CHAPTER 46

Myoclonus, Myoclonic Seizures, and Infantile Spasms

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DEFINITIONS AND DIAGNOSIS OF MYOCLONUS

Myoclonus (from the Greek *myo*, "muscle," and *klonus*, "agitation/violent contraction") has been defined as a "sudden, involuntary, brief, shock-like muscle contraction arising from the central nervous system" (CNS) [Fahn et al., 1986]. Myoclonus may be focal or generalized, single or repetitive, rhythmic or irregular. The origin of myoclonus may involve the spinal cord, cortex, brainstem, and cerebellum and provides the basis for several of the many classifications of myoclonic movements [Serratosa and Delgado-Escueta, 1993]. The range of myoclonic phenomena includes nonepileptic events such as sleep myoclonus, opsoclonus-myoclonus, and narcotic-induced myoclonus (Fig. 46-1). Epileptic myoclonus types include progressive disorders and nonprogressive syndromes such as juvenile myoclonic epilepsy.

This chapter presents the spectrum of myoclonic events observed in the neonate, infant, and child, to distinguish myoclonic seizure syndromes from other entities, and provides current information on and practical guidelines for the diagnosis and management of discrete types of myoclonic seizures. In addition, the diagnosis and management of infantile spasms, traditionally grouped with the myoclonic epilepsies, are discussed.

The electrophysiologic [Hallet, 1985] and location-related [Fahn et al., 1986; Halliday, 1967] classifications of myoclonus are complex and fall outside the scope of this chapter. In general, nonepileptic myoclonus is not associated with electroencephalographic correlates, whereas epileptic myoclonus is defined electrophysiologically as muscle jerks related temporally to an discharge on the electroencephalogram (EEG) recording and accompanied by a short-duration burst (50 to 100 milliseconds) on the electromyogram (EMG) recording [Hallet, 1985]. Epileptic myoclonus may be the major manifestation of an EEG-defined seizure or a minor component of other seizures such as classic absence. In a majority of circumstances, the distinction between nonepileptic and epileptic myoclonus in neonates, infants, and children can be based on the history and on observation. In this regard, the value of videotapes provided by the parents, permitting the clinician to evaluate infrequently occurring or nocturnal myoclonus, cannot be overemphasized.

Box 46-1 presents the major categories of nonepileptic myoclonus, based on age at presentation. Additionally, myoclonus should be distinguished from similar movement disorders, particularly tics. Table 46-1 enumerates features that discriminate between these two clinically similar entities.

CLASSIFICATION OF MYOCLONIC SEIZURES AND SYNDROMES

Myoclonic seizures are defined as events of CNS origin, consisting of rapid muscle movements that are caused by paroxysmal depolarization shift [Hallet, 1985]. As a group, the myoclonic seizures constitute one of the most prevalent and challenging seizure categories and can manifest in infancy, childhood, or adolescence (Table 46-2). They range from self-limiting "benign" disorders, through nonprogressive yet life-long entities (e.g., juvenile myoclonic epilepsy), to progressive myoclonic epilepsies associated with cognitive decline and death.

The diagnosis, classification, and management of myoclonic seizures have been evolving. The current International League Against Epilepsy classification of pediatric myoclonic seizures in the context of other epilepsy syndromes can be found in Chapter 40. A practical classification of myoclonic seizures is presented in Table 46-2, and of epilepsy syndromes, in Table 46-3, based on age at presentation. A useful distinction can be made between myoclonic *seizures*, a descriptive term based on the phenomenology of the seizure as confirmed by EEG, and myoclonic epilepsy *syndromes*. In addition to its associated seizure characteristics and EEG findings, a syndrome is characterized by distinct age at occurrence, natural evolution, associated features, and response to specific medications [Dreifuss, 1989]. A defined syndrome often is a homogeneous entity, with common etiology, genetic predisposition, or pathophysiology. Therefore, recognizing a seizure as belonging to a specific syndrome provides valuable information regarding its treatment and prognosis [Delgado-Escueta et al., 2003] (see Table 46-3).

MYOCLONIC SEIZURES OF THE NEONATAL PERIOD

Myoclonic seizures are a frequent type of neonatal seizures [Mizrahi and Kellaway, 1987; Tharp, 2002]. A majority of these seizures are symptomatic—that is, they occur in response to a wide variety of insults inflicted on the developing CNS either before or at the time of birth [Miller et al., 2002; Mizrahi and Clancy, 2000; Scher, 2002]. Thus, myoclonic seizures in the neonate merit the same evaluation process triggered by other neonatal seizures. Infection (congenital, prenatal, or perinatal), stroke and hemorrhage, hypoxia, and metabolic derangement all can be causative (see Table 46-2). A particularly malignant form of neonatal myoclonic seizures has been described in association with nonketotic hyperglycinemia in otherwise healthy newborns.

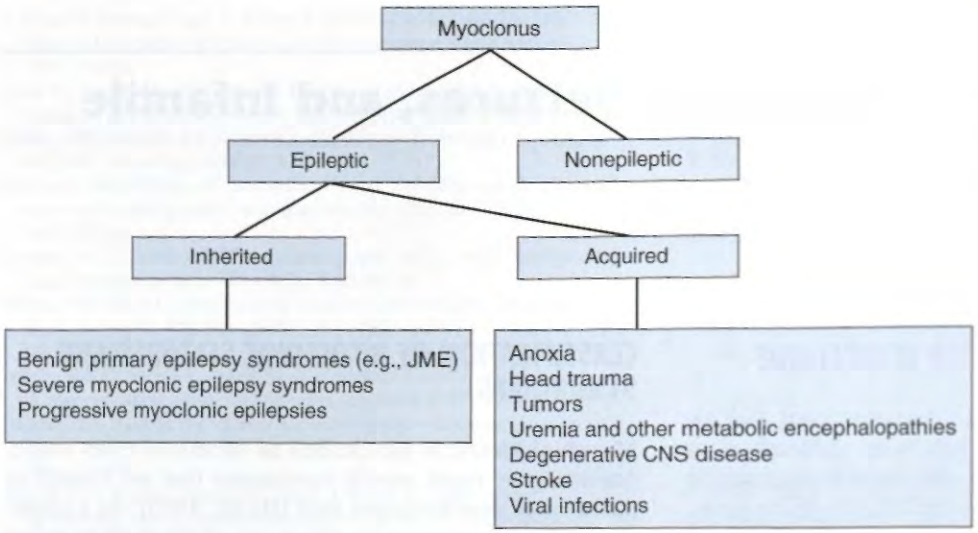


FIGURE 46-1. Overview of myoclonus categories. CNS, central nervous system; JME, juvenile myoclonic epilepsy. (From Leppik IE: Classification of the myoclonic epilepsies. Epilepsia 2003;44 [Suppl 11]:2-6. Reprinted with permission of Blackwell Publishing Ltd.)

Box 46-1 Differential Diagnosis of Nonepileptic Myoclonus by Age at Presentation

Neonates

Common
- Sleep myoclonus of preterm infant
- Sleep myoclonus of full-term infant
- Narcotic-induced myoclonus
- Drug withdrawal myoclonus
- Perinatal asphyxia
- Congenital infection, including AIDS
- Nonspecific, induced (startle) myoclonus

Rare
- Hyperekplexia (stiff baby syndrome) [Ryan et al., 1992]
- Metabolic myoclonus (e.g., uremia)
- Polyunsaturated fatty acid disease

Infants
- Sleep myoclonus
- Opsoclonus-myoclonus with or without neoplasm [Mitchell et al., 2002]
- CNS infections (e.g., coxackievirus infection)
- Concomitant genetic syndrome (e.g., startle myoclonus in Tay-Sachs)
- Benign familial (autosomal-dominant) myoclonus

Children
- Tics or chorea mimicking myoclonus
- CNS infections, opsoclonus-myoclonus, other entities listed for infants
- Drug-induced: penicillins, narcotics, some antihistamines, valproate, carbamazepine, phenytoin toxicity
- L-Dopa, chlorambucil, benzodiazepine withdrawal

AIDS, acquired immunodeficiency syndrome; CNS, central nervous system.

TABLE 46-1

Distinguishing Features of Tic and Myoclonus

TIC	MYOCLONUS
Complex or simple motion	Simple motion
Often variable location	Stereotypic: involving the same muscle group
Bilateral extremities rare; midline or lateralized	Typically in extremities, often bilateral
Vocalization frequent	Vocalization absent
Desire to move	No perceived urge
Can be transiently suppressed	Nonsuppressible
Incorporated in purposeful motion	Nonpurposeful

Determination of serum and cerebrospinal fluid glycine levels is therefore required [Chien et al., 2004].

Specific clinical syndromes of neonatal or early infantile myoclonic epilepsy with distinctive features that permit prognostication have been defined. Ohtahara, working alone [1976] and with Yamatogi [2003], and Aicardi [1978] described a severe form of myoclonic seizures with a burst-suppression EEG pattern. Clinically, massive axial bilateral myoclonia is seen in this early myoclonic encephalopathy syndrome, which typically commences during the first postnatal month. Although the etiology of this syndrome may be heterogeneous, the outcome for affected children is uniformly poor, including a high mortality rate (up to 60%) during the first year of life. In many cases, the seizures evolve to classic infantile spasms, and the EEG develops a hypsarrhythmic pattern.

Evaluation and Treatment

Because a majority of myoclonic seizures in the neonate are symptomatic, a search for a treatable cause is warranted. If levels of electrolytes, glucose, calcium, and magnesium are not revealing, evaluation should be directed by findings on

TABLE 46–2

Myoclonic Seizures of Neonates, Infants, Children, and Adolescence

Seizure or Syndrome	Additional Information [References]
Neonates	
Symptomatic myoclonic seizures	CNS insult: infection, hypoxia, stroke, drugs
Metabolic disorders with myoclonic seizures	Nonketotic hyperglycinemia [Dalla Bernardina and Dulac, 1994]
Early myoclonic encephalopathy	Burst-suppression EEG, poor prognosis [Aicardi and Goutieres, 1978]
Myoclonic epilepsy with CNS malformation	Aicardi's syndrome; lissencephaly; agyria-pachygyria; other migration disorders [Dalla Bernardina and Dulac, 1994]
Infants	
Early infantile epileptic encephalopathy	Burst-suppression; may overlap neonatal syndrome [Ohtahara and Yamatogi, 2003]
Benign myoclonic epilepsy of infancy	Rare; brief seizures, normal EEG background [Dravet et al., 1985a]
Severe myoclonic epilepsy of infancy	Rare; start as seizures with fever; positive family history [Dravet et al., 1985b]; sodium channelopathy [Claes et al., 2001]
Infantile spasms	Clusters of myoclonic jerks [Baram, 1993; Dulac and Plouin, 1994]
Storage disorders	GM_1, GM_2 gangliosidoses (Tay-Sachs disease, Sandhoff's disease); Niemann-Pick disease; Krabbe's disease; metachromatic leukodystrophy; neuronal ceroid lipofuscinosis (early and late infantile)
Mitochondrial disorders	MELAS; early Leigh's disease; other mitochondrial MERRF variants
Other metabolic disorders	Phenylketonuria and variants; Menkes's disease; others
Other progressive entities	Infantile Huntington's disease
Children and Adolescents	
Familial myoclonic epilepsy	
Myoclonic seizures in Lennox-Gastaut syndrome	Typically a minor component of the syndrome [Gastaut, 1985]
Absence with myoclonic features	EEG 3-sec spike-wave; prognosis guarded [Tassinari and Bureau, 1985]
Juvenile myoclonic epilepsy	Generalized seizures may precede myoclonus
Mitochondrial disorders	MERRF; myoclonus with MELAS, others [DiMauro and Moraes, 1993]
Progressive myoclonic epilepsies	Lafora body disease [Genton and Roger, 1993]; Baltic and Mediterranean types (Unverricht-Lundborg) [Delgado-Escueta et al., 2003]
Degenerative/storage disorders	Juvenile neuronal ceroid lipofuscinosis; Gaucher disease type 3 (juvenile neuropathic) [Nishimura et al., 1980]; sialidosis type I (cherry-red spot myoclonus) [Delgado-Escueta, 2003]

TABLE 46–3

Myoclonic Epilepsies in Infancy and Early Childhood

	DISORDER				
Feature	**Early Myoclonic Encephalopathy (Ohtahara's, Aicardi's Syndromes)**	**Severe Myoclonic Epilepsy of Infancy (SMEI) (Dravet's Syndrome)**	**Benign Myoclonic Epilepsy of Infancy [Dravet et al., 1985a]**	**Early Childhood Myoclonic-Astatic Epilepsy (MAE)**	**Myoclonic-Astatic Epilepsy (MAE) of Early Childhood (Doose's Syndrome)**
Age at onset	~1 mo	~6 mo to 1 yr	4 mo to 3 yr	1 to 4 yr	Peaks at 4 yr
Gender predominance	M:F	M:F	M:F	M:F	M:F
Psychomotor development	Variable	Slow	Normal	Normal	Variable
Family history; genetics		Positive in 50-60% of cases	Positive in 30% of cases	Positive in 60% of cases; maternal transmission?	Positive in 32% of cases, if EEG included
Seizure types	Massive axial bilateral myoclonia	Febrile and tonic-clonic → myoclonic, partial, atypical absence	Myoclonic; in adolescence, also tonic-clonic	Myoclonic, astatic (drop attacks), absence, rare tonic-clonic No tonic seizures	Onset: tonic-clonic (60%); astatic, myoclonic-astatic, or myoclonic/absence, SE common Nocturnal tonic seizures
EEG	Burst suppression	Generalized spike and polyspike waves; variable multifocal/ focal; slow background	Generalized polyspike and spike waves; normal background	Generalized 3- to 6-Hz spike/ polyspike waves mixed with classic 3-Hz waves; normal background	Irregular general spike/polyspike waves; multifocal spikes; slow background common
Prognosis	Grim: 60-80% mortality rate in first year	Unfavorable: drug resistance, low IQ, ataxia, tremors, dysarthria	Favorable with early treatment; may remit	Favorable with early therapy; typically persists	Variable; nocturnal seizures worsen prognosis

EEG, electroencephalogram, IQ, intelligence quotient, SE, status epilepticus. Modified from Delgado-Escueta AV, Perez-Gosiengfial KB, Bai D, et al. Recent developments in the quest for myoclonic epilepsy genes. Epilepsia 2003;44 (Suppl 11):13, with permission.

the history and the physical and neurologic examinations. Thus, required analyses include drug screens; determination of serum (and cerebrospinal fluid) amino acids, urea, lactate, and ammonia concentrations; and a congenital infection screen. In addition, neuroimaging studies should be performed. The EEG may be useful both for delineating specific syndromic categories (for example, a burst-suppression pattern in a nonmedicated neonate) and for prognosis [Scher, 1993; Tharp et al., 1989]. Treatment should focus on reversing the trigger for the seizures, if possible, and on seizure control [Wheless and Sankar, 2003]. Benzodiazepines should be used for myoclonic seizures in the neonate, and valproate avoided if possible, owing to the significant mortality associated with the latter medication in this age group [Bryant et al., 1996].

SYNDROMES OF INFANTS: INFANTILE SPASMS (WEST'S SYNDROME)

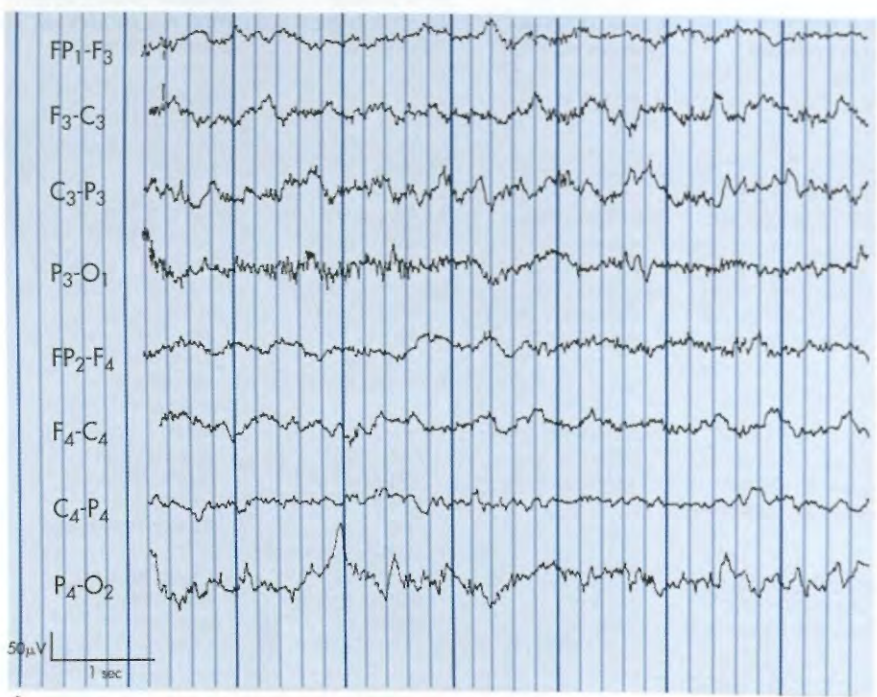
Often classified among the myoclonic epilepsies, infantile spasms constitute the most prevalent and perplexing entity that appears specifically in the infancy period of brain development (Table 46-2). Therefore, this syndrome is discussed in detail, followed by a review of other seizures consisting primarily of myoclonic events.

Infantile spasms occur primarily during the first year of life, especially between the third and eighth months, regardless of the timing of any instigating factors (e.g., intrauterine infection or stroke, tuberous sclerosis, perinatal asphyxia, postnatal insult). It is thus useful to consider infantile spasms a highly age-specific epileptic response of the infant brain to innumerable causes [Brunson et al., 2002]. This concept is consistent with the natural evolution of infantile spasms (with or without treatment), in which the spasms disappear or evolve into other seizures [Hrachovy et al., 1991; but see de Menezes and Rho, 2002]. Infantile spasms are relatively common, occurring in 1 per 2000 infants [Cowan and Hudson, 1991; Riikonen, 2001]. Because the outcome with infantile spasms, in terms of cognitive function and intellect, is poor (with mental retardation in 80% to 90% of children and epilepsy in greater than 50%), the economic and emotional burdens to society associated with this disorder are enormous. Early recognition and diagnosis, as well as new therapies, hold the most promise for this severe form of epilepsy in infants.

Infantile spasms were first brought to attention by Dr. W. J. West in 1841, who documented the disorder in his own son [West, 1841]. Other reports of this myoclonic epilepsy in infants with its poor neurodevelopmental outcome followed, and the term *West's syndrome* was coined in the early 1960s [Eling et al., 2002]. *Hypsarrhythmia*, the high-voltage, chaotic EEG abnormality associated with infantile spasms interictally, was defined in the 1950s [Gibbs and Gibbs, 1952]. The ictal correlates of the spasms themselves were delineated by Hrachovy and colleagues [1984]. The poor response of infantile spasms to conventional antiepileptic drugs [Aicardi, 1986; Holmes, 1987] led to the discovery of the efficacy of adrenocorticotropic hormone for treatment of this type of seizure [Sorel and Dusaucy-Bauloye, 1956]. Adrenocorticotropic hormone and also glucocorticoids (prednisone or hydrocortisone) have since been used as major therapeutic agents for infantile spasms (see later on) [Baram et al., 1996; Hrachovy and Frost, 1989; Lerman and Kivity, 1982; Mackay et al., 2004].

Clinical Features and Diagnosis

The syndrome of infantile spasms consists of a constellation of myoclonic-like seizures in infants whose EEG pattern is that of hypsarrhythmia or its variants [Jeavons, 1985]. The EEG



A

FIGURE 46-2. Samples of electroencephalograms (EEGs) from a normal infant and from a patient with hypsarrhythmia. **A,** Awake EEG from a normally developing 8-month-old male with a suspected seizure. Coherence of EEG waves is evident.

pattern, lack of response to conventional antiepileptic agents, and poor outcome distinguish infantile spasms from the similar epilepsies of infancy [Aicardi, 1986; Dreifuss, 1989; Lombroso, 1990]. Clinically, clusters of jerks, subtle or massive, occur mainly on awakening. The movements may consist of head, truncal, and hip flexion or extension or, most commonly, head and body flexion with leg extension [Hrachovy and Frost, 1989]. The number of jerks per cluster and of clusters per day are highly variable, as are associated features such asymmetry (typically in the presence of a focal brain lesion) [Kramer et al., 1997], autonomic phenomena (flushing, pallor), or a cry [Jeavons and Bower, 1964]. The location of the origin of these movements, and whether or not they truly are myoclonus, have been topics of debate [e.g., Pinard et al., 1993]. Arrest of development and loss of developmental milestones often accompany the onset of infantile spasms.

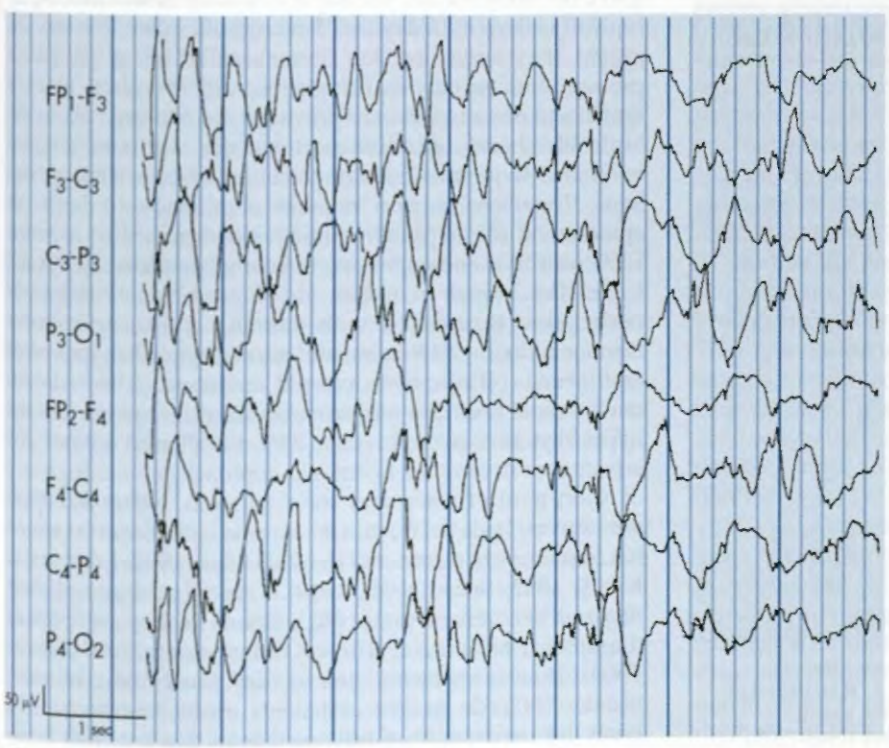
In a large majority of affected infants, infantile spasms are a symptom of an abnormally developing brain (symptomatic infantile spasms), as is evident from the history, examination, or diagnostic evaluation [Jeavons and Bower, 1964]. In a second, smaller group of infants, presence of an underlying CNS dysfunction is suggested by delayed development or abnormal findings on physical examination. Infantile spasms in this group have been defined as *cryptogenic*, and the prevalence of the disorder has been decreasing with the availability of better diagnostic modalities, which allow more infants to be classified in the symptomatic group. A minority of infants (approximately 10%) have an apparently normal CNS, as defined by normal development, imaging studies, and etiologic evaluation. Dulac and colleagues have coined the term *idiopathic* for the disorder in these infants to emphasize the important concept that with successful treatment, these are the infants with potentially excellent outcome [Caplan et al., 2002; Dulac et al., 1993; Ito et al., 2002; Kivity et al., 2004; Lombroso, 1983; Ohtsuka et al., 2000].

Because symptomatic infantile spasms arise from an abnormal CNS, the nature of the underlying insult or lesion may affect the phenomenology of the spasms (and often of other seizure types diagnosed before the onset of infantile spasms). In some children with infantile spasms, a focal seizure triggers or coincides with a generalized spasm [Carrazana et al., 1993], or the spasm may be strongly asymmetrical. In infants with generalized or multifocal brain dysfunction, the spasms typically are symmetric. It should be noted, however, that during the stage of CNS maturation of infants, generalized spasms may be generated by a localized epileptic focus [Acharya et al., 1997; Chugani et al., 1990; Dulac, 2001; Wyllie, 1996].

Clinical Laboratory Tests

The evaluation of an infant suspected of having infantile spasms should include a prolonged EEG, consisting of at least a full sleep-wake cycle. The EEG hallmark of infantile spasms is the presence of hypsarrhythmia (Fig. 46-2), a disorganized, high-voltage pattern with no normal background. The hypsarrhythmia may thus signify diffuse, abnormal neuronal activity interictally, perhaps contributing to the loss of milestones and poor outcome. The brief seizures typically are associated with "flattening" of the EEG pattern [Hrachovy et al., 1984]. The hypsarrhythmia may not be evident early in the course of infantile spasms or may be present only during deep sleep. Therefore, a prolonged EEG or, optimally, a video EEG may be required for diagnosis [Hrachovy and Frost, 1989].

An infant with suspected infantile spasms should have a search for treatable disorders or precipitating factors. Neuroimaging may reveal tuberous sclerosis or CNS malformations [Dulac et al., 1984]; the latter accounts for a significant percentage of cases of infantile spasms (20% to 30% in recent



B

FIGURE 46-2, cont'd. B, A hysparrhythmic EEG from a 10-month-old infant with sequelae of extreme prematurity (adjusted chronologic age of 7 months) and clinical infantile spasms. A disorganized pattern of very high voltage slow and sharp waves, without synchrony, predominates. Note the different voltage scale of the two samples. Horizontal bars = 1 second; vertical bars = 50 µV.

series) [Baram et al., 1996; Kramer et al., 1997; Riikonen, 2001]. Treatable causes such as tumors [Gabriel, 1983; Mimaki et al., 1983] or hydrocephalus [Baram et al., 1996] should be excluded. Stroke [Alvarez et al., 1987] and pre- or postnatal infection may be apparent on magnetic resonance imaging (MRI). A search for metabolic disorders is recommended [Kramer et al., 1997; Riikonen, 2001], and may be supported by abnormal basal ganglia signal on MRI [Desguerre et al., 2003].

Natural History

In a majority of cases, the hypsarrhythmia disappears over weeks to months, regardless of treatment, followed by waning of the spasms themselves. Even without treatment, 89% of patients have been reported to be spasm free by age 5 years [Hrachovy et al., 1991; but see de Meneses and Rho, 2002]. In many infants with infantile spasms who demonstrate diffuse or multifocal neuronal dysfunction, the disorder progresses to Lennox-Gastaut syndrome (see Chapters 40 and 44), with multiple seizure types and a typical EEG pattern. Among survivors of infantile spasms in whom lesions such as those of tuberous sclerosis were the trigger, the spasms often revert or evolve to a focal epilepsy [Chugani et al., 1990; Shields et al., 1999]. As mentioned earlier, the intellectual outcome in a majority of the survivors of infantile spasms is poor [Caplan et al., 2002; Dulac, 2001; Jeavons and Bower, 1964]. Therefore, the goal of optimal treatment of infantile spasms should focus not only on seizure control but also on improvement of cognitive outcome. To date, no single treatment mode has been documented to provide these therapeutic benefits for a majority of infants with infantile spasms. Adrenocorticotropic hormone therapy, use of newer antiepileptic drugs such as vigabatrin, and occasionally surgical resection of a focal lesion that triggers the spasms may offer the best results in appropriate patients.

Box 46-2 ACTH Treatment Regimen for Infantile Spasms

Two-Week Treatment Schedule

- ACTH (Acthar Gel) 75 U/m^2 of body surface area per dose, intramuscularly, twice a day (150 U/m^2/day)

Monitoring

- Plasma electrolytes and glucose at onset and end of treatment
- Blood pressure twice weekly, measured when child is not crying; expect diastolic pressure of >80 mm Hg in 50% of patients
- If kidneys are intact (need assessment in TS), continue medication

Tapering Schedule

- *For 3 days*: 30 U/m^2 in the morning
- *For 3 days*: 15 U/m^2 in the morning
- *For 3 days*: 10 U/m^2 in the morning
- *For 6 days*: 10 U/m^2 every other morning

ACTH, adrenocorticotropic hormone; TS, tuberous sclerosis.
Modified from Baram TZ, Mitchell WG, Tournay A, et al. High-dose corticotropin (ACTH) versus prednisone for infantile spasms: A prospective, randomized, blinded study. Pediatrics 1996;97:375, with permission.

Treatment

Whether early treatment of infantile spasms with rapid resolution of both spasms and the hypsarrhythmic EEG improves cognitive outcome is not fully resolved. Glaze and associates [1988], in a prospective study, did not find improved outcome in infants who received treatment within a month of onset of infantile spasms, compared with those in whom treatment was delayed. Overall success of treatment in that study was low, however. Other prospective [Kivity et al., 2004; Lombroso, 1983] and retrospective [Koo et al., 1992; Singer et al., 1980] studies concluded that prompt *successful* treatment, presumably through elimination of the hypsarrhythmia, promotes resumed acquisition of cognitive milestones and improved outcome. Currently recommended treatment for infantile spasms, based on information gathered over the past decade, involves adrenocorticotropic hormone, vigabatrin, or, in selected infants with focal lesions that trigger the spasms, surgical resection.

Adrenocorticotropic Hormone

In accordance with the results of several studies including both prospective randomized, controlled [Baram et al., 1996; Hrachovy et al., 1983, 1994], and uncontrolled studies [Snead et al., 1989], the American Academy of Neurology and the Child Neurology Society have issued a practice parameter recommending the use of adrenocorticotropic hormone for the treatment of infantile spasms [Mackay et al., 2004]. Because of the apparent increased efficacy of high doses of adrenocorticotropic hormone, the recommended therapy for infantile spasms consists of adrenocorticotropic hormone in depot formulation (e.g., Acthar Gel), at a dose of 150 U/m^2 body surface per day *in two daily doses* (Box 46-2), typically 80 to 90 U/day in a 5-month-old infant. Parents are taught the procedure for intramuscular injection; blood pressure and urinalysis for glucose are measured twice a week; and parents and care providers are educated about the high likelihood of adrenocorticotropic hormone-induced reversible hypertension, voracious appetite, irritability, and acne. Treatment success requires elimination of both the spasms and the hypsarrhythmia, as determined by a video EEG (or EEG) encompassing at least a complete sleep-wake cycle. The 2-week treatment is followed by a 12-day taper period (see Box 46-2), with morning adrenocorticotropic hormone dosing, to reinstate normal circadian peaks of endogenous adrenocorticotropic hormone. This adrenocorticotropic hormone regimen eliminates the spasms and the hypsarrhythmia in more than 85% of affected infants. Its advantages over other hormonal approaches are a high rate of short-term efficacy and short duration, which minimize the severe side effects of chronic adrenocorticotropic hormone/steroid treatment [Heiskala et al., 1996; Lerman and Kivity, 1982; Snead et al., 1989]. Thus, *high dose* and *short duration* of adrenocorticotropic hormone therapy may provide the optimal balance of efficacy and adverse effects [Baram, 2003]. If seizures recur, their identity should be confirmed, because infantile spasms commonly evolve to other seizure types that may require a different therapy. For recurrent infantile spasms, a second course of adrenocorticotropic hormone

has been successful [Baram, unpublished observations; Snead, 1993]. Although high adrenocorticotropic hormone doses are advocated in the United States and may be required for the neurobiologic mechanism of infantile spasm suppression [Brunson et al., 2002; Rho, 2004], much lower doses are suggested in Japan [e.g., Ito et al., 2002], where synthetic, highly brain-penetrating preparations, different population characteristics, or other factors may influence therapy success [Baram, 2001].

Vigabatrin

Vigabatrin, an inhibitor of γ-aminobutyric acid (GABA) degradation, has been extensively used in Europe, and its effectiveness, particularly for children with tuberous sclerosis–associated infantile spasms, has been demonstrated. In a multicenter retrospective study, 50% of all patients of infantile spasms and 27 of 28 infants with tuberous sclerosis–associated spasms responded to vigabatrin [Aicardi, 1996; Chiron et al., 1997]. A controlled randomized study of vigabatrin in the United States found an efficacy rate of only 35% using high-dose vigabatrin [Elterman et al., 2001; Lux et al., 2002]. Unlike adrenocorticotropic hormone, vigabatrin does not result in an all-or-none response, and increasing doses (to 150 to 200 mg/kg per day) gradually decrease spasm frequency. Remarkably, studies in France have suggested that vigabatrin may improve cognitive outcome of patients with tuberous sclerosis–associated infantile spasms [Chiron et al., 1997]. The duration of required treatment with vigabatrin is unclear, but a year or more has been recommended [Aicardi, 1996; Elterman et al., 2001]. Prolonged treatment may be associated with retinal changes and irreversible visual field constriction [Johnson et al., 2000; Krauss et al., 1998], effects that have resulted in lack of Food and Drug Administration (FDA) approval of the drug in the United States.

Surgical Treatment

The role of surgical treatment for infantile spasms has not been fully defined [Caplan et al., 2002; Chugani et al., 1990; Shields et al., 1999]. As discussed earlier, infantile spasms may be triggered by focal CNS lesions, and in affected infants, focal seizures often precede the onset of infantile spasms or trigger individual spasms. The natural history of these spasms typically consists of a recrudescence of focal seizures with a focal EEG [Kramer et al., 1997]. As with any "lesional" pediatric epilepsy, surgical resection of the focus may often be curative [Wyllie, 1996]. In the special case of tuberous sclerosis–associated infantile spasms, exciting novel technology may permit identification of the "epileptogenic" tuber, allowing resection [Juhasz et al., 2003]. Useful criteria for infants with infantile spasms who may benefit from surgical resection have been suggested [Kramer et al., 1997].

Other Treatments

Numerous additional treatments have been used for infantile spasms. These include therapy with nitrazepam, valproate, lamotrigine, topiramate [Conry 2004], zonisamide [Lotze and Willfong, 2004; Suzuki, 2001], neurosteroids [Kerrigan et al., 2000], pyridoxine [Ohtsuka et al., 2000], immunoglobulins, or thyrotropin-releasing hormone [Takeuchi et al., 2001] and the ketogenic diet [Kossoff et al., 2002; Nordli et al., 2001]. Variable efficacy has been reported for each. Because spasms disappear spontaneously at a rate of approximately 1% per week, effects of prolonged treatment should be carefully considered. Occasionally, treatment of the precipitating factor of infantile spasms (such as tumor or hydrocephalus) will eliminate the seizures.

Pathophysiology

Infantile spasms are associated with diverse genetic (e.g., Kato et al., 2004], teratogenic, perinatal, and postnatal etiologic factors. This diversity points to a "final common pathway" for the etiologic conditions, leading to infantile spasms only during the state of CNS maturation present in infancy. Mechanistic theories for the development of infantile spasms have included autoimmune or brainstem dysfunction [Hrachovy and Frost, 1989], developmental "arrest" [Riikonen, 1983], and cortical microdysplasia [Dalla Bernardina and Dulac, 1994; Vinters et al., 1992].

The recent improvement of the resolution of MRI has led to the identification of structural malformations in a relatively larger proportion of children with infantile spasms. Frequency of CNS malformations in infantile spasms has been reported to be 20% [Baram et al., 1996; Kramer et al., 1997] and 30% to 34% [Dalla Bernardina and Dulac, 1994]. These malformations may consist of a diffusely dysplastic brain, such as in pachygyria, or as relatively small regions of cortical dysplasia and even microscopic areas of microdysgenesis [Meencke and Gerhard, 1985]. A current hypothesis for the pathogenesis of infantile spasms suggests that abnormal excitability generated by the focal areas of dysplastic brain spreads throughout the cortex [Dulac et al., 1997] and is propagated to brainstem structures [Juhasz et al., 2002], leading to the generalized spasms. This spread of the epileptic activity happens only during infancy, a developmental period characterized by cortical excitability. Studies in excised dysplastic adult brain [Avoli et al., 2003] and in animal models of cortical dysplasia [Zhu and Roper, 2000] have provided evidence for epileptogenic neuronal activity within these regions. Foci of microdysgenesis, however, have been described in brains of normal persons examined postmortem [Lyon and Gastaut, 1985], casting doubt on the etiologic role of these regional heterotopias in infantile spasms. In addition, in a majority of infants with symptomatic infantile spasms, the underlying disorders do not include cortical dysplasias.

Theories for the pathogenesis of infantile spasms have to be consistent with the unique features of this disorder. For example, how can a single entity have so many causes? Why do infantile spasms arise only in infancy, even when a known insult had occurred prenatally, and why do they disappear? Why are infantile spasms associated with lasting cognitive dysfunction, and why do these seizures—unlike most others—respond to adrenocorticotropic hormone?

The unique response of infantile spasms to hormonal treatment with high doses of adrenocorticotropic hormone may provide a key for elucidating the pathophysiology of this disorder. In randomized, controlled blinded approaches, adrenocorticotropic hormone doses that are much higher than those required for maximal hormonal effects offer additional efficacy: elimination of the spasms and the hypsarrhythmia in 86% to 88% of infants within a week [Baram et al., 1996], compared with approximately 40% efficacy of

high-dose prednisone or lower doses of adrenocorticotropic hormone. Does adrenocorticotropic hormone have additional nonhormonal effects that ameliorate infantile spasms? Although analogs of adrenocorticotropic hormone without hormonal effects did not eliminate infantile spasms [Pentella et al., 1982; Willing and Lagenstein, 1982], suggesting that the hormonal actions of adrenocorticotropic hormone are necessary for efficacy, it is known that these analogs do not bind adrenocorticotropic hormone receptors within the brain [Brunson et al., 2001b, 2002]. Therefore, the additional efficacy of supramaximal adrenocorticotropic hormone doses is consistent with the hypothesis that the hormone exerts additional effects in the brain that are independent from the release of endogenous steroids. It is unlikely that these effects of adrenocorticotropic hormone are simply anticonvulsant: adrenocorticotropic hormone is not anticonvulsant in animal models [Baram and Schultz, 1995; Holmes, 1987]. In addition, the rapid, "all-or-none" and often permanent effects of adrenocorticotropic hormone on infantile spasms are not consistent with conventional anticonvulsant properties [Baram, 1993; Hrachovy and Frost, 1989]. Recent work has demonstrated that high doses of adrenocorticotropic hormone that permit penetration of the peptide across the blood-brain barrier reduce the levels of the seizure-promoting endogenous peptide corticotropin-releasing hormone in seizure-prone brain regions including the amygdala [Brunson et al., 2001b]. Thus, the efficacy of adrenocorticotropic hormone suggests a "final common pathway" for the mechanisms by which the many causes of infantile spasms trigger these seizures. This hypothesis suggests that infantile spasms occur in the context of an insulted and stressed developing CNS [Baram, 1993; Brunson et al., 2002]. The many causative disorders underlying infantile spasms all lead to activation of the stress response, including the stress neurohormone corticotropin-releasing hormone. Corticotropin-releasing hormone has been found, in infant animal models, to cause severe seizures and long-term deficits of learning and memory [Baram et al., 1992; Brunson et al., 2001a]. These effects of corticotropin-releasing hormone are restricted to infancy because the receptors for corticotropin-releasing hormone, which mediate its action on CNS neurons, are most abundant during this developmental period. Adrenocorticotropic hormone administration inhibits production and release of corticotropin-releasing hormone both through steroid release and a negative feedback mechanism and directly, by activation of brain adrenocorticotropic hormone receptors. Therefore, the efficacy of adrenocorticotropic hormone for infantile spasms may depend on its ability to decrease the levels of the seizure-promoting stress neurohormone corticotropin-releasing hormone. This supposition is consistent with the profile of adrenocorticotropic hormone effect, the myriad different "causes" of infantile spasms, the abnormal adrenocorticotropic hormone levels in the cerebrospinal fluid of affected infants [Baram et al., 1992, 1995; Nagamitsu et al., 2001], and the spontaneous disappearance of the seizures. Furthermore, if corticotropin-releasing hormone is responsible for the seizures and the worsened cognitive outcome in persons with infantile spasms, then drugs that block the actions of corticotropin-releasing hormone on its receptors may provide a better therapy for this disorder [Baram, 2003; Baram and Hatalski, 1998].

SEVERE MYOCLONIC EPILEPSY OF INFANCY

Myoclonic seizures are the major manifestation of several epileptic entities confined to the first 2 years of life. Dalla Bernardina and colleagues [1983], Dravet and associates [1985a, 1985b], Ohtahara working alone [1976] and with Yamatogi [2003], and others have defined clinical and EEG criteria to distinguish among these disorders—benign or severe myoclonic epilepsies of infancy—but significant clinical overlap among these syndromes remains. Thus, the prognosis for infants presenting with myoclonic epilepsy other than infantile spasms cannot be predicted with certainty. Specifically, in these rare syndromes, normal findings on the neurodevelopmental examination at presentation do not necessarily predict a good outcome, although in general, a normal-appearing interictal EEG is consistent with the benign syndrome described by Dravet and associates [1985a], with good response to valproate and a relatively low likelihood of development of other epilepsies.

Since the mid-1990s, a syndrome of severe myoclonic epilepsy of infancy has been characterized [Dravet, 1985b; Scheffler et al., 2001], and the molecular basis of this entity has been discovered. The onset of this disorder is typically with clonic seizures, provoked by fever, that progress to massive or subtle myoclonic events associated with other seizure types (absence, partial tonic-clonic). The clinical course is one of intractable seizures with cognitive deterioration and poor response to treatment. Because severe myoclonic epilepsy of infancy commonly manifests with febrile seizures and occurs in children from families with generalized epilepsy and febrile seizures (GEFS$^+$), severe myoclonic epilepsy of infancy has been considered a severe manifestation of the GEFS$^+$ spectrum (Scheffer et al., 2001]. Indeed, mutations in a sodium channel gene (*SCN1A*), leading to defective channel function, have been found in severe myoclonic epilepsy of infancy, as discovered also for GEFS$^+$ [Claes et al., 2003; Wallace et al., 2003]. Several related genes may be involved, and the severity of the clinical phenotype may depend on the location and type of the mutation (see Chapter 42 for a comprehensive discussion).

Symptomatic Myoclonic Epilepsies of Infancy

Several genetic disorders of lysosomal and other enzyme dysfunction may have their clinical onset during the first 2 years of life (see Tables 46-2 and 46-3). In these entities, seizures are rarely the major presenting symptom, and a thorough history and examination often reveal other stigmata of specific entities (e.g., organomegaly, spasticity, retinal cherry-red spot). Laboratory evaluation should be guided by the genetic background, associated features, and other aspects of the clinical presentation. Storage disorders that merit consideration include the two early-presenting variants of the neuronal ceroid lipofuscinoses (see Chapter 59). The infantile (Santauuori-Haltia) and late infantile (Jansky-Bielschowsky) forms are characterized by myoclonic and other seizures, developmental regression, visual loss, and a rapidly progressive course. Gangliosidoses manifesting at this age include GM_1 and GM_2, particularly in infants of Jewish Ashkenazi background (see Table 46-2). Among mitochondrial disorders, myoclonic epilepsy with ragged red

fibers rarely begins in the infancy period, as may other disorders related to mutation of mitochondrial genes (e.g., Leigh's syndrome).

MYOCLONIC EPILEPSIES OF CHILDREN AND ADOLESCENTS

Juvenile Myoclonic Epilepsy

The most common type of myoclonic epilepsy of childhood seen in adolescents is juvenile myoclonic epilepsy, a nonprogressive, genetically inherited disorder that accounts for 15% to 20% of all epilepsies at this age [Wheless and Kim, 2002]. Typically, onset is at or near the time of puberty, but many cases occur earlier or manifest in the early 20s. The heraldic event commonly is a generalized tonic-clonic seizure, and only careful history reveals that early-morning myoclonus, the cardinal feature of this disorder, has been present for some time. The myoclonia occurs as repetitive irregular or semirhythmic myoclonic jerks involving shoulders and arms, sometimes with dropping of objects, sometimes asymmetric or unilateral, and confined to the awakening minutes or hours. The myoclonia may be mistaken for "nervousness" and classically precedes the generalized tonic-clonic seizures, which can occur at any time of day or night and are found in 90% of patients. Alternatively, juvenile myoclonic epilepsy may evolve clinically from apparently typical childhood absence seizures [Delgado-Escueta et al., 2003; Wirrell et al., 1996]. The diagnosis is confirmed by the pathognomonic EEG pattern (Fig. 46-3). The myoclonia is precipitated by sleep deprivation and alcohol.

Evaluation and Diagnosis

EEG is the most useful test for the diagnosis of juvenile myoclonic epilepsy. EEG abnormalities are accentuated by sleep deprivation, and an early-morning EEG (with video) also may clarify the nature of "nervousness" on awakening. EEG background usually is normal, without slowing or disorganization. The characteristic abnormality consists of bursts of bifrontal or generalized, bilaterally synchronous, spike/polyspike-and-wave activity, typically at 3.5 to 4 Hz [Janz, 1989]. Fast spike-and-wave activity of 4 to 6 Hz also is frequently observed [Dreifuss, 1989]. Absence seizures (which occur in 30% of patients) are accompanied by typical spike-and-wave activity, but the frequency usually is faster than 3 Hz [Asconape and Penry, 1984; Delgado-Escueta, 2003]. Focal polyspike-and-wave activity accompanied by

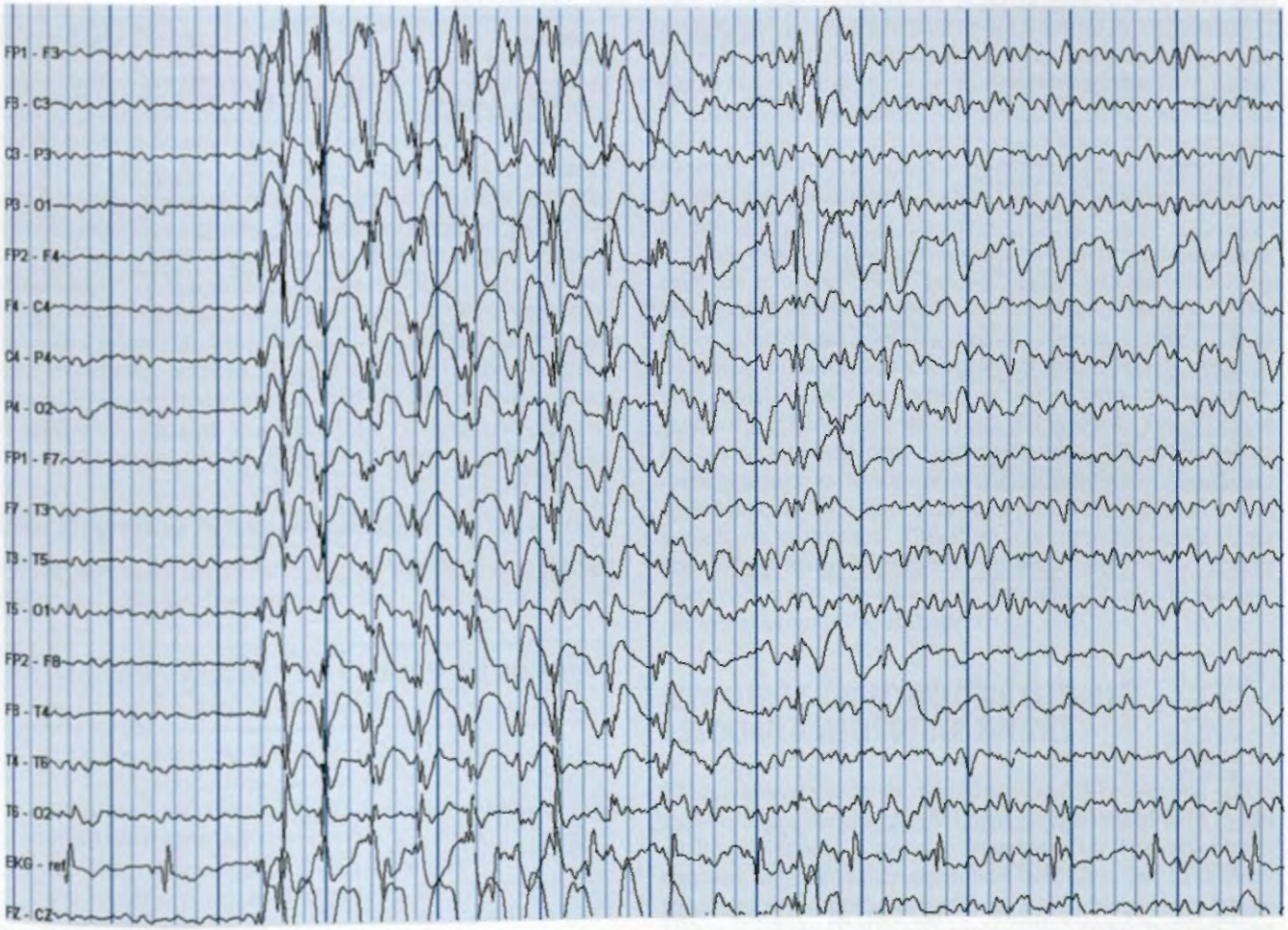


FIGURE 46-3. Sample of an electroencephalogram (EEG) from an adolescent with juvenile myoclonic epilepsy (JME). Generalized spike-wave discharge, maximal over the frontal leads, erupts suddenly from a normal background. The typical spike or polyspike discharges in JME are 3.5 to 4 Hz in frequency. (Courtesy of Dr. Howard Kim, University of California, Irvine.)

focal jerks also has been reported [Panayiotopoulos et al., 1991]. Photoparoxysmal response composed primarily of generalized or frontally predominant polyspike-and-wave activity occurs in approximately 30% to 35% of patients [Janz, 1989]. The myoclonic jerks themselves are accompanied by an EEG burst of 10 to 16 Hz polyspikes, followed by high-amplitude slowing at a frequency of 2 to 5 Hz. Juvenile myoclonic epilepsy clearly is a familial disorder, although the exact genes responsible have not been cloned [Minassian et al., 1995; Serratosa and Delgado-Escueta, 1993].

Treatment

The treatment of juvenile myoclonic epilepsy should focus on both avoidance of the precipitating factors, as well as on the use of antiepileptic medications. These life-long seizures are triggered by fatigue and alcohol; therefore, lifestyle management, such as ample sleep and avoidance of alcohol, significantly influences the likelihood of successful drug management. In adolescent girls, hormonal changes occuring with menstruation are a significant precipitant of the seizures, requiring special care in obtaining adequate sleep or increased medication dose. Valproate is reportedly effective in 86% to 90% of cases [Delgado-Escueta and Enrile-Bacsal, 1984]. When valproate is not effective or leads to unacceptable side effects, lamotrigine may provide an alternative option. Treatment of juvenile myoclonic epilepsy with felbamate, zonisamide, and clorazepate has been reported. Unlike most idiopathic seizures of the developing human, juvenile myoclonic epilepsy rarely remits, so that affected persons require medication for life. A relapse rate of 75% to 100% when medication is withdrawn has been documented [Delgado-Escueta and Enrile-Bacsal, 1984; Penry et al., 1989].

PROGRESSIVE MYOCLONIC EPILEPSIES

Progressive myoclonic epilepsies are rare genetic entities, accounting for approximately 1% of epilepsies in childhood. These syndromes typically consist of massive myoclonic seizures, cognitive deterioration, and other neurologic signs, often including ataxia (Table 46-4). Several of the progressive myoclonic epilepsy syndromes have been characterized clinically, have specific EEG characteristics, and

TABLE 46–4

Progressive Myoclonic Epilepsy (PME) Syndromes in Children and Adolescents

			SIGNS OF NEUROLOGIC DETERIORATION							
SYNDROME	ONSET AGE (yr)	SEIZURES AT ONSET	Visual	Cerebellar	Pyramidal Tract	Extra-pyramidal	Dementia	NEUROPATHOLOGY	GEOGRAPHIC DISTRIBUTION	DEATH
Unverricht-Lundborg PME	6-15	Generalized, myoclonus including face; stimulus sensitive	No	Worse on phenytoin	Rare, infrequent	Rare	Slow to develop	Vesicular changes in eccrine sweat glands	North Europe, U.S., Canada, Mediterranean countries	Age 50-60 yr
Lafora body disease	10-18	Generalized (absence; drops) then myoclonus; stimulus sensitive	Occipital seizures with visual hallucinations	Mid to late course	Common	Not common	Rapidly progressive (1-2 yr after onset)	PAS* cytoplasmic inclusions in skin, muscle, liver, and brain biopsies	Mediterranean, Middle East, Africa, India, Pakistan	Age 20-25 yr ~10 yr after onset
Neuronal ceroid lipofuscinoses: Batten (late infant) or Batten-Vogt-Spielmeyer disease	4-10	Face myoclonias seizures 1-4 yr later; generalized and absence; stimulus sensitive	Central visual loss heralds disease Retinitis pigmentosa	Not prominent	Common	Common	Rapidly progressive	Vacuolated lymphocytes fingerprint profiles and acurvilinear inclusion on skin biopsy	Scandinavia, U.S.	Late teens or early 20s
Adult ceroid lipofuscinosis (Kufs' disease)	11-50	Stimulus sensitive generalized and myoclonia late, or no seizures	—	Common	Common	Athetosis, dyskinesia common	Slowly progressive	Fingerprint profile; osmiophilic granular profiles in brain biopsy and lipofuscin deposits in liver biopsy specimen	Worldwide	10 yr from onset
Juvenile Gaucher's disease	~5-15; rarely later	Generalized, partial; photomyoclonic response	Abnormal eye movements, gaze palsies herald onset	Ataxia early in course	Common	Can be present	Early in course	Osteopenia, bone lesions; organomegaly; Gaucher's cells; diminished lucocerebrosidase activity	—	<10 yr from onset
Mitochondrial encephalo-myopathy with ragged red fibers (MERRF)	3-65	Generalized, partial; photosensitive	Rare optic atrophy	Can occur	Dysarthria ataxia	No	Slowly progressive	Lacticacidosis, myopathy, short stature, deafness; muscle biopsy; ragged red fibers; abnormal mitochondrial enzymes	Worldwide	3-30 yr from onset
Sialidosis (cherry-red spot myoclonus)	8-15	Facial myoclonus; generalized; no photosensitivity	Visual deficit	Ataxia	Present	No	Present	Painful neuropathy; increased urinary oligosaccharides; neuroaminidase deficit	Common in Italy	10-40 yr from onset
Juvenile GM_2 gangliosidosis	2-6	Generalized in mid-course	Optic atrophy and retinitis pigmentosa	Progressive ataxia	Early	No	Early with decerebrate rigidity	β-*N*-acetylhexosaminidase A deficit	Ashkenazi Jews—U.S., Israel	5-15 yr

PAS*, periodic acid-Schiff positive.

are known to be a result of specific genetic disturbance disorders (see Chapter 42). They are described briefly here. The distinguishing EEG features of the progressive myoclonic epilepsies are summarized in Box 46-3.

Unverricht-Lundborg Progressive Myoclonic Epilepsy

The Unverricht-Lundborg type of progressive myoclonic epilepsy is a disorder of autosomal recessive inheritance found in Finnish and other northern European populations along the Baltic seashore. This "Baltic myoclonus" (EPM1), with an incidence of 1:20,000, manifests typically between ages 6 and 15 years with stimulus-sensitive myoclonus, followed by ataxia, dysarthria, and slowly progressive cognitive decline. Unlike in juvenile myoclonic epilepsy, the EEG background often is slow, with irregular, generalized spike- or polyspike-and-slow-wave complexes maximal over the anterior head regions. A large majority of affected persons have photosensitive epileptiform EEG discharges and myoclonus. A similar, Mediterranean form of this disorder is common in North Africa. Both variants have been traced to the q22.3 band on chromosome 21 and may involve different mutations of the cystatin B gene [Lalioti et al., 1997a, 1997b; Malafosse et al., 1992]. Mechanistically, abnormalities of cystatin B, a cysteine protease inhibitor, hamper its ability to inactivate proteases that leak out of the lysosome.

Lafora Body Disease

Lafora body disease typically manifests between the ages of 6 and 18 years, with nonmyoclonic, generalized tonic-clonic seizures. Asymmetric myoclonic jerks follow, as well as progressive dementia, ataxia, and visual loss, with death in approximately 10 years. At presentation, the EEG may still show a normal background with isolated generalized spike-and-slow-wave discharges, but a slow background with predominance of irregular generalized spike- or polyspike-and-slow-wave discharges evolves rapidly. Pathologically, Lafora bodies are intracellular polyglucosan-containing inclusions in neurons, muscle, liver, and skin glands. The gene mutated in Lafora body disease, *EPM2A*, is located on chromosome 6 and encodes an intracellular tyrosine phosphatase, laforin [Minassian, 1998, 2000].

Other Progressive Myoclonic Epilepsies (see Table 46-4)

The juvenile and young adult forms of neuronal ceroid lipofuscinosis (Vogt-Spielmeyer [or Batten's] disease and Kufs' disease, respectively) also may present during adolescence, with myoclonic seizures (see Chapter 59). Juvenile neuronal ceroid lipofuscinosis, the form common in the United States, commences in late childhood with visual loss, often facial myoclonus, and progressive cognitive decline and seizures. The EEG deteriorates slowly, with abnormal visual-evoked potentials (VEPs) and electroretinograms. The adult form of neuronal ceroid lipofuscinosis can commence in the early teens, heralded by progressive myoclonic epilepsy and dementia, as well as extrapyramidal signs. Visual loss is rare.

The diagnosis of the neuronal ceroid lipofuscinosiss has progressed significantly. Each of the four age-dependent syndromes described here has typical neuropathologic features, with a distinctive pattern of intracellular inclusions. Genotype-phenotype analyses, however, have suggested 8 to 10 discrete entities, and recent genetic analyses suggested that at least some are a result of defects in lysosomal enzymes, including tripeptidylpeptidase I (TTPI), and palmitoyl protein thioesterase. These are encoded by a series of genes, named CLNs, located on several chromosomes: 1 (*CLN1*), 11 (*CLN2*), and so on [Wisniewski et al., 2001].

Among the mitochondrial disorders, myoclonic epilepsy with ragged red fibers [DiMauro and Moraes, 1993] may manifest as myoclonic seizures in children and adolescents. Syndrome phenotype and severity vary greatly, as is typical for this class of disorders, depending on the amount and tissue distribution of mutant mitochondrial DNA (mtDNA) in each affected person. Intention myoclonus, epilepsy, muscle weakness, neurosensory hearing loss, and ataxia are seen in various combinations. A mutation of the lysine transfer DNA (tRNA) gene commonly is the cause [DiMauro and Moraes, 1993]. The EEG features consist of slow background and generalized (or focal) irregular spike-and-wave or polyspike-and-wave discharges.

Other degenerative disorders in which myoclonus is present early or is a prominent feature include juvenile Gaucher's disease and sialidosis type I (see Tables 46-2 and 46-4). The latter, "cherry-red spot myoclonus," typically arises at 8 to 15 years. In addition to myoclonus (often facial), neuropathy, ataxia, and other seizures occur, with vertex spikes seen on the EEG (see Box 46-3, Table 46-4). Diagnosis is based on increased urine oligosaccharides. Although each of these entities is quite rare, the progressive myoclonic epilepsies in the aggregate comprise 1% of childhood/adolescent epilepsies. Therefore, children and adolescents presenting with myoclonic epilepsy that defies rapid diagnosis merit an evaluation for mitochondrial, storage, and other progressive disorders.

Box 46-3 EEG Characteristics in Patients with Progressive Myoclonic Epilepsies

- Generalized multiple spike (polyspike) waves
- Slow background, disorganized sleep
- Photosensitivity (even to single flashes: neuronal ceroid lipofuscinosis)
- Imperfect relation of spikes to myoclonus
- Giant somatosensory evoked potentials
- Focal, especially occipital, epileptiform discharges
- Vertex-positive spikes in sialidosis

EEG, electroencephalogram.

MYOCLONUS OR MYOCLONIC SEIZURES ASSOCIATED WITH OTHER ENTITIES

Classic absence seizures, with the typical 3-per-second spike-and-wave discharges on EEG, may be associated with eyelid or lip myoclonus (see also Chapter 43). The myoclonic features may be rather prominent and have led to debates regarding the boundaries between "true" absence and "myoclonic absence" [Delgado-Escueta et al., 2003; Tassinari and Bureau, 1985]. These controversies notwithstanding, it is generally agreed that the prognosis for absence may be worse

TABLE 46–5

Anticonvulsants Exacerbating Myoclonus and Myoclonic Seizures

DRUG	EPILEPSY SYNDROME
Carbamazepine	Acquired or cryptogenic myoclonic epilepsy
	Lennox-Gastaut syndrome (may evoke myoclonia)
	Angelman's syndrome
	Autosomal dominant cortical myoclonus and epilepsy
	Juvenile myoclonic epilepsy
	Severe myoclonic epilepsy in infancy
	Myoclonic-astatic epilepsy (Doose's syndrome)
Phenytoin	Myoclonic-astatic epilepsy, (Doose's syndrome)
	Lennox-Gastaut syndrome (may evoke myoclonia)
	Progressive myoclonic epilepsies
	Juvenile myoclonic epilepsy
Lamotrigine	Severe myoclonic epilepsy of infancy
	Lennox-Gastaut syndrome (may evoke myoclonia)
	Juvenile myoclonic epilepsy
Vigabatrin	Lennox-Gastaut syndrome (may evoke myoclonia)
	Myoclonic-astatic epilepsy (Doose's syndrome)
	Juvenile myoclonic epilepsy
	Severe myoclonic epilepsy in infancy
Gabapentin	Lennox-Gastaut syndrome
	Partial seizures

Data from Genton P. When antiepileptic drugs aggravate epilepsy. Brain Dev 2000;22:75, and Wheless JW, Sankar R. Treatment strategies for myoclonic seizures and epilepsy syndrome. Epilepsia 2003;44 (Suppl 11): 27.

if the myoclonic features predominate [Panayiotopoulos et al., 1989].

A syndrome of "drop attacks" with onset at ages 1 to 5 years accounts for about 2% of all childhood epilepsies. This entity occurs more commonly in males and likely is of genetic origin [Doose and Baier, 1987]. The seizures have been termed *myoclonic-astatic epilepsy*. The drop attack begins with a major myoclonic jerk and is followed by loss of body tone and a fall. These seizures typically arise in previously normal children, and response to medication and prognosis are variable. They are distinguished from Lennox-Gastaut syndrome by several features: (1) tonic seizures are not seen, except during sleep; (2) drop attacks predominate; (3) previous development is normal or only mildly delayed; and (4) the EEG background may be normal or often includes "absence-like" spike-and-wave discharges (see Table 46-2). By contrast, among the multiple seizure types of Lennox-Gastaut syndrome, "myoclonic" jerks are rarely prominent, and EMG studies suggest that a majority of such seizures likely are atonic. New onset of myoclonic seizures in a child with Lennox-Gastaut syndrome should prompt evaluation for an iatrogenic cause (see later on) (see Chapter 43 for a discussion of Lennox-Gastaut syndrome). The treatment of myoclonic-astatic epilepsy remains challenging, and no controlled studies have been undertaken. Felbamate, benzodiazepines, valproate, lamotrigine, and ethosuximide reportedly have been used (Wallace, 1995; Wheless and Sankar, 2003]. The combination of lamotrigine and topiramate has been successful in anecdotal reports.

Finally, subacute sclerosing panencephalitis is characterized by myoclonic seizures and progressive dementia, most commonly subsequent to measles infection or vaccination [Dyken et al., 1989]. The pathogenesis of this disorder involves persistence of a "defective" measles virus in the CNS [Asher, 1991]. The average latency period from measles infection or vaccination to the onset of symptoms is 8 years, although onset in infancy has been reported [Baram et al., 1994]. Clinical myoclonic seizures, often massive, are accompanied by semiperiodic sharp or slow waves on EEG, which occur every 3 to 4 seconds. The diagnosis depends on the demonstration of high cerebrospinal fluid measles titers [Asher, 1991]. Subacute sclerosing panencephalitis progresses over months or years to a vegetative state or death [Risk and Haddad, 1979]. Current available treatment is unsatisfactory, but antiviral treatment and interferons have been reported to yield stabilization or improvement of the clinical status [Gascon et al., 2003; Yalaz et al., 1992], so that early diagnosis and rapid initiation of treatment before severe neurologic deterioration are warranted.

APPROACH TO TREATMENT OF MYOCLONIC SEIZURES

The rational approach to the treatment of myoclonic seizures involves exclusion of nonepileptic myoclonus and, when feasible, treatment of reversible causes of symptomatic epileptic myoclonus. An additional step in the management of apparent myoclonic jerks with an epileptic EEG is the exclusion of atonic (rapid loss of muscle tone) or tonic (rapid muscle tightening) seizures, because these may respond better to different antiepileptic drugs from those useful for myoclonic seizures. The EEG correlates of myoclonic seizures often are high-amplitude multiple spikes followed by a slow wave, whereas atonic and tonic seizures generally are accompanied by spike/polyspike and "flattening" of the EEG pattern and by fast low-voltage activity with increasing amplitude, respectively.

The development of new myoclonic seizures in an infant or a child with known epilepsy should lead to the consideration of adverse effects of concomitant antiepileptic drugs [Bauer, 1996; Wheless and Sankar, 2003]. Carbamazepine and phenytoin have been reported to cause myoclonic seizures, as have newer anticonvulsants such as vigabatrin [Lortie et al., 1993], gabapentin [Vossler, 1996], lamotrigine, and pregabalin (Table 46-5). Dose reduction or elimination of the offending drug may stop these myoclonic seizures.

The management of specific myoclonic seizures such as infantile spasms and juvenile myoclonic epilepsy is discussed in the relevant sections. For other myoclonic seizures, the current therapeutic mainstays include valproate, benzodiazepines, lamotrigine, zonisamide, and felbamate, and nonpharmacologic approaches may be suitable for specific cases. Further discussion of specific antiepileptic drugs is found also in Chapter 49.

Valproate is very effective for myoclonic seizures, including those associated with other seizure types [Jeavons et al., 1977; Pellock, 1991]. It is the first-line drug for treatment of juvenile myoclonic epilepsy. High-dose valproate monotherapy, with plasma levels higher than 100 mg/dL,

may provide optimal results. Valproate therapy is associated with both dose-dependent and dose-independent side effects [Brodie and Dichter, 1996]. Moreover, 70 fatalities due to valproate-induced hepatotoxicity were reported in the United States between 1978 and 1996 [Bryant et al., 1996]. The highest risk for death (1:500 to 1:600) has been found in patients younger than 2 years of age who were on polytherapy regimens. Accordingly, although many myoclonic seizures that may respond to valproate manifest during the first 2 years of life, the use of valproate at this age should be undertaken with caution, and then only for monotherapy.

Several benzodiazepines including clonazepam have efficacy in the treatment of refractory myoclonic seizures [Hanson and Menkes, 1972], including severe myoclonic-astatic epilepsies. Benzodiazepines may be first-line drugs for treatment of myoclonic seizures (except for infantile spasms) in infants, in whom the use of valproate should be undertaken with caution. Sedation and the development of tolerance often limit the long-term usefulness of benzodiazepines, and high doses (e.g., greater than 3 mg/kg per day of clonazepam) often lead to congestion and accumulation of respiratory tract secretions, at least partially because of impaired swallowing [Wyllie et al., 1986].

Lamotrigine has been extensively used for myoclonic seizures in Europe and has been considered as effective as valproate [Wallace, 1995]. The drug has demonstrated excellent efficacy for myoclonic seizures in the context of Lennox-Gastaut syndrome, often including an improvement in interictal mental status [Besag et al., 1995; Wallace, 1995]. The major side effect of lamotrigine is a rash that can be severe. Therefore, the use of lamotrigine requires careful dose escalation and supervision. (The manufacturer currently does not advocate use of lamotrigine in children; see medication insert.) Dooley and colleagues [1996] have demonstrated that lamotrigine can be reinitiated in children whose rash had required temporary elimination of this medication. Use of zonisamide has been reported in the treatment of juvenile myoclonic epilepsy, as well as the progressive myoclonic epilepsies [Kyllerman et al., 1998]. In mitochondrial disorders with myoclonic seizures, coenzyme Q10 and/or carnitine might be helpful. The use of acetazolamide for myoclonic seizures has been debated [Resor et al., 1990], whereas adrenocorticotropic hormone [Snead et al., 1989] may result in temporary improvement in patients with myoclonic seizures.

Nonpharmacologic treatment approaches may be considered in severe cases: The ketogenic diet (see Chapter 50) may offer a useful alternative for management of refractory myoclonic seizures, with reported efficacy of up to 70% to 80% [Prasad et al., 1996]. Vagus nerve stimulation has been reported to be effective in reducing frequency of generalized tonic-clonic seizures in some myoclonic seizure types. Its efficacy in myoclonic seizures remains unclear [Wheless and Sankar, 2003]. Finally, corpus callosotomy has been advocated for debilitating massive myoclonic seizures that result in severe injury [Pinard et al., 1993; Smith et al., 1999; but see Cendes et al., 1993].

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