The myoclonic epilepsies of childhood

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A RELATIVELY important proportion of the epilepsies that occur during the first 5 to 8 years of life include frequently repeated seizures characterized clinically by brief muscular contraction or loss of tone, often resulting in multiple daily falls. Many such epilepsies are associated with variable degrees of neuromental dysfunction and show little sensitivity to antiepileptic drugs.

The electroencephalograhic (EEG) concomitants of such seizure disorders include interictal bilateral, but not necessarily symmetrical, spike-wave complexes, either slow (< 2.5 Hz) or fast (≥ 2.5 Hz), variably associated with other paroxysmal or nonparoxysmal abnormalities such as slow background rhythm, or focal or multifocal spikes or sharp waves. Some investigators term all such cases myoclonic epilepsy,[1] regardless of the type of EEG paroxysms and of the exact electroclinical type of seizures. Currently, most writers[2–6] prefer to subdivide this large group into at least two broad subgroups. The first subgroup features predominantly tonic and atonic seizures[7] usually associated with interictal slow spike-waves,[8–10] and corresponds roughly to the Lennox-Gastaut syndrome.[5,6,9,11,12] The second subgroup comprises primarily true myoclonic seizures,[13–16] most commonly featuring ictal or interictal fast spike-wave complexes on the EEG, and corresponds to the myoclonic epilepsies proper. Distinctions between the two subgroups, however, are not sharply defined, since several types of attacks, of both myoclonic and atonic-tonic nature, may occur in the same patient, and the EEG may include both fast and slow spike-wave activity, resulting in a number of intermediate and unclassifiable cases.[2]

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The nosological confusion is increased by the fact that some investigators do not use clinical and EEG criteria for subdivision of the epilepsies with tonic-atonic and myoclonic seizures, but rather utilize an etiologic criterion.[15] Cases unassociated with demonstrable brain damage but with frequent genetic antecedents of epilepsy are thus termed myoclonic-astatic epilepsy, while those demonstrating lesional damage are termed Lennox-Gastaut syndrome. We think that descriptive terms such as myoclonic or atonic should not be used to imply a specific mechanism or cause.

The present study deals only with the epilepsies characterized predominantly or exclusively by true myoclonic or myoclonic-atonic seizures, i.e., seizures marked clinically by very brief shock-like muscle contractions, and electrically by fast spike-wave or polyspike-wave complexes.[2,7] Other types of brief attacks, including tonic or atonic seizures associated with fast recruiting rhythms or slow spike-wave bursts on the EEG, might be associated with myoclonic attacks but could not be the dominant ictal manifestation.

More prolonged seizures, especially generalized tonic-clonic, unilateral clonic, or partial seizures were not uncommon. Forty-seven such patients were studied, and the results were compared with those of previously published series.[3,4,13–21]

PATIENTS AND METHODS

The 47 cases were collected during the period 1979 to 1985. Cases listed under the diagnostic category of myoclonic epilepsy were reviewed and incomplete records were discarded. Because myoclonic seizures may be difficult or impossible to distinguish by history from other brief epileptic attacks such as tonic seizures[2,7] or spasms,[22] the study included only those patients in

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whom electroclinical myoclonic attacks were associated with fast polyspike-waves. The occasional presence of other types of fits or the presence of some slow spike-wave activity was not a cause of exclusion. The exact proportion of myoclonic seizures necessary for inclusion in the study, the frequency of other types of attacks or the amount of slow spike-wave activity that would result in exclusion, were not quantified; clinical impressions had to be relied upon in some cases, thus resulting in unavoidable bias. True myoclonic seizures had to represent one major type of seizure and to be clearly predominant over other brief minor motor manifestations for the seizure disorder to be classified as myoclonic. The frequency of other seizure types such as generalized tonic-clonic seizures (GTCS) and unilateral tonic-clonic or clonic seizures was not considered critical in this regard, as such seizures are commonly seen in many types of childhood epilepsy. Patients with myoclonic jerks occurring only on intermittent photic stimulation were not included. Patients with evidence of progressive neurologic conditions [2,13] were excluded. The presence of fixed neurologic signs or of mental retardation antedating the onset of seizures was not a criterion for exclusion. The mean duration of follow-up was 65 months (range, 15 months to 20 years). At end of follow-up, patients were classified as intellectually normal, mildly or moderately retarded, or severely retarded on the basis of WISC or Brunet-Lézine tests or of clinical evaluation. Those patients who had had no seizures within one year of the end of follow-up were considered seizure-free.

RESULTS

The series was analyzed globally, then subdivided into three subgroups. Seven patients had severe developmental delay from birth in association with nonprogressive neurologic signs and were classified as cases of myoclonic epilepsy with fixed encephalopathy. The remaining 40 patients were separated into those for whom myoclonic seizures were the only type of brief seizures (Group I, including 19 patients), and those who had multiple types of seizures in addition to myoclonic attacks (Group II, including 21 patients). Group II was in turn subdivided into group IIa, consisting of 11 patients for whom onset was with tonic-clonic seizures, usually febrile, with only secondary occurrence of myoclonic seizures, often in association with other types of fits, and group IIb, consisting of 10 children with multiple types of brief attacks, often including tonic seizures and atypical absences, in addition to true myoclonic seizures. Generalized or unilateral tonic-clonic seizures of short duration occurred in all subgroups and were not a criterion for classification.

The seven patients with fixed encephalopathy were infants with anoxic-ischemic brain damage of probably prenatal and perinatal origin.[13] They had bilateral pyramidal tract signs and, usually, dystonia or choreoathetosis. Microcephaly of a moderate grade was common. These seven cases were not further analyzed. The 40 cases of myoclonic epilepsy without encephalopathy are presented below.

TABLE 1
CLINICAL AND ETIOLOGIC DATA IN STUDY GROUP (N = 40)

Finding	Number with finding	Percent with finding
Sex		
M	26	65
F	14	35
Abnormal gestation and/or perinatal period	4	10
Abnormal early development	11	27.5
Positive family history of convulsions or epilepsy	10	25
Occurrence of other types of seizure before myoclonic seizures	21	52.5
Occurrence of falls	21	52.5
Associated seizures	29	72.5
Neurologic signs	4	10
Abnormal CT scan	2	8*
Seizure-free at end of follow-up	14	35
Mental retardation	19	47.5
Abnormal behavior/learning/language difficulties	29	72.5
Mean age of onset of myoclonic seizures	29 mo	
Mean age at first seizure	24 mo	

* CT was performed in 24 patients

MYOCLONIC EPILEPSY—40 PATIENTS

The main clinical and etiologic data for the group as a whole are shown in *Table 1*.

The mean age at onset of epilepsy was 24 months (range, 4 months to 4 years); that of the myoclonic seizures was 29 months (range, 7 months to 4 years). Early development had been unremarkable, although mild delay in passing milestones was not unusual. Myoclonic seizures were frequent, occurring at least

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several times daily in 35 cases, although these myoclonic attacks were quite irregular in occurrence and could disappear without apparent cause for variable periods. Five patients had episodes of myoclonic status. The EEG characteristics included short-duration irregular bursts of arrhythmic polyspike-wave or fast spike-wave complexes in 42 patients. In 13 cases, more regular 3-Hz spike waves were present, in association with arrhythmic complexes. Four patients had slow spike-wave complexes together with fast ones. Other abnormalities included a slow background rhythm, at least in some tracings, in 17 cases (42.5%) and focal or multifocal spikes or sharp waves in seven cases. Photic stimulation was effective in 16 cases and hyperventilation in 14. The outcome for the group was relatively unfavorable with persistence of seizures at end of follow-up in 65% of the cases and with mental retardation, usually of mild to moderate degree, in 52.5% of the patients. The high proportion of behavioral disturbances (especially the hyperkinetic syndrome), language problems and learning difficulties was remarkable.

TABLE 2
CLINICAL AND ETIOLOGIC DATA IN GROUP I PATIENTS*

Finding	Number with finding	Percent with finding
Sex		
M	15	79
F	4	21
Abnormal gestation and/or perinatal period	2	10.5
Abnormal early development	4	21
Positive family history of convulsions or epilepsy	7	37
Occurrence of other types of seizure before myoclonic seizures	4	21
Occurrence of falls	8	42
Associated seizures	8	42
Neurologic signs	2	10.5
Abnormal CT scan	2	10.5
Seizure-free at end of follow-up	12	63
Mental retardation	4	21
Abnormal behavior learning/language difficulties	10	53
Age at onset of myoclonic seizure	32.3 mo	
Age at first seizure	43 mo	

* See text for definition

Analysis of Group I Cases

In 19 patients, true myoclonic seizures were the exclusive type of brief motor attacks. The characteristics of this group appear in *Table 2.*

Thirteen of these children also had occasional brief lapses of consciousness, not associated with clinically appreciable myoclonic jerks, which occurred concomitantly with bursts of irregular polyspike-wave complexes indistinguishable from those that occurred in association with myoclonic jerking. These lapses were not considered as a separate type of seizure, but merely as a mild variant of myoclonic attacks. Seven patients had infrequent tonic-clonic or clonic seizures in addition to myoclonic attacks. Tonic seizures or partial fits were not observed. Most patients had several types of myoclonic attacks, with a preponderance of bilateral symmetrical jerks that provoked repeated falls in eight cases. Myoclonic seizures were likely to supervene upon awakening and in 15 cases were very frequently repeated. Only one patient had an episode of myoclonic status. Four children had had other types of seizure before the occurrence of myoclonic jerks. In one case, these were febrile convulsions, and in three cases, isolated or infrequent afebrile generalized tonic-clonic seizures. Background EEG rhythm was normal in 72% of patients, and all had fast spike-wave complexes. Paroxysmal bursts were induced by photic stimulation in five and facilitated by hyperventilation in six patients. All children had normally passed milestones before the onset of seizures, and seven of nineteen (37%) had a positive family history of convulsions or epilepsy.

The outcome was relatively favorable in this group with only four patients moderately retarded at end of follow-up. However, 12 of 19 children (63%) had behavioral disturbances or language or learning difficulties. Sixty-three percent of patients were seizure-free at end of follow-up.

Analysis of Group II Cases

The 21 patients in this group were almost equally distributed between Group IIa (11 cases) and IIB (10 cases). The main features of these patients appear in *Table 3.*

Group IIa patients had a stereotyped course with onset of unilateral or generalized, tonic-clonic or clonic seizures, starting during the first year—and often the first semester—of life. These seizures were usually precipitated by minor infectious episodes with mild fever (< 38.5o) and were frequently repeated. In most

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TABLE 3
CLINICAL AND ETIOLOGIC DATA IN GROUP II PATIENTS*

Finding	Group IIa		Group IIb	
	Number with finding	Percent with finding	Number with finding	Percent with finding
Sex				
M	4	36	7	70
F	7	64	3	30
Abnormal gestation and/or perinatal period	1	9	1	10
Abnormal early development	4†	36	3	30
Positive family history of convulsions or epilepsy	1	9	2	20
Occurrence of other types of seizure before myoclonic seizures	11	100	6	60
Occurrence of falls	6	55	7	70
Associated seizures	11‡	100	10	100
Neurologic signs	2	18	0	0
Abnormal CT scan	0	0	0	0
Seizure-free at end of follow-up	0	0	2	20
Mental retardation	10§	91	5	50
Abnormal behavior/learning and language difficulties	10	91	9	90
Mean age at first seizure	6.9 mos		43 mos	
Mean age at onset of myoclonic seizures	16.2 mos		32.3 mos	

* See text for definition.
† Delay in passing motor milestones.
‡ Several seizure types in all patients.
§ 1 patient not evaluated.

patients, they were of long duration, even including episodes of status. Myoclonic seizures were never the first ictal manifestation but appeared mainly after the first year of life. They were usually associated with atypical absences, generalized or unilateral clonic seizures and partial seizures. Tonic seizures were observed in a few cases. EEG abnormalities included focal or multifocal paroxysmal abnormalities in 80% of patients. None of these chidren had slow spike-wave complexes. Intermittent photic stimulation was effective in five cases, and one child self-induced myoclonic attacks and atypical absences by fixating contrasted patterns. The outcome was poor, with mild to moderate mental retardation in virtually all cases and persistence of the seizures at end of follow-up in all patients.

Group IIb patients constituted a heterogeneous subset. Five patients of this subgroup had tonic seizures in addition to prominent myoclonic attacks, and could be classified as intermediate between myoclonic epilepsies and the Lennox-Gastaut syndrome, or as a "myoclonic variant" of the Lennox-Gastaut syndrome. However, interictal slow spike-wave complexes were present in the EEG of only two of these children whereas all had irregular bursts of fast spike-waves. In five patients, focal sharp or slow waves were present in one or several tracings. Hyperventilation was activating in six patients and photic stimulation in four. The epilepsy in this group was persistent in 80%, and mental retardation was apparent in half the patients. Ninety percent of them had behavioral or learning difficulties.

DISCUSSION

The present series confirms the heterogeneity of the myoclonic epilepsies, even when cases with predominantly tonic and atonic seizures (Lennox-Gastaut syndrome) are excluded. The distinction between the myoclonic epilepsies proper and the Lennox-Gastaut syndrome is far from being uniformly clear, as is illustrated by children in subgroup IIb. These patients had several types of brief tonic, myoclonic and atonic attacks, and their classification depended on the respective frequencies of the various ictal manifestations,

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a highly subjective evaluation which is, in addition, subject to variations with the course of the disease. The occurrence of true myoclonic seizures is well known in the Lennox-Gastaut syndrome,[5,6,9] and these may be especially prominent in some cases that have been identified as "myoclonic variants" of the syndrome.[4,13] It is interesting to note that some of the Group IIb children had tonic seizures without interictal slow spike-wave complexes, while others with purely myoclonic attacks had both interictal and even ictal slow spike-waves. Several authors who separate the myoclonic epilepsies from the Lennox-Gastaut syndrome have also found that tonic seizures can occur in cases of "true" myoclonic epilepsy,[17,18] and the presence of fast spike-wave activity in the Lennox-Gastaut syndrome is well recognized.[2,5,6,9] It is thus likely that the "true" myoclonic epilepsies and the Lennox-Gastaut syndrome represent the two extremities of a spectrum of epileptic conditions with many intermediate forms.[2] Differentiating the two syndromes, however, is not of purely academic interest. The outcome of the myoclonic epilepsies is clearly more favorable than that of the Lennox-Gastaut syndrome. The proportion of mental retardation in 55 cases of cryptogenic myoclonic epilepsy was 63%, and only 11% of the patients were severely retarded, whereas in 80 patients with the Lennox-Gastaut syndrome, the corresponding proportions were respectively 91% and 55%.[16]

The subgroups we have delineated on simple clinical criteria do not necessarily correspond to those proposed in previous studies using different criteria.[4,13,14] However, group IIa of the present series is very similar or identical in its clinical manifestations and poor prognosis to the syndrome of severe myoclonic epilepsy as defined by Dravet et al[19] and by Dalla Bernardina et al.[20] Of the 42 patients reported by Dravet et al, four died; all survivors were mentally retarded and had behavioral disturbances. The term myoclonic epilepsy, however, may not be the most appropriate for such cases, as the myoclonic seizures are but one of the ictal manifestations, not necessarily the most conspicuous. In fact, the prolonged clonic seizures often overshadow the relatively mild myoclonic attacks. Moreover, cases with similar onset and outcome may not include myoclonic attacks, or these may represent only a minor and transient feature. The term of polymorphic epilepsy of infancy following febrile convulsions, as proposed by Cavazzuti, is perhaps more appropriate although the initial seizures are not always associated with fever.[20]

Group I is relatively homogeneous and is similar in many respects to the "cryptogenic myoclonic epilepsy" previously studied by one of us.[14,16] However, these previous studies included cases with several types of brief seizures. Such cases were excluded from the present series in which only true myoclonic seizures associated with polyspike-wave or fast spike-wave complexes, brief lapses of consciousness with the same EEG concomitants as the jerks, and occasional GTCS were accepted. The group thus defined has common features with the "benign myoclonic epilepsy of infancy" described by the Marseilles school.[21] Certainly, the outcome for Group I cases is more favorable than for any other group, a fact which seems to justify separating such cases from other patients with myoclonic epilepsy. However, the outcome of our children was not uniformly favorable, as a few had mild mental retardation and many had learning, language and behavioral difficulties that amounted to a significant handicap in social life and schooling. Some patients of this group responded quite promptly to antiepileptic drugs such as ethosuximide or sodium valproate, a fact we had recognized in a previous series.[14] In these children, the disorder seemed to run a more favorable course than it did in the rest of the group. However, we were not able to recognize factors reliably predictive of a favorable outcome in these children, especially with regard to behavioral and learning difficulties.

Group IIB, on the other hand, is clearly heterogeneous and probably represents a mixture of different epileptic syndromes. In addition to cases that may correspond to the myoclonic variant of the Lennox-Gastaut syndrome[4,13] (although with atypical EEG characteristics), this subgroup includes transitional and unclassifiable cases. Dravet et al[4] also were unable to classify 34 of their 142 cases of myoclonic epilepsy. Such cases probably correspond to some of the cases of "cryptogenic myoclonic epilepsy"[14] and of "myoclonic-astatic epilepsy"[18] described by other investigators.

The etiology of the myoclonic epilepsies is multifactorial. Brain damage of a progressive or of a fixed nature may be the major factor, as in the seven patients with fixed encephalopathy presented here. The outlook for such patients is poor. In addition, myoclonic status may occur, especially during sleep.[23] In all series of myoclonic epilepsy, however, genetic factors play a major etiologic role. The figure of 25% in the present series is comparable to those of 26% to 38% quoted in the literature.[2,4] The highest proportion (37%) was found among Group I patients, which is in conformity with the probable absence of brain damage in most of these patients and consequent better prognosis. However,

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Dravet et al[19] found familial antecedents of epilepsy in 26% of their patients with "severe myoclonic epilepsy."

CONCLUSION

More definitive classification of the myoclonic epilepsies of infancy and early childhood must await elucidation of their causes and mechanisms. Meanwhile, a relatively simple classification, such as is used in this article, has practical usefulness for prognosis and treatment. The occurrence of several types of seizures, such as prolonged and early clonic or tonic-clonic seizures, and of frequent tonic seizures all herald an unfavorable outcome.

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