CHAPTER

41 Myoclonus and Myoclonic Seizures

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Myoclonus 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 CNS origin of myoclonus may involve the spinal cord, cortex, brainstem, and cerebellum and provides the basis for several of many classifications of myoclonic movements [Serratosa and Delgado-Escueta, 1993]. Myoclonic phenomena include both nonepileptic (e.g., sleep myoclonus, opsoclonus-myoclonus, and narcotic-induced myoclonus) and epileptic myoclonus syndromes, such as juvenile myoclonic epilepsy or infantile spasms. This chapter presents the range of myoclonic events observed in neonates, infants, and children, distinguishes myoclonic seizure syndromes from other conditions, and provides practical guidelines for the diagnosis and management of discrete types of myoclonic seizures.

The electrophysiologic or location-related classifications of myoclonus are complex and fall outside the scope of this chapter [Hallet, 1985; Halliday, 1967; Fahn et al., 1986]. In general, nonepileptic myoclonus is not associated with electroencephalographic (EEG) correlates, whereas epileptic myoclonus is defined electrophysiologically as muscle jerks related temporally to an EEG discharge and accompanied by short-duration bursts (50 to 100 milliseconds) on electromyography [Hallet, 1985]. Epileptic myoclonus may be the major manifestation of an EEG-defined seizure or a minor component of other seizures, such as classical absence epilepsy. In the majority of circumstances the distinction between nonepileptic and epileptic myoclonus in neonates, infants, and children can be based on patient history and on personal observation. The value of videotapes provided by the parents, permitting the clinician to evaluate infrequently occurring or nocturnal myoclonus, cannot be overemphasized. Box 41-1 presents the major categories of nonepileptic myoclonus, based on the age of presentation.

CLASSIFICATION OF MYOCLONIC SEIZURES AND SYNDROMES

As opposed to nonepileptic myoclonus, myoclonic seizures are associated with EEG correlates and comprise one of the most prevalent and challenging seizure categories in infants and children. The diagnosis, classification, and management of myoclonic seizures continue to evolve. The current International League Against Epilepsy classification of pediatric myoclonic seizures in the context of other epilepsy syndromes can be found in Chapter 37. Table 41-1 describes a more practical classification of myoclonic seizures and syndromes 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. A syndrome is characterized, in addition to the seizure and the EEG, by the distinct age of occurrence, progression, associated features, and response to specific medications. For a defined syndrome, information is often available regarding the etiology or genetic predisposition. Recognizing a seizure as belonging to a specific syndrome provides valuable information regarding treatment and prognosis [Dreifuss, 1989].

Myoclonic Seizures in the Neonatal Period

Myoclonic seizures are seen frequently in neonates [Mizrahi and Kellaway, 1987]. The majority of these seizures are symptomatic (i.e., they occur in response to a wide variety of insults inflicted on the developing CNS either before or around the time of birth). Myoclonic seizures in the neonate merit the same evaluation process triggered by other neonatal seizures. Infection (intrauterine or perinatal), stroke, hemorrhage, hypoxia, and metabolic derangements can all be causative (see Table 41-1). A particularly malignant form of neonatal myoclonic seizures has been described in association with nonketotic hyperglycinemia in otherwise healthy newborns [Murphy and Dehkharghani, 1994]. Serum and cerebrospinal fluid (CSF) glycine levels are therefore required.

Specific clinical syndromes of neonatal or early infantile myoclonic epilepsy with distinctive features that permit prognostication have been defined. Ohtahara [1976] and Aicardi [1978] independently described a severe form of myoclonic seizures with a burst-suppression EEG pattern. Some authorities consider these separate entities, with earlier onset and more prominent myoclonic seizures in Aicardi's series. Although the etiology of this syndrome may be heterogenous, the outcome is uniformly poor, including a high mortality rate (up to 60%) during the first year of life. In many patients the seizures evolve to classical infantile spasms.

Evaluation and Treatment. Because the majority of myoclonic seizures in the neonate are symptomatic, a search for a treatable cause is warranted. If electrolytes, glucose, calcium, and magnesium are normal, evaluation should proceed based on knowledge obtained from the history, physical examination, and neurologic examination. Thus blood urea nitrogen, lactate, and ammonia determinations; urine drug screens; serum, CSF, and urine screening for amino acid or organic acid disorders; screening for congenital infections; and neuroimaging should be considered. The EEG may be useful both for delineating specific syndromic categories (e.g., a burst-suppression pattern in a nonmedicated neonate) and for prognosis [Tharp et al., 1989; Scher, 1993]. Treatment should focus on reversing the effects of the underlying seizure disorder, if possible, and on seizure control. Benzodiazepines should be used for myoclonic seizures in the neonate and valproate avoided in this age group, if possible, because of the higher mortality associated with its use [Bryant et al., 1996].

Myoclonic Seizures and Seizure Syndromes in Infants

A number of myoclonic epilepsies appear to be age-specific to this period of brain development (see Table 41-1). The most prevalent, infantile spasms, is discussed in detail, followed by short summaries of other infant myoclonic syndromes, which may be idiopathic or associated with other CNS disorders.

The Syndrome of Infantile Spasms (West Syndrome). Infantile spasms occur 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, or postnatal insult). It is thus useful to consider infantile spasms a highly age-specific epileptic response of the infant brain to innumerable causes. 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]. Infantile spasms are relatively common, occurring in one in 2000 infants [Cowan and Hudson, 1991]. Because the outcome of infantile spasms in terms of cognitive function and intellect is grim (80% to 90% with mental retardation, greater than 50% with epilepsy), the economic and emotional burdens to society associated with this disorder are enormous. Early recognition and diagnosis and new therapies hold the most promise for this severe form of epilepsy.

Infantile spasms were first described by WJ West in 1841. He documented the disorder in his own son [West, 1841]. Other reports of this myoclonic epilepsy in infants with its poor neurodevelopmental outcome followed, under the names West syndrome, Salaam epilepsy, and others. Hypsarrhythmia, the high-voltage, chaotic EEG 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 et al. [1984]. The poor response of infantile spasms to conventional antiepileptics [Aicardi, 1986; Holmes, 1987] led to the discovery of the efficacy of adrenocorticotropic hormone (ACTH) for this type of seizure [Sorel and Dusaucy-Bauloye, 1956]. The hormone ACTH, as well as glucocorticoids (prednisone or hydrocortisone), have since been consistently used as the major therapeutic agents for infantile spasms [Lerman and Kivity, 1982; Hrachovy and Frost, 1989; Baram et al., 1996].

Clinical features and diagnosis. The syndrome of infantile spasms consists of a constellation of myoclonic seizures in an infant whose EEG pattern is that of hypsarrhythmia or its variants [Jeavons, 1985]. The EEG pattern, response to therapy, and poor outcome distinguish infantile spasms from the other myoclonic epilepsies of infancy [Aicardi, 1986; Dreifuss, 1989; Lombroso, 1990]. Clinically, clusters of myoclonic jerks, subtle or massive, occur mainly on awakening. The movements may consist of head, body, and hip flexion, 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 is highly variable, as are associated features, such as an asymmetry of the myoclonus (in the presence of a focal brain lesion) [Kramer et al., 1997], autonomic phenomena (flushing, pallor), or a cry [Jeavons and Bower, 1964]. Arrest of development and loss of developmental milestones often accompany the onset of infantile spasms. In the largest group 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]. A second group of infants are assumed to have (undiagnosed) underlying CNS dysfunctions based on delayed

BOX 41-1
Differential Diagnosis of Nonepileptic Myoclonus By Age of Presentation

Neonates
Common
Sleep myoclonus in premature infants
Sleep myoclonus in full-term infants
Narcotic-induced myoclonus
Drug withdrawal myoclonus
Perinatal asphyxia
Congenital infection, including acquired immunodeficiency syndrome
Nonspecific induced (startle) myoclonus
Rare
Hyperekplexia (stiff baby syndrome) [Ryan, 1992]
Metabolic myoclonus (e.g., uremia)
Polyunsaturated fatty acid disease

Infants
Sleep myoclonus
Opsoclonus-myoclonus with or without neoplasm
CNS infections (e.g., coxsackievirus)
Genetic syndromes (e.g., startle myoclonus in Tay-Sachs disease)
Benign familial (autosomal-dominant) myoclonus

Children
Tics or chorea mimicking myoclonus
Drug induced: Dopa, penicillin and related antibiotics, narcotics, some antihistamines, valproate, carbamazepine, phenytoin, chlorambucil, benzodiazepine withdrawal

Table 41-1 Myoclonic Seizures of Neonates, Infants, and Children

SEIZURE OR SYNDROME	ADDITIONAL INFORMATION AND REFERENCES
Neonates	
Symptomatic myoclonic seizures	CNS insult: infection, hypoxia, stroke, drugs
Metabolic disorders with myoclonic seizures	Nonketotic hyperglycemia [DallaBernadina 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 [Dulac et al., 1984]; other migration disorders [DallaBernadina and Dulac, 1994]
Infants	
Early infantile epileptic encephalopathy	Burst-suppression; may overlap neonatal syndrome
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
Infantile spasms	Clusters of myoclonic jerks [Baram, 1993; Dulac and Plouin, 1994]
Storage disorders	GM_1, GM_2 (Tay-Sachs disease, Sandhoff); Niemann-Pick disease; Krabbe's disease
Mitochondrial disorders	MELAS; early Leigh syndrome
Other metabolic disorders	Phenylketonuria and variants; Menkes' disease; other disorders
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	Myoclonic epilepsy with ragged red fibers (MERRF); myoclonus with MELAS; other phenotypes [DiMauro and Moraes, 1993]
Progressive myoclonic epilepsies	Lafora body [Genton and Roger, 1993]; Baltic and Mediterranean types (Unverricht-Lundborg) [Genton and Roger, 1993]
Degenerative/storage disorders	Juvenile neuronal ceroid lipofuscinosis; Gaucher type III (juvenile neuropathic) [Nishimura et al., 1980]; sialidosis type I (cherry-red spot myoclonus) [Serratosa and Delgado-Escueta, 1993]

development or an abnormal examination. This group has been defined as cryptogenic, and the prevalence of this second group 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 (~10%) have an apparently normal CNS, as defined by normal development, imaging studies, and etiologic evaluation. Dulac has coined the term *idiopathic* for these infants, to emphasize the important concept that given appropriate treatment, these infants have potentially excellent outcomes [Lombroso, 1983; Dulac et al., 1993].

Since 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 individuals with infantile spasms a focal seizure triggers or coincides with a generalized spasm or the spasm may be strongly asymmetric [Donat and Wright, 1991; Carrazana et al., 1993]. In infants with generalized or multifocal brain dysfunction the spasms are typically symmetric. It should be noted, however, that during the stage of CNS maturation present in the infant, generalized myoclonus may be generated by a localized epileptic focus [Wyllie, 1996; Acharya et al., 1997].

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 (Figure 41-1), a disorganized, high-voltage pattern with no normal background. Hypsarrhythmia may thus signify diffuse, abnormal neuronal activity between the seizures, perhaps contributing to the loss of milestones and poor outcome. The brief myoclonic seizures are typically associated with a flattening of the EEG [Hrachovy et al., 1984]. Hypsarrhythmia may not be evident early in the course of infantile spasms, or it may be present only during deep sleep, so that a prolonged EEG, or optimally, a video EEG may be required for diagnosis [Hrachovy and Frost, 1989].

A second line of evaluation in infants with suspected infantile spasms should be to search for treatable etiologies or precipitating factors. Neuroimaging may reveal congenital CNS malformations [Dulac et al., 1984], which accounted for about 20% of infantile spasm cases in recent series [Baram et al., 1996; Kramer et al., 1997]. 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], infection, or tuberous sclerosis, an important instigator of infantile spasms, may be apparent on MRI. A search for metabolic disorders is recommended, since these have accounted for 4% of the patients with infantile spasm [Kramer et al., 1997].

Natural history of infantile spasms. In the majority of infants, hypsarrhythmia disappears over weeks to months, irrespective of treatment, followed by waning of the spasms. Even without treatment, 89% of patients have been reported to be spasm-free by age 5 years [Hrachovy et al., 1991]. Many infants, in whom infantile spasms were associated with diffuse or multifocal neuronal dysfunction, progress to Lennox-Gastaut syndrome. Infantile spasm survivors in whom a focal lesion triggered their spasms often revert to a focal epilepsy clinically and on EEG [Chugani et al., 1990]. The intellectual outcome of the majority of infantile spasm survivors is poor. Therefore the goal of optimal infantile spasm treatment should focus not only on seizure control but also on alteration of cognitive outcome. To date, no single treatment has been documented to provide these therapeutic benefits for the majority of patients with infantile spasms. However, the hormone ACTH, newer antiepileptics, such as vigabatrin, and occasionally surgical resection of a focal lesion, which triggers the spasms, may offer the best results in selected patients.

Treatment of infantile spasms. Whether early treatment of infantile spasms (i.e., rapid resolution of both the spasms and the hypsarrhythmic EEG) improves cognitive outcome is not fully resolved. In a prospective study, Glaze et al. [1988] did not find improved outcome in infants treated within a month of infantile spasm onset, compared with those in whom treatment was delayed. However, other prospective [Lombroso, 1983] and retrospective [Singer et al., 1980; Koo et al., 1992] studies concluded that prompt treatment, presumably via elimination of the hypsarrhythmia, may permit a resumption of development and an improved outcome. Current recommended treatment for infantile spasms based on information gathered over the past decade involves hormonal approaches, vigabatrin, or, in selected infants with focal lesions that trigger the spasms, surgical resection.

ACTH. Based on the results of a prospective, randomized, controlled study [Baram et al., 1996], and older uncontrolled ones [Snead et al., 1989], the recommended therapy for infantile spasms consists of ACTH in depot formulation (e.g., ACTHAR-GEL, Rhone-Poulenc Rorer) at a dose of 150 U/m^2 of body surface per day for 2 weeks, with a rapid taper. For the typical 5-month-old infant, this dose is equivalent to 80 to 90 U/day. Parents are taught the procedure for intramuscular injection, blood pressure is measured twice a week, and parents and care-providers are educated about the high likelihood of ACTH-induced reversible hypertension, voracious appetite, irritability, and acne. Parents are requested to keep seizure calendars, although their validity has been questioned [Hrachovy et al., 1996]. 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 (Box 41-2). It is important that single daily tapering doses are given in the morning to accentuate the normal circadian peak of endogenous ACTH. If seizures recur, their identity should be confirmed, since infantile spasms typically evolve to other seizures that may require different therapy. For recurrent infantile spasms, a second course of ACTH has been successful [Snead, 1993]. This ACTH regimen, delineated in Box 41-2, has been demonstrated to eliminate both the infantile spasms and the hypsarrhythmia in more than 85% of affected infants. Its advantages over other hormonal approaches are its high short-term efficacy and its short duration, which minimize the severe side effects of chronic ACTH/steroid treatment [Lerman and Kivity, 1982; Snead et al., 1989; Heiskala et al., 1996].

Vigabatrin (an inhibitor of GABA degradation) has been extensively used in Europe, and its effectiveness, particularly for children with infantile spasms associated with tuberous sclerosis, has been demonstrated. In a multicenter retrospective study, 50% of all infantile spasms and 27 of 28 infants with tuberous sclerosis–associated spasms responded to vigabatrin [Aicardi, 1996; Chiron et al., 1997]. Unlike ACTH, vigabatrin does not result in an all-or-none response, and increasing doses (up to 150 mg/kg/day) gradually decrease spasm frequency. However, the retrospective European multicenter study revealed a short median response time (3 to 7 days) to high-dose vigabatrin [Aicardi, 1996]. The duration of required treatment with vigabatrin is unclear, but a year or more has been recommended [Aicardi, 1996]. Preliminary studies have suggested that vigabatrin may alter cognitive outcome of individuals with tuberous sclerosis–associated infantile spasms [Chiron et al., 1997].

The role of surgical treatment for infantile spasms has not been fully defined [Chugani et al., 1990; Chugani et al., 1993]. Infantile spasms may be triggered by focal CNS lesions. In these infants, focal seizures often precede the onset of infantile spasms or trigger individual spasms. The natural history of these spasms typically consists of an evolution back to focal seizures and a focal EEG [Kramer et al., 1997]. As with any pediatric epilepsy that is secondary to a focal lesion, surgical resection of the focus may often be curative [Wyllie, 1996]. Updated and useful criteria for consideration of infants with infantile spasms who may benefit from surgical resection have recently been presented [Kramer et al., 1997].

Numerous additional treatments have been used for infantile spasms. Since the spasms disappear spontaneously at a rate of ~1% per week, any prolonged treatment may appear efficacious. Although the scope of this chapter does not permit detailed discussion of specific treatment modalities, high-dose valproate, pyridoxine, immunoglobulins, nitrazepam, and the ketogenic diet have been reported to be effective therapies for infantile spasms. Occasionally, treatment of the precipitating factor of infantile spasms (e.g., tumor or hydrocephalus) eliminates the seizures.

The pathophysiology of infantile spasms. Infantile spasms are associated with diverse genetic, teratogenic, perinatal, and

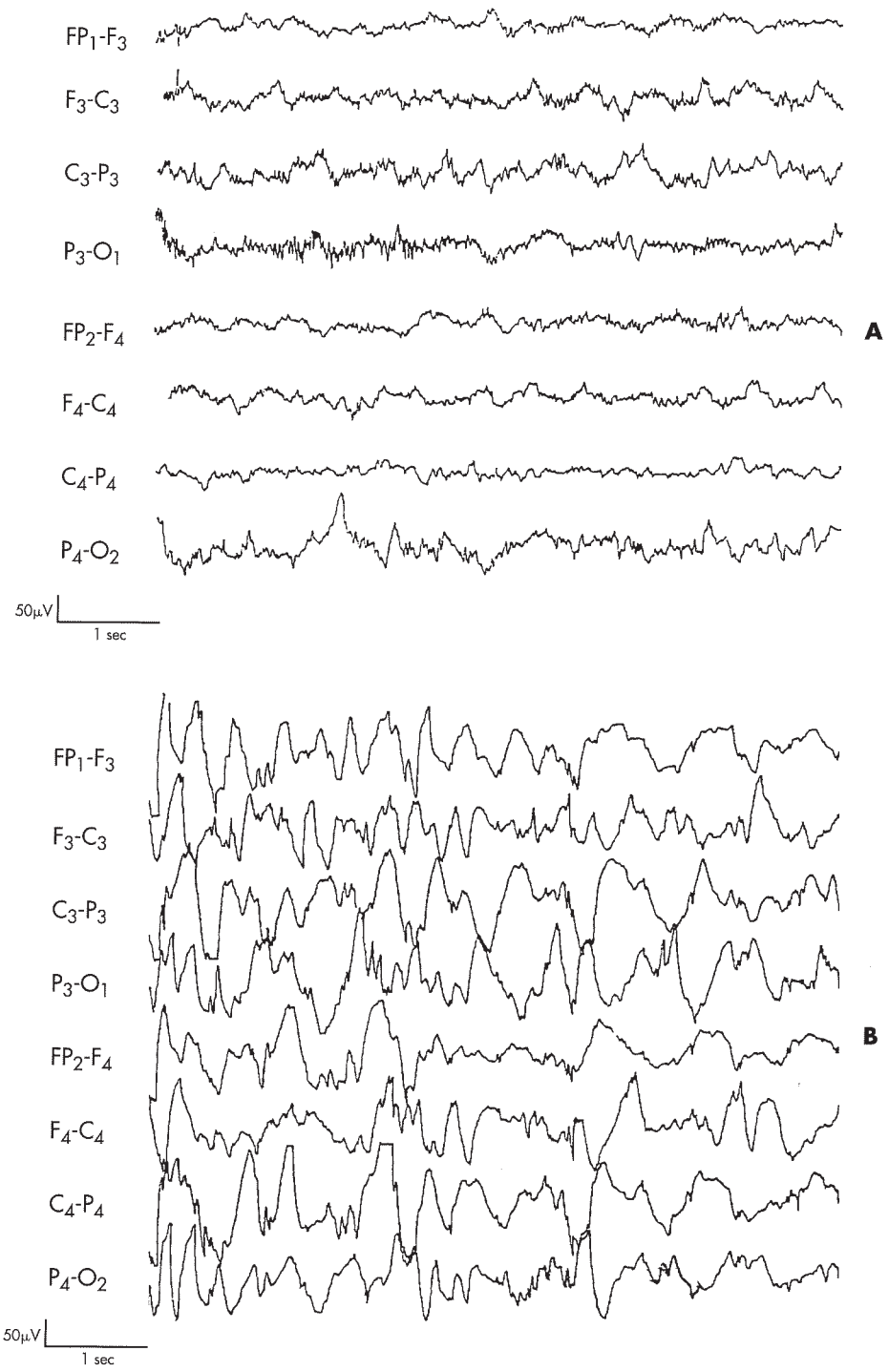

FIGURE 41-1 Samples of a normal infant electroencephalogram (EEG) and of hypsarrhythmia. **A,** Awake EEG from a normally developing 8-month-old boy with a suspected seizure. Coherence of EEG waves is evident. **B,** A hypsarrhythmic EEG from a 10-month-old infant with sequelae of extreme prematurity (adjusted chronologic age 7 months) and clinical infantile spasms. A disorganized pattern of high-voltage slow and sharp waves, without synchrony, dominates. Note the different voltage scale of the two samples. Horizontal bars = 1 second; vertical bars = 50 μV.

postnatally acquired etiologic factors. This fact has suggested that there must be a "final common pathway" for these etiologies, 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 [Vinters et al., 1992; DallaBernadina and Dulac, 1994]. Recent improvements in the resolution of MRI have led to the identification of structural malformations in a relatively larger proportion of individuals with infantile spasms. The frequency of CNS malformations in infantile spasms ranges from 20% to 35% [Baram et al., 1996; Kramer et al., 1997; DallaBernadina and Dulac, 1994]. These malformations consist not only of a diffusely dysplastic brain, such as in pachygyria, but of focal, relatively small regions of cortical dysplasia [Chugani et al., 1990] and even microscopic areas

BOX 41-2
ACTH Treatment Regimen for Infantile Spasms

2-week treatment schedule
ACTH: 75 U/m^2 twice a day, intramuscularly, using ACTHAR-GEL
Monitor: a. Plasma electrolytes and glucose at onset and end of treatment
b. Blood pressure twice a week
Mandate measurement when child not crying. Expect diastolic >80 mmHg in 50%.
If kidneys intact (need assessment in tuberous sclerosis), 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

Modified from Baram et al. [1996], with permission.

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, leading to generalized myoclonic seizures (i.e., infantile spasms). This spread of the epileptic activity happens only during infancy, a developmental period characterized by cortical excitability [Dulac et al., 1997]. Studies in excised dysplastic adult brain [Avoli et al., 1997] and in animal models of cortical dysplasia [Luhmann, 1996] have provided evidence for abnormal and epileptogenic neuronal activity within these regions. However, foci of microdysgenesis have been described in postmortem examination of brains of normal individuals [Lyon and Gastaut, 1985], casting doubt on the etiologic role of these regional heterotopias in infantile spasms. Furthermore, the majority of infants with symptomatic infantile spasms have etiologies that do not include cortical dysplasias.

Any theory concerning the pathogenesis of infantile spasms has to account for (or be consistent with) the unique features of this seizure disorder. For example, how can a single entity have so many etiologies? Why do infantile spasms occur only in infancy, even when a known insult has 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 ACTH?

The unique response of infantile spasms to hormonal treatment by ACTH and prednisone has been used as a key for elucidating the pathophysiology of this disorder [Hrachovy et al., 1994]. A recent prospective, controlled, randomized study suggests that high doses of ACTH eliminate the spasms and the hypsarrhythmia in up to 88% of infants [Baram et al., 1996]. ACTH may accelerate CNS myelination and dendritic formation, and thus may shorten a hypothetical period of vulnerability to infantile spasms [Riikonen, 1983]. However, the hormonal actions of ACTH (as opposed to other potential effects) have been demonstrated to be necessary for efficacy, since analogues of ACTH without hormonal effects do not eliminate infantile spasms [Pentella et al., 1982; Willing and Lagenstein, 1982]. Furthermore, the rapid (median response time of 2 days), all-or-none, and often permanent effects of ACTH on infantile spasms are not consistent with conventional antiepileptic properties [Hrachovy and Frost, 1989; Baram, 1993; Baram et al., 1996]. The established hormonal role of ACTH in human physiology is to function in the neuroendocrine cascade through which the human organism responds to all manner of stressful stimuli. A hypothesis suggesting that infantile spasms occur in the context of an insulted and stressed developing CNS has been formulated [Baram, 1993]. The many etiologies of infantile spasms all lead to activation of the stress response, including the stress neurohormone corticotropin releasing hormone (CRH). Corticotropin releasing hormone has been demonstrated, in infant animal models, to cause severe seizures and death of neurons in areas involved with learning and memory [Baram and Schultz, 1991; Baram and Ribak, 1995]. These effects of CRH 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. ACTH administration is known to inhibit production and release of CRH via a negative feedback mechanism. Therefore the efficacy of ACTH for infantile spasms may depend on its ability to decrease the levels of the seizure-promoting stress-neurohormone CRH [Baram et al., 1992; 1995]. Furthermore, if CRH is responsible for infantile spasms and the worsened cognitive outcome of individuals with infantile spasms, then drugs that block the actions of CRH on its receptors may provide a better therapy for this disorder [Baram, 1993; Baram and Hatalski, 1997].

Other Myoclonic Epilepsy Syndromes in Infancy. Myoclonic seizures are the major manifestation of several other epileptic entities confined to the first 2 years of life. DallaBernadina et al. [1983], Dravet et al. [1985a; 1986b], Ohtahara et al. [1987], and others have defined clinical and EEG criteria to distinguish among these disorders—benign or malignant myoclonic epilepsies of infancy—but significant overlap among these syndromes remains. Thus the prognosis of infants presenting with myoclonic epilepsy other than infantile spasms cannot be predicted with certainty. Specifically, in these rare syndromes a normal neurodevelopmental examination on presentation does not necessarily predict a good outcome. In general a normal interictal EEG is consistent with the benign syndrome described by Dravet et al. [1985a], with good response to valproate and a relatively low likelihood of development of other epilepsies. In contrast, simple clonic seizures that are provoked by fever and evolve to massive or subtle myoclonic events associated with other seizure types are typical of the severe form of infantile myoclonic epilepsy and have a grave prognosis [Dravet et al., 1985b]. Treatment should be tailored to the seizure types of the individual patient.

Symptomatic Myoclonic Epilepsies of Infancy. Numerous genetic disorders of lysosomal and other enzyme dysfunction have their clinical onset during the first 2 years of life and may present with, or be associated with, myoclonic seizures. These seizures are rarely the major symptom of most degenerative disorders. A thorough history and examination should focus on other stigmata of specific entities (e.g., organomegaly, spasticity, or a retinal cherry-red spot). Laboratory evaluation should be guided by the genetic background, associated features, and other aspects of the clinical presentation.

Myoclonic Epilepsies of Children and Adolescents

Juvenile Myoclonic Epilepsy. The onset of juvenile myoclonic epilepsy is typically around puberty, ranging from 12 to 18 years of age. The cardinal feature of this disorder is repetitive irregular or semi-rhythmic myoclonic jerks involving shoulders and arms, sometimes with dropping of objects. Myoclonia occurs on awakening and may be mistaken for nervousness. Generalized tonic-clonic seizures, which can occur at any time of day or night, are found in 90% of patients and may precede the myoclonus. The diagnosis is often delayed and is confirmed by the pathognomonic EEG pattern. 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) may also clarify the nature of nervousness on awakening. The EEG background is usually normal with no evidence of slowing or disorganization. The characteristic abnormality consists of bursts of bifrontal or generalized, bilaterally synchronous, spike/polyspike-and-wave activity [Janz, 1989]. Fast spike-and-wave activity of 4 to 6 Hz is also frequently observed [Dreifuss, 1989]. Absence seizures (which occur in 30% of patients) are accompanied by typical spike-and-wave activity, but the frequency

is usually faster than 3 Hz [Asconape and Penry, 1984]. Focal polyspike-and-wave activity accompanied by focal jerks has also 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 are accompanied with an EEG burst of 10- to 16-Hz polyspikes, followed by high-amplitude slowing at a frequency of 2 to 5 Hz [Janz, 1989].

Treatment of juvenile myoclonic epilepsy should focus on both the avoidance of the precipitating factors, particularly sleep deprivation and alcohol intake, as well as treatment with valproate. In adolescent females, hormonal changes around menstruation are a significant precipitant of the seizures, requiring special care in obtaining adequate sleep or an increased medication dose. The use of 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 and clonazepam provide alternative therapies. Unlike most idiopathic seizures of the developing human, juvenile myoclonic epilepsy rarely remits, so that affected individuals 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]. Juvenile myoclonic epilepsy is clearly a familial disorder, although the precise gene(s) responsible have not been isolated [Serratosa and Delgado-Escueta, 1993; Minassian et al., 1995].

Progressive Myoclonic Epilepsies. Progressive myoclonic epilepsies are rare genetic entities, with an autosomal-recessive mode of inheritance, congregating in discrete populations. For example, populations with high prevalence of the Unverricht-Lundborg type of progressive myoclonic epilepsies are found in northern Europe, along the Baltic sea shore. 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 [Malafosse et al., 1992; Lalioti et al., 1997a; b]. For Baltic-Mediterranean progressive myoclonic epilepsies, the onset is in the second decade. The myoclonic jerks can typically be provoked and worsen as the disease progresses, with development of ataxia, tremor, and loss of ambulation.

Lafora body disease, also an autosomal-recessive disorder, typically presents with nonmyoclonic seizures. Myoclonic events are commonly of small amplitude but are associated with progressive dementia, visual loss, and debilitation, with death after about 10 years. Linkage of this disorder to the short arm of chromosome 6 has been reported [Serratosa et al., 1995]. The juvenile form of neuronal ceroid lipofuscinosis (Batten disease) may also present with myoclonic seizures associated with visual loss. Other degenerative disorders in which myoclonus is present early or is a prominent feature include sialidosis type I and the myoclonic epilepsy–ragged-red fibers (MERRF) phenotype of mitochondrial disorders [DiMauro and Moraes, 1993]. Thus children and adolescents presenting with myoclonic epilepsy that does not conform to juvenile myoclonic epilepsy should be evaluated for mitochondrial or other progressive disorders.

Myoclonus or Myoclonic Seizures with Other Entities. Classic absence seizures, with the typical 3-per-second spike-wave discharges on EEG, may be associated with eyelid or lip myoclonus (also see Chapter 38). The myoclonic features may be rather prominent and have led to debates regarding the boundaries between true absence and myoclonic absence [Tassinari and Bureau, 1985]. These controversies notwithstanding, it is generally agreed that the prognosis for absence seizures may be worse if the myoclonic features predominate [Panayiotopoulos et al., 1989].

A syndrome of drop attacks with onset at the age of 1 to 5 years accounts for about 2% of all childhood epilepsies. This entity occurs more commonly in males and is probably of genetic origin [Doose and Baier, 1987]. The seizures have been termed *myoclonic-astatic* and consist of a major myoclonic jerk followed by loss of body tone and a fall. These seizures typically arise in previously normal children, and their responses to medication and their prognoses are variable.

The multiple seizure types of Lennox-Gastaut syndrome often include myoclonic jerks. However, EMG studies suggest that the majority of such seizures are likely atonic, and Gastaut did not consider myoclonic seizures a significant component of the syndrome [Gastaut, 1985]. See Chapter 38 for a discussion of Lennox-Gastaut syndrome.

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 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 CSF 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 intraventricular interferon has been reported to yield stabilization or improvement of the clinical status [Yalaz et al., 1992]; thus early diagnosis and rapid initiation of treatment before severe neurologic deterioration are warranted.

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 important 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, since these may respond better to different antiepileptics than myoclonic seizures. The EEG correlates of myoclonic seizures are often high-amplitude multiple spikes followed by a slow wave, whereas atonic and tonic seizures are generally accompanied by spike/polyspike waves and a flattening of the EEG and by fast low-voltage activity with increasing amplitude, respectively.

The development of new myoclonic seizures in an infant or child with known epilepsy should lead to the consideration of adverse effects of concomitant antiepileptics [Bauer, 1996]. Carbamazepine and phenytoin have been reported to cause myoclonic seizures, as have newer antiepileptics, such as vigabatrin [Lortie et al., 1993; Wallace, 1995]. 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, has been discussed in the relevant sections. Even when a clear-cut myoclonic epilepsy syndrome has been established, such as with juvenile myoclonic epilepsy, life-style management, such as ample sleep and avoidance of alcohol, significantly influences the likelihood of successful drug management. For other myoclonic seizures the current therapeutic mainstays include valproate, benzodiazepines, and lamotrigine. Further discussion of specific antiepileptics is found in Chapter 44.

Valproate is exceptionally effective for myoclonic seizures, including patients in whom these seizures are associated with other seizure types [Jeavons et al., 1977; Pellock, 1991]. High-dose valproate monotherapy, with plasma levels higher than 100 μg/ml, may provide optimal results. Valproate therapy is associated with both dose-dependent and dose-independent side effects [Brodie and Dichter, 1996]. Moreover, 70 fatalities resulting from valproate-induced hepatotoxicity have been reported in the United States between 1978 and 1996 [Bryant et al., 1996]. The highest risk for death (1:500 to 600) has been found in patients under the age of 2 who were on polytherapy regimens. Thus although many myoclonic seizures that may respond to valproate present during the first 2 years of life, the use of valproate at this age should be undertaken with caution and as monotherapy.

Among the benzodiazepines, clonazepam has demonstrated efficacy in the treatment of refractory myoclonic seizures [Hanson and Menkes, 1972; Panayiotopoulos et al., 1994]. Clonazepam has

been advocated particularly for the severe myoclonic-astatic epilepsies but has been useful in a variety of myoclonic seizures. It is the first-line drug 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 clonazepam. In addition, clonazepam at high doses (typically more than 0.3 mg/kg/day) often leads 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 equally effective to valproate [Wallace, 1995]. The drug has demonstrated excellent efficacy for myoclonic seizures in the context of Lennox-Gastaut syndrome, often including an improvement of interictal mental status [Besag et al., 1995; Wallace, 1995]. The major side effect of lamotrigine is a rash, which can be severe and which occurs more commonly in patients taking valproate. Therefore use of lamotrigine requires exceptionally careful and slow-dose escalation and supervision. Dooley et al. [1996] have demonstrated that lamotrigine can be re-initiated in a child whose rash had required temporary elimination of this medication.

In addition to the established therapeutic approaches described, acetazolamide and ACTH have resulted in temporary improvements of myoclonic seizures [Snead et al., 1989]. Likewise, the ketogenic diet (see Chapter 45) may offer a useful alternative for refractory myoclonic seizures, with reported efficacy of up to 70% to 80% [Prasad et al., 1996].

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