GEFS+ spectrum. However, in Dravet syndrome the mutations lead to loss of function and thus to a more severe phenotype. There are several milder variants of Dravet syndrome that manifest some but not all of the above features and that are referred to as Dravet syndrome spectrum or Borderland. Mutations in other genes may also cause Dravet syndrome or GEFS+ phenotypes.

The majority of patients who had prolonged febrile seizures and encephalopathy after vaccination and who had been presumed to have suffered from **vaccine encephalopathy** (seizures and psychomotor regression occurring after vaccination and presumed to be caused by it) turn out to have Dravet syndrome mutations, indicating that their disease is caused by the mutation and not secondary to the vaccine. This has raised doubts about the very existence of the entity termed vaccine encephalopathy.

EVALUATION

Figure 593-1 delineates the general approach to the patient with febrile seizures. Each child who presents with a febrile seizure requires a detailed history and a thorough general and neurologic examination. Febrile seizures often occur in the context of otitis media, roseola and human herpesvirus (HHV) 6 infection, shigella, or similar infections, making the evaluation more demanding. In patients with febrile status, HHV-6B (more frequently) and HHV-7 infections were found to account for one-third of the cases. Several laboratory studies need to be considered in evaluating the patient with febrile seizures.

Lumbar Puncture

Meningitis should be considered in the differential diagnosis, and lumbar puncture should be performed for all infants younger than 6 mo of age who present with fever and seizure, or if the child is ill-appearing or at any age if there are clinical signs or symptoms of concern. A lumbar puncture is an option in a child 6-12 mo of age who is deficient in *Haemophilus influenzae* type b and *Streptococcus pneumoniae* immunizations or for whom immunization status is unknown. A lumbar puncture is an option in children who have been pretreated with antibiotics. *In patients presenting with febrile status epilepticus in the absence of a central nervous system infection, a nontraumatic lumbar puncture rarely shows cerebrospinal fluid (CSF) pleocytosis (96% have <3 nucleated cells in the CSF) and the CSF protein and glucose are usually normal.*

CDTS -> cần phân biệt vs viêm màng não
Nelson 2016: chỉ định CDTS
(1) tất cả trẻ < 6 tháng tuổi có sốt và co giật (fever + seizure)
(2) lâm sàng trẻ có dấu hiệu gợi ý viêm màng não
(3) trẻ 6-12m nếu chưa vaccin Hib, phế cầu hoặc không rõ chủng ngừa
(4) đã điều trị KS trước đó

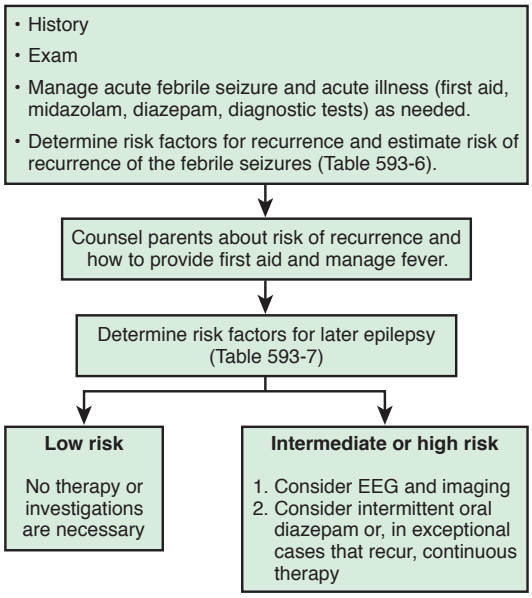

Figure 593-1 Management of febrile seizures. *(Modified from Mikati MA, Rahi A: Febrile seizures: from molecular biology to clinical practice,* Neurosciences (Riyadh) *10:14–22, 2004.)*

with antibiotics. *In patients presenting with febrile status epilepticus in the absence of a central nervous system infection, a nontraumatic lumbar puncture rarely shows cerebrospinal fluid (CSF) pleocytosis (96% have <3 nucleated cells in the CSF) and the CSF protein and glucose are usually normal.*

sốt co giật đơn giản lần đầu và không có bất thường sk gì hết: EEG không cần thực hiện. EEG không dự đoán sốt co giật trong tương lai và động kinh nếu kết quả bất thường

Electroencephalogram

If the child is presenting with the first simple febrile seizure and is otherwise neurologically healthy, an EEG need not normally be performed as part of the evaluation. An EEG would not predict the future recurrence of febrile seizures or epilepsy even if the result is abnormal. Spikes during drowsiness are often seen in children with febrile seizures, particularly those older than age 4 yr, and these do not predict later epilepsy. EEGs performed within 2 wk of a febrile seizure often have nonspecific slowing, usually posteriorly. Thus, in many cases, if an EEG is indicated, it is delayed until or repeated after more than 2 wk have passed. An EEG should, therefore, generally be restricted to special cases in which epilepsy is highly suspected, and, generally, it should be used to delineate the type of epilepsy rather than to predict its occurrence. If an EEG is done, it should be performed for at least 20 min in wakefulness and in sleep according to international guidelines to avoid misinterpretation and drawing of erroneous conclusions. At times, if the patient does not recover immediately from a seizure, then an EEG can help distinguish between ongoing seizure activity and a prolonged postictal period, sometimes termed a **nonepileptic twilight state.** EEG can also be helpful in patients who present with febrile status epilepticus because the presence of focal slowing present on the EEG obtained within 72 hr of the status has been shown to be highly associated with MRI evidence of acute hippocampal injury.

EEG: để xếp loại động kinh hơn là dự đoán tái phát

trạng thía động kinh có sốt: nên làm EEG

Blood Studies

Blood studies (serum electrolytes, calcium, phosphorus, magnesium, and complete blood count) are not routinely recommended in the work-up of a child with a first simple febrile seizure. Blood glucose should be determined in children with prolonged postictal obtundation or with poor oral intake (prolonged fasting). Serum electrolyte values may be abnormal in children after a febrile seizure, but this should be suggested by precipitating or predisposing conditions elicited in the history and reflected in abnormalities of the physical examination. If clinically indicated (e.g., in a history or physical examination

ion, calci, P, Mg, công thức máu: k làm thường qui ở trẻ SỐT CO GIẬT ĐƠN GIẢN LẦN ĐẦU
glucose: trẻ có trạng thái sau cơn kéo dài hoặc giảm ăn uống
ion đồ máu: khi khám thấy tình trạng mất nước

suggesting dehydration), these tests should be performed. A low sodium level is associated with higher risk of recurrence of the febrile seizure within the following 24 hr.

CT, MRI: k được khuyến cáo ở trẻ sốt co giật đơn giản lần đầu

Neuroimaging

A CT or MRI is not recommended in evaluating the child after a first simple febrile seizure. The work-up of children with complex febrile seizures needs to be individualized. This can include an EEG and neuroimaging, particularly if the child is neurologically abnormal. Approximately 11% of children with febrile status epilepticus are reported to have (usually) unilateral swelling of their hippocampus acutely, which is followed by subsequent long-term hippocampal atrophy. Whether these patients will ultimately develop temporal lobe epilepsy remains to be determined.

TREATMENT

In general, antiepileptic therapy, continuous or intermittent, is not recommended for children with 1 or more simple febrile seizures. Parents should be counseled about the relative risks of recurrence of febrile seizures and recurrence of epilepsy, educated on how to handle a seizure acutely, and given emotional support. If the seizure lasts for longer than 5 min, acute treatment with diazepam, lorazepam, or midazolam is needed (see Chapter 593.8 for acute management of seizures and status epilepticus). Rectal diazepam is often prescribed to be given at the time of reoccurrence of a febrile seizure lasting longer than 5 min (see Table 593-12 for dosing). Alternatively, buccal or intranasal midazolam may be used and is often preferred by parents. Intravenous benzodiazepines, phenobarbital, phenytoin, or valproate may be needed in the case of febrile status epilepticus. If the parents are very anxious concerning their child's seizures, intermittent oral diazepam (0.33 mg/kg every 8 hr during fever) or intermittent rectal diazepam (0.5 mg/kg administered as a rectal suppository every 8 hr), can be given during febrile illnesses. Intermittent oral nitrazepam, clobazam, and clonazepam (0.1 mg/kg/day) have also been used. Such therapies help reduce, but do not eliminate, the risks of recurrence of febrile seizures. Other therapies have included continuous phenobarbital (4-5 mg/kg/day in 1 or 2 divided doses), and continuous valproate (20-30 mg/kg/day in 2 or 3 divided doses). *In the vast majority of cases, it is not justified to use continuous therapy owing to the risk of side effects and lack of demonstrated long-term benefits, even if the recurrence rate of febrile seizures is expected to be decreased by these drugs.*

Antipyretics can decrease the discomfort of the child but do not reduce the risk of having a recurrent febrile seizure, probably because the seizure often occurs as the temperature is rising or falling. Chronic antiepileptic therapy may be considered for children with a high risk for later epilepsy. Currently available data indicate that the possibility of future epilepsy does not change with or without antiepileptic therapy. Iron deficiency is associated with an increased risk of febrile seizures, and thus screening for that problem and treating it appears appropriate.

Bibliography is available at Expert Consult.

593.2 Unprovoked Seizures

Mohamad A. Mikati and Abeer J. Hani

HISTORY AND EXAMINATION

Acute evaluation of a first seizure includes assessment of vital signs and respiratory and cardiac function, and institution of measures to normalize and stabilize them as needed. Signs of head trauma, abuse, drug intoxication, poisoning, meningitis, sepsis, focal abnormalities, increased intracranial pressure, herniation, neurocutaneous stigmata, brainstem dysfunction, and/or focal weakness should all be sought because they could suggest an underlying etiology for the seizure.

The **history** should also include details of the seizure manifestations, particularly those that occurred at its initial onset. These could give clues to the type and brain localization of the seizure. One should also probe for previous signs or symptoms of other seizures in the preceding weeks, or longer, that the parents may have overlooked and did not report. In some instances, if the events have been going on for a time and there is a question about their nature (e.g., sleep myoclonus vs seizures), then the family could video record the patient and make the video available to the healthcare provider. Having the parents imitate the seizure can also be helpful. Seizure patterns (e.g., clustering), precipitating conditions (e.g., sleep or sleep deprivation, television, visual patterns, mental activity, stress), exacerbating conditions (e.g., menstrual cycle, medications), frequency, duration, time of occurrence, and other characteristics need to be carefully documented (see Chapter 593.9). Parents often overlook, do not report, or underreport absence, complex partial, or myoclonic seizures. A history of personality change or symptoms of increased intracranial pressure can suggest an intracranial tumor. Similarly, a history of cognitive regression can suggest a degenerative or metabolic disease. Certain medications such as stimulants or antihistamines, particularly sedating ones, can precipitate seizures. A history of prenatal or perinatal distress or of developmental delay can suggest etiologic congenital or perinatal brain dysfunction. Details of the spells can suggest nonepileptic paroxysmal disorders that mimic seizures (see Chapter 594).

DIFFERENTIAL DIAGNOSIS

This involves consideration of nonepileptic paroxysmal events (see Chapter 594), determination of the seizure type, as classified by the new ILAE system (see Table 593-1) and consideration of potential underlying etiologies. Some seizures might begin with **auras**, which are sensory experiences reported by the patient and not observed externally. These can take the form of visual (e.g., flashing lights or seeing colors or complex visual hallucinations), somatosensory (tingling), olfactory, auditory, vestibular, or experiential (e.g., déjà vu, déjà vécu feelings) sensations, depending upon the precise localization of the origin of the seizures.

Motor seizures can be **tonic** (sustained contraction), **clonic** (rhythmic contractions), **myoclonic** (rapid shock-like contractions, usually <50 msec in duration, that may be isolated or may repeat but usually are not rhythmic), **atonic**, or **astatic**. **Astatic** seizures often follow myoclonic seizures and cause a very momentary loss of tone with a sudden fall. **Atonic** seizures, on the other hand, are usually longer and the loss of tone often develops more slowly. Sometimes it is difficult to distinguish among tonic, myoclonic, atonic, or astatic seizures based on the history alone when the family reports only that the patient "falls"; in such cases, the seizure may be described as a **drop attack**. Loss of tone or myoclonus in only the neck muscles results in a milder seizure referred to as a **head drop**. Tonic, clonic, myoclonic, and atonic seizures can be focal (including 1 limb or 1 side only), focal with secondary generalization, or primary generalized. Epileptic **spasms** (axial spasms, these terms being preferred over infantile spasms because they can occur beyond infancy) consist of flexion or extension of truncal and extremity musculature that is sustained for 1-2 sec, shorter than what is seen in tonic seizures, which last longer than 2 sec. Focal motor clonic and/or myoclonic seizures that persist for days, months, or even longer are termed **epilepsia partialis continua**.

Absence seizures are generalized seizures consisting of staring, unresponsiveness, and eye flutter lasting usually for few seconds. **Typical absences** are associated with 3 Hz spike–and–slow-wave discharges and with petit mal epilepsy, which has a good prognosis. **Atypical absences** are associated with 1-2 Hz spike–and–slow-wave discharges, and with head atonia and myoclonus during the seizures. They occur in Lennox-Gastaut syndrome, which has a poor prognosis. **Juvenile absences** are similar to typical absences but are associated with 4-5 Hz spike-and-slow waves and occur in juvenile myoclonic epilepsy. Seizure type and other EEG and clinical manifestations determine the type of **epilepsy syndrome** with which a particular patient is afflicted (Table 593-8; see Chapter 593.3 and 593.4).

Family history of certain forms of epilepsy, like benign neonatal seizures, can suggest the specific epilepsy syndrome. More often, however, different members of a family with a positive history of epilepsy have different types of epilepsy. Head circumference can indicate

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Table 593-8 Selected Epilepsy Syndromes by Age of Onset

NEONATAL PERIOD
Benign familial neonatal seizures (BFNS)
Early myoclonic encephalopathy (EME)
Ohtahara syndrome
INFANCY
Epilepsy of infancy with migrating focal seizures
West syndrome
Myoclonic epilepsy in infancy (MEI)
Benign infantile seizures
Benign familial infantile epilepsy
Dravet syndrome
Myoclonic encephalopathy in nonprogressive disorders
CHILDHOOD
Febrile seizures plus (FS+) (can start in infancy; this can be with generalized [GEFS+] or with focal seizures)
Early-onset benign childhood occipital epilepsy (Panayiotopoulos type)
Epilepsy with myoclonic atonic (previously astatic) seizures
Benign epilepsy with centrotemporal spikes (BCECTS)
Late-onset childhood occipital epilepsy (Gastaut type)
Autosomal dominant nocturnal frontal lobe epilepsy (AD-NFLE)
Epilepsy with myoclonic absences
Lennox-Gastaut syndrome
Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)
Landau-Kleffner syndrome
Childhood absence epilepsy (CAE)
ADOLESCENCE–ADULT
Juvenile absence epilepsy (JAE)
Juvenile myoclonic epilepsy (JME)
Epilepsy with generalized tonic–clonic seizures alone
Progressive myoclonus epilepsies (PME)
Autosomal dominant epilepsy with auditory features (ADEAF)
Other familial temporal lobe epilepsies
AGE-RELATED (AGE OF ONSET LESS SPECIFIC)
Familial focal epilepsy with variable foci (childhood to adult)
Reflex epilepsies
SEIZURE DISORDERS THAT ARE NOT TRADITIONALLY GIVEN THE DIAGNOSIS OF EPILEPSY
Benign neonatal seizures (BNS)
Febrile seizures (FS)
EPILEPTIC ENCEPHALOPATHIES
EME
Ohtahara syndrome
Migrating partial seizures of infancy
West syndrome
Dravet syndrome
Myoclonic encephalopathy in nonprogressive disorders
Epilepsy with myoclonic astatic seizures
Lennox-Gastaut syndrome
Epileptic encephalopathy with CSWS
Landau-Kleffner syndrome
OTHER SECONDARY GENERALIZED EPILEPSIES
Generalized epilepsy secondary to neurodegenerative disease
Progressive myoclonus epilepsies

Modified from Berg AT, Berkovic SF, Bordie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia *51:676–685, 2010.*

Table 593-9 Proposed Diagnostic Scheme for People with Epileptic Seizures and with Epilepsy

Epileptic seizures and epilepsy syndromes are to be described and categorized according to a system that uses standardized terminology and that is sufficiently flexible to take into account the practical and dynamic aspects of epilepsy diagnosis:

- Axis 1: Ictal phenomenology, used to describe ictal events with any degree of detail needed.
- Axis 2: Seizure type, from the List of types of Epileptic Seizures. Localization within the brain and precipitating stimuli for reflex seizures should be specified when appropriate.
- Axis 3: Syndrome, from the List of Epilepsy Syndromes, with the understanding that a syndromic diagnosis may not always be possible.
- Axis 4: Etiology, from a Classification of Diseases Frequently Associated with Epileptic Seizures or Epilepsy Syndromes when possible, genetic defects, or specific pathologic substrates for symptomatic focal epilepsies.
- Axis 5: Impairment; this is often useful to make sure one does not overlook the consequences of epilepsy, such as medication side effects, and learning and socialization difficulties.

Modified from Engel J. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE task force on classification and terminology. Epilepsia. 2001;42:796–803.

the presence of microcephaly or of macrocephaly. Eye exam may show optic disc edema, retinal hemorrhages, chorioretinitis, colobomata (associated with brain malformations), a cherry-red spot, optic atrophy, macular changes (associated with genetic neurodegenerative and storage diseases), or phakomas (associated with tuberous sclerosis). Skin exam could show a trigeminal V_1 distribution capillary hemangioma (associated with Sturge-Weber syndrome), hypopigmented lesions (sometimes associated with tuberous sclerosis and detected more reliably by viewing the skin under UV light), or other neurocutaneous manifestations such as Shagreen patches and adenoma sebaceum (associated with tuberous sclerosis), or whorl-like hypopigmented areas (hypomelanosis of Ito, associated with hemimegalencephaly). Subtle asymmetries on the exam such as drift of 1 of the extended arms, posturing of an arm on stress gait, slowness in rapid alternating movements, small hand or thumb and thumb nail on 1 side, or difficulty in hopping on 1 leg relative to the other can signify a subtle hemiparesis associated with a lesion on the contralateral side of the brain.

Guidelines on the evaluation of a **first unprovoked nonfebrile** seizure include a careful history and physical examination and brain imaging by head CT or MRI. Emergency head CT in the child presenting with a first unprovoked nonfebrile seizure is often useful for acute management of the patient. Laboratory studies are recommended in specific clinical situations: Spinal tap is considered in patients with suspected meningitis or encephalitis, in children without brain swelling or papilledema, and in children in whom a history of intracranial bleeding is suspected without evidence of such on head CT. In the second of these, examination of the CSF for xanthochromia is essential. Electrocardiography (ECG) to rule out long QT or other cardiac dysrhythmias and other tests directed at disorders that could mimic seizures may be needed (see Chapter 594). EEG is highly recommended to assess for focal abnormalities and predict seizure recurrence.

LONG-TERM APPROACH TO THE PATIENT AND ADDITIONAL TESTING

The approach to the patient with epilepsy is based on the diagnostic scheme proposed by the ILAE Task Force on Classification and Terminology and presented in Table 593-9. This emphasizes the total approach to the patient, including identification, if possible, of the underlying etiology of the epilepsy and the impairments that result from it. The impairments are very often just as important as, if not more important than, the seizures themselves. Most epilepsy syndromes are potentially caused by any 1 of multiple underlying or still undetermined etiologies. However, in addition, there are many epilepsy syndromes that are associated with specific gene mutations (see Table 593-2). Different mutations of the same gene can result in different epilepsy syndromes, and mutations of different genes can cause the same epilepsy syndrome phenotype. The clinical use of gene testing in the diagnosis and management of childhood epilepsy has been limited to patients manifesting specific underlying malformational, metabolic, or degenerative disorders, patients with severe named epilepsy syndromes (such as West and Dravet syndromes and progressive

myoclonic epilepsies), and to patients with syndromes of mendelian inheritance (see Table 593-2).

Patients with **recurrent seizures**, specifically with 2 seizures spaced apart by longer than 24 hr, warrant further work-up directed at the underlying etiology. In patients with drug-resistant epilepsy, or in infants with new-onset epilepsy in whom the initial testing did not reveal an underlying etiology, a full metabolic work-up, including amino acids, organic acids, biotinidase, and CSF studies, is needed. Additional testing can include, depending on the case, some or most of the following:

1. Measurement of serum lactate, pyruvate, acyl carnitine profile, creatine, very-long-chain fatty acids, and guanidino-acetic acid.
2. Blood and serum sometimes need to be tested for white blood cell lysosomal enzymes, serum coenzyme Q levels, and serum copper and ceruloplasmin levels (for Menkes syndrome).
3. Serum immune isoelectric focusing is performed for carbohydrate-deficient transferrin.
4. CSF glucose testing looks for glucose transporter deficiency, and CSF can be examined for cells and proteins (for parainfectious and postinfectious syndromes, and for Aicardi-Goutières syndrome, which also shows cerebral calcifications and has a specific gene defect test available).
5. Other laboratory studies include immunoglobulin (Ig) G index, NMDA (*N*-methyl-D-aspartate) receptor antibodies, and measles titers.
6. CSF tests can also confirm with, the appropriate clinical setup, the diagnosis of cerebral folate deficiency, pyridoxine dependency, pyridoxal dependency, mitochondrial disorders, nonketotic hyperglycinemia, neopterin/biopterin metabolism disorders, adenylosuccinate lyase deficiency, and neurotransmitter deficiencies. In infants who do not respond immediately to antiepileptic therapy, vitamin B_6 (100 mg intravenously) is given as a therapeutic trial to help diagnose pyridoxine-responsive seizures, with precautions to guard against possible apnea. The trial is best done with continuous EEG monitoring, including a preadministration baseline recording period. Prior to the vitamin B_6 trial, a pipecolic acid level and urine and CSF α-aminoadipic acid semialdehyde levels should be drawn, because they often elevated in this rare syndrome and the therapeutic trial result may not be definitive. Some patients are pyridoxal phosphate, rather than pyridoxine, dependent. Also patients with cerebral folate deficiency can have intractable seizures. Thus trials of pyridoxal phosphate given orally (up to 50 mg/kg) and folinic acid (up to 3 mg/kg) over several weeks can help diagnose these rare disorders while waiting for the definitive diagnosis from CSF or genetic testing for these disorders. Certain EEG changes such as continuous spike–and–slow-wave seizure activity and burst-suppression patterns may also suggest these vitamin-responsive syndromes.
7. Urine may also need to be tested for urinary sulfites indicating molybdenum cofactor deficiency and for oligosaccharides and mucopolysaccharides. MR spectroscopy is performed for lactate and creatine peaks to rule out mitochondrial disease and creatine transporter deficiency.
8. Gene testing looks for specific disorders that can manifest with seizures, including *SCN1A* mutations in Dravet syndrome; *ARX* gene for West syndrome in boys; *MECP2, CDKL5,* and protocadherin 19 for Rett syndrome and similar presentations; syntaxin binding protein for Ohtahara syndrome; and polymerase G for West syndrome and other seizures in infants. Gene testing can also be performed for other dysmorphic or metabolic syndromes.
9. Muscle biopsy can be performed for mitochondrial enzymes and coenzyme Q10 levels, and skin biopsy for inclusion bodies seen in neuronal ceroid lipofuscinosis and Lafora body disease is sometimes needed.
10. Genetic panels are available that include multiple genes that can cause epilepsy at specific ages; whole-exome sequencing is also available. These can be helpful in selected patients.

Most patients do not require a work-up anywhere near the above described extensive testing. The pace and extent of the work-up must depend critically upon the clinical epileptic and nonepileptic features, the family and antecedent personal history of the patient, the medication responsiveness of the seizures, the likelihood of identifying a treatable condition, and the wishes and need of the family to assign a specific diagnosis to the child's illness.

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593.3 Partial Seizures and Related Epilepsy Syndromes

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Partial (now referred to as focal) seizures account for approximately 40% of seizures in children and can be divided into **simple partial seizures** (currently referred to in the most recent ILAE classification as **focal seizures without impairment of consciousness**), in which consciousness is not impaired, and **complex partial seizures** (currently referred to as **focal seizures with impairment of consciousness**, also called **focal dyscognitive seizures**), in which consciousness is affected. Simple and complex partial seizures can each occur in isolation, one can temporally lead to the other (usually simple to complex), and/or each can progress into **secondary generalized seizures** (tonic, clonic, atonic, or most often tonic–clonic).

FOCAL SEIZURES WITHOUT IMPAIRMENT OF CONSCIOUSNESS

These can take the form of sensory seizures (auras) or brief motor seizures, the specific nature of which gives clues as to the location of the seizure focus. Brief motor seizures are the most common and include focal tonic, clonic, or atonic seizures. Often there is a motor (jacksonian) march from face to arm to leg, adversive head and eye movements to the contralateral side, or postictal (Todd) paralysis that can last minutes or hours, and sometimes longer. Unlike tics, motor seizures are not under partial voluntary control; seizures are more often stereotyped and less likely than tics to manifest different types in a given patient.

FOCAL SEIZURES WITH IMPAIRMENT OF CONSCIOUSNESS

These seizures usually last 1-2 min and are often preceded by an **aura**, such as a rising abdominal feeling, déjà vu or déjà vécu, a sense of fear, complex visual hallucinations, micropsia or macropsia (temporal lobe), generalized difficult-to-characterize sensations (frontal lobe), focal sensations (parietal lobe), or simple visual experiences (occipital lobe). Children younger than 7 yr old are less likely than older children to report auras, but parents might observe unusual preictal behaviors that suggest the experiencing of auras. Subsequent manifestations consist of decreased responsiveness, staring, looking around seemingly purposelessly, and automatisms. **Automatisms** are automatic semipurposeful movements of the mouth (oral, alimentary such as chewing) or of the extremities (manual, such as manipulating the sheets; leg automatisms such as shuffling, walking). Often there is salivation, dilation of the pupils, and flushing or color change. The patient might appear to react to some of the stimulation around him or her but does not later recall the epileptic event. At times, walking and/or marked limb flailing and agitation occur, particularly in patients with frontal lobe seizures. Frontal lobe seizures often occur at night and can be very numerous and brief, but other complex partial seizures from other areas in the brain can also occur at night, too. There is often contralateral dystonic posturing of the arm and, in some cases, unilateral or bilateral tonic arm stiffening. Some seizures have these manifestations with minimal or no automatisms. Others consist of altered consciousness with contralateral motor, usually clonic, manifestations. After the seizure, the patient can have postictal automatisms, sleepiness, and/or other transient focal deficits such as weakness (Todd paralysis) or aphasia.

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SECONDARY GENERALIZED SEIZURES

Seizures of this type were previously known as focal seizures with impairment of consciousness evolving to bilateral convulsive seizures. Secondary generalized seizures can start with generalized clinical phenomena (from rapid spread of the discharge from the initial focus), or as simple or complex partial seizures with subsequent clinical generalization. There is often adversive eye and head deviation to the side contralateral to the side of the seizure focus followed by generalized tonic, clonic, or tonic–clonic activity. Tongue biting, urinary and stool incontinence, vomiting with risk of aspiration, and cyanosis are common. Fractures of the vertebrae or humerus are rare complications. Most such seizures last 1-2 min. Tonic focal or secondary generalized seizures often manifest adversive head deviation to the contralateral side, or fencing, hemi- or full figure-of-four arm, or Statue of Liberty postures. These postures often suggest frontal origin, particularly when consciousness is preserved during them, indicating that the seizure originated from the medial frontal supplementary motor area.

EEG in patients with focal/partial seizures usually shows focal spikes or sharp waves in the lobe where the seizure originates. A sleep-deprived EEG with recording during sleep increases the diagnostic yield and is advisable in all patients whenever possible (Fig. 593-2). Despite that, approximately 15% of children with epilepsy initially have normal EEGs because the discharges are relatively infrequent or the focus is deep. If repeating the test does not detect paroxysmal findings, then longer recordings in the laboratory or using ambulatory EEG or even inpatient 24-hr video EEG monitoring may be helpful. The latter is particularly helpful if the seizures are frequent enough, because it then can allow visualization of the clinical events and the corresponding EEG tracing.

Brain imaging is critical in patients with focal seizures. In general, MRI is preferable to CT, which misses subtle but occasionally potentially clinically significant lesions. MRI can show pathologies such as changes as a result of previous strokes or hypoxic injury, malformations, medial temporal sclerosis, arteriovenous malformations, inflammatory pathologies, or tumors (Fig. 593-3).

BENIGN EPILEPSY SYNDROMES WITH FOCAL SEIZURES

The most common such syndrome is **benign childhood epilepsy with centrotemporal spikes** which typically starts during childhood (ages 3-10 yr) and is outgrown in adolescence. The child typically wakes up at night owing to a focal (simple partial) seizure causing buccal and throat tingling and tonic or clonic contractions of 1 side of the face, with drooling and inability to speak but with preserved consciousness and comprehension. Dyscognitive focal (complex partial) and secondary generalized seizures can also occur. EEG shows typical broad-based centrotemporal spikes that are markedly increased in frequency during drowsiness and sleep. MRI is normal. Patients respond very well to antiepileptic drugs (AEDs) such as carbamazepine. In some patients who only have rare and mild seizures treatment might not be needed.

Benign epilepsy with occipital spikes can occur in early childhood (**Panayiotopoulos type**) and manifests with complex partial seizures with ictal vomiting, or they appear in later childhood (**Gastaut type**) with complex partial seizures, visual auras, and migraine headaches. Both are typically outgrown in a few years. Manifestations may include visual hallucinations and postictal headache (epilepsy–migraine sequence).

In infants, several less-common **benign infantile familial convulsion syndromes** have been reported. For some of these, the corresponding gene mutation and its function are known (see Tables 593-2 and 593-5), but for others, the genetic underpinnings are yet to be determined. Specific syndromes include benign infantile familial convulsions with parietooccipital foci linked to chromosomal loci 19q and 2q, benign familial infantile convulsions with associated choreoathetosis linked to chromosomal locus 16p12-q12, and benign

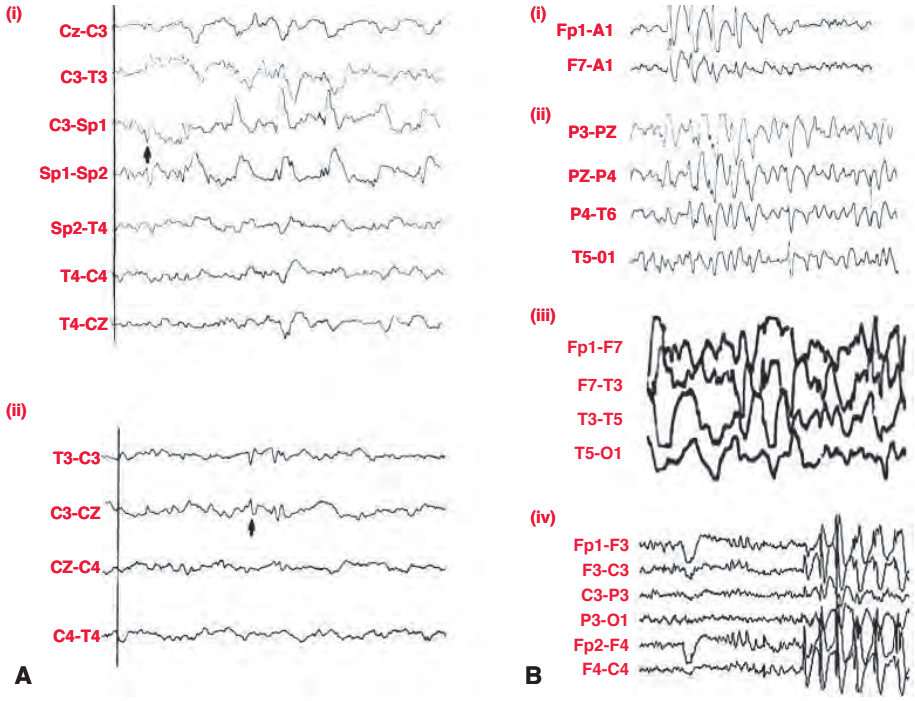

Figure 593-2 **A,** Representative EEG associated with partial seizures: (i) Spike discharges from the left temporal lobe *(arrow)* in a patient with complex partial seizures caused by mesial temporal sclerosis; (ii) left central-parietal spikes *(arrow)* characteristic of benign partial epilepsy with centrotemporal spikes. **B,** Representative EEGs associated with generalized seizures: (i) 3/sec spike-and-wave discharge of absence seizures with normal background activity; (ii) 1-2/sec interictal slow spike waves in a patient with Lennox-Gastaut syndrome; (iii) hypsarrhythmia with an irregular multifocal high-voltage spike and wave activity with chaotic high-voltage slow background; (iv) juvenile myoclonic epilepsy EEG showing 4-6/sec spike and waves enhanced by photic stimulation.

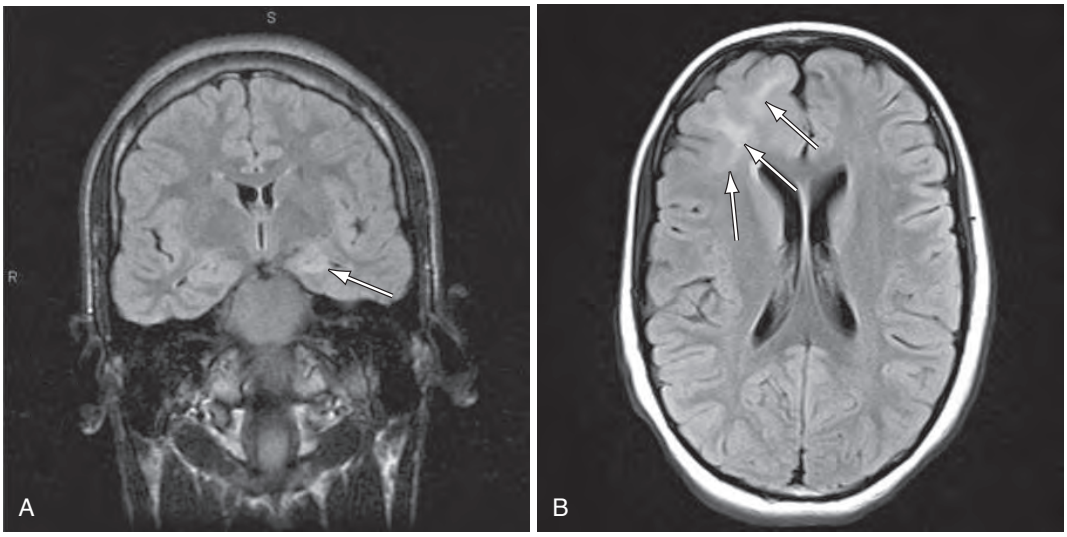

Figure 593-3 **A,** Coronal fluid-attenuated inversion-recovery (FLAIR) MRI scan of a 13 yr old with intractable seizures and mesial temporal sclerosis (MTS). The *arrow* points at the hippocampus with the high-intensity signal characteristic of MTS. **B,** Axial FLAIR MRI of a 7 yr old with intractable seizures and right frontal cortical dysplasia. The *arrows* point at the high-intensity signal corresponding to the dysplasia. *(**A** from Lee JYK, Adelson PD: Neurosurgical management of pediatric epilepsy,* Pediatr Clin North Am *51:441–456, 2004.)*

infantile familial convulsions with hemiplegic migraine linked to chromosome 1. A number of **benign infantile nonfamilial syndromes** have been reported, including dyscognitive focal (complex partial) seizures with temporal foci, secondary generalized tonic–clonic seizures with variable foci, tonic seizures with midline foci, and partial seizures in association with mild gastroenteritis. All of these have a good prognosis and respond to treatment promptly, often necessitating only short-term (e.g., 6 mo), if any, therapy. **Nocturnal autosomal dominant frontal lobe epilepsy** has been linked to acetylcholine-receptor gene mutations and manifests with nocturnal seizures with dystonic posturing and agitation, screaming, kicking that respond promptly to carbamazepine. Several other less-frequent familial benign epilepsy syndromes with different localizations have also been described, some of which occur exclusively or predominantly in adults (see Table 593-2).

SEVERE EPILEPSY SYNDROMES WITH FOCAL SEIZURES

Symptomatic structural/metabolic epilepsy secondary to focal brain lesions has a higher chance of being severe and refractory to therapy than idiopathic genetic epilepsy. It is important to note that many patients with focal lesions, for example, old strokes or brain tumors, either never have seizures or have well-controlled epilepsy. In infants, drug-resistant epilepsy with focal seizures is often caused by severe metabolic problems, hypoxic–ischemic injury, or congenital malformations. In addition, in this age group, a syndrome of multifocal severe partial seizures with progressive mental regression and cerebral atrophy called **migrating partial seizures of infancy** has been described. In infants and older children, several types of lesions, which can occur in any lobe, can cause intractable epilepsy and seizures and some cases may be secondary to mutations in the calcium sensitive potassium channel KCNT1. Brain malformations causing focal epilepsy include focal cortical dysplasia, hemimegalencephaly, Sturge-Weber hemangioma, tuberous sclerosis, and congenital tumors such as ganglioglioma, and dysembryoplastic neuroepithelial tumors, as well as others. The intractable seizures can be simple partial, complex partial, secondary generalized, or combinations thereof. If secondary generalized seizures predominate and take the form of absence-like seizures and drop attacks, the clinical picture can mimic the generalized epilepsy syndrome of Lennox-Gastaut syndrome and has been termed by some **pseudo–Lennox-Gastaut syndrome**.

Temporal lobe epilepsy can be caused by any temporal lobe lesion. A common cause is **mesial** (also termed **medial**) **temporal sclerosis**, a condition often preceded by febrile seizures and, rarely, genetic in origin. Pathologically, these patients have atrophy and gliosis of the hippocampus and, in some, of the amygdala. It is the most common cause of surgically remediable partial epilepsy in adolescents and adults. Occasionally, in patients with other symptomatic or cryptogenic partial or generalized epilepsies, the focal discharges are so continuous that they cause an epileptic encephalopathy. Activation of temporal discharges in sleep can lead to loss of speech and verbal auditory agnosia (**Landau-Kleffner epileptic aphasia syndrome**). Activation of frontal and secondary generalized discharges in sleep leads to more global delay secondary to the **syndrome of continuous spike waves in slow-wave sleep** (>85% of slow-wave sleep recording dominated by discharges).

The syndrome of **Rasmussen encephalitis** is a form of chronic encephalitis that manifests with unilateral intractable partial seizures, epilepsia partialis continua, and progressive hemiparesis of the affected side, with progressive atrophy of the contralateral hemisphere. The etiology is usually unknown. Some cases have been attributed to cytomegalovirus and others to anti-NMDA receptor autoantibodies.

593.4 Generalized Seizures and Related Epilepsy Syndromes

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ABSENCE SEIZURES

Typical absence seizures usually start at 5-8 yr of age and are often, owing to their brevity, overlooked by parents for many months even though they can occur up to hundreds of times per day. Unlike complex partial seizures they do not have an aura, usually last for only a few seconds, and are accompanied by eye lid flutter or upward rolling of the eyes but typically not by the usually more florid automatisms of complex partial seizures (absence seizures can have simple automatisms like lip-smacking or picking at clothing and the head can minimally fall forward). Absence seizures do not have a postictal period and are characterized by immediate resumption of what the patient was doing before the seizure. Hyperventilation for 3-5 min can precipitate the seizures and the accompanying 3 Hz spike–and–slow-wave

discharges. The presence of periorbital, lid, perioral or limb myoclonic jerks with the typical absence seizures usually predicts difficulty in controlling the seizures with medications. Early onset absence seizures (before the age of 4 yr) should trigger evaluation for glucose transporter defect that is often associated with low CSF glucose levels and an abnormal sequencing test of the transporter gene.

Atypical absence seizures have associated myoclonic components and tone changes of the head (head drop) and body and are also usually more difficult to treat. They are precipitated by drowsiness and are usually accompanied by 1-2 Hz spike–and–slow-wave discharges.

Juvenile absence seizures are similar to typical absences but occur at a later age and are accompanied by 4-6 Hz spike–and–slow-wave and polyspike–and–slow-wave discharges. These are usually associated with juvenile myoclonic epilepsy (see "Benign Generalized Epilepsies").

GENERALIZED MOTOR SEIZURE

The most common generalized motor seizures are generalized tonic–clonic seizures that can be either primarily generalized (bilateral) or secondarily generalized (as described in Chapter 593.3) from a unilateral focus. If there is no partial component, then the seizure usually starts with loss of consciousness and, at times, with a sudden cry, upward rolling of the eyes, and a generalized tonic contraction with falling, apnea, and cyanosis. In some, a clonic or myoclonic component precedes the tonic stiffening. The tonic phase is followed by a clonic phase that, as the seizure progresses, shows slowing of the rhythmic contractions until the seizure stops usually 1-2 min later. Incontinence and a postictal period often follow. The latter usually lasts for 30 min to several hours with semicoma or obtundation and postictal sleepiness, weakness, ataxia, hyper- or hyporeflexia, and headaches. There is a risk of aspiration and injury. First aid measures include positioning the patient on his or her side, clearing the mouth if it is open, loosening tight clothes or jewelry, and gently extending the head and, if possible, insertion of an airway by a trained professional. The mouth should not be forced open with a foreign object (this could dislodge teeth, causing aspiration) or with a finger in the mouth (this could result in serious injury to the examiner's finger). Many patients have single **idiopathic generalized tonic–clonic seizures** that may be associated with intercurrent illness or with a cause that cannot be ascertained (see Chapter 593.2). Generalized tonic, atonic, and astatic seizures often occur in severe generalized pediatric epilepsies. Generalized myoclonic seizures can occur in either benign or difficult-to-control generalized epilepsies (see "Benign Generalized Epilepsies" and "Severe Generalized Epilepsies").

BENIGN GENERALIZED EPILEPSIES

Petit mal epilepsy typically starts in mid-childhood, and most patients outgrow it before adulthood. Approximately 25% of patients also develop generalized tonic–clonic seizures, half before and half after the onset of absences. **Benign myoclonic epilepsy of infancy** consists of the onset of myoclonic and other seizures during the 1st yr of life, with generalized 3 Hz spike–and–slow-wave discharges. Often, it is initially difficult to distinguish this type from more-severe syndromes, but follow-up clarifies the diagnosis. **Febrile seizures plus syndrome** manifests febrile seizures and multiple types of generalized seizures in multiple family members, and at times different individuals within the same family manifest different generalized and febrile seizure types (see Chapter 593.1).

Juvenile myoclonic epilepsy (Janz syndrome) is the most common generalized epilepsy in young adults, accounting for 5% of all epilepsies. It has been linked to mutations in many genes including *CACNB4; CLNC2; EJM2, 3, 4, 5, 6, 7, 9; GABRA1; GABRD;* and *Myoclonin1/EFHC1* (see Table 593-2). Typically, it starts in early adolescence with 1 or more of the following manifestations: myoclonic jerks in the morning, often causing the patient to drop things; generalized tonic–clonic or clonic–tonic–clonic seizures upon awakening; and juvenile absences. Sleep deprivation, alcohol (in older patients), and photic stimulation, or, rarely, certain cognitive activities can act as precipitants. The EEG usually shows generalized 4-5 Hz polyspike–and–slow-wave discharges. There are other forms of generalized epilepsies such as **photoparoxysmal epilepsy**, in which generalized tonic–clonic, absence or myoclonic generalized seizures are precipitated by photic stimuli such as strobe lights, flipping through TV channels and viewing video games. Other forms of **reflex** (i.e., **stimulus-provoked**) **epilepsy** can occur; associated seizures are usually generalized, although some may be focal (see Table 593-1 and Chapter 593.9).

SEVERE GENERALIZED EPILEPSIES

Severe generalized epilepsies are associated with intractable seizures and developmental delay. **Early myoclonic infantile encephalopathy** starts during the 1st 2 mo of life with severe myoclonic seizures and burst suppression pattern on EEG. It is usually caused by inborn errors of metabolism such as non-ketotic hyperglycinemia. **Early infantile epileptic encephalopathy (Ohtahara syndrome)** has similar age of onset and EEG but manifests tonic seizures and is usually caused by brain malformations or syntaxin binding protein 1 mutations. Severe **myoclonic epilepsy of infancy (Dravet syndrome)** starts as focal febrile status epilepticus or focal febrile seizures and later manifests myoclonic and other seizure types (see Chapter 593.1).

West syndrome starts between the ages of 2 and 12 mo and consists of a triad of infantile epileptic spasms that usually occur in clusters (particularly in drowsiness or upon arousal), developmental regression, and a typical EEG picture called **hypsarrhythmia** (see Fig. 593-2). Hypsarrhythmia is a high-voltage, slow, chaotic background with multifocal spikes. Patients with cryptogenic (sometimes called idiopathic, now referred to as unknown etiology) West syndrome have normal development before onset, while patients with symptomatic West syndrome have preceding developmental delay owing to perinatal encephalopathies, malformations, underlying metabolic disorders, or other etiologies (see Chapter 593.2). In boys, West syndrome can also be caused by *ARX* gene mutations (often associated with ambiguous genitalia and cortical migration abnormalities). West syndrome, especially in cases of unknown etiology (cryptogenic cases, i.e., cases that are not symptomatic of metabolic or structural brain disorder), is a medical emergency because diagnosis delayed for 3 wk or longer can affect long-term prognosis. The spasms are often overlooked by parents and by physicians, being mistaken for startles caused by colic or for other benign paroxysmal syndromes (see Chapter 594).

Lennox-Gastaut syndrome typically starts between the ages of 2 and 10 yr and consists of a triad of developmental delay, multiple seizure types that as a rule include atypical absences, myoclonic, astatic, and tonic seizures. The tonic seizures occur either in wakefulness (causing falls and injuries) or also, typically, in sleep. The third component is the EEG findings (see Fig. 593-2): 1-2 Hz spike–and–slow waves, polyspike bursts in sleep, and a slow background in wakefulness. Patients commonly have myoclonic, atonic, and other seizure types that are difficult to control, and most are left with long-term cognitive impairment and intractable seizures despite multiple therapies. Some, but not all, patients start with Ohtahara syndrome, develop West syndrome, and then progress to Lennox-Gastaut syndrome. **Myoclonic astatic epilepsy** is a syndrome similar to, but milder than, Lennox-Gastaut syndrome that usually does not have tonic seizures or polyspike bursts in sleep. The prognosis is more favorable than that for Lennox-Gastaut syndrome. Another syndrome characterized by atonic seizures causing head nodding as well as tonic, clonic and stimulus sensitive seizures is the **nodding syndrome**, which is a recently described epidemic type of epilepsy seen in some African countries and often associated with encephalopathy, stunted growth, and variable degrees of cognitive deficits. The underlying etiology is unknown.

Progressive myoclonic epilepsies are a group of epilepsies characterized by progressive dementia and worsening myoclonic and other seizures. **Type I** or **Unverricht-Lundborg disease** (secondary to a cystatin B mutation) is more slowly progressive than the other types and usually starts in adolescence. **Type II** or **Lafora body disease** can have an early childhood onset but usually starts in adolescence, is more quickly progressive, and is usually fatal within the 2nd or 3rd decade. It can be associated with photosensitivity, manifests periodic acid–Schiff-positive Lafora inclusions on muscle or skin biopsy (in eccrine

sweat gland cells), and has been shown to be caused by laforin *(EPM2A)* or malin *(EPM2B)* gene mutations. Other causes of progressive myoclonic epilepsy include myoclonic epilepsy with ragged red fibers, sialidosis type I, neuronal ceroid lipofuscinosis, juvenile neuropathic Gaucher disease, dentatorubral-pallidoluysian atrophy, and juvenile neuroaxonal dystrophy.

Myoclonic encephalopathy in nonprogressive disorders is an epileptic encephalopathy that occurs in some congenital disorders affecting the brain, such as Angelman syndrome, and consists of almost continuous and difficult-to-treat myoclonic and, at times, other seizures.

Landau-Kleffner syndrome is a rare condition of unknown cause characterized by loss of language skills attributed to auditory agnosia in a previously normal child. At least 70% have associated clinical seizures, but some do not. The seizures when they occur are of several types, including focal, generalized tonic–clonic, atypical absence, partial complex, and, occasionally, myoclonic seizures. High-amplitude spike-and-wave discharges predominate and tend to be bitemporal. In the later evolutionary stages of the condition, the EEG findings may be normal. The spike discharges are always more apparent during non–rapid eye movement sleep; thus, a child in whom Landau-Kleffner syndrome is suspected should have an EEG during sleep, particularly if the awake record is normal. CT and MRI studies typically yield normal results. In the related but clinically distinct epilepsy syndrome with **continuous spike waves in slow-wave sleep**, the discharges are more likely to be frontal or generalized and the delays more likely to be global. The approach and therapy to the 2 syndromes are similar. Valproic acid is often the anticonvulsant that is used first to treat the clinical seizures and may help the aphasia. Some children respond to clobazam, to the combination of valproic acid and clobazam, or to levetiracetam. For therapy of the aphasia, nocturnal diazepam therapy (0.2-0.5 mg/kg PO at bedtime for several months) is often used as first- or second-line therapy, as are oral steroids. Oral prednisone is started at 2 mg/kg/24 hr for 1 mo and decreased to 1 mg/kg/24 hr for an additional month. With clinical improvement, the prednisone is reduced further to 0.5 mg/kg/24 hr for up to 6-12 mo. Long-term therapy is often needed irrespective of what the patient responds to. If the seizures and aphasia persist after diazepam and steroids trials, then a course of intravenous immunoglobulins should be considered. It is imperative to initiate speech therapy and maintain it for several years, because improvement in language function occurs over a prolonged period.

Amenably treatable metabolic epilepsies are becoming increasingly recognized. **Pyridoxine-dependent epilepsy** typically presents as neonatal encephalopathy shortly after birth with, at times, report of increased fetal movements (seizure) in utero. There are associated gastrointestinal symptoms with emesis and abdominal distention, neurologic irritability, sleepless and facial grimacing along with recurrent partial motor seizure, generalized tonic seizures, and myoclonus. Seizures are usually refractory and may progress to status epilepticus if no pyridoxine is used. Some cases start in infancy or in childhood. Diagnosis is confirmed by the presence of elevated plasma, urine and CSF α-aminoadipic semialdehyde and elevated plasma and CSF pipecolic acid levels. The presence of either homozygous or compound heterozygous mutations in ALDH7A1 alleles (which encode the protein antiquitin) confirms the diagnosis. The use of pyridoxine 100 mg daily orally (up to 600 mg/day) or intravenously helps stop the seizures. **Pyridoxal phosphate responsive neonatal epileptic encephalopathy** (Pyridox[am]ine 5′-phosphate oxidase [PNPO] deficiency) may present similarly in the absence of gastrointestinal symptoms. Diagnostically, there are reduced pyridoxal phosphate levels in the CSF with increased levels of CSF levodopa and 3-methoxytyrosine along with decreased CSF homovanillic acid and 5-hydroxyindolacetic acid. The EEG may show a burst suppression pattern and treatment is by enteral administration of pyridoxal phosphate (up to 60 mg/kg/day). **Folinic acid–responsive seizures** may also present with neonatal epileptic encephalopathy and intractable seizures. These patients have a similar diagnostic profile as pyridoxine-dependent epilepsy patients and are caused by the same gene mutations but respond to folinic acid supplementation in addition to pyridoxine use. **Cerebral folate deficiency**, which also responds to high doses of folinic acid (2-3 mg/kg/day), may manifest with epilepsy, intellectual disability, developmental regression, dyskinesias, and autism. CSF 5-methyltetrahydrofolate levels are decreased with normal plasma and red blood cell folate levels. There are usually mutations in the folate receptor *(FOLR1)* gene or blocking autoantibodies against membrane-associated folate receptors of the choroid plexus. **Tetrahydrobiopterin deficiencies** with or without hyperphenylalaninemia may present with epilepsies, and symptoms resulting from deficiencies of dopamine (parkinsonism, dystonia), noradrenaline (axial hypotonia), serotonin (depression, insomnia, temperature changes) and folate (myelin formation, basal ganglia calcifications, and seizures). Treatment is by substitution therapy with tetrahydrobiopterin and neurotransmitter precursors started as early as possible. **Creatine deficiency syndromes** present typically with developmental delay, seizures, autistic features, and movement disorders and are diagnosed by abnormal levels of urine creatine and guanidinoacetic acid and/or, depending on the type of underlying genetic etiology, with absent creatine peak on MR spectroscopy of the brain. Use of creatine monohydrate and dietary restrictions are helpful. **Biotinidase deficiency** presenting as developmental delay, seizures, ataxia, alopecia, and skin rash and often associated with intermittent metabolic acidosis and organic profile of lactic and propionic acidemia, responds to the use of biotin. Serine biosynthesis defects with low serine levels in plasma or CSF amino acids often present with congenital microcephaly, intractable seizures, and psychomotor retardation and respond to supplemental serine and glycine use. **Developmental delay, epilepsy, and neonatal diabetes** is caused by activating mutations in the adenosine triphosphate-sensitive potassium channels. Sulfonylurea drugs that block the potassium channel treat the neonatal diabetes and probably also favorably affect the central nervous system (CNS) symptoms and affect seizures. Hyperinsulinism-hyperammonemia syndrome is caused by activating mutations of the glutamate dehydrogenase encoded by the *GLUD1* gene. Patients present with hypoglycemic seizures after a protein-rich meal with hyperammonemia (ammonia levels 80-150 μmol/L). They are managed with a combination of protein restriction, AEDs, and diazoxide (a potassium channel agonist that inhibits insulin release). **GLUT-1 deficiency syndrome** classically presents with infantile-onset epilepsy, developmental delay, acquired microcephaly, and complex movement disorders. It causes impaired glucose transport to the brain typically diagnosed by genetic testing or finding of low CSF lactate and CSF glucose, or low CSF to serum glucose ratios (less than 0.4). The manifestations of the disease are usually responsive to ketogenic diet.

593.5 Mechanisms of Seizures

Mohamad A. Mikati and Abeer J. Hani

One can distinguish in the pathophysiology of epilepsy 4 distinct, often sequential, mechanistic processes. First is the **underlying etiology**, which is any pathology or pathologic process that can disrupt neuronal function and connectivity and that eventually leads to the second process (epileptogenesis) which makes the brain epileptic. The underlying etiologies of epilepsy are diverse and include, among other entities, brain tumors and malformations, strokes, scarring, or mutations of specific genes. These mutations can involve voltage-gated channels (Na^+, K^+, Ca^{2+}, Cl^-, and HCN [hydrogen cyanide]), ligand-gated channels (nicotinic acetylcholine and γ-aminobutyric acid A receptors [$GABA_A$]) or other proteins. In some but not in all such mutations, the molecular and cellular deficits caused by the mutations have been identified. For example, in Dravet syndrome, the loss of function mutation in the *SCN1A* gene causes decreased excitability in inhibitory GABAergic interneurons, leading to increased excitability and epilepsy. In human cortical dysplasia, the expression of the NR2B subunit of the NMDA receptor is increased, leading to excessive depolarizing currents. In many other epileptic conditions, a clear etiology is still lacking and in others the etiology may be known, but it is still not

known how the identified underlying genetic etiology or brain insult results in epileptogenesis.

Second, **epileptogenesis** is the mechanism through which the brain, or part of it, turns epileptic. The presence of this process explains why some patients with the above pathologies develop epilepsy and some do not. **Kindling** is an animal model for human focal epilepsy in which repeated electrical stimulation of selected areas of the brain with a low-intensity current initially causes no apparent changes but with repeated stimulation results in epilepsy. This repetitive stimulation can lead to temporal lobe epilepsy, for example, through activation of metabotropic and ionotropic glutamate receptors (by glutamate), as well as the tropomyosin-related kinase B receptor (by brain-derived neurotrophic factor and neurotrophin-4). This leads to an increase in the intraneuronal calcium, which, in turn, activates calcium calmodulin–dependent protein kinase and calcineurin, a phosphatase, resulting eventually in calcium-dependent epileptogenic gene expression (e.g., c-fos) and promotion of mossy fiber sprouting. **Mossy fibers** are excitatory fibers that connect the granule cells to the CA3 region within the hippocampus, and their pathologic sprouting underlies increased excitability in medial temporal lobe epilepsy associated with mesial temporal sclerosis in humans and in animal models. The cell loss in the CA3 region that is a characteristic of mesial temporal sclerosis (presumably resulting from an original insult such as a prolonged febrile status epilepticus episode or hypoxia) leads to a pathologic attempt at compensation by sprouting of the excitatory mossy fibers. Consequently, mossy fiber sprouting, which has been demonstrated in humans also, leads to increased excitability and to epilepsy. Complex febrile seizures in rats induce hyperactivation of, paradoxically excitatory, $GABA_A$ receptors leading to granule cell ectopia and to subsequent temporal lobe epilepsy. Possibly similar yet to be fully characterized epileptogenesis mechanisms may underlie other focal epilepsies.

Lately, the role of large-scale molecular cell signaling pathways in epileptogenesis, namely the mammalian target of rapamycin (mTOR), the Ras/ERK, and repressor element 1 (RE1)-silencing transcription factor (REST; also known as neuron-restrictive silencer factor) pathways have been implicated in the mechanisms leading to epilepsy. The mTOR pathway in tuberous sclerosis, hemimegalencephaly and cortical dysplasia-related epilepsies, Ras/ERK in a number of syndromes, and REST in epileptogenesis after acute neuronal injury.

The third process is the resultant **epileptic state of increased excitability** that is present in all patients irrespective of the underlying etiology or mechanism of epileptogenesis. In a seizure focus, each neuron has a stereotypic synchronized response called **paroxysmal depolarization shift** that consists of a sudden depolarization phase, resulting from glutamate and calcium channel activation, with a series of action potentials at its peak followed by an after-hyperpolarization phase, resulting from activation of potassium channels and GABA receptors that open chloride channels. When the after-hyperpolarization is disrupted in a sufficient number of neurons, the inhibitory surround is lost and a population of neurons fire at the same rate and time, resulting in a seizure focus. In childhood absence epilepsy, the discharging neurons also develop a paroxysmal depolarization shift similar to the one found in partial epilepsy. However, the mechanism of paroxysmal depolarization shift generation is different because it involves thalamocortical connections bilaterally. T-type calcium channels on thalamic relay neurons are activated during hyperpolarization by GABAergic interneurons in the reticular thalamic nucleus, which results in enhancement of synchronization in the thalamocortical loop and consequently in the typical generalized spike-wave pattern. In tumor-related epilepsy, particularly in that related to oligodendroglioma, the voltage-gated sodium channels are present on the surface of tumor cells at a higher density than on normal cells, and their inactivation is impaired by the alkaline pH present in this condition. In hypothalamic hamartoma causing gelastic seizures, clusters of GABAergic interneurons spontaneously fire, thus synchronizing the output of the hypothalamic hamartoma neurons projecting to the hippocampus.

The fourth process is **seizure-related neuronal injury** as demonstrated by MRI in patients after prolonged febrile and afebrile status epilepticus. Many such patients show acute swelling in the hippocampus and long-term hippocampal atrophy with sclerosis on MRI. Nonetheless in most patients with seizure-related MRI abnormalities, the findings are transient. In experimental models, the mechanisms of such injuries have been shown to involve both apoptosis and necrosis of neurons in the involved regions. There is evidence from surgically resected epileptic tissue that apoptotic pathways are activated in foci of intractable epilepsy.

In infantile spasms, recently developed animal models suggest that increases in stress-related corticotropin-releasing hormone, sodium channel blockade, and NMDA receptor stimulation are contributing mechanisms. Prior positron emission tomography data suggest that an interaction between focal cortical lesions and the brainstem raphe nuclei is important at least in some infantile spasms patients.

Bibliography is available at Expert Consult.

593.6 Treatment of Seizures and Epilepsy

Mohamad A. Mikati and Abeer J. Hani

DECIDING ON LONG-TERM THERAPY

After a *first seizure*, if the risk of recurrence is low, such as when the patient has normal neurodevelopmental status, EEG, and MRI (risk approximately 20%), then treatment is usually not started. If the patient has abnormal EEG, MRI, development, and/or neurologic exam, and/or a positive family history of epilepsy, then the risk is higher and often treatment is started. Other considerations are also important, such as motor vehicle driving status and type of employment in older patients or the parents' ability to deal with recurrences or AED drug therapy in children. The decision is therefore always individualized. All aspects of this decision-making process should be discussed with the family. Figure 593-4 presents an overview of the approach to the treatment of seizures and epilepsy.

COUNSELING

An important part of the management of a patient with epilepsy is educating the family and the child about the disease, its management, and the limitations it might impose and how to deal with them. It is important to establish a successful therapeutic alliance. Restrictions on driving (in adolescents) and on swimming are usually necessary (Table 593-10). In most states, the physician is not required to report the epileptic patient to the motor vehicle registry; this is the responsibility of the patient. The physician then is requested to complete a specific form for patients who are being cleared to drive. Also in most states, a seizure-free period of 6 mo, and in some states longer, is required before driving is allowed. Often swimming in rivers, lakes, or sea, and underwater diving are prohibited, but swimming in swimming pools may be allowable. When swimming, even patients with epilepsy that is under excellent control should be under the continuous supervision of an observer who is aware of their condition and capable of lifeguard-level rescue.

The physician, parents, and child should jointly evaluate the risk of involvement in athletic activities. To participate in athletics, proper medical management, good seizure control, and proper supervision are crucial to avoid significant risks. Any activity where a seizure might cause a dangerous fall should be avoided; these activities include rope climbing, use of the parallel bars, and high diving. Participation in collision or contact sports depends on the patient's condition. Epileptic children should not automatically be banned from participating in hockey, baseball, basketball, football, or wrestling. Rather, individual consideration should be based on the child's specific case (see Table 593-10).

Counseling is helpful to support the family and to educate them about the resources available in the community. Educational and, in some cases, psychologic evaluation may be necessary to evaluate for possible learning disabilities or abnormal behavioral patterns that might coexist with the epilepsy. Epilepsy does carry a risk of increased

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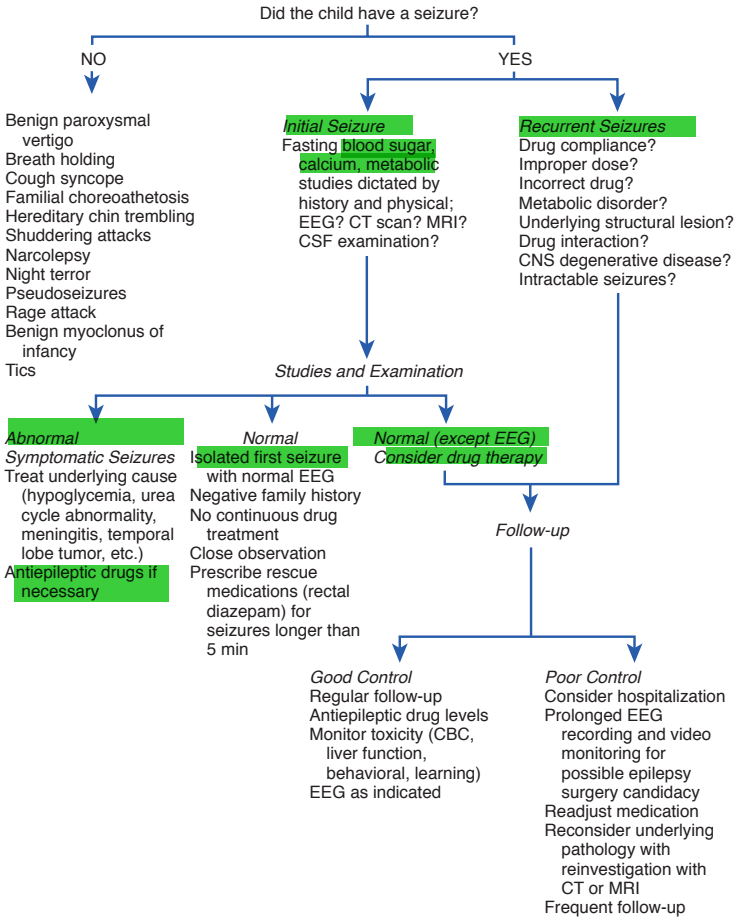

Figure 593-4 Approach to the child with a suspected convulsive disorder.

Table 593-10 Sports and Special Considerations for the Child with Epilepsy*

SPORTS TYPE	SPECIAL CONSIDERATIONS
Body contact sports	If there are more than occasional seizures, physician evaluation of benefits and risks of participation should be made based on the child's condition. No contraindications in general except for boxing.
Noncontact sports	Generally recommended. Anxiety and fatigue can cause a problem in some children. Individualization based on clinical history must be the rule.
Gymnastics	A fall can result if the child experiences a sudden seizure, especially with trampolines, parallel bars, and rope climbing, which should be avoided. Individual consideration remains the basic determinant.
Swimming	The child should always be under supervision, and scuba diving should be discouraged in poorly controlled epileptics.

*Specific advice should be individualized depending on the patient's clinical condition. Many patients actually have fewer seizures when they are active than when they are idle.

Modified from Committee on Children with Handicaps: The epileptic child and competitive school athletics, Pediatrics *42:700–702, 1968; and Knowles BD: Athletes with seizure disorders,* Curr Sports Med Rep *11(1):16–20, 2012, Table 1.*

mortality (2 or more times the standardized mortality rates of the general population) and of sudden unexpected death. This is mostly related to the conditions associated with or underlying the epilepsy (e.g., tumor, metabolic diseases), to poor seizure control (e.g., in patients with severe epileptic encephalopathies, or drug-resistant seizures), and to poor compliance with prescribed therapies. Thus, family members can usually be informed about this increased risk without inappropriately increasing their anxiety. Many family members feel they need to observe the patient continuously in wakefulness and sleep and have the patient sleep in the parents' room to detect seizures. There are currently advertised seizure-detection equipment that use motion sensors placed under the mattress to detect seizures. Some are disappointing and ineffective in detecting seizures, whereas data from other equipment are encouraging in that they were useful in detecting a majority of generalized tonic–clonic seizures during sleep (see bibliography for details). Whether such measures can reduce sudden unexpected death in epilepsy (SUDEP) risk remains to be seen and the parents need to guard against being overprotective to avoid adversely affecting the psychology of the child. Education about what to do in case of seizures, the choices of treatment or no treatment and of medications and their side effects, and potential complications of epilepsy should be provided to the parents and, if the child is old enough, to the child.

MECHANISMS OF ACTION OF ANTIEPILEPTIC DRUGS

AEDs reduce excitability by interfering with the sodium, potassium or calcium ion channels, by reducing excitatory neurotransmitter release

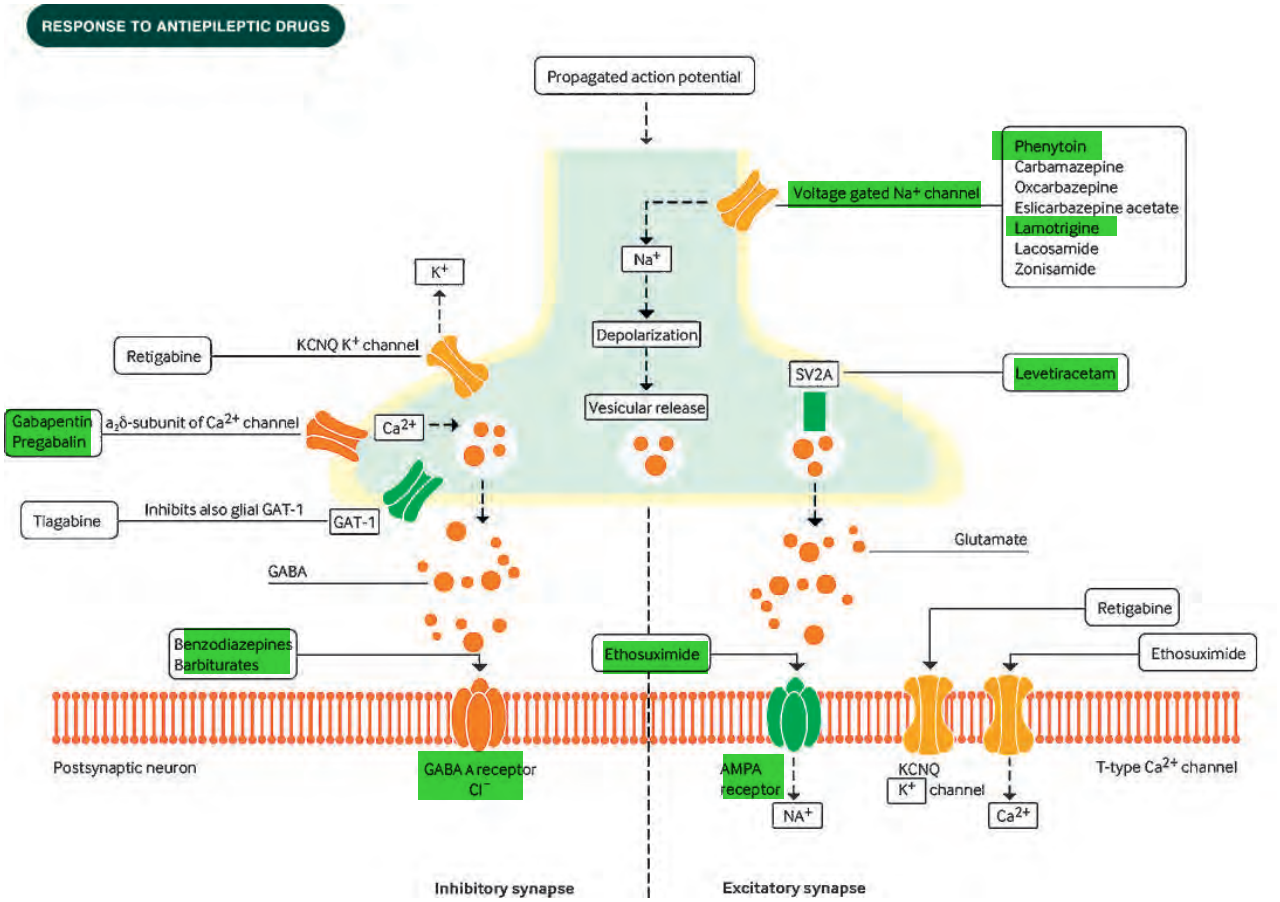

Figure 593-5 Mechanisms of action of antiepileptic drugs, which act by diverse mechanisms, mainly involving modulation of voltage activated ion channels, potentiation of GABA, and inhibition of glutamate. Approved antiepileptic drugs have effects on inhibitory *(left hand side)* and excitatory *(right hand side)* nerve terminals. The antiepileptic efficacy in trials of most of these drugs as initial add-on does not differ greatly, indicating that seemingly similar antiseizure activity can be obtained by mechanisms aimed at diverse targets. However, putative mechanisms of action were determined only after discovering the antiseizure effects; mechanism driven drug discovery has been largely ignored. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; GABA, γ-aminobutyric acid; GAT-1, sodium-dependent and chloride-dependent GABA transporter 1; SV2A, synaptic vesicle glycoprotein 2A. *(From Schmidt D, Schachter SC: Drug treatment of epilepsy in adults. BMJ, 348:bmj.g254, 2014.)*

or function, or by enhancing GABAergic inhibition (Fig. 593-5). Most medications have multiple mechanisms of action, and the exact mechanism responsible for their activity in human epilepsy is usually not fully understood. Often, medications acting on sodium channels are effective against partial seizures, and medications acting on T-type calcium channels are effective against absence seizures. Voltage-gated sodium channels are blocked by felbamate, valproate, topiramate, carbamazepine, oxcarbazepine, lamotrigine, phenytoin, rufinamide, lacosamide, and zonisamide. T-type calcium channels, found in the thalamus area, are blocked by valproate, zonisamide, and ethosuximide. Voltage-gated calcium channels are inhibited by gabapentin, pregabalin, lamotrigine, and felbamate. N-type calcium channels are inhibited by levetiracetam. Ezogabine/retigabine opens KCNQ/Kv7 voltage-gated potassium channels.

$GABA_A$ receptors are activated by phenobarbital, benzodiazepines, topiramate, felbamate, and levetiracetam. Tiagabine, by virtue of its binding to GABA transporters 1 (GAT-1) and 3 (GAT-3), is a GABA reuptake inhibitor. GABA levels are increased by vigabatrin via its irreversible inhibition of GABA transaminases. Valproate inhibits GABA transaminases, acts on $GABA_B$ presynaptic receptors (also done by gabapentin), and activates glutamic acid decarboxylase (the enzyme that forms GABA).

Glutaminergic transmission is decreased by felbamate that blocks NMDA and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid)/kainate receptors. Topiramate also blocks AMPA/kainate receptors. Levetiracetam binds to the presynaptic vesicle protein SV2A found in all neurotransmitter vesicles and possibly results in inhibition of presynaptic neurotransmitter release in a use-dependent manner. Perampanel blocks glutamate AMPA receptors.

CHOICE OF DRUG ACCORDING TO SEIZURE TYPE AND EPILEPSY SYNDROME

Drug therapy should be based on the type of seizure and the epilepsy syndrome as well as on other individual factors. In general, the **drugs of first choice** for focal seizures and epilepsies are oxcarbazepine and carbamazepine; for absence seizures, ethosuximide; for juvenile myoclonic epilepsy, valproate and lamotrigine; for Lennox-Gastaut syndrome, clobazam, valproate, topiramate, lamotrigine, and, most recently, as add on, rufinamide; and for infantile spasms, adrenocorticotropic hormone (ACTH). There is significant controversy about these choices, and therapy should always be individualized (see Choice of Drug: Other Considerations below and Table 593-10).

West syndrome is best treated with ACTH. There are several protocols that range in dose from high to intermediate to low. The recommended regimen of ACTH (80 mg/mL) is a daily dose of 150 units/m^2 (divided into twice-daily intramuscular injections of 75 units/m^2, the lot number is recorded) administered over a 2-wk period with a subsequent gradual taper over a 2-wk period (30 units/m^2 in the morning

for 3 days; 15 units/m^2 in the morning for 3 days; 10 units/m^2 in the morning for 3 days; and 10 units/m^2 every other morning for 6 days, then stop). The increase in price of ACTH gel in the United States has led many physicians to use the lower-dose regimen because it may be just as effective (initial: 20 units/day for 2 wk, if patient responds, taper and discontinue over a 1-wk period; if patient does not respond, increase dose to 30 units/day for 4 wk then taper and discontinue over a 1-wk period). Response is usually observed within the 1st 7 days; however, if no response is observed within 2 wk, the lot is changed. During the tapering period of any regimen, and especially in symptomatic patients, relapse can occur. Remediation entails increasing the dose to the previously effective dose for 2 wk and then beginning the taper again. Synthetic ACTH has also been used: Synacthen Depot intramuscular 0.25 mg/mL or 1 mg/mL is used; 1 mg is considered to have the potency of 100 IU in stimulating the adrenal gland.

Awake and asleep EEGs are often done 1, 2, and 4 wk after the initiation of ACTH to monitor the patient's response, with the aim of clearing the EEG from hypsarrhythmia and of stopping the seizures. Side effects, more common with the higher doses, include hypertension, electrolyte imbalance, infections, hyperglycemia and/or glycosuria, and gastric ulcers. All should be carefully monitored for and prophylactic therapy for ulcers is desirable. ACTH is generally thought to offer an added advantage, particularly in cryptogenic cases, over vigabatrin and possibly over prednisone and other steroids.

Vigabatrin is considered by some as a drug of second choice for infantile spasms and by some even as an alternative to ACTH as a drug of first choice. Its principal side effect is retinal toxicity that is seen in approximately 30% of the patients, with resultant visual field defects that persist despite withdrawal of the drug. The level of evidence for its efficacy is weaker than that for ACTH but stronger than that of other alternative medications, including valproate, benzodiazepines like nitrazepam and clonazepam, topiramate, lamotrigine, zonisamide, pyridoxine, ketogenic diet, and intravenous gamma globulin (IVIG). None of these alternative drugs offers uniformly satisfactory results. However, they are useful for decreasing the frequency and severity of seizures in patients with symptomatic infantile spasms and as adjunctive therapy in patients with cryptogenic infantile spasms who do not respond completely to ACTH or vigabatrin.

Lennox-Gastaut syndrome is another difficult-to-treat epilepsy syndrome. Treatment of seizures in Lennox-Gastaut syndrome varies according to the preponderant seizure type. For drop attacks (tonic, atonic, or myoclonic astatic seizures), valproate, lamotrigine, topiramate, clobazam, felbamate, and rufinamide are considered to be effective. Felbamate is used as a last resort medication because of its potential toxicity. These drugs might control other types of seizures (partial, generalized tonic–clonic, atypical absence, other tonic, myoclonic) as well. For patients who have a preponderance of atypical absence seizures, lamotrigine or ethosuximide are often suitable drugs to try because they are relatively less toxic than many of the alternative drugs. Valproate is helpful against these seizures, too. Clonazepam is often helpful but produces significant sedation, hyperactivity, and drooling, and often tolerance to its antiepileptic effects develops in a few months. Consequently, clonazepam is often used as a rescue medication for clusters of seizures (disintegrating tablet preparation). In resistant cases of Lennox-Gastaut syndrome and related epilepsies, zonisamide, levetiracetam, acetazolamide, methsuximide, corticosteroids, ketogenic diet, or IVIG can be used.

Dravet syndrome is usually treated with valproate and benzodiazepines such as clobazam or clonazepam. The ketogenic diet can also be useful in patients with this syndrome, including cases with refractory status. Stiripentol, which is available in some countries, is useful, particularly if used in combination with valproate and clobazam, but doses need to be adjusted, since stirpentol can increase clobazam levels and valproate can increase stirpentol levels. Other medications include zonisamide and topiramate. Lamotrigine, carbamazepine, and phenytoin are reported to exacerbate seizures. Barbiturate use during status epilepticus in this syndrome is suspected to be associated with adverse outcomes; consequently, alternative acute therapies in such cases need to be considered.

Very rare cases of patients who have neonatal, infantile, or early childhood seizures who have **pyridoxine-dependent epilepsy** (demonstrated to be caused by antiquitin gene mutation) respond to pyridoxine 10-100 mg/day orally (up to 600 mg/day has been used) within 3-7 days of the initiation of oral therapy and almost immediately if given parenterally. Some patients have seizures that are intractable from onset, but others have seizures that show an initial but transient response to traditional AEDs. Some of these patients also require concurrent folinic acid (5-15 mg/day). Other patients require the active form of vitamin B_6, specifically, pyridoxal phosphate (50 mg/day initial dose that can be increased gradually up to 15 mg/kg every 6 hr) owing to their deficiency of **PNPO**. In both the PNPO-deficient/pyridoxal phosphate–dependent and the pyridoxine-dependent forms, hypotonia and hypopnea can occur after initiation of vitamin therapy. Pyridoxine has also been used by some, specifically in Japan, early in the treatment of West syndrome. Patients with **cerebral folate deficiency** can respond to folinic acid supplementation (usually at doses of 2-3 mg/kg/day). Traditionally these entities have been diagnosed by giving the vitamin B_6 or folinic acid in therapeutic trials, but currently laboratory testing is available to confirm the diagnosis (see Chapter 593.4).

Absence seizures are most often initially treated with ethosuximide, which is, as effective as, but less toxic than, valproate and more effective than lamotrigine. Alternative drugs of first choice are lamotrigine and valproate, especially if generalized tonic–clonic seizures coexist with absence seizures, as these 2 medications are effective against the latter seizures whereas ethosuximide is not. Patients resistant to ethosuximide might still respond to valproate or to lamotrigine. In absence seizures, the EEG is usually helpful in monitoring the response to therapy and is often more sensitive than the parents' observations in detecting these seizures. The EEG often normalizes when complete seizure control is achieved. This is usually not true for partial epilepsies. Other medications that could be used for absence seizures include acetazolamide, zonisamide, or clonazepam.

Benign myoclonic epilepsies are often best treated with valproate, particularly when patients have associated generalized tonic–clonic and absence seizures. Benzodiazepines, clonazepam, lamotrigine, and topiramate are alternatives for the treatment of benign myoclonic epilepsy. **Severe myoclonic epilepsies** are treated with medications effective for Lennox-Gastaut syndrome such topiramate, clobazam, and valproate, as well as zonisamide. Levetiracetam may also have efficacy in myoclonic epilepsies.

Partial and secondary generalized tonic and clonic seizures can be treated with oxcarbazepine, levetiracetam, carbamazepine, phenobarbital, topiramate, valproic acid, lamotrigine, clobazam, or clonazepam (see Table 593-8). Oxcarbazepine, levetiracetam, carbamazepine (United States), or valproate (Europe) are often being used first. One study favored lamotrigine as initial monotherapy for partial seizures and valproate for generalized seizures. Almost any of these medications has been used as first or second choice. depending on the individualization of the therapy.

CHOICE OF DRUG: OTHER CONSIDERATIONS

Because there are many options for each patient, the choice of which drug to use is always an individualized decision based on comparative effectiveness data from randomized controlled trials and on several other considerations delineated below.

Comparative effectiveness (Table 593-11) and **potential for paradoxical seizure aggravation** by some AEDs (e.g., precipitation of myoclonic seizures by lamotrigine in Dravet syndrome and exacerbation of absence seizures by carbamazepine and tiagabine) must be considered.

- **Comparative tolerability** (see Table 593-14): Adverse effects can vary according to the profile of the patient. The most prominent example is the increased risk of liver toxicity for valproate therapy in children who are younger than 2 yr of age, on polytherapy, and/or have metabolic disorders. Thus, if metabolic disorders are suspected, other drugs should be considered first and valproate should not be started until the metabolic disorders are ruled out by normal amino acids, organic acids, acylcarnitine profile, lactate,

Table 593-11 Comparison of Recommendations for the Treatment of Pediatric Epilepsy

SEIZURE TYPE OR EPILEPSY SYNDROME	FDA APPROVED	SIGN (2005)	NICE (2012)	AAN (2004)	ILAE (2013)*	PEDIATRIC EXPERT CONSENSUS SURVEY (NORTH AMERICA–2005)	PEDIATRIC EXPERT CONSENSUS SURVEY (EUROPE–2007)
Partial-onset	CBZ, ezogabine, lacosamide, LEV, LTG, OXC, PB, perampanel, PHT, TPM, VGB	CBZ, CLB, LTG, OXC, PHT, TPM, VGB, VPA	CBZ, LEV, LTG, OXC, VPA	CBZ, GBP, LTG, OXC, PB, PHT, TPM	A: OXC B: None C: CBZ, PB, PHT, TPM, VGB, VPA D: CLB, CZP, LTG, ZNS	CBZ, OXC	CBZ, OXC
BCECT	None	Not specifically mentioned	CBZ, LEV, LTG, OXC, VPA	Not surveyed	A, B: None C: CBZ, VPA D: GBP, LEV, OXC, STM	CBZ, OXC	VPA
Childhood absence epilepsy	ESM, VPA	ESM, LTG, VPA	ESM, LTG, VPA	LTG	A: ESM, VPA B: None C: LTG D: None	ESM	VPA
Juvenile myoclonic epilepsy	LEV, LTG, TPM	VPA	LEV, LTG, TPM, VPA	Not surveyed	A, B, C: None D: TPM, VPA	LTG, VPA	VPA
Lennox-Gastaut syndrome	CLB, FLB, LTG, rufinamide (atonic), TPM	CLB, LTG, VPA	VPA	Not surveyed	Not reviewed	LTG, VPA	VPA
Infantile spasms	VGB	Nitrazepam, TPM, VGB, VPA	Corticosteroids, VGB	ACTH, VGB (updated IS guidelines 2012)	Not reviewed	ACTH, VGB	VGB
Primary generalized tonic-clonic seizures	LEV, LTG, TPM	TPM, VPA	LTG, TPM, VPA	No evidence given	A: None B: None C: CBZ, PB, PHT, TPM, VPA D: OXC		

*ILAE recommendations are listed according to levels of evidence supporting the efficacy of the options. Level A: ≥1 class I randomized controlled trial (RCT) or ≥2 class II RCTs; Level B: 1 class II RCT or ≥2 class III RCTs; Level C: ≥2 class III RCTs; Level D: 1 class III double-blind or open-label study *or* 1 class IV clinical study *or* data from expert committee reports, opinions from experienced clinicians.

AAN, American Academy of Neurology; ACTH, adrenocorticotropic hormone; BCECT, benign childhood epilepsy with centrotemporal spikes; CBZ, carbamazepine; CLB, clobazam; CZP, clonazepam; ESM, ethosuximide; FDA, Food and Drug Administration; FLB, felbamate; GBP, gabapentin; ILAE, International League against Epilepsy; LEV, levetiracetam; LTG, lamotrigine; NICE, National Institute for Clinical Excellence; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; SIGN, Scottish Intercollegiate Guidelines Network; STM, sulthiame; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; ZNS, zonisamide.

Modified and updated from Wheless JW, Clarke DF, Arzimanoglou A, et al: Treatment of pediatric epilepsy: European expert opinion, Epileptic Disord *9:353–412, 2007; and Perucca E, Tomson T; ILAE Subcommission on AED Guidelines. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes.* Epilepsia *54(3):551–563, 2013.*

pyruvate, liver function tests, and perhaps other tests. The choice of an AED can also be influenced by the likelihood of occurrence of nuisance side effects such as weight gain (valproate, carbamazepine), gingival hyperplasia (phenytoin), alopecia (valproate), hyperactivity (benzodiazepines, barbiturates, levetiracetam, valproate, gabapentin). Children with behavior problems and/or with attention-deficit disorder can become particularly hyperactive with GABAergic drugs mentioned above. This often affects the choice of medications.

- **Cost and availability:** The cost of the newer AEDs often precludes their use, particularly in developing countries where cost is a major issue. Also, many drugs are not available in many countries either because they are too expensive, because, paradoxically, they are too inexpensive (lower profit margin), or because of regulatory restrictions. AEDs have a narrow therapeutic range and thus switching from brand name to generic formulations, or from one generic to another, can result in changes in levels that could result in breakthrough seizures or side effects. Thus, generic substitution is generally best avoided, particularly in fragile patients, if a brand name drug has already proved efficacious.
- **Ease of initiation** of the AED: Medications that are started very gradually such as lamotrigine and topiramate should not be chosen in situations when there is a need to achieve a therapeutic level quickly. In such situations, medications that have intravenous preparations or that can be started and titrated more quickly, such as valproate, phenytoin, or levetiracetam, should be considered instead.
- **Drug interactions** and presence of background medications: An example is the potential interference of enzyme-inducing drugs with many chemotherapeutic agents. In those cases, medications like gabapentin or levetiracetam are used. Also, valproate inhibits the metabolism and increases the levels of lamotrigine, phenobarbital, and felbamate. It also displaces protein-bound phenytoin from protein-binding sites, increasing the free fraction, and, thus, the free and not the total level needs to be checked when both medications are being used together. Enzyme inducers like phenobarbital, carbamazepine, phenytoin, and primidone reduce levels of lamotrigine, valproate, and, to a lesser extent, topiramate and zonisamide. Medications exclusively excreted by the kidney like levetiracetam and gabapentin are not subject to such interactions.

Table 593-12 Teratogenesis and Perinatal Outcomes of Antiepileptic Drugs

FINDING	RECOMMENDATION	LEVEL OF RECOMMENDATION
VPA as part of polytherapy and possibly monotherapy probably contributes to the development of major congenital malformations and adverse cognitive outcome	If possible, avoidance of valproate polytherapy during the 1st trimester of pregnancy should be considered so as to decrease the risk of major congenital malformations and adverse cognitive outcome	B
AED polytherapy, as compared to monotherapy, regimens probably contribute to the development of major congenital malformations and to adverse cognitive outcomes	If possible, avoidance of AED polytherapy during the 1st trimester of pregnancy should be considered to decrease the risk of major congenital malformations and adverse cognitive outcome	B
Monotherapy exposure to phenytoin or phenobarbital possibly increases the likelihood of adverse cognitive outcomes	If possible, avoidance of phenytoin and phenobarbital during pregnancy may be considered to prevent adverse cognitive outcomes	C
Neonates of women with epilepsy taking AEDs probably have an increased risk of being small for gestational age and possibly have an increased risk of a 1 min Apgar score of <7	Pregnancy risk stratification should reflect that the offspring of women with epilepsy taking AEDs are probably at increased risk for being small for gestational age (level B) and possibly at increased risk of 1 min Apgar scores of <7	C

Levels of recommendation: A: strongest recommendation; based on class 1 evidence; B and C: lower levels of recommendations.

Types of malformations: Prior studies had reported the occurrence of spina bifida with valproate and carbamazepine therapy, and of cardiac malformation and cleft palate after carbamazepine, phenytoin, and phenobarbital exposure. There is variability from study to study. However, in general the relative incidence of major malformations of approximately 10% for valproate monotherapy, higher with valproate polytherapy, and in the range of 5% for monotherapy with the other above 3 AEDs and higher with polytherapy.

FDA categories: Valproate, phenobarbital, carbamazepine, and phenytoin are classified by the FDA as category D. Ethosuximide, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide are category C. Category C: Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women or no animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women. Category D: Studies, adequate, well-controlled, or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy might outweigh the potential risk.

AED, antiepileptic drug; VPA, valproate.

Data from Harden CI, Meador KJ, Pennell PB, et al: Practice parameter update: management issues for women with epilepsy—focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes. Report of the Quality Standards Subcommittee and Therapeutics and Technology Subcommittee of the American Academy of Neurology and American Epilepsy Society, Neurology *73(2):133–141, 2009.*

- **The presence of comorbid conditions:** For example, the presence of migraine in a patient with epilepsy can lead to the choice of a medication that is effective against both conditions such as valproate or topiramate. In an obese patient, a medication such as valproate might be avoided, and a medication that decreases appetite such as topiramate might be used instead. In adolescent girls of child-bearing potential, enzyme-inducing AEDs are often avoided because they can interfere with birth control pills; other AEDs, particularly valproate, can increase risks for fetal malformations (Table 593-12). Valproic acid may unmask or exacerbate certain underlying metabolic disorders; these include nonketotic hyperglycinemia, DNA polymerase γ mutations *(POLG)* with mitochondrial DNA depletion (also known as Alpers-Huttenlocher syndrome), other mitochondrial disorders (Leigh syndrome; mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes [MELAS]; myoclonic epilepsy with ragged red fibers; myoclonic epilepsy-myopathy-sensory ataxia syndrome), and hyperammonemic encephalopathies. Manifestations may include hepatotoxicity or encephalopathy.
- **Coexisting seizures:** In a patient with both absence and generalized tonic–clonic seizures, a drug that has a broad spectrum of antiseizure effects such as lamotrigine or valproate could be used rather than medications that have a narrow spectrum of efficacy, such as phenytoin and ethosuximide.
- **History of prior response** to specific AEDs: For example, if a patient or a family member with the same problem had previously responded to carbamazepine, carbamazepine could be a desirable choice.
- **Mechanism of drug actions:** At present, the current understanding of the pathophysiology of epilepsy does not allow specific choice of AEDs based on the assumed pathophysiology of the epilepsy. However, in general, it is believed that it is better to avoid combining medications that have similar mechanisms of action, such as phenytoin and carbamazepine (both work on sodium channels). A number of medications, such as lamotrigine and valproate or topiramate and lamotrigine, are reported to have synergistic effects, possibly because they have different mechanisms of action.
- **Ease of use:** Medications that are given once or twice a day are easier to use than medications that are given 3 or 4 times a day. Availability of a pediatric liquid preparation, particularly if palatable, also plays a role.
- **Ability to monitor the medication** and adjust the dose: Some medications are difficult to adjust and to follow, requiring frequent blood levels. The prototype of such medications is phenytoin, but many of the older medications also require blood level monitoring for optimal titration. However, monitoring in itself can represent a practical or patient satisfaction disadvantage for the older drugs as compared to the newer AEDs, which generally do not require blood-level monitoring except to check for compliance.
- **Patient's and family's preferences:** All things being equal, the choice between 2 or more acceptable alternative AEDs might also depend on the patient's or family's preferences. For example, some patients might want to avoid gingival hyperplasia and hirsutism as side effects but might tolerate weight loss, or vice versa.
- **Genetics** and genetic testing: A genetic predisposition to developing AED-induced side effects is another factor that may be a consideration. For example, there is a strong association between the human leukocyte antigen HLA-B*1502 allele and severe cutaneous reactions induced by carbamazepine, phenytoin, or lamotrigine in Chinese Han patients and, to a lesser extent, South East Asian populations; hence these AEDs should be avoided in genetically susceptible persons after testing for the allele. The testing for other alleles that predispose to such allergies in other populations is not yet clinically useful. Mutations of the *SCN1A* sodium channel gene indicating Dravet syndrome could also lead to avoiding lamotrigine, carbamazepine, and phenytoin, and to the use of the more appropriate valproate, clobazam, or stiripentol.

- **Teratogenic profiles:** Some AEDs, including valproate and to a lesser extent carbamazepine, phenobarbital, and phenytoin, are associated with teratogenic effects (see Table 593-12).

Some of these considerations can be addressed by resorting to expert opinion surveys (see Table 593-11) or to guidelines developed by concerned societies such as the ILAE, National Institute for Clinical Excellence (NICE) in England, Scottish Intercollegiate Guidelines Network (SIGN), or the American Academy of Neurology (AAN). Some guidelines are totally evidence based (AAN, ILAE), and others (NICE, SIGN) incorporate other considerations as well. However, no guideline is able to incorporate all the considerations relevant to each patient.

INITIATING AND MONITORING THERAPY

In nonemergency situations, or when loading is not necessary, the **maintenance dose** of the chosen AED is started (Table 593-13). With some medications (e.g., carbamazepine and topiramate), even smaller doses are initially started then **gradually increased** up to the maintenance dose to build tolerance to adverse effects such as sedation. For example, the starting dose of carbamazepine is usually 5-10 mg/kg/day. Increments of 5 mg/kg/day can be added every 3 days until a therapeutic level is achieved and a therapeutic response is established or until unacceptable adverse effects occur. With other medications such as zonisamide, phenobarbital, phenytoin, or valproate, starting at the maintenance dose is usually tolerated. With some, such as levetiracetam and gabapentin, either approach can be used. Patients should be counseled about potential adverse effects, and these should be monitored during follow-up visits (Table 593-14).

Titration

Levels of many AEDs should usually be determined after initiation to ensure compliance and therapeutic concentrations. Monitoring is most helpful for the older AEDs such as phenytoin, carbamazepine, valproate, phenobarbital, and ethosuximide. After starting the maintenance dosage or after any change in the dosage, a steady state is not reached until 5 half-lives have elapsed, which, for most AEDs, is 2-7 days (half-life: 6-24 hr). For phenobarbital, it is 2-4 wk (mean half-life: 69 hr). For zonisamide it is 14 days during monotherapy and less than that during polytherapy with enzyme inducers (half-life: 63 hr in monotherapy and 27-38 hr during combination therapy with enzyme inducers). If a therapeutic level has to be achieved faster, a **loading dose** may be used for some drugs, usually with a single dose that is twice the average maintenance dose per half-life. For valproate it is 25 mg/kg, for phenytoin it is 20 mg/kg, and for phenobarbital it is 10-20 mg/kg. A lower loading dosage of phenobarbital is sometimes given in older children (5 mg/kg, which may be repeated once or more in 24 hr), to avoid excessive sedation.

Only 1 drug should be used initially and the dose increased until complete control is achieved or until side effects prohibit further increases. Then, and only then, may another drug be added and the initial drug subsequently tapered. Control with 1 drug (**monotherapy**) should be the goal, although some patients eventually need to take

Table 593-13 Dosages of Selected Antiepileptic Drugs

MEDICATION	FDA APPROVAL (AGE APPROVED)	MAINTENANCE ORAL DOSAGE (mg/kg/day) UNLESS OTHERWISE SPECIFIED	USUAL DOSING	THERAPEUTIC LEVELS	PREPARATIONS
Acetazolamide	Absence seizures (adults)	1-12 mo; 10 <1 yr: 20-30	bid or tid	10-15 mg/L	125, 250, 500 mg tabs
Bromide		50-100	bid or qd	10-15 mEq/L	Supplied as triple bromide soln (240 mg/mL of bromide salt)
Carbamazepine*	Partial and GTC (all ages)	10-20	tid or qid SR usually bid	3-12 mg/L	150, 300 mg ER caps 100, 200, 400 mg ER tabs 100 mg chewable tabs 200 mg tabs 100 mg/5 mL susp
Clobazam†	LGS (all ages above 2 yr)	10-20 mg/day	bid or tid	60-200 µg/L	5 mg, 10 mg, 20 mg tabs 2.5 mg/mL soln
Clonazepam†	Absence sz, LGS, myoclonic sz (all ages)	0.05-0.2	bid or tid	25-85 µg/L	0.5, 1, 2 mg tabs 0.125, 0.25, 0.5 mg orally disintegrating tabs
Diazepam	Partial sz (all ages >6 mo)	0.25-1.5 0.01-0.25 IV 0.2-0.5 mg/kg rectal (according to age; see Table 593-15)	bid or tid	100-700 µg/L	2, 5, 10 mg tabs 5 mg/mL, 5 mg/5 mL soln Rectal gel that can be dialed to dispense 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20 mg
Ethosuximide	Absence sz (>3 yr)	20-30	bid or tid	40-100 mg/L	250 mg caps 250 mg/5 mL syrup, soln
Ezogabine	Partial sz (adults)	No pediatric dose approved	tid	—	50, 200, 300, 400 mg tabs
Felbamate	LGS (>2 yr) Partial sz (>14 yr)	15-45	bid or tid	50-110 mg/L	400, 600 mg tabs 600 mg/5 mL susp
Gabapentin‡	Partial sz (>3 yr)	30-60	tid	2-20 mg/L	100, 300, 400 mg caps, 600, 800 mg tabs
Lacosamide	Partial sz (>17 yr)	No FDA approved dose. 4-12	bid	<= 15 µg/L	50, 100, 150, 200 mg tabs 10 mg/mL oral soln

Table 593-13 Dosages of Selected Antiepileptic Drugs—cont'd

MEDICATION	FDA APPROVAL (AGE APPROVED)	MAINTENANCE ORAL DOSAGE (mg/kg/day) UNLESS OTHERWISE SPECIFIED	USUAL DOSING	THERAPEUTIC LEVELS	PREPARATIONS
Lamotrigine	LGS, partial and tonic–clonic sz (age >2 yr)	5-15[§] 1-5[¶]	tid bid	1-15 mg/L	25, 100, 150, 200 mg tabs 5, 25 mg chewable dispersible tabs 25, 50, 100, 200 mg ODTs 25, 50, 100, 200, 250, 300 mg ER tabs
Levetiracetam[†]	Myoclonic, partial and tonic–clonic sz (age >4-6 yr)	20-40	bid or tid	6-20 mg/L	250, 500, 750 mg tabs 100 mg/mL soln 500, 750 mg SR (ER) tabs
Lorazepam	Status epilepticus (all ages)	0.05-0.1	bid or tid	20-30 µg/L	0.5, 1, 2 mg tabs 2 mg/mL soln
Methsuximide (or methsuximide)	Absence sz (children and older)	10-30	bid or tid	10-50 mg/L	150, 300 mg caps
Nitrazepam	–	0.25-1	bid or tid	<200 µg/L	5 mg tabs
Oxcarbazepine[*]	Partial sz (>2 yr)	20-40	bid	13-28 mg/L	150, 300, 600 mg tabs 300 mg/5 mL susp
Perampanel	Partial sz (>12 yr)	2-12 mg per day (older than 12 yr)	qhs	-	2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg tabs
Phenobarbital	Myoclonic, partial, and tonic–clonic sz and status (all ages)	<5 yr, 3-5 >5 yr, 2-3	bid or qd	10-40 mg/L	15, 30, 60, 90, 100 mg tabs 4 mg/mL soln
Phenytoin	Partial, tonic–clonic sz and status (all ages)	<3 yr, 8-10 >3 yr, 4-7	tabs, susp: tid caps: qd	5-20 mg/L	50 mg tabs 30,100 mg caps 125 mg/5 mL susp
Pregabalin	Partial sz (adults)	2-14	bid	Up to 10 µg/mL	25, 50, 75, 100, 150, 200, 225, 300 mg caps 20 mg/mL soln
Primidone	Partial and tonic–clonic sz (all ages)	10-20	bid or tid	4-13 mg/L	50, 250 mg tabs, susp
Rufinamide[†]	LGS (age >4 yr)	30-45	bid	<60 µg/mL	200, 400 mg tabs
Sulthiame[‖]		5-15	bid or tid	1.5-20 µg/mL	50, 200 mg caps Not available in all countries
Tiagabine	Partial sz (age >2 yr)	0.5-2	bid, tid, qid	80-450 µg/L	2, 4, 12, 16 mg tabs
Topiramate[†]	LGS, partial and tonic–clonic sz (all ages)	3-9, slow titration	bid or tid	2-25 mg/L	25, 100, 200 mg tabs 15, 25 mg sprinkle caps
Valproate	Absence, myoclonic, partial and tonic–clonic sz (age >2 yr)	15-40. Higher doses are used if the patient is on enzyme inducers (up to 60 kg/day)	Sprinkle caps: bid Soln: tid	50-100 mg/L	250 mg caps 125 mg sprinkle caps 125, 250, 500 mg tabs 250 mg/5 mL soln
Vigabatrin	Infantile spasms and partial sz (age >1 mo)	50-150	bid	20-160 µg/mL	500 mg tabs 500 mg powder for soln
Zonisamide	Partial sz (age >16 yr)	4-8	bid or qd	10-40 mg/L	100 mg caps

Unless specified otherwise, as above, one would usually target the lower range of therapeutic dose then adjust as needed depending on response and/or levels. Dosing schedule (e.g., bid or tid) can depend on if a sustained release preparation is available and if the patient is on enzyme inducers (e.g., carbamazepine) or inhibitors (e.g., valproic acid) that could affect that drug (as indicated in the dosing in the table and in the text).

*Usually start by one-fourth maintenance dose and increase by one-fourth every 2-3 days to full dose.

[†]Usually start with one-fourth maintenance dose and increase by one-fourth every 7 days to full dose.

[‡]Usually start with one-fourth maintenance dose and increase by one-fourth every day to full dose.

[§]Child on enzyme inducers.

[‖]Available in some European countries.

[¶]Child on valproate.

cap, capsule; ER, extended release; GTC, generalized tonic–clonic; LGS, Lennox-Gastaut syndrome; ODT, orally disintegrating tablet; soln, solution; SR, sustained release; susp, suspension; sz, seizure(s); tab, tablet.

Table 593-14 Some Common Adverse Effects of Antiepileptic Drugs*

ANTIEPILEPTIC DRUG	SIDE EFFECT(S)
Acetazolamide	Nuisance: dizziness, polyuria, electrolyte imbalance Serious: Stevens-Johnson syndrome
Benzodiazepines	Nuisance: dose-related neurotoxicity (drowsiness, sedation, ataxia), hyperactivity, drooling, increased secretions Serious: apnea
Bromide	Nuisance: irritability, spurious hyperchloremia (falsely high chloride owing to bromide) Serious: psychosis, rash, toxicity developing slowly owing to the very long half-life
Carbamazepine	Nuisance: tics, transient leukopenia; hyponatremia, weight gain, nausea; dizziness Serious: Stevens-Johnson syndrome, agranulocytosis, aplastic anemia, liver toxicity
Ezogabine	Nuisance: dizziness, somnolence tremor, abnormal coordination, disturbance in attention, memory impairment, blurred vision, gait disturbance, and dysarthria Serious: blue discoloration of the skin and retinal pigmentation that requires close ophthalmologic monitoring in follow up, urinary retention
Felbamate	Nuisance: anorexia, vomiting, insomnia, hyperactivity, dizziness Serious: major risks for liver and hematologic toxicity requiring close monitoring (1 in 500 in children >2 yr with complex neurological disorders)
Gabapentin	In children: acute onset of aggression, hyperactivity In adults: euphoria and behavioral disinhibition, weight gain
Lacosamide	Nuisance: diplopia, headache, dizziness, nausea Serious: possibly cardiac arrhythmias (if predisposed)
Lamotrigine	Nuisance: CNS side effects: headache, ataxia, dizziness, tremor, but usually less than other AEDs Serious: Stevens-Johnson syndrome, rarely liver toxicity
Levetiracetam	CNS adverse events: somnolence, asthenia, dizziness, but usually less than other AEDs In children: behavioral symptoms are common In adults: depressive mood
Oxcarbazepine	Somnolence, headache, dizziness, nausea, apathy, rash, hypertrichosis, gingival hypertrophy, hyponatremia
Perampanel	Dizziness, somnolence, fatigue, irritability, falls, nausea, weight gain, vertigo, ataxia, gait disturbance, and balance disorder
Phenobarbital and other barbiturates	Nuisance: neurotoxicity, insomnia, hyperactivity, signs of distractibility, fluctuation of mood, aggressive outbursts Serious: liver toxicity, Stevens-Johnson syndrome
Phenytoin and other hydantoins	Nuisance: gingival hyperplasia, coarsening of the facies, hirsutism, cerebellovestibular symptoms (nystagmus and ataxia) Serious: Stevens-Johnson syndrome, liver toxicity
Pregabalin	Nuisance: dizziness, peripheral edema, blurred vision, weight gain, thrombocytopenia Serious: hypersensitivity reactions, rhabdomyolysis
Primidone	Nuisance: CNS toxicity (dizziness, slurred speech, giddiness, drowsiness, depression) Serious: liver toxicity, Stevens-Johnson syndrome
Rufinamide	Nuisance: somnolence, vomiting Serious: contraindicated in familial short QT interval
Succinimides	Nuisance: nausea, abdominal discomfort, anorexia, hiccups Serious: Stevens-Johnson syndrome, drug-induced lupus
Tiagabine	Nuisance: dizziness, somnolence, asthenia, headache and tremor, precipitation of absence or myoclonic seizures Serious: precipitation of nonconvulsive status epilepticus
Topiramate	Nuisance: cognitive dysfunction, weight loss, renal calculi, hypohidrosis, fever Serious: precipitation of glaucoma
Valproic acid	Nuisance: weight gain; hyperammonemia tremor, alopecia, menstrual irregularities Serious: hepatic and pancreatic toxicity
Vigabatrin	Nuisance: hyperactivity Serious: irreversible visual field deficits, retinopathy that requires frequent ophthalmologic evaluations and follow up
Zonisamide	Fatigue, dizziness, anorexia, psychomotor slowing, ataxia, rarely hallucinations, hypohidrosis and fever

*Essentially all AEDs can cause CNS toxicity and potentially rashes and serious allergic reactions.
AED, antiepileptic drug; CNS, central nervous system.

multiple drugs. When appropriate, levels should also be checked upon addition (or discontinuation) of a second drug because of potential drug interactions. During follow-up, repeating the EEG every few months may be helpful to evaluate changes in the predisposition to seizures. This is especially true in situations where tapering off of medication is contemplated in any seizure type and during follow-up to assess response for absence seizures, as the EEG mirrors response in such patients.

Monitoring

For the older AEDs, before starting treatment, **baseline laboratory studies,** including complete blood count, platelets, liver enzymes, and possibly kidney function tests and urinalysis, are often obtained and repeated periodically. Laboratory monitoring is more relevant early on, because idiosyncratic adverse effects such as allergic hepatitis and agranulocytosis are more likely to occur in the 1st 3-6 mo of therapy. These laboratory studies are usually initially checked once or twice during the 1st mo, then every 3-4 mo thereafter. Serious concerns have been raised about the real usefulness of routine monitoring (in the absence of clinical signs) because the yield of significant adverse effects is low and the costs may be high. There are currently many advocates of less-frequent routine monitoring.

In approximately 10% of patients, a reversible dose-related leukopenia may occur in patients on carbamazepine or on phenytoin. This adverse effect responds to decreasing the dose or to stopping the medication and should be distinguished from the much-less-common idiosyncratic aplastic anemia or agranulocytosis. One exception requiring frequent (even weekly) monitoring of liver function and of blood counts throughout the therapy is felbamate, owing to the high incidence of liver and hematologic toxicity (1 in 500 children under 2 yr of age with complex neurological disorders who are on the drug). The gum hyperplasia that is seen with phenytoin necessitates good oral hygiene (brushing teeth at least twice per day and rinsing the mouth after taking the phenytoin); in a few cases, it may be severe enough to warrant surgical reduction and/or change of medication. Allergic rash can occur with any medication, but is probably most common with lamotrigine, carbamazepine, and phenytoin.

SIDE EFFECTS

During follow-up the patient should be monitored for **side effects**. Occasionally, a Stevens-Johnson–like syndrome develops, probably most commonly with lamotrigine; it also has been found to be particularly common in Chinese patients who have the allele HLA-B*1502 and are taking carbamazepine and lamotrigine.

Other potential side effects are rickets from phenytoin, phenobarbital, primidone, and carbamazepine (enzyme inducers that reduce 25-hyrdroxy-vitamin D level by inducing its metabolism) and hyperammonemia from valproate. Skeletal monitoring is warranted in patients on chronic AED therapy because it is often associated with vitamin D abnormalities (low bone density, rickets, and hypocalcemia) in children and adults, particularly those on enzyme-inducing medications. Thus, counseling the patient about sun exposure and vitamin D intake, monitoring its levels, and, in most cases, vitamin D supplementation are recommended. There is currently no consensus on the dose to be used for supplementation or prophylaxis, but starting doses of 400-2,000 IU/day with follow-up of the levels are reasonable.

Irreversible hepatic injury and death are particularly feared in young children (<2 yr old) who are on valproate in combination with other AEDs, particularly those who might have inborn errors of metabolism such as acidopathies and mitochondrial disease. Virtually all AEDs can produce sleepiness, ataxia, nystagmus, and slurred speech with toxic levels.

The FDA has determined that the use of AEDs may be associated with an increased risk of suicidal ideation and action and has recommended counseling about this side effect before starting these medications. This is obviously more applicable to adolescents and adults.

When adding a new AED, the doses used are often affected by the background medications. For example, if the patient is on enzyme inducers, the doses needed of valproate and lamotrigine are often double the usual maintenance doses. On the other hand, if the patient is on valproate, the doses of phenobarbital or lamotrigine are approximately half of what is usually needed. Thus, changes in the dosing of the background medication are often done as the interacting medication is being started. Genetic variability in enzymes that metabolize AEDs, and in the presence of inducible multidrug resistance genes, **pharmacogenomics**, might account for some of the variation among individuals in responding to certain AEDs. Although numerous variants of the cytochrome P450 enzymes have been characterized and although several multidrug resistance genes have been identified, the use of this new knowledge is currently largely restricted to research investigations, and it has yet to be applied in routine clinical practice.

Additional Treatments

The principles of monotherapy indicate that a second medication needs to be considered after the first either is pushed as high as tolerated and still does not control the seizures or results in intolerable adverse effects. In those cases, a second drug is started and the first is tapered and then discontinued. The second drug is then again pushed to the dose that controls the seizure or that results in intolerable side effects. If the second drug fails, monotherapy with a third drug or **dual (combination) therapy** is considered.

Patients with **drug-resistant** (previously referred to as intractable or refractory) **epilepsy** (those who have failed at least 2 fair trials of appropriate medications) warrant a careful diagnostic reevaluation to look for degenerative, metabolic, or inflammatory underlying disorders (e.g., mitochondrial disease, Rasmussen encephalitis; see Chapter 593.2) and to investigate them for candidacy for epilepsy surgery. Treatable metabolic disorders that can manifest as intractable epilepsy include pyridoxine-dependent and pyridoxal-responsive epilepsy; folinic acid–responsive seizures (demonstrated to be the same disorder as pyridoxine-dependent epilepsy); cerebral folate deficiency; neurotransmitter disorders; biotinidase deficiency; glucose transporter 1 deficiency (responds to the ketogenic diet); serine synthesis defects; creatine deficiency syndromes; untreated phenylketonuria; developmental delay, epilepsy and neonatal diabetes; and hyperinsulinemia–hyperammonia. Often patients who do not respond to AEDs are candidates for steroids, IVIG, or the ketogenic diet.

Steroids, usually given as ACTH (see the discussion of West syndrome in "Severe Generalized Epilepsies" in Chapter 593.4) or as prednisone 2 mg/kg/day (or equivalent), are often used in epileptic encephalopathies such as West, Lennox-Gastaut, myoclonic astatic, continuous spike-waves in slow-wave sleep, and Landau-Kleffner syndromes. The course usually is for 2-3 mo with a taper over a similar period. Because relapses occur commonly during tapering, and in such syndromes as Landau-Kleffner and continuous spike-waves in slow-wave sleep, therapy for longer than 1 yr is often needed.

IVIG has also been reported to be similarly effective in non–immunodeficient patients with West, Lennox-Gastaut, Landau-Kleffner, and continuous spike-waves in slow-wave sleep syndromes and may also have efficacy in partial seizures. One should check the IgA levels before starting the infusions (to assess the risk for allergic reactions, because these are increased in patients with complete IgA deficiency) and guard against allergic reactions during the infusion. Low IgA, low IgG_2, and male sex are reported to possibly predict favorable response. The usual regimen is 2 g/kg divided over 4 consecutive days followed by 1 g/kg once a month for 6 mo. The mechanism of action of steroids and of IVIG are not known but is presumed to be antiinflammatory, because it has been demonstrated that seizures increase cytokines and that these, in turn, increase neuronal excitability by several mechanisms, including activation of glutamate receptors. Steroids and ACTH might also stimulate brain neurosteroid receptors that enhance GABA activity and might reduce corticotrophin-releasing hormone, which is known to be epileptogenic.

The **ketogenic diet** is believed to be effective in glucose transporter protein 1 deficiency, pyruvate dehydrogenase deficiency, myoclonic–astatic epilepsy, tuberous sclerosis complex, Rett syndrome, severe myoclonic epilepsy of infancy (Dravet syndrome), and infantile spasms. There is also suggestion of possible efficacy in selected

mitochondrial disorders—glycogenosis type V, Landau-Kleffner syndrome, Lafora body disease, and subacute sclerosing panencephalitis. The diet is absolutely contraindicated in carnitine deficiency (primary); carnitine palmitoyltransferase I or II deficiency; carnitine translocase deficiency; β-oxidation defects; medium-chain acyl dehydrogenase deficiency; long-chain acyl dehydrogenase deficiency; short-chain acyl dehydrogenase deficiency; long-chain 3-hydroxyacyl-coenzyme A deficiency; medium-chain 3-hydroxyacyl-coenzyme A deficiency; pyruvate carboxylase deficiency; and porphyrias. Thus, an appropriate metabolic work-up, depending on the clinical picture, usually needs to be performed before starting the diet (e.g., acyl carnitine profile, total and free carnitine levels). The diet has been used for refractory seizures of various types (partial or generalized) and consists of an initial period of fasting followed by a diet with a 3:1 or 4:1 fat:nonfat ratio, with fats consisting of animal fat, vegetable oils, or medium-chain triglycerides. Many patients do not tolerate it owing to diarrhea, vomiting, hypoglycemia, dehydration, or lack of palatability. Diets such as the low-glycemic-index diet and the Atkins diet are easier to institute, do not require hospitalization, and are also useful, but it is not known yet if they are as effective as the classic diet.

APPROACH TO EPILEPSY SURGERY

If a patient has failed 3 drugs, the chance of achieving seizure freedom using AEDs is generally <10%. Therefore, proper evaluation for surgery is necessary as soon as patients fail 2 or 3 AEDs, usually within 2 yr of the onset of epilepsy and often sooner than 2 yr. Performing epilepsy surgery in children at an earlier stage (e.g., <5 yr of age) allows transfer of function in the developing brain. Candidacy for epilepsy surgery requires proof of resistance to AEDs used at maximum, tolerably nontoxic doses; absence of expected unacceptable adverse consequences of surgery, and a properly defined **epileptogenic zone** (area that needs to be resected to achieve seizure freedom). The epileptogenic zone is identified by careful analysis, by an expert team of epilepsy specialists in an epilepsy center, of the following parameters: seizure semiology, interictal EEG, video-EEG long-term monitoring, neuropsychologic profile, and MRI. Other techniques, such as invasive EEG (depth electrodes, subdurals), single-photon emission CT, magnetoencephalography, and positron emission tomography are also often needed when the epileptogenic zone is difficult to localize or when it is close to eloquent cortex. To avoid resection of eloquent cortex, several techniques can be used, including the **Wada test**. In this test, intracarotid infusion of amobarbital is used to anesthetize 1 hemisphere to lateralize memory and speech by testing them during that unilateral anesthesia. Other tests to localize function include functional MRI, magnetoencephalography, and subdural electrodes with cortical stimulation. Developmental delay or psychiatric diseases must be considered in assessing the potential impact of surgery on the patient. The usual minimal presurgical evaluation includes EEG monitoring, imaging, and age-specific neuropsychologic assessment.

Epilepsy surgery is often used to treat refractory epilepsy of a number of etiologies, including cortical dysplasia, tuberous sclerosis, polymicrogyria, hypothalamic hamartoma, Landau-Kleffner syndrome, and hemispheric syndromes, such as Sturge-Weber syndrome, hemimegalencephaly, and Rasmussen encephalitis. Patients with intractable epilepsy resulting from metabolic or degenerative problems are not candidates for resective epilepsy surgery. **Focal resection** of the epileptogenic zone is the most common procedure. **Hemispherectomy** is used for diffuse hemispheric lesions; **multiple subpial transection**, a surgical technique in which the horizontal connections of the epileptic focus are partially cut without resecting it, is sometimes used for unresectable foci located in eloquent cortex such as in Landau-Kleffner syndrome. In Lennox-Gastaut syndrome, **corpus callosotomy** is used for drop attacks. **Vagal nerve stimulation** is often used for intractable epilepsies of various types and for seizures of diffuse focal or multifocal anatomic origin that do not yield themselves to resective surgery. Focal resection and hemispherectomy result in a high rate (50-80%) of seizure freedom. Corpus callosotomy and vagal nerve stimulation result in lower rates (5-10%) of seizure freedom; however, these procedures do result in significant reductions in the frequency and severity of seizures, decrease in medication requirements, and meaningful improvements in the patient's quality of life in approximately half or more of eligible patients.

DISCONTINUATION OF THERAPY

Discontinuation of AEDs is usually indicated when children are free of seizures for at least 2 yr. In more-severe syndromes, such as temporal lobe epilepsy secondary to mesial temporal sclerosis, Lennox-Gastaut syndrome, or severe myoclonic epilepsy, a prolonged period of seizure freedom on treatment is often warranted before AEDs are withdrawn, if withdrawal is attempted at all. In self-limited (benign) epilepsy syndromes, the duration of therapy can often be as short as 6 mo.

Many factors should be considered before discontinuing medications, including the likelihood of remaining seizure-free after drug withdrawal based on the type of epilepsy syndrome and etiology; the risk of injury in case of seizure recurrence (e.g., if the patient drives); and the adverse effects of AED therapy. Most children who have not had a seizure for 2 yr or longer and who have a normal EEG when AED withdrawal is initiated, remain free of seizures after discontinuing medication, and most relapses occur within the 1st 6 mo.

Certain risk factors can help the clinician predict the prognosis after AED withdrawal. The most important risk factor for seizure relapse is an abnormal EEG before medication is discontinued. Children who have remote structural (symptomatic) epilepsy are less likely to be able to stop AEDs than are children who have a benign genetic (idiopathic) epilepsy. In patients with absences or in patients treated with valproate for primary generalized epilepsy, the risk of relapse might still be high despite a normal EEG because valproate can normalize EEGs with generalized spike-wave abnormalities. Thus, in these patients, repeating the EEG during drug taper can help identify recurrence of the EEG abnormality and associated seizure risk before clinical seizures recur. Older age of epilepsy onset, longer duration of epilepsy, presence of multiple seizure types, and need to use more than 1 AED are all factors associated with a higher risk of seizure relapse after AED withdrawal.

AED therapy should be discontinued gradually; often over a period of 3-6 mo. Abrupt discontinuation can result in withdrawal seizures or status epilepticus. Withdrawal seizures are especially common with phenobarbital and benzodiazepines; consequently, special attention must be given to a prolonged tapering schedule during the withdrawal of these AEDs. Seizures that occur more than 2-3 mo after AEDs are completely discontinued indicate relapse, and resumption of treatment is usually warranted.

The decision to attempt AED withdrawal must be assessed mutually among the clinician, the parents, and the child depending on the child's age. Risk factors should be identified and precautionary measures should be taken. The patient and family should be counseled fully on what to expect, what precautions to take (including cessation of driving for a period of time), and what to do in case of relapse. A prescription for rectal diazepam or of intranasal midazolam to be given at the time of seizures that might occur during and after tapering is usually warranted (see Table 593-12 for dosing).

Sudden Unexpected Death in Epilepsy

SUDEP is the most common epilepsy related mortality in patients with chronic epilepsy; the incidence is unknown but ranges from 1-5 per 1,000 people with epilepsy. Although the precise etiology is unknown, risk factors include polypharmacology, poorly controlled generalized tonic–clonic seizures, male gender, age younger than 16 yr, long duration of epilepsy, and frequent seizures. Patients are usually found dead in their bed in a prone position with evidence suggesting a recent seizure. Potential mechanisms of SUDEP include respiratory arrest or dysfunction, drug-induced cardiac toxicity, CNS dysfunction (hypoventilation, arrhythmia, suppression of brain electrical activity), or pulmonary edema. Table 593-15 lists possible preventive measures.

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Table 593-15 Measures in Clinical Practice to Reduce the Risk of SUDEP

- **Reduction of tonic–clonic seizures:** optimum treatment, good drug compliance, lifestyle advice (e.g., alcohol intake, sleep deprivation)
- **Treatment changes:** change in a gradual staged manner; when switching drugs, introduce the new drug before withdrawing the old drug; the patients should have access to immediate advice in the event of worsening seizures during periods of change
- **Supervision at night for patients at high risk:** attendance, use of alarms (balancing the benefits of independent living and the penalties of intrusive monitoring)
- **Choice of drugs:** caution with antiepileptic drugs with potential cardiorespiratory adverse effects
- **Act on ictal warning signs:** tonic–clonic seizures that are prolonged, associated with marked cyanosis, severe bradycardia or apnea, and postictal EEG suppression; complex partial seizures with marked atonia (drop attacks); seizure in those with preexisting cardiac or respiratory impairment
- **Supervision after a tonic–clonic seizure:** continuous attendance until full consciousness is restored; call emergency services for high-risk seizures
- **Counseling on the risks:** lifestyle and treatment decisions are the patient's prerogative and the physician's role is to provide a risk-vs-benefit analysis

EEG, electroencephalogram; SUDEP, sudden unexpected death in epilepsy.
From Shorvan S, Tomson T: Sudden unexpected death in epilepsy. Lancet *378:2028–2036, 2011.*

593.7 Neonatal Seizures

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Seizures are possibly the most important and common indicator of significant neurologic dysfunction in the neonatal period. Seizure incidence is higher during this period than in any other period in life: 57.5 per 1,000 in infants with birth weights <1,500 g and 2.8 per 1,000 in infants weighing between 2,500 and 3,999 g have seizures.

PATHOPHYSIOLOGY

The immature brain has many differences from the mature brain that render it more excitable and more likely to develop seizures. Based predominantly on animal studies, these are delay in Na^+, K^+-adenosine triphosphatase maturation and increased NMDA and α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptor density. In addition, the specific types of these receptors that are increased are those that are permeable to calcium (GLUR2 AMPA receptors). This contributes to increased excitability and to the long-term consequences associated with seizures, particularly those resulting from perinatal hypoxia. Medications that block AMPA receptors, such as topiramate, may thus prove useful in this clinical setup.

Another difference is delay in the development of inhibitory GABAergic transmission. In fact, GABA in the immature brain has an excitatory function as the chloride gradient is reversed relative to the mature brain, with higher concentrations of chloride being present intracellularly than extracellularly. Thus, opening of the chloride channels in the immature brain results in depolarizing the cell and not in hyperpolarizing it. This phenomenon appears to be more prominent in male neonates, perhaps explaining their greater predisposition to seizures. The reason for this is that the Cl^- transporter, NKCC1, is predominantly expressed in the neonatal period, leading to transport of Cl^- into the cell at rest, and then to cellular depolarization upon activation of $GABA_A$ receptors and opening of Cl^- channels with chloride efflux. This is important for neuronal development but renders the neonatal brain hyperexcitable. With maturation, expression of NCCK1 decreases and KCC2 increases. KCC2 transports Cl^- out of the cell, resulting in reduction of intracellular chloride concentration so that when $GABA_A$ receptors are activated, Cl^- influx and hyperpolarization occur. Bumetanide, a diuretic that blocks NKCC1, can prevent excessive GABA depolarization and avert the neuronal hyperexcitability underlying neonatal seizures. It also prevents, in rats, complex febrile seizure induced hyperactivation of excitatory $GABA_A$ receptors and the resultant granule cell ectopia and temporal lobe epilepsy.

Although it is susceptible to developing seizures, the immature brain appears to be more resistant to the deleterious effects of seizures than the mature brain, as a result of increases in calcium binding proteins that buffer injury-related increases in calcium, increased extracellular space, decreased levels of the second messenger inositol triphosphate, and the immature brain's ability to tolerate hypoxic conditions by resorting to anaerobic energy metabolism.

Many animal studies indicate that seizures are detrimental to the immature brain. Human studies also suggest harmful effects of seizures as shown by MRI and by the association of worse prognosis in neonates with seizures even when correcting for confounding factors. Even electrographic seizures without clinical correlates have been shown to be associated with worse prognosis. However, it is not definite that this association is causal: It is difficult in human studies to distinguish among effects of seizures, of the underlying insult responsible for the seizures (clinical or electrographic), and of the AEDs used to stop the seizures. Most physicians currently believe that it is favorable to control clinical as well as electrographic seizures.

TYPES OF NEONATAL SEIZURES

There are 5 main neonatal seizure types: subtle, clonic, tonic, spasms, and myoclonic. Spasms, focal clonic, focal tonic, and generalized myoclonic seizures are, as a rule, associated with electrographic discharges (epileptic seizures), whereas motor automatisms, the subtle, generalized tonic and multifocal myoclonic episodes are frequently not associated with discharges and thus are thought to often represent release phenomena with abnormal movements secondary to brain injury rather than true epileptic seizures (Table 593-16). To determine clinically whether such manifestations are seizures or release phenomena is often difficult, but precipitation of such manifestations by stimulation and aborting them by restraint or manipulation would suggest that they are not seizures. One needs to keep in mind, however, that epileptic seizures can also be induced by stimulation. Thus, in many cases, specifically in sick neonates with history of neurologic insults, continuous bedside EEG monitoring helps make this distinction. Such monitoring has become the standard of care in most intensive care nurseries.

Subtle Seizures

Subtle seizures include transient eye deviations, nystagmus, blinking, mouthing, abnormal extremity movements (rowing, swimming, bicycling, pedaling, and stepping), fluctuations in heart rate, hypertension episodes, and apnea. Subtle seizures occur more commonly in premature than in full-term infants.

Clonic Seizures

Clonic seizures can be focal or multifocal. Multifocal clonic seizures incorporate several body parts and are migratory in nature. The migration follows a nonjacksonian trend; for example, jerking of the left arm can be associated with jerking of the right leg. Generalized clonic seizures that are bilateral, symmetric, and synchronous are uncommon in the neonatal period presumably due to decreased connectivity associated with incomplete myelination at this age.

Tonic Seizures

Tonic seizures can be focal or generalized (generalized are more common). Focal tonic seizures include persistent posturing of a limb or posturing of trunk or neck in an asymmetric way often with persistent horizontal eye deviation. Generalized tonic seizures are bilateral tonic limb extension or tonic flexion of upper extremities often associated with tonic extension of lower extremities.

Spasms

Spasms are sudden generalized jerks lasting 1-2 sec that are distinguished from generalized tonic spells by their shorter duration and by

Table 593-16 Clinical Characteristics, Classification, and Presumed Pathophysiology of Neonatal Seizures

CLASSIFICATION	CHARACTERIZATION
Focal clonic	Repetitive, rhythmic contractions of muscle groups of the limbs, face, or trunk May be unifocal or multifocal May occur synchronously or asynchronously in muscle groups on 1 side of the body May occur simultaneously but asynchronously on both sides Cannot be suppressed by restraint Pathophysiology: epileptic
Focal tonic	Sustained posturing of single limbs Sustained asymmetrical posturing of the trunk Sustained eye deviation Cannot be provoked by stimulation or suppressed by restraint Pathophysiology: epileptic
Generalized tonic	Sustained symmetrical posturing of limbs, trunk, and neck May be flexor, extensor, or mixed extensor/flexor May be provoked or intensified by stimulation May be suppressed by restraint or repositioning Presumed pathophysiology: nonepileptic
Myoclonic	Random, single, rapid contractions of muscle groups of the limbs, face, or trunk Typically not repetitive or may recur at a slow rate May be generalized, focal, or fragmentary May be provoked by stimulation Presumed pathophysiology: may be epileptic or nonepileptic
Spasms	May be flexor, extensor, or mixed extensor/flexor May occur in clusters Cannot be provoked by stimulation or suppressed by restraint Pathophysiology: epileptic
Motor automatisms	
Ocular signs	Random and roving eye movements or nystagmus (distinct from tonic eye deviation) May be provoked or intensified by tactile stimulation Presumed pathophysiology: nonepileptic
Oral-buccal-lingual movements	Sucking, chewing, tongue protrusions May be provoked or intensified by stimulation Presumed pathophysiology: nonepileptic
Progression movements	Rowing or swimming movements Pedaling or bicycling movements of the legs May be provoked or intensified by stimulation May be suppressed by restraint or repositioning Presumed pathophysiology: nonepileptic
Complex purposeless movements	Sudden arousal with transient increased random activity of limbs May be provoked or intensified by stimulation Presumed pathophysiology: nonepileptic

From Mizrahi EM, Kellaway P. Diagnosis and management of neonatal seizures. *Philadelphia, 1998, Lippincott-Raven. Tab 4, p. 21.*

the fact that spasms are usually associated with a single, very brief, generalized discharge.

Myoclonic Seizures

Myoclonic seizures are divided into focal, multifocal, and generalized types. Myoclonic seizures can be distinguished from clonic seizures by the rapidity of the jerks (<50 msec) and by their lack of rhythmicity. Focal myoclonic seizures characteristically affect the flexor muscles of the upper extremities and are sometimes associated with seizure activity on EEG. Multifocal myoclonic movements involve asynchronous twitching of several parts of the body and are not commonly associated with seizure discharges on EEG. Generalized myoclonic seizures involve bilateral jerking associated with flexion of upper and occasionally lower extremities. The latter type of myoclonic jerks is more commonly correlated with EEG abnormalities than the other types.

Seizures vs Jitteriness

Jitteriness can be defined as rapid motor activities, such as a tremor or shake, that can be ended by flexion or holding the limb. Seizures, on the other hand, generally do not end with tactile or motor suppression. Jitteriness, unlike most seizures, is usually induced by a stimulus. Also unlike jitteriness, seizures often involve eye deviation and autonomic changes.

ETIOLOGY

Table 593-17 lists causes of neonatal seizures.

Hypoxic–Ischemic Encephalopathy

This is the most common cause of neonatal seizures, accounting for 50-60% of patients. Seizures secondary to this encephalopathy occur within 12 hr of birth.

Vascular Events

These include intracranial bleeds and ischemic strokes and account for 10-20% of patients. Three types of hemorrhage can be distinguished: primary subarachnoid hemorrhage, germinal matrix–intraventricular hemorrhage, and subdural hemorrhage. Patients with arterial strokes or venous sinus thrombosis can present with seizure and these can be

Table 593-17 Causes of Neonatal Seizures According to Common Age of Presentation

AGES 1-4 DAYS
Hypoxic–ischemic encephalopathy
Drug withdrawal, maternal drug use of narcotic or barbiturates
Drug toxicity: lidocaine, penicillin
Intraventricular hemorrhage
Acute metabolic disorders
• Hypocalcemia
• Sepsis
• Maternal hyperthyroidism, or hypoparathyroidism
• Hypoglycemia
• Perinatal insults, prematurity, small for gestational age
• Maternal diabetes
• Hyperinsulinemic hypoglycemia
• Hypomagnesemia
• Hyponatremia or hypernatremia
• Iatrogenic or inappropriate antidiuretic hormone secretion
Inborn errors of metabolism
• Galactosemia
• Hyperglycinemia
• Urea cycle disorders
Pyridoxine deficiency and pyridoxal-5-phosphate deficiency (must be considered at any age)
AGES 4-14 DAYS
Infection
• Meningitis (bacterial)
• Encephalitis (enteroviral, herpes simplex)
Metabolic disorders
• Hypocalcemia
• Diet, milk formula
• Hypoglycemia, persistent
• Inherited disorders of metabolism
• Galactosemia
• Fructosemia
• Leucine sensitivity
• Hyperinsulinemic hypoglycemia, hyperinsulinism, hyperammonemia syndrome
• Anterior pituitary hypoplasia, pancreatic islet cell tumor
• Beckwith syndrome
Drug withdrawal, maternal drug use of narcotics or barbiturates
Benign neonatal convulsions, familial and nonfamilial
Kernicterus, hyperbilirubinemia
Developmental delay, epilepsy, neonatal diabetes syndrome
AGES 2-8 WK
Infection
• Herpes simplex or enteroviral encephalitis
• Bacterial meningitis
Head injury
• Subdural hematoma
• Child abuse
Inherited disorders of metabolism
• Aminoacidurias
• Urea cycle defects
• Organic acidurias
• Neonatal adrenoleukodystrophy
Malformations of cortical development
• Lissencephaly
• Focal cortical dysplasia
Tuberous sclerosis
Sturge-Weber syndrome

diagnosed by neuroimaging. Venous sinus thrombosis could be missed unless MR or CT venography studies are requested.

Intracranial Infections

Bacterial and nonbacterial infections account for 5-10% of the cases of neonatal seizures and include bacterial meningitis, TORCH (*t*oxoplasmosis, *o*ther infections, *r*ubella, *c*ytomegalovirus, *h*erpes simplex virus) infections, particularly herpes simplex encephalitis.

Brain Malformations

Brain malformations account for 5-10% of neonatal seizure cases. An example is **Aicardi syndrome**, which affects girls only and consists of retinal lacunae, agenesis of the corpus callosum, and severe seizures including subsequent infantile spasms with hypsarrhythmia that is sometimes initially unilateral on EEG.

Metabolic Disturbances

Metabolic disturbances include disturbances in glucose, calcium, magnesium, other electrolytes, amino acids, or organic acids and pyridoxine dependency.

Hypoglycemia can cause neurologic disturbances and is very common in small neonates and neonates whose mothers are diabetic or prediabetic. The duration of hypoglycemia is very critical in determining the incidence of neurologic symptoms.

Hypocalcemia occurs at 2 peaks. The first peak corresponds to low-birthweight infants and is evident in the 1st 2-3 days of life. The second peak occurs later in neonatal life and often involves large, full-term babies who consume milk that has an unfavorable ratio of phosphorus to calcium and phosphorus to magnesium. **Hypomagnesemia** is often associated with hypocalcemia. **Hyponatremia** can cause seizures and is often secondary to inappropriate antidiuretic hormone secretion.

Local anesthetic intoxication seizures can result from neonatal intoxication with local anesthetics administered into the infant's scalp.

Neonatal seizures can also result from disturbances in **amino acid or organic acid** metabolism. These are usually associated with acidosis and/or hyperammonemia. However, even in the absence of these findings, if a cause of the seizures is not immediately evident, then ruling out metabolic causes requires a full metabolic work-up (see Chapter 593.2) including examination of serum amino acids, acyl carnitine profile, lactate, pyruvate, ammonia, very-long-chain fatty acids (for neonatal adrenoleukodystrophy and Zellweger syndrome), examination of urine for organic acids, α-aminoadipic acid semialdehyde and sulfocysteine, as well as examination of CSF for glucose, protein, cells, amino acids, lactate, pyruvate, α-aminoadipic acid semialdehyde, pyridoxal phosphate, 5-MTHF (5-methyltetrahydrofolate), succinyladenosine, and CSF neurotransmitter metabolites. This is because many inborn errors of metabolism, such as nonketotic hyperglycinemia, can manifest with neonatal seizures (often mistaken initially for hiccups that these patients also have) and can be detected only by performing these tests. Definitive diagnosis of **nonketotic hyperglycinemia**, for example, requires measuring the ratio of CSF glycine to plasma glycine.

Pyridoxine and **pyridoxal dependency disorders** can cause severe seizures. These seizures, which are often multifocal clonic, usually start during the 1st few hr of life. Cognitive impairment is often associated if therapy is delayed (see Chapter 593.6).

Drug Withdrawal

Seizures can rarely be caused by the neonate's passive addiction and then drug withdrawal. Such drugs include narcotic analgesics, sedative–hypnotics, and others. The associated seizures appear during the 1st 3 days of life.

Neonatal Seizure Syndromes

Seizure syndromes include **benign idiopathic neonatal seizures (fifth day fits)**, which are usually apneic and focal motor seizures that start around the fifth day of life. Interictal EEG shows a distinctive pattern called *theta pointu alternant* (runs of sharp 4-7 Hz activity), and ictal EEG shows multifocal electrographic seizures. Patients have a good response to medications and a good prognosis. Autosomal dominant **benign familial neonatal seizures** have onset at 2-4 days of age and usually remit at 2-15 wk of age. The seizures consist of ocular deviation, tonic posturing, clonic jerks, and, at times, motor automatisms. Interictal EEG is usually normal. These are caused by mutations in the *KCNQ2* and *KCNQ3* genes. Approximately 16% of patients develop later epilepsy. **Early myoclonic encephalopathy** and **early infantile epileptic encephalopathy (Ohtahara syndrome)** are discussed in Chapter 593.4.

Miscellaneous Conditions

Miscellaneous conditions include benign neonatal sleep myoclonus and hyperekplexia, which are nonepileptic conditions (see Chapter 594).

DIAGNOSIS

Some cases can be correctly diagnosed by simply taking the prenatal and postnatal history and performing an adequate physical examination. Depending on the case, additional tests or procedures can be performed. EEG is considered the main tool for diagnosis. It can show paroxysmal activity (e.g., sharp waves) in between the seizures and electrographic seizure activity if a seizure is captured. However, some neonatal seizures might not be associated with EEG abnormalities as noted above either because they are "release phenomena" or alternatively because the discharge is deep and is not detected by the scalp EEG. Additionally, electrographic seizures can occur without observed clinical signs (**electroclinical dissociation**). This is presumed to be caused by the immaturity of cortical connections, resulting, in many cases, in no or minimal motor manifestations. Continuously monitoring the EEG at the bedside in the neonatal intensive care unit for neonates at risk for neonatal seizures and brain injury is part of routine clinical practice in most centers, providing real-time measurements of the brain's electrical activity and identifying seizure activity. Many centers apply EEG monitoring to at-risk babies even before seizures develop, which is often desirable; others monitor patients who have manifested or are suspected of having seizures. In addition, there are currently attempts to develop methods for continuous monitoring of cerebral activity with automated detection and background analysis of neonatal seizures, similar to the continuous ECG monitoring in intensive care facilities. In infants started on hypothermia protocols following suspected hypoxic–ischemic injuries, it is recommended to continuously monitor the EEG during the cooling and rewarming periods to detect clinical and subclinical events in this high-risk population. The American Clinical Neurophysiology Society recommends continuous EEG monitoring in the neonatal intensive care unit to monitor evolution of EEG background to help with prognostication, to guide titration of anticonvulsant therapy for infants with established seizures, to screen for seizures among infants deemed to be at risk (hypoxic ischemic encephalopathy, stroke, meningitis, intraventricular hemorrhage, metabolic disorders, and congenital cerebral malformations), to screen for seizures among infants who are paralyzed, to characterize clinical events suspected to represent seizures, and to detect impending cerebral ischemia or hemorrhage.

Careful neurologic examination of the infant might uncover the cause of the seizure disorder. Examination of the **retina** might show the presence of chorioretinitis, suggesting a congenital TORCH infection, in which case titers of mother and infant are indicated. The **Aicardi syndrome** is associated with coloboma of the iris and retinal lacunae. Inspection of the **skin** might show hypopigmented lesions characteristic of tuberous sclerosis (seen best on UV light examination) or the typical crusted vesicular lesions of incontinentia pigmenti; both neurocutaneous syndromes are often associated with generalized myoclonic seizures beginning early in life. An unusual body or urine odor suggests an inborn error of metabolism.

Blood should be obtained for determinations of glucose, calcium, magnesium, electrolytes, and blood urea nitrogen. If hypoglycemia is a possibility, serum glucose testing is indicated so that treatment can be initiated immediately. Hypocalcemia can occur in isolation or in association with hypomagnesemia. A lowered serum calcium level is often associated with birth trauma or a CNS insult in the perinatal period. Additional causes include maternal diabetes, prematurity, DiGeorge syndrome, and high-phosphate feedings. Hypomagnesemia (<1.5 mg/dL) is often associated with hypocalcemia and occurs particularly in infants of malnourished mothers. In this situation, the seizures are resistant to calcium therapy but respond to intramuscular magnesium, 0.2 mL/kg of a 50% solution of $MgSO_4$. Serum electrolyte measurement can indicate significant hyponatremia (serum sodium <115 mEq/L) or hypernatremia (serum sodium >160 mEq/L) as a cause of the seizure disorder.

A **lumbar puncture** is indicated in virtually all neonates with seizures, unless the cause is obviously related to a metabolic disorder such as hypoglycemia or hypocalcemia. The latter infants are normally alert interictally and usually respond promptly to appropriate therapy. The CSF findings can indicate a bacterial meningitis or aseptic encephalitis. Prompt diagnosis and appropriate therapy improve the outcome for these infants. Bloody CSF indicates a traumatic tap or a subarachnoid or intraventricular bleed. Immediate centrifugation of the specimen can assist in differentiating the 2 disorders. A clear supernatant suggests a traumatic tap, and a xanthochromic color suggests a subarachnoid bleed. Mildly jaundiced normal infants can have a yellowish discoloration of the CSF that makes inspection of the supernatant less reliable in the newborn period.

Many **inborn errors of metabolism** cause generalized convulsions in the newborn period. Because these conditions are often inherited in an autosomal recessive or X-linked recessive fashion, it is imperative that a careful family history be obtained to determine if there is consanguinity or whether siblings or close relatives developed seizures or died at an early age. Serum ammonia determination is useful for screening for the hypoglycemic hyperammonemia syndrome and for suspected urea cycle abnormalities. In addition to having generalized clonic seizures, these latter infants present during the 1st few days of life with increasing lethargy progressing to coma, anorexia and vomiting, and a bulging fontanel. If the blood gases show an anion gap and a metabolic acidosis with the hyperammonemia, urine organic acids should be immediately determined to investigate the possibility of methylmalonic or propionic acidemia.

Maple syrup urine disease should be suspected when a metabolic acidosis occurs in association with generalized clonic seizures, vomiting, bulging fontanel, and muscle rigidity during the 1st wk of life. The result of a rapid screening test using 2,4-dinitrophenylhydrazine that identifies keto derivatives in the urine is positive in maple syrup urine disease.

Additional metabolic causes of neonatal seizures include nonketotic hyperglycinemia, an intractable condition characterized by markedly elevated plasma and CSF glycine levels, prominent hiccups, persistent generalized seizures, and lethargy rapidly leading to coma; ketotic hyperglycinemia in which seizures are associated with vomiting, fluid and electrolyte disturbances, and a metabolic acidosis; and Leigh disease suggested by elevated levels of serum and CSF lactate or an increased lactate : pyruvate ratio. Biotinidase deficiency should also be considered. A comprehensive description of the diagnosis and management of these metabolic diseases is discussed in Part XI, Metabolic Disorders.

Unintentional **injection of a local anesthetic** into a fetus during labor can produce intense tonic seizures. These infants are often thought to have had a traumatic delivery because they are flaccid at birth, have abnormal brainstem reflexes, and show signs of respiratory depression that sometimes require ventilation. Examination may show a needle puncture of the skin or a perforation or laceration of the scalp. An elevated serum anesthetic level confirms the diagnosis. The treatment consists of supportive measures and promotion of urine output by administering intravenous fluids with appropriate monitoring to prevent fluid overload.

Benign familial neonatal seizures, an autosomal dominant condition, begins on the 2nd-3rd day of life, with a seizure frequency of 10-20/day. Patients are normal between seizures, which stop in 1-6 mo. These are caused by mutations in the voltage-sensitive potassium channel genes *Kv7.2*, and *Kv7.3* (*KCNQ2* and *KCNQ3*). Other mutations in the *Kv7.2* gene cause severe neonatal epileptic encephalopathy. **Fifth-day fits** occur on day 5 of life (4-6 days) in normal-appearing neonates. The seizures are multifocal and are often present for <24 hr. The diagnosis requires exclusion of other causes of seizures and sequencing of the above genes. The prognosis is good for the benign form.

Pyridoxine dependency, a rare disorder, must be considered when seizures begin shortly after birth with signs of fetal distress in utero and are resistant to conventional anticonvulsants such as phenobarbital or phenytoin. The history may suggest that similar seizures

occurred in utero. When pyridoxine-dependent seizures are suspected, 100-200 mg of pyridoxine or pyridoxal phosphate should be administered intravenously during the EEG, which should be promptly performed once the diagnosis is considered. The seizures abruptly cease, and the EEG often normalizes in the next few hours or longer. Not all cases of pyridoxine dependency respond dramatically to the initial bolus of IV pyridoxine. Therefore, a 6-wk trial of oral pyridoxine (100-200 mg/day) or preferably pyridoxal phosphate (as pyridoxine does not help infants with the related but distinct syndrome of pyridoxal dependency) is recommended for infants in whom a high index of suspicion continues after a negative response to IV pyridoxine. Measurement of serum pipecolic acid and α-aminoadipic acid semialdehyde (elevated) and CSF pyridoxal-5-phosphate (decreased) needs to be performed before initiation of the trials without delay. These children require lifelong supplementation of oral pyridoxine (100 mg/day at times with folinic acid) or pyridoxal phosphate (15-60 mg/kg/day). Cerebral folate deficiency should also be ruled out by medication trial (folinic acid 1-3 mg/kg/day) and by CSF levels of 5-methyltetrahydrofolate assay. Gene sequencing can confirm the diagnosis (see Chapter 593.4). The earlier the therapy is initiated in these vitamin responsive disorders, the more favorable the outcome.

Drug-withdrawal seizures can occur in the newborn nursery but can take several weeks to develop because of prolonged excretion of the drug by the neonate. The incriminated drugs include barbiturates, benzodiazepines, heroin, and methadone. The infant may be jittery, irritable, and lethargic, and can have myoclonus or frank clonic seizures. The mother might deny the use of drugs; a serum or urine drug screen might identify the responsible agent.

Infants with focal seizures, suspected stroke or intracranial hemorrhage, and severe **cytoarchitectural abnormalities** of the brain (including lissencephaly and schizencephaly) who clinically may appear normal or microcephalic should undergo MRI or CT scan. Indeed, it is appropriate to recommend imaging of all neonates with seizures unexplained by serum glucose, calcium, or electrolyte disorders. Infants with chromosome abnormalities and adrenoleukodystrophy are also at risk for seizures and should be evaluated with investigation of a karyotype and serum very-long-chain fatty acids, respectively.

PROGNOSIS

Over the last few decades, prognosis of neonatal seizures has improved owing to advancements in obstetric and intensive neonatal care. Mortality has decreased from 40% to 20%. The correlation between EEG and prognosis is very clear. Although neonatal EEG interpretation is very difficult, EEG was found to be highly associated with the outcome in premature and full-term infants. An abnormal background is a powerful predictor of less-favorable later outcome. In addition, prolonged electrographic seizures (>10 min/hr), multifocal periodic electrographic discharges, and spread of the electrographic seizures to the contralateral hemisphere also correlate with poorer outcome. The underlying etiology of the seizures is the main determinant of outcome. For example, patients with seizures secondary to hypoxic–ischemic encephalopathy have a 50% chance of developing normally, whereas those with seizures caused by primary subarachnoid hemorrhage or hypocalcemia have a much better prognosis.

TREATMENT

A mainstay in the therapy of neonatal seizures is the diagnosis and treatment of the underlying etiology (e.g., hypoglycemia, hypocalcemia, meningitis, drug withdrawal, trauma), whenever one can be identified. There are conflicting approaches regarding the control of neonatal seizures. Most experts advocate complete control of clinical as well electrographic seizures. Others argue for treating clinical seizures only. Most centers favor the first approach. An important consideration before starting anticonvulsants is deciding, based on the severity duration and frequency of the seizures if the patient needs to receive intravenous therapy and loading with an initial bolus or can simply be started on maintenance doses of a long-acting drug. Patients often require assisted ventilation after receiving intravenous or oral loading doses of AEDs, and thus precautions for observations and for needed interventions are necessary.

Lorazepam

The initial drug used to control acute seizures is usually lorazepam. Lorazepam is distributed to the brain very quickly and exerts its anticonvulsant effect in <5 min. It is not very lipophilic and does not clear out from the brain very rapidly. Its action can last 6-24 hr. Usually, it does not cause hypotension or respiratory depression. The dose is 0.05 mg/kg (range: 0.02-0.10 mg/kg) every 4-8 hr.

Diazepam

Diazepam can be used as an alternative initial drug. It is highly lipophilic, so it distributes very rapidly into the brain and then is cleared very quickly out, carrying the risk of recurrence of seizures. Like other intravenous benzodiazepines, it carries a risk of apnea and hypotension, particularly if the patient is also on a barbiturate, so patients need to be observed for 3-8 hr after administration. The usual dose is 0.1-0.3 mg/kg IV over 3-5 min, given every 15-30 min to a maximum total dose of 2 mg. However, because of the respiratory and blood pressure limitations and because the intravenous preparation contains sodium benzoate and benzoic acid, it is currently not recommended as a first-line agent.

Midazolam

Midazolam can be used as an initial drug as a bolus or as a second- or third-line drug as a continuous drip for patients who did not respond to phenobarbital and/or to phenytoin. The doses used have been in the range of 0.05-0.1 mg/kg IV initial bolus, with a continuous infusion of 0.5-1 μg/kg/min IV that can then be gradually titrated upward, if tolerated, every 5 min or longer, to a maximum of approximately 33 μg/kg/min (2 mg/kg/hr).

Phenobarbital

Phenobarbital is considered by many as the first choice long-acting drug in neonatal seizures. Whether to use a benzodiazepine first depends on the clinical situation. The usual loading dose is 20 mg/kg. If this dosage is not effective, then additional doses of 5-10 mg/kg can be given until a dose of 40 mg/kg is reached. Respiratory support may be needed after phenobarbital loading. Twenty-four hours after starting the loading dose, maintenance dosing can be started at 3-6 mg/kg/day usually administered in 2 separate doses. Phenobarbital is metabolized in the liver and is excreted through kidneys. Thus, any abnormality in the function of these organs alters the drug's metabolism and can result in toxicity. In infants with acidosis or critical illness that might alter serum protein content, free (i.e., not protein bound) levels of the drug should be followed carefully.

Phenytoin and Fosphenytoin

For ongoing seizures, if a total loading dose of 40 mg/kg of phenobarbital was not effective, then a loading dose of 15-20 mg/kg of phenytoin can be administered intravenously. The rate at which the dose should be given must not exceed 0.5-1.0 mg/kg/min so as to prevent cardiac problems, and the medication needs to be avoided in patients with significant heart disease. Heart rate should be monitored while administrating the drug. It is not possible to mix phenytoin or fosphenytoin with dextrose solutions. Owing to its reduced solubility, potentially severe local cutaneous reactions, interaction with other drugs, and possible cardiac toxicity, intravenous phenytoin is not widely used.

Fosphenytoin, which is a phosphate ester prodrug, is preferable. It is highly soluble in water, and can be administered very safely intravenously and intramuscularly, without causing injury to tissues. Fosphenytoin is administered in phenytoin equivalents (PE). The usual loading dose of fosphenytoin is 15-20 PE/kg administered over 30 min. Maintenance doses of 4-8 PE/kg/day can be given. As is the case for phenobarbital, free levels of the drug should be monitored in neonates whose serum pH or protein content might not be normal.

Other Medications

Approximately 45% of neonates respond to the first drug used if it is phenobarbital or phenytoin and an additional 15% respond to the second agent. Levetiracetam (which can be given intravenously with later convenient conversion to oral solution) and topiramate (oral) are reported to be the drugs of second and third choice for approximately half of surveyed pediatric neurologists and some have used them even before phenobarbital or phenytoin in selected cases. The dosages used are 10-30 mg/kg/day of levetiracetam, at times higher, and up to 20 mg/kg/day of topiramate. Bumetanide has been used as an adjunct drug, particularly with phenobarbital, because of its effect on the chloride gradient, as discussed above. Lidocaine is another medication used for resistant cases. Primidone, carbamazepine, valproate, and lamotrigine use, although reported in some studies, is rarely warranted. Valproate, for example, is more likely to be toxic in children younger than 2 yr of age than in older children.

Duration of Therapy

Duration of therapy is related to the risk of developing later epilepsy in infants suffering from neonatal seizures, which ranges from 10-30% and depends on the individual neurologic examination, the etiology of the seizures, and the EEG at the time of discharge from the hospital. In general, if the EEG at the time of discharge does not show evidence of epileptiform activity, then medications are usually tapered at that time. If the EEG remains paroxysmal, then the decision is usually delayed for several months after discharge.

Bibliography is available at Expert Consult.

593.8 Status Epilepticus

Mohamad A. Mikati and Abeer J. Hani

Status epilepticus is a medical emergency that should be anticipated in any patient who presents with an acute seizure. It is defined as continuous seizure activity or recurrent seizure activity without regaining of consciousness lasting for more than 5 min as part of an operational definition put forth within the past few years. In the past, the cutoff time was 30 min, but this has been reduced to emphasize the risks involved with the longer durations. The ILAE defines status epilepticus as "a seizure which shows no clinical signs of arresting after a duration encompassing the great majority of seizures of that type in most patients or recurrent seizures without resumption of baseline central nervous system function interictally." The measures used to treat status epilepticus have to be started in any patient with acute seizures that do not stop within a few minutes. The most common type is **convulsive status epilepticus** (generalized tonic, clonic, or tonic–clonic), but other types do occur, including **nonconvulsive status** (complex partial, absence), myoclonic status, epilepsia partialis continua, and neonatal status epilepticus. The incidence of status epilepticus ranges between 10 and 60 per 100,000 population in various studies. Status epilepticus is most common in children younger than 5 yr of age, with an incidence in this age group of >100 per 100,000 children.

Approximately 30% of patients presenting with status epilepticus are having their first seizure, and approximately 40% of these later develop epilepsy. Febrile status epilepticus is the most common type of status epilepticus in children. In the 1950s and 1960s, mortality rates of 6-18% were reported after status epilepticus; currently, with the recognition of status epilepticus as a medical emergency, a lower mortality rate of 4-5% is observed, most of it secondary to the underlying etiology rather than to the seizures. Status epilepticus carries an approximately 14% risk of new neurologic deficits, most of this (12.5%) secondary to the underlying pathology.

Nonconvulsive status epilepticus manifests as a confusional state, dementia, hyperactivity with behavioral problems, fluctuating impairment of consciousness with at times unsteady sitting or walking, fluctuating mental status, confusional state, hallucinations, paranoia, aggressiveness catatonia, and or psychotic symptoms. It should be considered in any of these situations, especially in an unresponsive or encephalopathic child. Epilepsia partialis continua has been defined previously and can be caused by tumor, vascular etiologies, mitochondrial disease (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes [MELAS]), and Rasmussen encephalitis.

Refractory status epilepticus is status epilepticus that has failed to respond to therapy, usually with at least 2 (such as a benzodiazepine and another medication) medications. Currently, the trend is not to assign a minimum duration, whereas in the past a minimum duration of 30 min, 60 min, or even 2 hr was cited. **New-onset refractory status epilepticus** has been identified as a distinct entity that can be caused by almost any of the causes of status epilepticus in a patient without prior epilepsy. It also is often of unknown etiology, presumed to be encephalitic or postencephalitic, can last several weeks or longer, and often, but not always, has a poor prognosis. Devastating epileptic encephalopathy in school-age children, also called **fever-induced refractory epileptic encephalopathy in school age children (FIRES)** is a syndrome of refractory status epilepticus that is associated with acute febrile infections, appears to be parainfectious in nature, and to be highly drug resistant but responsive to the ketogenic diet.

ETIOLOGY

Etiologies include new-onset epilepsy of any type; drug intoxication (e.g., tricyclic antidepressants) in children and drug and alcohol abuse in adolescents; drug withdrawal or overdose in patients on AEDs; hypoglycemia; hypocalcemia; hyponatremia; hypomagnesemia; acute head trauma; encephalitis; meningitis; autoimmune encephalitis (such as anti-NMDA receptor and anti–voltage-gated potassium channel complex antibody syndromes); ischemic (arterial or venous) stroke; intracranial hemorrhage; folinic acid and pyridoxine and pyridoxal phosphate dependency (these usually present in infancy but childhood onset is also possible); inborn errors of metabolism (see Chapter 593.2) such as nonketotic hyperglycinemia in neonates and mitochondrial encephalopathy with lactic acidosis (MELAS) in infants, children, and adolescents; ion channel–related epilepsies (e.g., sodium and potassium channel mutations reviewed in the sections above); hypoxic–ischemic injury (e.g., after cardiac arrest); systemic conditions (such as hypertensive encephalopathy, posterior reversible encephalopathy, renal or hepatic encephalopathy); brain tumors; and any other disorders that can cause epilepsy (such as brain malformations, neurodegenerative disorders, different types of progressive myoclonic epilepsy, storage diseases).

A rare condition called **hemiconvulsion-hemiplegia-epilepsy syndrome** consists of prolonged febrile status epilepticus presumably caused by focal acute encephalitis with resultant atrophy in the involved hemisphere, contralateral hemiplegia, and chronic epilepsy. It should be suspected early on to attempt to control the seizures as early as possible. This and the somewhat similar condition mentioned above called FIRES are likely to be have a parainfectious-autoimmune etiology. Rasmussen encephalitis often causes epilepsia partialis continua (see Chapter 593.3) and sometimes convulsive status epilepticus. Several types of infections are more likely to cause encephalitis with status epilepticus, such as herpes simplex (complex partial and convulsive status), *Bartonella* (particularly nonconvulsive status), Epstein-Barr virus, and mycoplasma (postinfectious encephalomyelitis with any type of status epilepticus). Postinfectious encephalitis and acute disseminated encephalomyelitis are common causes of status epilepticus, including refractory status epilepticus. HHV6 can cause a distinct epileptic syndrome with limbic status epilepticus in immune-suppressed patients.

MECHANISMS

The mechanisms leading to the establishment of sustained seizure activity seen in status epilepticus appear to involve (1) failure of desensitization of AMPA glutamate receptors, thus persistence of increased excitability, and (2) reduction of GABA-mediated inhibition as a result of intracellular internalization of $GABA_A$ receptors. This explains the

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clinical observation that status epilepticus is often less likely to stop in the next specific period of time the longer the seizure has lasted and why benzodiazepines appear to be decreasingly effective the longer seizure activity lasts. During status epilepticus there is increased cerebral metabolic rate and a compensatory increase in cerebral blood flow that, after approximately 30 min, is not able to keep up with the increases in cerebral metabolic rate. This leads to a transition from adequate to inadequate cerebral oxygen tensions and, together with other factors, contributes to neuronal injury resulting from status epilepticus. Status epilepticus can cause both neuronal necrosis and apoptosis. The mechanisms of apoptosis are thought to be related to increases in intracellular calcium and proapoptotic factors such as ceramide, Bax, and apoptosis-inducing factor. In addition, inflammation through the cytokines (such as interleukin-1β) released during seizure activity can modify neuronal excitability by modifying neurotransmitter function in a number of ways, such as through phosphorylation of the NR2B subunit rendering the NMDA receptors more permeable to calcium influx, increased expression of highly calcium-permeable AMPA receptors, and induction of endocytosis of $GABA_A$ receptors. Prostaglandins (such as prostaglandin E_2) can increase glutamate release and reduce potassium currents leading to increased excitability.

THERAPY

Status epilepticus is a medical emergency that requires initial and continuous attention to securing airway, breathing, and circulation (with continuous monitoring of vital signs including ECG) and determination and management of the underlying etiology (e.g., hypoglycemia). Laboratory studies, including glucose, sodium, calcium, magnesium, complete blood count, basic metabolic panel, CT scan, and continuous EEG, are needed for all patients. Blood and spinal fluid cultures, toxic screens, and tests for inborn errors of metabolism are often needed. AED levels need to be determined in all patients known already to be taking these drugs. Lumbar puncture, comprehensive toxicologic screens, MRI, and other laboratory tests are performed depending on clinical suspicion and need. EEG is helpful in ruling out **pseudo–status epilepticus** (psychologic conversion reaction mimicking status epilepticus) or other movement disorders (chorea, tics), rigors, clonus with stimulation, and decerebrate/decorticate posturing. The EEG can also be helpful in identifying the type of status epilepticus (generalized vs focal), which can guide further testing for the underlying etiology and further therapy. EEG can also help distinguish between postictal depression and later stages of status epilepticus in which the clinical manifestations are subtle (e.g., minimal myoclonic jerks) or absent (electroclinical dissociation), and can help in monitoring the therapy, particularly in patients who are paralyzed and intubated. Neuroimaging must be considered after the child has been stabilized, especially if it is indicated by the clinical manifestations, by an asymmetric or focal nature of the EEG abnormalities, or by lack of knowledge of the underlying etiology. The EEG manifestations of status epilepticus show several stages that consist of initial distinct electrographic seizures (stage I) followed by waxing and waning electrographic seizures (stage II), continuous electrographic seizures (stage III; many patients start with this directly), continuous ictal discharges punctuated by flat periods (stage IV), and periodic epileptiform discharges on flat background (stage V). The last 2 stages are often associated with subtle clinical manifestations and with a lower chance of response to medications.

The initial **emergent** therapy usually involves intravenous diazepam, lorazepam, or midazolam. Diazepam is at least as effective as intravenous lorazepam but has fewer side effects (Table 593-18). The use of midazolam autoinjector as initial therapy for acute seizures was found to be at least as useful and safe as the use intravenous lorazepam and results in earlier response. If intravenous access is not available, buccal or intranasal midazolam, intranasal lorazepam, or rectal diazepam are effective options. Intramuscular midazolam is equally effective as intravenous lorazepam. With all options, respiratory depression is a potential side effect for which the patient should be monitored and managed as needed. In some infants, a trial of pyridoxine may be warranted. The strongest evidence for initial and emergent therapy is for diazepam or

Table 593-18 Doses of Commonly Used Antiepileptic Drugs in Status Epilepticus

DRUG*	ROUTE	DOSAGE
Lorazepam	Intravenous Intranasal	0.1 mg/kg up to 4 mg total, may repeat in 5-10 min 0.1 mg/kg
Midazolam	Intravenous Intramuscular Intranasal Buccal	0.2 mg/kg up to 10 mg total dose, may repeat in 5-10 min 0.08-0.23 mg/kg/hr maintenance 0.2 mg/kg 0.2 mg/kg 0.5 mg/kg
Diazepam	Intravenous Rectal	0.15 mg/kg up to a max total dose of 10 mg, may repeat in 5-10 min 2-5 yr: 0.5 mg/kg 6-11 yr: 0.3 mg/kg ≥12 yr: 0.2 mg/kg
Fosphenytoin	Intravenous	20 mg/kg PE, then 3-6 mg/kg/24 hr, loading rate up to 50 mg PE per min
Phenobarbital†	Intravenous	5-20 mg/kg
Pentobarbital coma†	Intravenous	13.0 mg/kg, then 1-5 mg/kg/hr
Propofol†	Intravenous	1 mg/kg (bolus), then 1-15 mg/kg/hr (infusion)
Thiopental†	Intravenous	5 mg/kg/1st hr, then 1-2 mg/kg/hr
Valproate†	Intravenous	Loading: 25 mg/kg, then 30-60 mg/kg/24 hr
Lacosamide†	Intravenous	Loading: 4 mg/kg then 4-12 mg/kg/24 hr
Levetiracetam	Intravenous	20-60 mg/kg
Topiramate	Enterally	5-10 mg/kg/24 hr (loading dose) then same or lower for maintenance

*Reflects current trends in use which may not be FDA approved. For FDA indications, see Table 593-13.
†May cause PR prolongation.
PE, phenytoin sodium equivalents.

lorazepam, followed by phenytoin/fosphenytoin and phenobarbital, then valproate and levetiracetam.

After the emergent therapy usually with a benzodiazepine, the subsequent **urgent therapy** medication is usually fosphenytoin, and the loading dose is usually 15-20 PE/kg. A level is usually taken 2 hr later to ensure achievement of a therapeutic concentration. Depending on the level, maintenance dose can be started right away or, more commonly, in 6 hr. With phenytoin and phenobarbital, each 1 mg/kg (1 PE/kg for fosphenytoin) increases the serum concentration by approximately 1 μg/mL; for valproate, each 1 mg/kg increases the serum concentration by approximately 4 μg/mL. Precautions about the rate of infusion of fosphenytoin and phenytoin (not >0.5-1.0 mg/kg/min) and the other medications need to be followed because side effects often depend on infusion rate. The subsequent medication is often phenobarbital. The dose used in neonates is usually 20 mg/kg loading dose, but in infants and children the dose is often 5-10 mg/kg (to avoid respiratory depression), with the dose repeated if there is not an adequate response. Current evidence for the urgent therapy is strongest for valproate, followed by phenytoin/fosphenytoin and midazolam continuous infusion, followed by phenobarbital and levetiracetam, the last of which are currently being increasingly used.

After the second or third medication is given, and sometimes before that, the patient might need to be intubated. All patients with status epilepticus, even the ones who respond, need to be admitted to the ICU for completion of therapy and monitoring. Ideally, emergent and urgent therapies should have been received within less than 30 min so as to initiate the subsequent therapy soon, thus reducing the chances of sequelae. For **refractory status epilepticus treatment**, an intravenous bolus followed by continuous infusion of midazolam, propofol, pentobarbital, or thiopental is used. This is done in the ICU. Subsequent boluses and adjustment of the rate of the infusion are usually made depending on clinical and EEG responses. Because most of these patients need to be intubated and paralyzed, the EEG becomes the method of choice by which to follow them. The goal is to stop electrographic seizure activity before reducing the therapy. Usually this implies achievement of complete flattening of the EEG. Some consider that achieving a burst suppression pattern may be enough, and the periods of flattening in such a case need to be 8-20 sec to ensure interruption of electrographic seizure activity. However, this is an area that is in need of further study. Currently, the level of the evidence for refractory treatment is strongest for midazolam and valproate, followed by propofol and pentobarbital/thiopental, followed by levetiracetam, phenytoin/fosphenytoin, lacosamide, topiramate, and phenobarbital.

Patients on these therapies require careful attention to blood pressure and to systemic complications, and some develop multiorgan failure. It is not unusual for patients put into pentobarbital coma to have to be on multiple pressors to maintain their blood pressure during therapy.

The choice among the above options to treat refractory status epilepticus often depends on the experience of the specific center. Midazolam probably has fewer side effects, but is less effective, and barbiturate coma is more effective, but carries a higher risk of side effects. On propofol, some patients develop a propofol infusion syndrome with lactic acidosis, hemodynamic instability, and rhabdomyolysis with higher infusion rates (>67 μg/kg/min). Thus electrolytes, creatine phosphokinase, and organ function studies need to be monitored. Often, barbiturate coma and similar therapies are maintained for 1 or more days before it is possible to gradually taper the therapy, usually over a few days. However, in some cases, including cases of new-onset refractory status epilepticus (new-onset refractory status epilepticus), such therapies need to be maintained for several weeks or even months. Even though the prognosis in new-onset refractory status epilepticus cases is often poor and many patients do not survive, meaningful recovery despite a prolonged course is still possible. This also appears to apply to the FIRES syndrome. Occasionally, inhalational anesthetics are useful. Probably isoflurane is preferable because halothane can increase intracranial pressure and enflurane can induce seizures. Other therapies have included ketamine, corticosteroids (e.g., for Rasmussen encephalitis, Hashimoto encephalopathy, or other autoimmune encephalitides), immunoglobulins, and plasma exchange (e.g., in Rasmussen or other autoimmune encephalitides), ketogenic diet (in patients with FIRES and Landau-Kleffner syndrome), vagus nerve stimulation in catastrophic epilepsy in infants, hypothermia, electroconvulsive therapy, magnetic transcranial stimulation, and surgical management with focal resection. Another potential therapy under study for convulsive status epilepticus is induction of acidosis (e.g., by hypercapnia), which could reduce neuronal excitability.

For nonconvulsive status epilepticus and epilepsia partialis continua, therapy needs to be tailored according to the clinical manifestations and often consists of trials of sequential oral or sometimes parenteral AEDs without resorting to barbiturate coma or overmedication that could result in respiratory compromise. The approach to complex partial status epilepticus is sometimes similar to the approach to convulsive status epilepticus and sometimes intermediate between the approach for epilepsia partialis and that for convulsive status, depending on severity. Long-term consequences after complex partial status epilepticus do occur, but the complications are often less severe than those after convulsive status epilepticus of similar duration. Prolonged nonconvulsive complex partial status epilepticus can last for as long as 12 wk, with patients manifesting psychotic symptoms and confusional states. These cases can be resistant to therapy. Despite that, patients still can have a full recovery. Some of these cases appear to improve with the use of steroids or IVIG, which are used if an autoimmune, parainfectious etiology is suspected.

Bibliography is available at Expert Consult.

593.9 Reflex Seizures (Stimulus Precipitated Seizures)

Robert M. Kliegman

Many patients with epilepsy can identify precipitating or provoking events that predispose them to having a seizure. Common events in patients with epilepsy include stress, lack of sleep, fever, or fatigue.

There is another group of patients who have seizures in response to a very specific, identifiable sensory stimulus or activity and are considered to have reflex seizures. Although no known "reflex" may be involved, more appropriate terms may be sensory precipitated or stimulus sensitive seizures (see Table 593-1). Stimuli may be external (light, patterns, music, brushing teeth) or internal (math, reading, thinking, self-induced). Reflex seizures may be generalized, partial, nonconvulsive, absence or myoclonic. One common pattern is photomyoclonic seizures characterized by forehead muscle twitching or repetitive eye opening or closing.

Photosensitive or pattern-induced seizures are a well-recognized disorder stimulated by bright or flashing lights (TV, video games, discotheques, concert light shows) or by patterns (TV, video games, lines on the road while traveling). Visual sensitivity may occur in 0.3-3% of the population, while photosensitive or pattern-induced seizures may occur in 1 in 4,000 people in the at-risk age group of 5-25 yr. When Japanese children were exposed to a Pokémon cartoon that induced seizures, only 24% had a history of spontaneous seizures. Patients tend to outgrow photosensitive or pattern-induced seizures in their 30s. Photoparoxysmal responses, with an abnormal EEG response to photic stimulation may be more common than photic-induced seizures. There are some photo-induced responses that do not demonstrate EEG abnormalities (nonconvulsive).

For patients with isolated photosensitive or pattern-induced seizures, avoidance or modification of stimuli is the initial approach. Such activities may include blue or polarized sunglasses, avoiding high-contrast flashing-light video games, avoiding discotheques, use a TV remote or watch TV in a well-lit room at a distance of >8 feet, and covering 1 eye when in a provocative situation.

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Table 593-19 Consensus Case Definition and Modified Consensus Case Definition for Nodding Syndrome—Uganda, 2012-2013*

TYPE OF CASE	CONSENSUS CASE DEFINITION	MODIFIED CONSENSUS CASE DEFINITION
Suspected case	Reported head nodding (repetitive involuntary drops of the head toward the chest on 2 or more occasions) in a previously normal person	Reported head nodding (repetitive involuntary drops of the head toward the chest on 2 or more occasions) in a previously normal person
Probable case	Suspected case of head nodding, with both major criteria: • Age of onset of nodding ranging from 3-18 yr • Frequency of nodding 5-20 per minute Plus at least 1 of the following minor criteria: • Other neurologic abnormalities (cognitive decline, school dropout because of cognitive or behavioral problems, other seizures or neurologic abnormalities) • Clustering in space or time with similar cases • Triggering by food or cold weather • Stunting or wasting • Delayed sexual or physical development • Psychiatric symptoms	Suspected case of head nodding, with 1 major criterion: • Age of onset of nodding ranging from 3-18 yr Plus at least 1 of the following minor criteria: • Other neurologic abnormalities (cognitive decline, school dropout because of cognitive or behavioral problems, other seizures or neurologic abnormalities) • Clustering in space or time with similar cases • Triggering by food or cold weather • Stunting or wasting • Psychiatric symptoms
Confirmed case	Probable case, with documented nodding episode • Observed and recorded by a trained healthcare worker, *or* • Videotaped nodding episode, *or* • Video/EEG/EMG documenting head nodding as atonic seizures	Probable case, with documented nodding episode • Observed and recorded by a trained healthcare worker, *or* • Videotaped nodding episode, *or* • Video/EEG/EMG documenting head nodding as atonic seizures

*The consensus case definition was drafted at the first International Scientific Meeting on Nodding Syndrome, held July 30–August 1, 2012, in Kampala, Uganda. Meeting report available at http://www.who.int/neglected_diseases/diseases/Nodding_syndrom_Kampala_Report_2012.pdf. The modified consensus case definition was developed during the March 2013 single-stage cluster survey conducted by Centers for Disease Control and Prevention (CDC) and the Ugandan Ministry of Health to assess prevalence of nodding syndrome in Uganda.

EEG, electroencephalographic; EMG, electromyographic.

From Iyengar PJ, Wamala J, Ratto J, et al: Prevalence of nodding syndrome–Uganda, 2012-2013. MMWR Morb Mortal Wkly Rep *63:603–606, 2014, Table 1.*

593.10 Nodding Syndrome

Robert M. Kliegman

Nodding syndrome appears to be an epidemic progressive epilepsy encephalopathy syndrome of unknown etiology seen predominantly in Uganda, Liberia, Tanzania, and the southern Sudan, with a prevalence of approximately 6.8 per 1,000 children. Age of onset is 6-13 yr. Nodding episodes are characterized by at least daily, rapid, paroxysmal forward head bobbling spells lasting several minutes; some patients are unresponsive whereas others may respond to commands or continue what they were doing before the episode. Children were previously healthy, although there may be a family history of seizures. In addition to episodes of nodding, there may be associated definable generalized tonic–clonic or absence seizures. Furthermore, patients go on to demonstrate severe and global cognitive impairment (see Table 593-19 for case definitions).

The EEG demonstrates a disorganized slow background and interictal generalized 2.5-3.0 Hz spike and slow waves. During a nodding episode, the EEG demonstrates generalized electrodecrement and paraspinal electromyography dropout suggestive of an atonic seizure. Cerebral spinal fluid analysis is usually negative, while the MRI shows cerebral and cerebellar atrophy.

Nodding episodes may be triggered during meals while eating hot foods or drinking cold liquids; cold environmental temperature may also trigger a nodding episode.

Treatment of seizures are indicated; however, the response to treatment is poor.

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Chapter 594

Conditions That Mimic Seizures

Mohamad A. Mikati and Makram M. Obeid

The misdiagnosis of epilepsy is estimated to be as high as 5-40%, implying that many patients may be subjected to unnecessary therapy and tests. Often all that is needed to differentiate nonepileptic paroxysmal disorders from epilepsy is a careful and detailed history in addition to a thorough exam; but sometimes an electroencephalogram (EEG) or more advanced testing may be necessary. The ready availability of video recording on mobile phones and other devices at home or at school can provide invaluable information. Nonepileptic paroxysmal disorders can be classified according to the age of presentation and the clinical manifestations: (1) syncope and other generalized paroxysms, (2) movement disorders and other abnormal movements and postures, (3) oculomotor abnormalities and visual hallucinations, and (4) sleep-related disorders (Table 594-1).

SYNCOPE AND OTHER GENERALIZED PAROXYSMS

Apnea

Apneic episodes in neonates are usually associated with bradycardia as is usually apnea resulting from brainstem compression. In contrast, apnea associated with seizures is usually accompanied by tachycardia. Of note, exceptions do occur as bradycardia can occur during epileptic seizures, and severe apnea of any cause can be followed by anoxic seizures.

Table 594-1 Conditions That Mimic Seizures According to Age of Presentation

AGE	SYNCOPE AND OTHER GENERALIZED PAROXYSMS	MOVEMENT DISORDERS AND OTHER ABNORMAL MOVEMENTS	OCULOMOTOR ABNORMALITIES	SLEEP DISORDERS
Neonate	Apnea Paroxysmal extreme pain disorder	Jitteriness Hyperekplexia Paroxysmal dystonic choreoathetosis	Paroxysmal tonic up gaze Alternating hemiplegia of childhood	Benign neonatal sleep myoclonus Sleep transition disorders
Infants	Reflex anoxic seizures Breath-holding spells Benign paroxysmal vertigo Paroxysmal extreme pain disorder	Jitteriness Sandifer Paroxysmal dystonic choreoathetosis Benign myoclonus of early infancy Pathologic startle Shuddering attacks Benign paroxysmal torticollis Psychologic disorders Alternating hemiplegia of childhood Jactatio capitis head banging Drug reactions	Paroxysmal tonic upgaze Oculomotor apraxia Spasmus nutans Opsoclonus myoclonus syndrome	Non-REM partial arousal disorders REM sleep disorders Narcolepsy Sleep transition disorders (somnambulism, somniloquy)
Children and adolescents	Benign paroxysmal vertigo Compulsive Valsalva Familial hemiplegic migraine Syncope (long QT, vasovagal, vagovagal, orthostatic, migraine-induced) Psychogenic seizures Transient global amnesia Hyperventilation spells	Tics Tremor Pathologic startle Paroxysmal dyskinesias Alternating hemiplegia of childhood Benign paroxysmal torticollis Episodic ataxia Psychologic disorders including factitious disorder imposed on another, malingering Masturbation Psychogenic seizures Cataplexy Jactatio capitis (head banging) Episodic rage Drug reactions	Daydreaming Drug reactions	Non-REM partial-arousal disorders REM sleep disorders Narcolepsy Sleep transition disorders (somnambulism, somniloquy) Sleep myoclonus Restless legs syndrome

REM, rapid eye movement.
From Obeid M, Mikati MA: Expanding spectrum of paroxysmal events in children: potential mimickers of epilepsy, Pediatr Neurol *37(5):309–316, 2007.*

Breath-Holding Spells

The term *breath-holding spells* is actually a misnomer, as these are not self-induced, but result from the immaturity of the autonomic system and occur in 2 different forms. The first type is the **pallid breath-holding spell**, which is caused by reflex vagal–cardiac bradycardia and asystole. The second type is the **cyanotic,** or **"blue," breath-holding spell**, which does not occur during inspiration, but results from prolonged expiratory apnea and intrapulmonary shunting. Episodes usually start with a cry (often, in the case of the pallid type, a "silent" cry with marked pallor), and progress to apnea and cyanosis. Spells usually begin between 6 and 18 mo of age. Syncope, tonic posturing, and even reflex anoxic seizures may follow the more-severe episodes, particularly in breath-holding spells of the pallid type. Injury, anger, and frustration, particularly with surprise, are common triggers. Education and reassurance of the parents is usually all that is needed, as these episodes are, as a rule, self-limited and are outgrown within a few years. However, treatment of coexisting iron deficiency is needed if it is present as the spells are made worse by iron-deficiency anemia. Anticholinergic drugs (e.g., atropine sulfate 0.01 mg/kg/24 hr in divided doses with a maximum daily dose of 0.4 mg), or antiepileptic drug therapy for coexisting anoxic seizures that are recurrent and not responding to other measures may, rarely, be needed. It is important also to educate parents on how to handle more-severe spells by first-aid measures, or even basic CPR when needed. In severe cases of asystole, a cardiac pacemaker implantation may be needed. All parents should be taught not to provide secondary gain when the episodes occur, because this can reinforce the episodes. Also, preparation for unpleasant experiences (such as receiving a shot) rather than surprising the child with them, can help limit the number of spells (see Chapter 69).

Compulsive Valsalva

In children with intellectual disability, including Rett syndrome, syncopal convulsions may be self-induced by maneuvers like Valsalva. In this case, true breath-holding occurs, and it usually lasts for approximately 10 sec during inspiration. Some clinicians advocate the use of naloxone in such cases.

Neurally Mediated Syncope

Syncope can present with drop attacks and can also lead to generalized convulsions, termed *anoxic seizures*. These convulsions, triggered by a sudden reduction of oxygen to the brain, are clinically similar to and can be misdiagnosed as generalized epileptic seizures. **Vasovagal (neurocardiogenic) syncope** is one of the most common mimickers of generalized tonic–clonic seizures and is usually triggered by dehydration, heat, standing for a long time without movement, hot showers, the sight of blood, pain, swallowing, vomiting, and or sudden stress. History is usually the clue to distinguishing syncope from epileptic seizures: There is initially pallor and sweating followed by blurring of vision, dizziness, nausea, and then gradual collapse with loss of consciousness. These symptoms are present in most, although not necessarily all patients with syncope and can sometimes be manifestations of complex partial seizures. Much more important is the fact that such prodromal features have an insidious onset and build up gradually, often arising from a state of malaise when they precede syncope. However when they precede an epileptic convulsion, such features usually start suddenly are short in duration, paroxysmal and are followed by other manifestations of complex partial seizures such as stereotyped automatisms. Abdominal pain, a common aura in temporal lobe epilepsy, occurs in vasovagal syncope, and can be a trigger or a consequence of that process (intestinal vagal discharge). Urinary incontinence and a brief period of convulsive jerks are not uncommon in vasovagal syncope. These occur with a frequency of 10% and 50%, respectively. Postictal confusion only rarely occurs, and the rule is the occurrence of only brief postictal tiredness with a subsequent remarkable ability to resume planned activities. Most children with vasovagal syncope have an affected 1st-degree relative; reports demonstrate

autosomal dominant inheritance at least in some families. The EEG is normal and the tilt test has been used for diagnostic purposes in selected cases. In most cases with typical history, this test is not needed. **Vagovagal syncope** can progress to convulsive seizure if the asystole is sufficiently prolonged. Sudden cold exposure to the face or to the body can also trigger vagal syncope. Syncope has been reported (rarely) to occur in association with cough, tight hair braiding, and hair combing. **Orthostatic hypotension and orthostatic intolerance** manifest symptoms that develop during upright standing and can be relieved by recumbence. **Postural tachycardia syndrome,** the pathophysiology of which presumably involves an excessive sympathetic discharge resulting in increased heart rate and vasoconstriction that can lead to decreased peripheral perfusion, is usually a disease of adolescent females that is characterized by upright syncope/near syncope, and tachycardia with normal or even increased blood pressure during the episode. Primary autonomic failure is rare in children, and familial dysautonomia is the only relatively common form. **Familial dysautonomia** is a disease common in Ashkenazi Jews and is characterized by absence of overflow emotional tears, depressed patellar reflexes, and lack of a flare reaction following intradermal histamine. **Dopamine β-hydroxylase deficiency** is a very rare cause of primary autonomic failure, and is characterized by a complicated perinatal course (hypotension, hypotonia, hypothermia), ptosis, highly arched palate, hyperflexible joints, impaired ejaculation, and nocturia. The tilt test causes a drop in both blood pressure and heart rate in patients with classic vasovagal syncope. It results in a blood pressure drop with minimal change in heart rate in autonomic failure, and in blood pressure drop and an increase in heart rate in postural tachycardia syndrome. Management of syncope centers on avoidance of precipitating factors (maintenance of hydration, avoidance of standing still, rising slowly from sitting, first-aid measures, raising of the legs, positioning) and treatment of any accompanying or underlying medical conditions (anemia, adrenal insufficiency, cardiac, etc.). In addition, **salt supplementation (2-4 g/day),** β-blockers (e.g., metoprolol at a starting dose of 1-2 mg/kg once per day up to a maximum of 6 mg/kg/day), or fluorohydrocortisone (0.05-0.1 mg/day) therapy may be needed in selected cases.

Cardiac Syncope

See Chapter 435.5.

Long QT syndromes (LQT) can cause life-threatening "pallid" or white syncope. Accompanying this are ventricular arrhythmias, usually torsades de pointes or even ventricular fibrillation. There are more than 10 types of prolonged QT syndrome. When accompanied by congenital deafness, it is part of the autosomal recessive Jervell and Lange-Nielson syndrome (type 1, LQT 1, associated with *KvLQT1* potassium channel mutation). The Romano-Ward syndrome is an autosomal dominant syndrome with incomplete penetrance that is characterized by episodes of lying still like a dead body for several seconds before the anoxic convulsive episode (LQT 2 associated with an *HERG* potassium channel mutation). LQT 3 is associated with an *SCN1A* sodium channel mutation, LQT 4 with ankyrin protein mutation, LQT 5 (milder form) with *KCNE1* mutations, LQT 6 with *KCNE2* potassium gene mutations, LQT 9 with caveolin sodium channel–related protein mutations, and LQT 10 with *SCN4B* sodium channel mutations. LQT 7 and LQT 8 are of particular interest because of associated clinical and neurologic manifestations. LQT 7 (Andersen-Tawil) syndrome is associated with periodic paralysis, skeletal developmental abnormalities, clinodactyly, low-set ears, and micrognathia (mutations in *KCNJ2* gene). LQT 8 or the Timothy syndrome (mutations in the calcium channel gene *CACNA1c*) manifests congenital heart disease, autism, syndactyly, and immune deficiency. All family members of an affected LQT syndrome individual should be investigated. Affected individuals need insertion of cardiac defibrillators, and their families should be taught CPR. As a rule, children with new-onset seizure disorder should get an electrocardiogram to rule out LQT syndrome masquerading as seizure disorder. Cardiac syncope is usually sudden without the gradual onset and the symptoms that accompany vagal syncope. Aortic stenosis can cause sudden syncope at the height of the exercise (usually hypertrophic), or directly at the end (usually valvular) and, if suspected, warrants an echocardiogram.

Other Causes of Syncope

Syncope that is not neurally mediated or cardiac in origin is caused by a decrease in blood volume, or a mechanical disruption of brain perfusion. Systemic diseases that lead to syncope by affecting blood volume (e.g., adrenal insufficiency) are usually first brought to medical attention by other accompanying signs and symptoms. In **stretch syncope**, which occurs mostly in adolescents while stretching the neck and the trunk backward and the arms outward, or during flexion of the neck, the presumed mechanism is mechanical disruption of brain perfusion caused by compression of the vertebral arteries. In some cases, this may be associated with an abnormally prolonged stylomastoid process compressing the carotids. If the latter condition is suspected, then neuroimaging (CT, MRI) is required for proper diagnosis of the stylomastoid anomaly.

Sporadic and Familial Hemiplegic Migraine

This is a rare type of migraine with a motor aura of weakness. Attacks begin as early as 5-7 yr of age. In a genetically susceptible person, attacks may be precipitated by head trauma, exertion, or emotional stress. The 3 genes so far identified are *SCN1A* (neuronal sodium channel subunit), *CACNA1*A (neuronal calcium channel subunit), and *ATP1A2* (sodium potassium adenosine triphosphatase subunit). However at least a quarter of the affected families, and most of the sporadic cases do not carry a mutations in these 3 genes. Headaches occur in all attacks in most patients. The presence of negative phenomena (e.g., numbness, visual scotomas) in addition to positive phenomena (pins and needles, flickering lights), and the progressive and successive occurrence of visual, sensory, motor, aphasic, and basilar signs and symptoms, in that order, help differentiate these attacks from epileptic seizures. Persistent cerebellar deficits (e.g., nystagmus, ataxia) may be present. Verapamil, acetazolamide, and lamotrigine have been successfully used to prevent attacks and verapamil and ketamine have been used for the acute episode, while ergot derivatives, nimodipine, Midrin (isometheptene mucate, dichloralphenazone, and paracetamol), and probably triptans and propranolol are to be avoided because of concerns of exacerbating the attacks. Interestingly, the co-occurrence of epileptic seizures has been reported in a minority of patient with hemiplegic migraine. It is important also to note that recurrent attacks akin to hemiplegic migraine can be symptomatic of Sturge-Weber syndrome or various metabolic diseases (e.g., mitochondrial encephalopathy with lactic acidosis and stroke-like episodes).

Benign Paroxysmal Vertigo of Childhood

This is a common migraine equivalent that consists of brief seconds-to-minutes episodes of vertigo that is often accompanied by postural imbalance and nystagmus. It is important to note that vertigo does not always refer to a spinning motion; it can also refer to a backward or forward motion (vertigo titubant) where children sometimes report that objects are moving toward them. The child appears frightened during the episode. Diaphoresis, nausea, vomiting, and, rarely, tinnitus may be present. Episodes usually remit by 6 yr of age. MRI and EEG are normal, but caloric testing, if done, can show abnormal vestibular function. Diphenhydramine, 5 mg/kg/day (maximum of 300 mg/day) may be used for a cluster of attacks. Preventive therapy with cyproheptadine may be rarely needed for frequent attacks.

Cyclic Vomiting Syndrome

This syndrome is another related periodic migraine variant that can respond to antimigraine or antiepileptic drugs. This and other periodic syndromes have been associated with mutations that also can cause hemiplegic migraine.

The "Alice in Wonderland" Syndrome

This is the episodic experience of transient distortions of body image or visual images that, most often, constitute a migraine equivalent. It also can be an epileptic phenomenon.

Migraine-Induced Syncope

Migraine, usually of the basilar variety, can trigger vasovagal syncope and, less commonly, epileptic seizures. Careful elicitation of the history of a migrainous prelude to the syncope helps in identifying these phenomena.

Psychologic Disorders

Psychogenic nonepileptic seizures are conversion reactions that are usually suspected clinically based on the characteristics of the spells (Table 594-2). The diagnosis can be confirmed by video EEG with capture of an episode to eliminate any residual doubts about their nature, as they can often occur in patients who also have epileptic seizures. They are best managed acutely by reassurance about their relatively benign nature and by a supportive attitude while at the same time avoiding positive reinforcement of the episodes. Psychiatric evaluation and follow-up are needed to uncover underlying psychopathology, and to establish continued support as psychogenic seizures can persist over long periods of time. **Malingering** and **factitious disorder imposed on another (formerly called Munchausen syndrome by proxy)** are often difficult to diagnose but an approach similar to that for psychogenic seizures, including video-EEG monitoring, is often helpful.

Paroxysmal Extreme Pain Disorder

Paroxysmal extreme pain disorder was previously called familial rectal pain syndrome. This syndrome (caused by the *SCN9A* sodium channel gene mutation) usually starts in the neonatal period or infancy and persists throughout life. Autonomic manifestations predominate initially, with skin flushing in all cases and harlequin color change and tonic attacks in most. Dramatic syncope with bradycardia and sometimes asystole are common. Later, the disorder is characterized by attacks of excruciating deep burning pain often in the rectal, ocular, or jaw areas, but also diffusely in some. Attacks are triggered by defecation, cold, wind, eating, and emotion. Carbamazepine is used, but the response is often incomplete. Gain-of-function Na(v)1.7 mutations are known to cause two neuropathic **pain** syndromes: inherited **erythromelalgia** and **paroxysmal extreme pain syndrome**. These syndromes are inherited in a dominant trait; they usually begin in childhood or infancy, and are characterized by attacks of severe neuropathic **pain** accompanied with autonomic symptoms. In addition, small fiber neuropathy and chronic nonparoxysmal **pain** have been described in patients harboring gain-of-function mutations in Na(v)1.7 channel. Loss-of-function mutations in Na(v)1.7 are extremely rare and invariably cause **congenital inability to perceive pain.**

Autonomic Storms (Diencephalic Seizures)

Spells of hyperhidrosis, changes in blood pressure, temperature and autonomic instability occur in patients with severe diffuse brain injury or localized hypothalamic injury and have been termed autonomic storms. The term *diencephalic seizures* is discouraged as these are not truly seizures. Therapy is difficult and has included, with mixed results, clonidine, anticonvulsants, cyproheptadine, morphine, and sympathectomy. Serotonin syndrome caused by antidepressants, stimulants, opioids, certain herbs like St. John's Wart and some other medications can produce similar symptoms, and if not recognized, can at times be fatal as can be the similar neuroleptic malignant syndrome caused by antipsychotic medications.

MOVEMENT DISORDERS AND OTHER ABNORMAL MOVEMENTS AND POSTURES

Neonatal Jitteriness and Clonus

Jitteriness consists of equal backward and forward movements of limbs, occurring spontaneously, or triggered by touch or loud sounds. Movement suppression by stimulus removal or by relaxing the affected limbs, the lack of autonomic symptoms, and the clear difference from the 2-phased (fast contraction, slow relaxation) clonic activity and the very quick myoclonic jerks, point to a nonepileptic event.

Table 594-2 Comparison of Generalized Seizures and Some Disorders That Can Mimic Them

CONDITION	PRECIPITANTS (MAY NOT APPLY TO ALL PATIENTS)	PRODROME	ICTAL SYMPTOMS	POSTICTAL SYMPTOMS
Generalized seizures	Sleep deprivation, television, video games, visual patterns, and photic stimulation	Rarely irritability or nonspecific behavioral changes	Usually 2-3 min Consciousness might be preserved if atonic, or in some, tonic seizures Synchronous bilateral movements Tongue biting	Delayed recovery with postictal depression, incontinence (may be ictal also)
Syncope: vasovagal Syncope with reflex anoxic seizures Syncope: trigeminal vagal Syncope: orthostatic	Fatigue, emotional stress, dehydration, vomiting, choking, swallowing Minor bump to head, upsetting surprises Cold water on face Standing up, bathing, awakening	Blurring of vision, tinnitus, dizziness Crying in breath-holding spells	Loss of consciousness for seconds, pallor and rarely reflex anoxic seizures	Rapid recovery with no postictal depression
Hyperekplexia	Auditory and tactile stimuli	None	Tonic stiffening, cyanosis if severe, nonfatigable nose-tap–induced startles	Depending on severity, may have postictal depression
Cardiac	Exercise	None	Loss of consciousness, often only few seconds, pallor	Rarely
Psychogenic	Suggestion, stress	None	Eyes closed Asynchronous flailing limb movements that vary between attacks No injury, closed eyelids May respond to suggestion during "loss of consciousness" Usually longer than 2-3 min	No postictal depression

Adapted from Obeid M, Mikati MA: Expanding spectrum of paroxysmal events in children: potential mimickers of epilepsy, Pediatr Neurol *37(5):309–316, 2007.*

Hypocalcemia, hypoglycemia, drug withdrawal, and hypoxic–ischemic encephalopathy are possible etiologies. **Clonus** as a result of corticospinal tract injury usually occurs in later infancy and childhood and can be stopped by change in position.

Hyperekplexia (Stiff Baby Syndrome) and Pathologic Startles

Hyperekplexia is a rare, sporadic or dominantly inherited disorder with neonatal onset of life-threatening episodes of tonic stiffening that precipitate apnea and convulsive hypoxic seizures.

Stiffness may result in difficulty in swallowing, choking spells, hip dislocations, umbilical or inguinal hernias, and delayed motor development. Stiffness in the neonatal form improves by 1 yr of age and may disappear during sleep.

The genetic cause is a defect in the α or β subunits of the strychnine-sensitive glycine receptors. It is characterized by a triad of generalized stiffness, nocturnal myoclonus, and later a pathologic startle reflex. A specific diagnostic sign can be elicited by tapping the nose, which produces a nonfatigable startle reflex with head retraction. Bathing, sudden awakening, and auditory or tactile stimuli can induce attacks. The differential diagnosis includes congenital stiff person syndrome, startle epilepsy, myoclonic seizures, neonatal tetany, phenothiazine toxicity, and Schwartz-Jampel syndrome. Making a prompt diagnosis is extremely important to initiate treatment with clonazepam as hypoxic brain injury can result from a prolonged episode. Other antiepileptics have also been effective. Repeatedly flexing the baby at the neck and hips (the Vigevano maneuver) can abort the episodes.

In other children after brain injury, and in many patients with cerebral palsy, an exaggerated startle reflex can occur. This is more common than hyperekplexia. In Tay-Sachs disease and similar gangliosidoses, exaggerated startle to sound occurs and has been, inappropriately, interpreted as hyperacusis.

Benign Paroxysmal Torticollis of Infancy

This condition typically presents as morning episodes of painless retrocollis, and later, torticollis, often triggered by changes in posture. Attacks may start with abnormal ocular movements, and progress to stillness in an abnormal posture. This usually lasts for minutes or hours and, at times, days. Neurologic exam between attacks, EEG, and neuroimaging are normal. It affects girls more than boys (3:1), often begins before 3 mo of age, and spontaneously remits before the age of 5 yr. Medical therapy is not needed. It is considered to be a migraine equivalent and cosegregates with migraine in families.

Sandifer Syndrome

Gastroesophageal reflux in infants may cause paroxysmal episodes of generalized stiffening and opisthotonic posturing that may be accompanied by apnea, staring, and minimal jerking of the extremities. Episodes often occur 30 min after a feed. In older children, this syndrome manifests with episodic dystonic or dyskinetic movements consisting of latero-, retro-, or torticollis, the exact pathophysiology of which remains elusive.

Alternating Hemiplegia of Childhood

This is a rare, often severe, disorder that consists of attacks of flaccid hemiplegia affecting 1 or both sides lasting minutes to days, starting in the 1st 18 mo of life. Earlier manifestations include paroxysmal nystagmus, which is often monocular and ipsilateral to the hemiplegia. Dystonic and tonic spells often occur and can be confused with seizures and the hemiplegia with Todd paralysis. Attacks can be triggered by bathing, cold, fatigue, hyperthermia, and emotional stress, and they remit during sleep and for about 15 minutes or so after waking up. Most cases are caused by mutations in the *ATP1A3* gene while, rarely, a similar clinical picture can occur as a result of mutations in *ATP1A2* or in the glucose transporter 1 *(GLUT1/SLC2AI)* gene mutations. Flunarizine 2.5-15 mg/day reduces the frequency of the attacks. Most children ultimately develop ataxia, developmental delay, and persistent choreoathetosis.

Paroxysmal Dyskinesias and Other Movement Disorders

These disorders are characterized by sudden attacks that consist of choreic, dystonic, ballistic, or mixed movements (Table 594-3). A sensation of fatigue or weakness confined to 1 side may herald an attack. Consciousness is preserved and patients may be able perform a motor activity, like walking, despite the attack. The variability in the pattern of severity and localization between different attacks may also help in differentiating them from seizures. The frequency of attacks increases in adolescence, and steadily decreases in the 3rd decade. Neurologic exam between attacks, EEG, laboratory investigations, and imaging studies are normal. These dyskinesias often respond to phenytoin, carbamazepine, clonazepam, or to antidopaminergic drugs such as haloperidol. **Drug reactions** can result in abnormal movements such as **oculogyric crisis** with many antiemetics, choreoathetosis with phenytoin, dystonia and facial dyskinesias with antidopaminergic drugs, and tics with carbamazepine. Strokes, focal brain lesions, connective tissue disorders (e.g., systemic lupus erythematosus), vasculitis, or metabolic and genetic disorders can also cause movement disorders. Mutations of the glucose transporter 1 *(GLUT1/SLC2AI)* gene have been described in patients with **exercise-induced dyskinesia**.

Motor Tics

These are movements that are under partial control, and are associated with an urge to do them and with a subsequent relief. They are usually exacerbated by emotions, and often change in character over time. In patients with tics who have Tourette syndrome, there is often a family history of tics and/or obsessive compulsive disorder or personality traits.

Episodic Ataxias

Episodic ataxia encompasses 7 clinically and genetically heterogeneous syndromes, only 2 of which (types 1 and 2) have been described in a large number of families. Type 1 is caused by mutations in the voltage-gated potassium channel Kv1.1. It consists of brief episodes (seconds to minutes) of cerebellar ataxia, and occasional partial seizures with interictal myokymia as a main diagnostic feature. Type 2 is characterized by longer attacks (minutes to hours) and interictal cerebellar signs. It is caused by mutations in the voltage-gated calcium channel gene *CACNA1A*. This type is more responsive than type 1 to acetazolamide that reduces the frequency and severity of attacks, but not the interictal signs and symptoms.

Benign Myoclonus of Early Infancy, Shuddering Attacks, and Chin Trembling

Benign myoclonus consists of myoclonic jerks of the extremities in wakefulness and sometimes also in sleep. It has been suggested by some that these attacks are in the same spectrum as shuddering attacks. **Shuddering attacks** are characterized by rapid tremor of the head, shoulder, and trunk, lasting a few seconds, often associated with eating, and recurring many times a day. Others have considered shuddering as an early manifestation of essential tremor as family history of essential tremor is often present. The clinical events in either of these can be mistaken for infantile spasms, but ictal and interictal EEG, MRI, and development are normal. Spontaneous remission occurs in both usually within a few months. **Hereditary chin trembling** at a frequency faster than 3 Hz starting shortly after birth and precipitated by stress has been described in several families.

A novel type of nonepileptic attack with infantile onset characterized in 3 patients as clusters of repeated head drops, mimicking epileptic negative myoclonus of the neck, accompanied by crying. The episodes occurred for 5 or 6 mo and disappeared by the end of the 1st yr. Language and cognition were normal This is a different form of myoclonic activity that may complicate the diagnosis of infantile spasms and West syndrome; thorough EEG investigation is needed in such cases.

Brainstem Dysfunction

Decorticate or decerebrate posturing that mimics epileptic tonic seizures may be secondary to decompensated hydrocephalus,

Table 594-3 Differential Diagnoses of Various Types of Paroxysmal Dyskinesia

Features	PKD	PNKD MR1+	PNKD MR1–	PED	PHD
Nomenclature	PKC	PDC, FPC	PDC, FPC	PEDt	ADNFLE
Inheritance	AD–16q	AD–2q35	AD–2q13	AD/AR	AD–20q13, 15q24, 1q21, 8p21
Age at onset (yr)	1-20	<1-12	1-23	Usually childhood	Usually childhood
Triggers	Sudden whole-body movement	Coffee, alcohol, stress	Exercise	After 10-15 minutes of exercise	Sleep
Clinical features	Chorea, athetosis, ballismus, dystonia	Chorea, athetosis, dystonia, ballismus	Chorea, athetosis, dystonia, ballismus	Mainly leg dystonia	Wakes up with dystonic posture
Usual duration	<1-5 min	10 min to 1 hr	10 min to 2-3 hr	10-15 min	<1 min
Frequency	1-20/day	1/week	1/week	Unclear	Several/night
Associations	Infantile seizures, migraine, writer's cramp, essential tremor	Migraine	Epilepsy	RE-PED-WC	
Medication	Carbamazepine Phenytoin Oxcarbazepine	Clonazepam Benzodiazepine	Clonazepam Benzodiazepine	Acetazolamide L-DOPA	Carbamazepine Oxcarbazepine
Prognosis	Excellent	Excellent, worse than PKD	Minimally worse than PNKD MR1+	Poor medication response	Excellent

AD, autosomal-dominant; ADNFLE, autosomal-dominant nocturnal frontal lobe epilepsy; AR, autosomal-recessive; FPC, familial paroxysmal choreoathetosis; MR1+, myofibrillogenesis regulator 1-positive; MR1–, myofibrillogenesis regulator 1-negative; PDC, paroxysmal dystonic choreoathetosis; PED, paroxysmal exercise-induced dyskinesia; PEDt, paroxysmal exercise-induced dystonia; PHD, paroxysmal hypnogenic dyskinesia; PKC, paroxysmal kinesigenic choreoathetosis; PKD, paroxysmal kinesigenic dyskinesia; PNKD, paroxysmal nonkinesigenic dyskinesia; RE-PED-WC, rolandic epilepsy–paroxysmal exercise-induced dystonia–writer's cramp.

From Friedman NR, Ghosh D, Moodley M: Syncope and paroxysmal disorders other than epilepsy. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors: Swaiman's pediatric neurology, ed 5, Philadelphia, 2012, WB Saunders, Table 65-1.

hemorrhage, or other causes of sudden rises in intracranial pressure that lead to brainstem dysfunction. In addition, crowding of the posterior fossa and near herniation, the so-called cerebellar fits can also lead to abnormal extensor posturing, drop attacks, and varying degrees of altered consciousness and respiratory compromise. Historically secondary to undiagnosed posterior fossa tumors in the preneuroimaging era, "cerebellar fits" mostly occur in the context of Chiari I malformations.

Psychologic Disorders

Many psychologic disorders can be mistaken for epileptic seizures. Pleasurable behavior similar to masturbation may occur from infancy onward, and may consist of rhythmical rocking movement in a sitting or lying position, or rhythmic hip flexion and adduction. **Masturbation** may occur in girls 2-3 yr of age and is often associated with perspiration, irregular breathing, and grunting, but no loss of consciousness. Occasionally this is associated with child abuse or with other psychopathology. **Stereotypies,** or repetitive movements that are more complex than tics and do not change and wax and wane like tics (e.g., head banging, head rolling, body rocking, and hand flapping), usually occur in neurologically impaired children. **A mannerism** is a pattern of socially acceptable, situational behavior that is seen in particular situations such as gesturing when talking. Mannerisms should not be confused with stereotypies which are generally pervasive over almost every other activity such as head-shaking or hand-flapping in multiple situations. Stereotypies, unlike mannerisms, increase with stress. Unlike tics and mannerisms, stereotypies usually start before the age of 3 yr, involve more body parts, are more rhythmic and most importantly occur with engrossment with an object or activity of interest and do not have a premonitory urge that increases with attempts to suppress them as children rarely try to suppress stereotypies. **Panic and anxiety attacks** have been described in children; at times, these may be clinically indistinguishable from actual epileptic seizures, and therefore may necessitate video-EEG monitoring. **Rage attacks** usually occur in patients with personality disorder and are usually not seizures although rare cases of partial seizures can manifest as rage attacks. **Hyperventilation spells** can be precipitated by anxiety and are associated with dizziness, tingling, and, at times, carpopedal spasm. **Transient global amnesia** consists of isolated short-term memory loss for minutes to hours that occurs mostly in the elderly. The etiology can be epileptic, vascular, or drug related.

OCULOMOTOR ABNORMALITIES AND VISUAL HALLUCINATIONS

Paroxysmal Tonic Upgaze of Childhood

This usually starts before 3 mo of age, and consists of protracted attacks (hours to days) of continuous or episodic upward gaze deviation, during which horizontal eye movements are preserved. A downbeating nystagmus occurs on downward gaze. Symptoms are reduced or relieved by sleep, exacerbated by fatigue and infections, and spontaneously remit after a few years. Up to 50% of patients may have psychomotor and language delay. Imaging, laboratory, and neuropsychologic examinations are usually nonrevealing. Therapy with low-dose levodopa/carbidopa may be helpful.

Oculomotor Apraxia and Saccadic Intrusions

In oculomotor apraxia saccadic eye movements are impaired. Sudden head turns compensating for lateral gaze impairment mimic seizures. This disorder may be idiopathic (Cogan oculomotor apraxia) or may occur in the context of ataxia telangiectasia or lysosomal storage diseases. Genetic defects in DNA repair mechanisms have been implicated in at least 4 spinocerebellar ataxia disorders that are accompanied by oculomotor apraxia. A selective loss of Purkinje cells required to suppress omnipause neurons and initiate saccadic eye movement is believed to occur in those disorders. Saccadic intrusions are involuntary sudden conjugate eye movements away from the desired eye position. These are not necessarily pathologic.

Spasmus Nutans

This disorder presents with a triad of nystagmus, head tilt, and head nodding. If diurnal fluctuation occurs, symptoms may look like epileptic seizures. Brain MRI should be performed, as the triad has been

associated with masses in the optic chiasm and third ventricle. Retinal disease should also be ruled out. In the absence of these associations, remission occurs before 5 yr of age.

Opsoclonus Myoclonus Syndrome

The so-called dancing eyes refers to continuous, random, irregular, and conjugate eye movements that may fluctuate in intensity. They usually accompany myoclonus and ataxia ("dancing feet"). Encephalitis and neuroblastoma are possible causes. Therapy is by treating the underlying etiology, but adrenocorticotropic hormone (ACTH), corticosteroids, and clonazepam may be needed. Rituximab has been studied and preliminary trials suggest it may be effective as well.

Daydreaming and Behavioral Staring

Staring may be a manifestation of absence seizures, which should be differentiated from daydreaming, behavioral staring because of fatigue, and inattention. Episodes of staring only in certain settings (e.g., school) are unlikely to be seizures. In addition, responsiveness to stimulation such as touch and lack of interruption of playing activity characterizes nonepileptic staring.

Visual Hallucinations

Visual perceptions in the absence of external stimuli, or visual hallucinations, are usually accompanied by other neurologic signs and symptoms when they occur in the context of seizures. An exception is occipital seizures, which can manifest with isolated and unformed visual hallucinations and may be accompanied by headache and nausea, making them difficult to differentiate from migraine. However, occipital seizures are characterized by colorful, shapes, circles and spots lasting seconds and confined to 1 hemifield, while migrainous auras usually last minutes, and consist of black-and-white lines, scotomas, and or fortification spectra that start in the center of vision. Hallucinations can also be secondary to drug exposure, midbrain lesions, and psychiatric illnesses. In addition, retinal-associated hallucinations can occur in the form of flashes of light in the context of inflammatory etiologies, trauma, or optic nerve edema.

SLEEP DISORDERS

Paroxysmal nonepileptic sleep events are more common in epileptic patients than in the general population, which makes their diagnosis difficult. Semiology, timing of events, and if needed video-EEG and polysomnography help in distinguishing epileptic from nonepileptic events. Parasomnias typically occur less than once or twice a night; more frequent episodes suggest epileptic seizures. Of note, the EEG pattern of frontal lobe epileptic seizures may be similar to the one seen in a normal arousals, making their diagnosis challenging, especially that they have nonspecific hypermotor manifestations such as thrashing, body rocking, kicking, boxing, pedaling, bending, running, and various vocalizations. The diagnosis of such epileptic seizures is made on the basis of highly stereotyped events arising several times a night from nonrapid eye movement sleep.

Benign Sleep Myoclonus and Neonatal Sleep Myoclonus

Neonatal sleep myoclonus consists of repetitive, usually bilateral rhythmic jerks involving the upper and lower limbs during nonrapid eye movement sleep, sometimes mimicking clonic seizures. A slow (1 Hz) rocking of the infant in a head-to-toe direction is a specific diagnostic test that may reproduce the myoclonus. The lack of autonomic changes, occurrence only in sleep, and suppression by awakenings may help in differentiating these events from epileptic seizures. Remission is spontaneous at 2-3 mo of age. In older children and adults, sleep myoclonus consists of random myoclonic jerks of the limbs.

Nonrapid Eye Movement Partial Arousal Disorders

Brief **nocturnal confusional arousals** occurring 1-2 hr after sleep in stage 4 sleep are normal in children. Such episodes can vary from chewing, sitting up, and mumbling to agitated sleep walking, and usually last for 10-15 min. **Night terrors** similarly occur a few hours after going to sleep in stage 3 or 4 of sleep, most often at 2-7 yr of age and more so in boys. The child screams; appears terrified; has dilated pupils, tachycardia, tachypnea, unresponsiveness, agitation, and thrashing that increase with attempts to be consoled; is difficult to arouse; and may have little or no vocalization. In older children with persistent night terrors, an underlying psychologic etiology may be present. Diagnosis is based on the history. However, rarely, video EEG monitoring may be needed. At times, the use of bedtime diazepam (0.2-0.3 mg/kg) or clonazepam (0.01 mg/kg) may help control the problem while psychologic factors are being investigated. **Restless leg syndrome** can cause painful leg dysesthesias that cause nocturnal arousals and insomnia. It can be either genetic or associated with iron deficiency, systemic illness, or some drugs. Therapy depends upon treating the underlying cause and, if needed, on dopaminergic drugs such as levodopa/carbidopa, or antiepileptics like gabapentin.

Rapid Eye Movement Sleep Disorders

Nightmares and **sleep paralysis** are common disorders. Unlike night terrors, nightmares tend to occur later during the night and the child has a memory of the event.

Sleep Transition Disorders

Nocturnal head banging (**jactatio capitis nocturna**), rolling, or body rocking often occurs in infants and toddlers as they are trying to fall asleep. These usually remit spontaneously by 5 yr of age. No specific therapy is needed.

Narcolepsy-Cataplexy Syndrome

Narcolepsy is characterized by excessive daytime sleepiness, cataplexy, sleep paralysis, hypnogogic hallucinations, and disturbed nighttime sleep. The persistence of rapid eye movement sleep atonia upon awakening or its intrusion during wakefulness lead to sleep paralysis or cataplexy, respectively. Loss of tone in cataplexy occurs in response to strong emotions, and spreads from the face downwards leading to a fall in a series of stages rather than a sudden one. Consciousness is maintained in cataplexy. A selective loss of hypocretin-secreting neurons in the hypothalamus is at the origin of this disorder. The fact that DQB1*0602 is a predisposing HLA allele identified in 85-95% of patients with narcolepsy-cataplexy suggests an autoimmune-mediated neuronal loss. Diagnosis is based on the **multiple sleep latency test**, and therapy relies on scheduled naps, amphetamines, methylphenidate, tricyclic antidepressants, and counseling about precautions in work and driving.

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