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EPILEPSY SYNDROMES IN DEVELOPMENT

Malignant migrating partial seizures in infancy: An epilepsy syndrome of unknown etiology

Giangennaro Coppola

Clinic of Child Neuropsychiatry, Second University of Naples, Naples, Italy

Summary

The syndrome of malignant migrating partial seizures in infancy was first reported in 1995, and is now included among the childhood epilepsy syndromes in development in the proposal of the revision of the International League Against Epilepsy (ILAE) classification of the epilepsies and epilepsy syndromes. The main clinical features are seizure onset in the first 6 months of life, occurrence of almost continuous migrating polymorphous focal seizures, combined with multifocal ictal electroencephalography (EEG) discharges, and progressive deterioration of psychomotor development. Etiology is so far unknown. Seizures are markedly drug resistant and outcome is generally severe. Based on age at onset, migrating partial seizures in infancy (MMPEI) may be placed between early epileptic encephalopathies (early myoclonic encephalopathy [EME] and early infantile epileptic encephalopathy [EIEE]) and infantile spasms.

KEY WORDS: Migrating partial seizures, Epileptic encephalopathy, Refractory epilepsy.

The syndrome of malignant migrating partial seizures in infancy was first reported in 1995 (Coppola et al., 1995). Since then, approximately 50 patients have been reported worldwide (Coppola et al., 1995; Gérard et al., 1999; Okuda et al., 2000; Wilmshurst et al., 2000; Veneselli et al., 2001; Gross-Tsur et al., 2004; Marsh et al., 2005; Coppola et al., 2006; Hmaimess et al., 2006; Coppola et al., 2007; Hahn et al., 2007; Caraballo et al., 2008). This syndrome has been included among the childhood epilepsy syndromes in development in the proposal of revision of the International League of Epilepsy (ILAE) Classification of the epilepsies and epilepsy syndromes (Engel, 2001).

Clinical symptoms

The natural history of this syndrome allows recognition of three distinct phases, as described in the first report in 1995 (Coppola et al., 1995). A first phase, generally starting in the first semester after birth, is often characterized by sporadic seizures, usually recurring in a few weeks or months. Seizure onset may also occur since the first day of life (Hmaimess et al., 2006). Seizures are mainly focal motor with rapid secondary generalization; autonomic manifestations such as apnea, flushing, or cyanosis frequently occur. This phase usually lasts a few weeks or months. However, sometimes seizures occur at the onset of the second phase. Interictal electroencephalography (EEG) in this first period shows increasing diffuse slowing of background activity with prevalence of slow waves often shifting from one hemisphere to the other. Shortly, multifocal discharges poorly activated by sleep are present in all cases.

The second phase could also be defined as a "stormy phase." At an age ranging from about 1–12 months, focal polymorphous seizures shortly become very frequent, occurring in clusters of 5–30 several times a day or being almost continuous for more days. Based on the origin of focal ictal discharges, seizure semiology more often includes lateral deviation of the head and eyes, twitches of the eyelids, clonic or tonic jerks of one or both limbs on one side, apnea, flushing and/or cyanosis of the face, chewing movements, mastication, and secondary tonic–clonic generalization. Milder clinical manifestations may be easily overlooked by parents/caregivers, and detection of frequent subclinical ictal manifestations is made possible only by long lasting video-EEG recordings. Seizures usually last 1–4 min, but often they last enough to qualify as status epilepticus. In this period, focal EEG discharges are typically migrating, starting from a cortical area and remaining localized or expanding to contiguous regions,

Address correspondence to Giangenaro Coppola, M.D., Clinic of Child Neuropsychiatry, Second University of Naples, Naples, Italy. E-mail: giangennaro.coppola@unina2.it

whereas others independently develop in different areas of the same or the opposite hemisphere. Prolonged video-EEG recordings show a clear correlation between the topography of the EEG ictal discharges and the clinical features. Therefore, occipital EEG seizures correlate with lateral deviation of head and eyes, rolandic ictal discharges correspond to contralateral clonic or tonic jerks, temporal lobe seizures are associated with flushing or chewing manifestations, and frontal seizures lead to bilateral limb hypertonia. In the second phase, ictal and interictal EEGs almost overlap. The wave pattern consists of rhythmic theta activity beginning in one region and progressively involving adjacent areas; meanwhile, other focal discharges may independently appear in other regions, while the original patterns tend to persist or to fade and be replaced by new patterns, thus producing a very complex multifocal status epilepticus (Fig. 1). Recently, Caraballo et al. (2008), analyzing the electroclinical patterns in 17 new cases, distinguished three different clinical patterns: (1) recurrence of ample rhythmic focal spikes or rhythmic sharp theta or alpha activity over the contralateral rolandic region; (2) polymorphic theta–delta activity over a temporooccipital region; (3) initial flattening or small discharge of ample fast polyspikes in one hemisphere. No relationship between these three patterns and outcome was found.

With increasing age, the amplitude of the ictal discharge tends to increase, and frontal areas are more frequently affected (Dulac, 2005). One patient developed only infantile spasms (Coppola et al., 1995). The age at onset of the third phase may vary highly, ranging from the end of the first year to 5 years of age and over. This phase is a relatively seizure-free period, although spontaneous intercurrent illnesses would easily trigger clusters of seizures or occasional status epilepticus.

Neuroradiological, biochemical, and other investigations

Computed tomography (CT) and magnetic resonance imaging (MRI) are generally normal at the beginning of the illness. During follow-up there may be a mild to moderate enlargement of both subarachnoid and ventricular spaces. Caraballo et al. (2008) reported mesial temporal lobe sclerosis in 3of 17 patients, whereas Coppola et al.

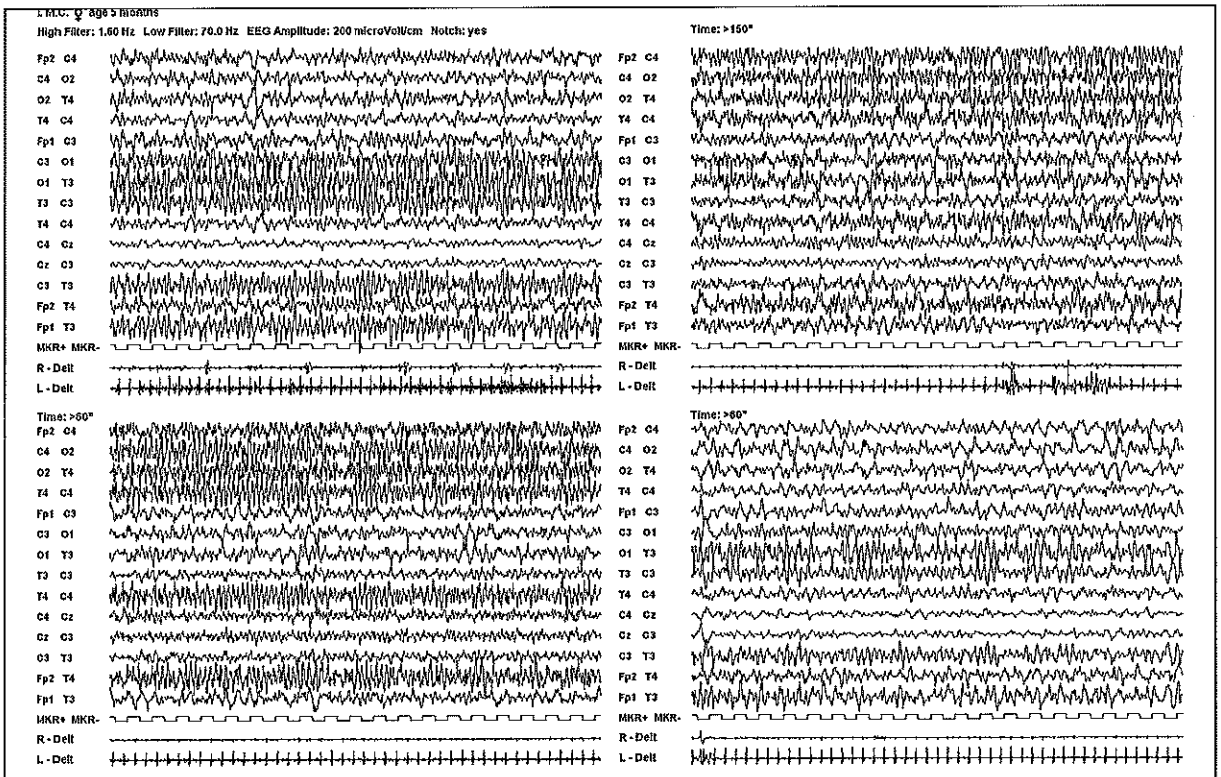

Figure 1.
(A–D). A 5-month-old boy with left temporooccipital discharge ending when another one starts on the right frontocentral and temporal areas with different frequency and then on the left temporal area.
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(2007) found left temporal lobe dual pathology in a child, including hippocampal sclerosis and cortical–subcortical blurring. In another patient (Gross-Tsur et al., 2004) MR brain spectroscopy revealed decreased *N*-acetyl aspartate in the frontal cortex and basal ganglia.

All biochemical studies including skin, liver, muscle examination, and respiratory chain function are negative; autopsy done in three patients disclosed no brain abnormalities in one (Wilmshurst et al., 2000), and neuronal gliosis of the CA1 sector of the pyramidal layer of the hippocampus in two (Coppola et al., 1995).

Etiology

The etiology of this syndrome is unknown. A role of genetic factors such as ion-channel mutations, cannot be ruled out. Recently, a first attempt of mutational scanning of *KCNQ2, KCNQ3, SCN1A, SCN2A, and CLCN2* genes failed to detect significant results (Coppola et al., 2006). Familial recurrence has not been reported.

Outcome and prognosis

Overall, the long-term outcome of migrating focal seizures in infancy, with reference to seizures and psychomotor development, remains very severe. Even when it becomes possible to shorten the duration of migrating status epilepticus and/or increase the intervals between active phases with different combination therapies, psychomotor abilities are poor, inevitably evolving into mental retardation. Only children whose seizures are brought under control acquire the ability to reach for objects and walk. Language is regularly absent. Furthermore, most patients develop an acquired microcephaly, showing a reduction of the cranial circumference of less than 2 standard deviations (SDs) by the end of the first year of age. A number of patients die before the end of the first year of age or later in the course of the follow-up, mainly because of intercurrent infections and respiratory failure. In a few cases, long-term outcome may be less severe than expected (Marsh et al., 2005; Caraballo et al., 2008).

Management

Migrating malignant partial seizures in infancy is so far markedly pharmacoresistant, and any attempt to control migrating seizures is often frustrating, especially in the stormy period. Overall, old and new antiepileptic drugs (AEDs) in monotherapy or in various combinations are ineffective. In some cases potassium bromide may lead to seizure control or to a significant seizure reduction, generally in a few weeks (Okuda et al., 2000; Coppola et al., 2007). Stiripentol together with clonazepam and levetiracetam are other potential treatment options (Perez et al., 1999; Hmaimess et al., 2006). The ketogenic diet has been tried with poor results (François et al., 2003).

Acknowledgments

We have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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