

<h2>Myoclonic Astatic Epilepsy of Early Childhood</h2> <p><i>Hermann DOOSE</i> Epilepsy Centre 2313 Raisdorf, Germany</p>	ARTICLE SECTIONS Summary Introduction General Seizure Symptomatology EEG findings Course and prognosis Differential diagnosis Treatment Conclusion
---	--

Myoclonic Astatic Epilepsy of Early Childhood

Hermann DOOSE

Summary

Myoclonic astatic epilepsy belongs to the epilepsias with primarily generalized seizures and thus stands in one line with absence-epilepsias, juvenile myoclonic epilepsy, as well as the infantile and juvenile idiopathic epilepsy with generalized tonic clonic seizures. Like these types of epilepsy, myoclonic astatic epilepsy is polygenically determined with little nongenetic variability. The disease is characterized by the following criteria: genetic predisposition (high incidence of seizures and/or genetic EEG patterns in relatives); mostly normal development and no neurological deficits before onset: primarily generalized myoclonic, astatic or myoclonic astatic seizures, short absences and mostly generalized tonic clonic seizures: no tonic seizures or tonic drop attacks during daytime (except for some rare cases with a most unfavourable course): generalized EEG patterns (spikes and waves, photosensitivity, 4-7 c/s rhythms), no multifocal EEG-abnormalities (but often pseudofoci). There is an overlap with other syndromes, such as benign and severe myoclonic epilepsy in infants (Dravet et al. 1985a, b), and myoclonic epilepsy of infancy and early childhood (Aicardi 1986). Differential diagnosis has to regard the Lennox-Gastaut syndrome in the stricter sense, and the atypical benign partial epilepsy or pseudo-Lennox syndrome. The course of this epileptic syndrome is variable. Spontaneous remission as well as a malignant course with dementia can be seen.



TOP

Introduction

There is hardly another field in pediatric epileptology presenting such terminological uncertainty and confusion as is to be found in the domain of epileptic syndromes with generalized minor seizures of early childhood. Though in adolescents and adults, the distinction between primarily and secondarily generalized seizures is regarded as a matter of course, this differentiation is not as clearly defined in generalized minor seizures of early childhood. The reason for that probably lies in the fact that the clinical and bioelectrical reaction patterns of the immature brain are relatively uniform: the myoclonic flexor spasms, the astatic fit, the generalized tonic clonic seizure (GTCS) as well as the tonic seizure can occur as a symptom of pathophysiologically different mechanisms: they can be primarily or secondarily generalized in origin.

Those deliberations precipitated our own researches in 1964 (Doose, 1964a, b). At that time, we separated infantile spasms from epilepsias with primarily generalized myoclonic seizures which are not accompanied by hypersarrhythmia but by generalized irregular spikes and waves. In contrast to infantile spasms, it was impossible to prove a secondary generalization for this kind of epilepsy. Epilepsias with this seizure type have been designated as myoclonic petit mal of

more often affected than in cases with minor seizures only. This difference is mainly due to early onset GTCS. This result is in agreement with the observation of Dravet et al. (1985a, b) in the benign and severe myoclonic epilepsy.



TOP

Seizure symptomatology

Myoclonic seizures consist of usually symmetrical jerking of the arms and shoulders, often with simultaneous nodding of the head. Some myoclonic jerks are violent, with arms being flung upwards, some are so mild that they are palpable rather than visible. Accompanying vocalization is rare. Violent generalized myoclonic jerks can lead to abrupt falling to the ground (drop attacks by myoclonias). Besides these symmetrical myoclonic jerks, irregular myoclonic twitching of the facial muscles, especially of the oral and ocular region may occur in severe cases. Rarely myoclonic attacks are precipitated by fright or light stimuli.

Astatic seizures. Astatic seizures with abrupt loss of muscle tonus only rarely occur as the sole symptom of the disorder. Without any precursory signs, the patient suddenly falls vertically to the ground. The direction of the fall depends on the position of the centre of gravity of the body when the seizure occurs. Mild astatic attacks may appear as brief head nodding and as a slight knee-bending of the erect child. These atonic astatic seizures, caused by the sudden breakdown of muscle tonus, have to be distinguished from tonic astatic seizures due to sudden generalized tonic spasms of axial muscles (Egli et al., 1985). In MAE, these tonic astatic seizures occur only in extremely unfavourable cases in the late course of the disorder.

Myoclonic astatic seizures. More often than myoclonic and astatic seizures, a combination can be observed. The more or less pronounced loss of muscle tonus is preceded by symmetrical myoclonias of the arms or irregular twitching of the face (postmyoclonic amyotonia, Gastaut & Regis, 1961).

Absences. In more than half of the cases myoclonic and astatic symptoms are accompanied by a short loss of consciousness: absences with myoclonic jerks and irregular myoclonias of the face and/or total or partial loss of postural tone.

Status of minor seizures. A status of myoclonic astatic seizures and accompanying absences is especially characteristic for MAE (36 per cent of our cases). The condition is characterized by apathy or even stupor. Careful observation reveals irregular twitching of the facial muscles and the extremities. Astatic seizures and head nodding can appear serially. The facial expression is slack, saliva drools, and speech is slurred or disappears completely. The status may last for hours or even days. Mostly there is a marked dependence on the sleeping-waking cycle, as short status regularly occur after awakening in the morning or in the afternoon. Status of pure myoclonic Fits seems to be extremely rare.

Febrile and afebrile GTCS. In two-thirds of our cases epilepsy started with febrile or afebrile GTCS. Initially, the GTCS or clonic seizures occur almost exclusively during daytime, and only in the later course also during the night. In severe cases the GTCS show an alternating lateralization.

Tonic seizures. Axial tonic seizures characteristically occur almost exclusively during the night, especially between 4 and 6 a.m. As can be demonstrated by long-term EEG, they can occur serially. Tonic seizures during daytime and a status of tonic seizures represent a rarity which can be observed only in the late course of the most unfavourable cases.

Focal seizures. Focal seizures are not characteristic of myoclonic astatic epilepsy. They can occur as a facilitative phenomenon in those rare cases with a primary brain lesion or, on the other hand, in the late course of unfavourable cases.



TOP

EEG Findings

In cases with febrile or afebrile GTCS as the presenting symptom, the EEG can be normal at onset or shows only

early childhood *Cmyoklonisches Kleinkind-Petit mal*, Doose, 1964a), later distinctly described as benign and severe myoclonic epilepsy by Dravet et al. (1985a, b) and attributed to the epilepsies presenting primarily generalized minor seizures (absences, impulsive petit mal). In the same way we later established the difference between primarily generalized myoclonic-astatic petit mal of early childhood and the Lennox syndrome (Gastaut et al., 1966). As it follows from the study of Gastaut et al. (1966), the Lennox syndrome comprises only a small subgroup which presents all the characteristics of an epilepsy with primarily generalized seizures, whereas the majority of the cases with this syndrome have to be classified as symptomatic in origin.

Since 1951 we collected 117 cases with primarily generalized myoclonic and myoclonic-astatic seizures. This large number of such a rare condition might be explained by the wide referral source of the epilepsy Centre at Kiel. Based on these 117 observations, the clinical picture can be described as follows.



TOP

General

Incidence. According to an epidemiological study of Doose & Sinepu (1983), primarily generalized myoclonic and myoclonic-astatic seizures occur in 1-2 percent of all childhood epilepsies up to age 9.

Sex ratio. The number of affected boys is at least twice as high as that of girls (in our group 86 boys and 31 girls).

Aetiological factors. Exogenous factors which could be aetiologicaly relevant, are rarely found. Only 16 per cent of 117 children showed signs of a developmental retardation before the onset of epilepsy or indications of definite high-risk factors in their history.

Genetics. The investigation of the families of 107 patients demonstrates the outstanding pathogenetic importance of hereditary factors (Doose et al., 1970; Doose & Baier, 1987a). In 32 per cent of the cases seizures were reported in parents, parents' siblings and/or in probands' siblings (Table 1). In detail, the incidence turned out to be higher in siblings (15 per cent) than in parents (6 per cent). The incidence was higher in relatives of female than of male probands. The seizure types registered in the relatives were predominantly afebrile or febrile GTCS. Absences, mostly with onset before the fifth birthday, were seen in only 25 per cent of the affected siblings. Myoclonic or myoclonic-astatic seizures occurred in only three out of 160 siblings (2 per cent = about 200 times more often than in the general population). Among the seizures in relatives, those manifesting before the 5th birthday (including febrile convulsions) were more prevalent than those of a later onset. Furthermore, in the family study of Doose & Baier (1987a), it could be demonstrated that genetic disposition to seizures of early childhood onset is a very important factor in the pathogenesis of myoclonic-astatic epilepsy (MAE). This so-called A-liability could be proven as genetically different from the genetic liability to manifest later onset epilepsy, e.g. absence epilepsies (B-liability). Obviously, MAE and absence epilepsy of later onset have to be regarded as genetically different, although they have some genetic factors in common, as can be seen by identical EEG findings in siblings. The frequency of electroencephalographic markers of a genetic liability to convulsions such as photosensitivity, 4-7 c/s rhythms, and spikes and waves, was distinctly increased in siblings and parents (Doose & Baier, 1987a). MAE is a paradigmatic example of a multifactorially determined disease (Doose & Baier, 1987a, 1989a). A number of genetically distinct and partly mutually independent factors (Baier & Doose, 1987), some of which expressed as special EEG patterns, others by certain clinical characteristics (A- and B-liability), are interacting and mutually augmentative. The multitude of aetiological genetic factors and of possible interactions explains the large variability of epileptic symptoms in relatives, and even in patients with MAE (cases with and without GTCS, with predominantly myoclonic or myoclonic-astatic seizures). Assuming a multifactorial pathogenesis, this is not surprising, but has to be expected. The hypothesis of a multifactorial pathogenesis has been exemplified by family observations (Doose & Baier, 1987b). Two children of a woman with former MAE manifested seizures during early childhood, but while the daughter again suffered from MAE, the son manifested a benign myoclonic epilepsy. This observation is in agreement with the assumption of polygenicity. The type of manifestation will depend on the special set of 'polygenes', which are inherited in the individual case. On the other hand, identical stimulus-sensitive myoclonic seizures with a benign course are observed in monozygotic twins. In the clinically healthy family a variety of genetic EEG anomalies could be registered. This observation is suggestive for a polygenically determined disease, which shows very little non-genetic variability.

A further argument for multifactorial determination of MAE are the family findings in groups with different clinical courses (Doose & Baier, 1987b). In cases with GTCS as the presenting symptom the parental generation is significantly

monomorphic theta rhythms with parietal accentuation as well as occipital 4 c/s rhythms, constantly blocked by opening the eyes. During this early stage, irregular spikes and waves are absent, and they appear with some delay; at First only during sleep. Regularly spikes and waves can be found, when minor seizures appear. The type of EEG pattern depends on the seizure type: in cases with predominantly or exclusively myoclonic seizures short paroxysms of irregular spikes and waves and polyspike waves are most typical. On the other hand, in children with atstatic or myoclonic atstatic seizures the record is characterized by 2-3 c/s spikes and waves and spike wave variants. Usually, they are of irregular shape, only rarely grouped in rhythmic sequences but interrupted by high amplitude slow waves. A lateralization of spikes and waves can often be seen, then simulating a spike focus or multifocal spikes ('pseudofoci'). The accentuation, however, mostly changes from one side to the other. Constantly localized foci are very rare. They can occur especially in the rare cases with primary brain damage, but they never dominate the EEG for a longer time. During sleep, spikes and waves are regularly activated. Most cases show photoparoxysmal response at least between the age of 5 and 15 years, i.e. at the age of maximal expressivity of the pattern. The background activity usually is dominated by 4-7 c/s rhythms with parietal accentuation (for literature see Doose & Baier, 1988). Often groups of theta rhythms immediately precede or follow the spike-wave paroxysms. During stages with a high frequency of seizures a polymorphous slowing instead of theta rhythms is dominant. In unfavourable cases the 4-7 c/s rhythms can persist until puberty and adulthood (Gundel et al., 1981a, b).

During status, the EEG shows 2-3 c/s spikes and waves and, especially in younger children very irregular polymorphous hypersynchronous activity, sometimes resembling hypsarrhythmia in West syndrome. In very rare cases with myoclonic status the EEG is dominated by polyspike waves. Nocturnal tonic seizures are accompanied by typical 10-15 c/s spike series.



TOP

Course and prognosis

A representative sample for the course of the disease cannot be derived from our material because the cases were collected over 30 years and have been treated by different regimens. Furthermore, our centre is consulted by a selection of unfavourable cases. Follow-up studies of 115 cases showed complete seizure control for at least 2 years in 54 per cent of the children beyond the age of 7 years.

Apparently, there is a wide range of possible developments. In very rare cases the disease resolves spontaneously. After some months, myoclonic or myoclonic atstatic seizures disappear without any therapy; the development of the children is quite normal. Such cases can be designated as benign myoclonic epilepsy of infancy (Dravet et al., 1985a). In other cases, minor seizures can disappear rapidly under valproate therapy.

If epilepsy starts during the first year of life with afebrile and febrile GTCS, generally the course of the disease is unfavourable. GTCS, often of long duration, can recur frequently. Their accentuation can change from one side of the body to the other, and after a short time they even appear during sleep, a prognostically unfavourable sign. Prognosis of children suffering from long-lasting status of minor seizures is particularly poor. This status can rapidly lead to dementia (Doose et al., 1970; Doose & Voizke, 1979). The younger the children are when the status appears, the higher is the risk of dementia. In these cases and in children suffering from frequent GTCS even neurological defects can be observed in the later course: slight ataxia, poorly differentiated coarse motor function, clumsiness among others. Nocturnal tonic seizures are another characteristic of unfavourable courses. Often they can be detected only by long-term EEG monitoring. Because the clinical symptomatology of tonic seizures may be minimal, they may not be noticed by the patient himself or even by the parents.

As a rule, the following criteria can be identified as prognostically unfavourable: frequent febrile or afebrile GTCS, petit mal status and onset of epilepsy during the First 18 months of life with GTCS. Regarding the EEG, the persistence of a rhythmic slowing until adolescence and adulthood and missing development of a stable occipital alpha-rhythm is a very important criterion of an unfavourable course (Gundel et al., 1981a,b).



TOP

Differential diagnosis

Differentiating between myoclonic epilepsies and infantile spasms is essential. This is usually possible without difficulty. Infantile spasms usually affect children with brain damage, the seizures typically occur in series, and the EEG shows hypsarrhythmia.

Delineation of the Lennox-Gastaut syndrome, is more difficult. However, the discussion of differential diagnosis must take into account the fact that the syndrome described by Gastaut et al. (1966) includes a subgroup with cases which show the above mentioned characteristics of generalized epilepsy. If those cases are excluded from the Lennox-Gastaut syndrome in the stricter sense, the following criteria diagnostic of MAE hold true:

- genetic predisposition (high incidence of seizures and genetic EEG patterns in relatives).
- mostly normal development before onset:
- never neurometabolic or degenerative diseases;
- mostly no neurological deficits at onset of the epilepsy;
- primarily generalized myoclonic, atonic or myoclonic atonic seizures, short absences and mostly generalized tonic-clonic seizures:
- rarely focal seizures;
- no atypical absences:
- tonic seizures during night in unfavourable cases;
- no tonic seizures or tonic drop attacks during daytime, except for some rare cases with a most unfavourable course;
- primarily generalized EEG patterns: generalized spikes and waves, photosensitivity, 4-7 c/s rhythms;
- no multifocal EEG abnormalities (but often pseudofoci).

Occasionally, it may be difficult to differentiate MAE from the atypical benign partial epilepsy (Aicardi & Chevrie, 1982) also called pseudo-lennox syndrome (Doose & Baier, 1989b). This epilepsy, too, usually affects primarily normally developed children and may be accompanied by drop attacks. Just as in MAE and, in contrast to Lennox-Gastaut syndrome, these drop attacks are atonic in nature. Tonic drop attacks do never occur. The EEG in these children shows focal and generalized sharp slow waves and sometimes also spikes and waves. The sharp slow waves have the shape characteristic of benign partial epilepsies, and they are activated during slow sleep, sometimes as a bioelectrical status (Tassinari et al., 1985). It could be demonstrated by family studies (Doose, 1989; Doose & Baier, 1989b) that the pseudo-lennox syndrome and the rolandic epilepsy in the stricter sense have a common genetic background (Doose & Baier, 1989b).

Discussion of the differential diagnosis has to consider another crucial point. Keeping in mind a multifactorial background of the epilepsies, an occasional coincidence of genetic with lesional factors has to be expected which may then lead to clinical expressions more or less similar to symptomatic epilepsies, i.e. Lennox-Gastaut syndrome. The existence of such intermediate types is as much an argument against the above mentioned nosographic concept as it is an argument against the syndromatic approach in general. From the pathogenetic point of view, however, these intermediate types are especially interesting because they exemplify an instructive model of the multifactorial aetiology of the epilepsy.



TOP

Treatment

Valproate is the drug of first choice. If its effect is insufficient, ethosuximide should be added. If there are still GTCS, primidone (better than phenobarbitone) has to be prescribed as a second or third substance. In cases with persistent severe GTCS bromide should be given without delay (40-60 mg/kg body weight, blood level 140 to 190 mg/100 ml) (Ernst et al., 1988). In cases with refractory minor seizures and in all patients with minor status ACTH is indicated (initial dose 15 U/m² body surface; if ineffective after 2 weeks the dose should be doubled). In some cases a status can be interrupted by acetazolamide. Clonazepam may activate tonic seizures and even provoke a tonic status.



TOP

Conclusion

MAE of early childhood belongs to the epilepsies with primarily generalized seizures and thus stands in one line with absence epilepsies, juvenile myoclonic epilepsy, as well as the infantile and juvenile idiopathic epilepsy with GTCS. The similarity of EEG findings in families of patients with different kinds of these idiopathic generalized epilepsies points to common genetic factors as part of a multifactorial system. The different clinical symptomatology and age-dependence of these syndromes may only be the expression of a special constellation of different factors and, in cases of MAE, the effect of the mentioned special genetic disposition to early onset seizures (A-liability, Doose & Baier, 1987a, b). So the lack of an elevated incidence of juvenile myoclonic epilepsy in the relatives of patients with myoclonic epilepsy of early childhood (Delgado-Escueta et al., 1991) is no argument against a genetic relationship between both conditions. Maybe future linkage analyses in MAE will, amongst others, detect the chromosome-6-locus which could be demonstrated for juvenile myoclonic epilepsy (Weissbecker et al., 1991; Durner et al., 1991).

A substantial literature exists dealing with epilepsies of early childhood with myoclonic and myoclonic astatic seizures. A number of special disorders or 'syndromes' were described in this group. All these syndromes do partly overlap each other, some are even equivalent (Lennox, 1945; Lennox & Davis, 1950; Doose, 1964a, b; Harper, 1968; Kruse, 1968; Aicardi & Chevria, 1971; Loiseau et al., 1974; Jeavons, 1977; Aicardi, 1980; Dalla Bernardina et al., 1982; Aicardi & Chevria, 1982; Dravet et al., 1985a, b; Aicardi, 1986). However, it was not intended to present MAE here as a rigidly defined syndrome, and it was not intended to conduct its defence against other proposed entities. It seems to make more sense to realize the wide clinical and bioelectrical variability of idiopathic generalized epilepsies of early childhood which is due to their multifactorial aetiopathogenetic background. To divide and subdivide this group of disorders into more and more entities and subentities may be a never-ending story: epilepsies with prevalingly myoclonic fits, with myoclonic astatic seizures, with prevailing absences, epilepsies with or without GTCS or even with GTCS as their sole symptom (Ernst et al., 1988), and, finally, each of these syndromes with or without additional environmental pathogenetic factors. By following this kind of syndromic approach, we are circling around the tips of icebergs. Admittedly, this iceberg strategy (Cloninger, 1985) may be useful for clinical practice if it is related to therapeutic considerations. Studying the biology of epilepsy, however, will only succeed, if we step down from these iceberg peaks to the submarine level representing the pathogenetic basis, and only that will be the precondition for a sensible classification of the epilepsies.



TOP