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Pronounced microcephaly in a patient with malignant migrating partial seizures in infancy

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ABSTRACT – Malignant migrating partial seizures in infancy is an age-specific epilepsy syndrome, resistant to conventional antiepileptic drugs in most cases. Since the first description of 14 infants in 1995, only 16 additional patients have been reported. We add a further case and present a video that shows a typical generalizing tonic seizure arising from the right temporo-occipital area and slowly spreading about both hemispheres. In addition to other symptoms previously described, almost complete arrest of brain growth with onset of seizures and evolution of distinctive secondary microcephaly were striking features in this patient.
[Published with video sequences]

Key words: malignant migrating partial seizures, infancy, microcephaly

Malignant migrating partial seizures in infancy (MMPSI) was first described by Coppola 10 years ago (Coppola *et al.* 1995). Its electroclinical features have been recently reviewed by Dulac in 2002. MMPSI affects boys and girls equally and no familial cases are on record. It is characterized by normal development before the onset of seizures, onset of epilepsy before 6 months of age, predominantly focal motor seizures at onset, daily polymorphous seizures during course, severe neuro-mental impairment, resistance to antiepileptic medication, and no definable etiology (Coppola *et al.* 1995, Dulac 2002).
The small number of patients reported since 1995 may indicate that this epilepsy syndrome is frequently overlooked. However, despite the polymorphous seizure symptomatology, MMPSI follows a typical course and has a characteristic electroclinical pattern that allows a confidant diagnosis.

Case report

The patient is the first child of healthy, unrelated German parents. He was born at term after an uneventful pregnancy and without any complications. Birth weight was 3070 g, length 50 cm, and head circumference 35 cm (50th percentile). Family history revealed a first cousin with BECTS.
His early development was judged as normal by the parents and his pediatrician. Clonic seizures of one or both legs lasting for 30 seconds to three minutes started at age three months. Initial EEGs were normal. MRI and extensive neuro-metabolic work-up revealed no abnormalities.

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After 4-6 weeks, seizures became considerably more frequent. Besides multifocal clonic generalizing seizures, daily tonic seizures with head and gaze deviation lasting for 1-4 minutes, sometimes occurring in series were noticed (*see video sequence*). At age 5 1/2 months, the boy was referred to our department. Head circumference had dropped to the 10th percentile (42.5 cm) *(figure 1)*. Neurological examination revealed muscular hypotonia and a profound delay of psychomotor development. The child had neither eye contact nor grasped, and was not able to turn over. In addition, more subtle ictal manifestations consisting of irregular breathing, increased salivation, mastication, eye deviation or eye lid twitching were also observed.

Interictal EEGs displayed a somewhat slowed background activity with additional fluctuating regional slowings and multifocal sharp waves. Ictal recordings revealed a monomorphic fast theta- or alpha-activity originating from different regions, spreading to adjacent areas, and propagating over both hemispheres (*see video sequence*). Frequently, two consecutive seizures arising from different regions were recorded during a single routine-EEG *(figure 2)*.

The infant was treated with pyridoxine, pyridoxal phosphate, folinic acid, phenobarbital, oxcarbazepine, valproate, topiramate, vigabatrin, sulthiame, and levetiracetam (60 mg/kg bw) as monotherapy and at several combinations. Steroid pulses and the ketogenic diet were also tried.

Overall, no substantial improvement of the patient's condition could be achieved by the various therapy regimes applied, but seizures tended to become less frequent from age eight months. At this time, the head circumference had dropped to the third percentile (43 cm) and a second MRI revealed brain atrophy with fronto-temporal preponderance *(figure 1)*. In addition to axial hypotonia, dystonic movements and the virtual absence of any psychomotor development were prominent findings. At this point, his parents became reluctant to pursue further therapy and the boy was discharged home with valproate and oxcarbazepine. At last follow-up by phone at age 18 months, he showed small psychomotor progression, but still suffers from daily seizures.

Discussion

The patient reported here matches other cases with MMPSI as described by Coppola and Dulac (Coppola *et al.* 1995, Dulac 2002).

The diagnosis of MMPSI may be missed due to the various seizure types encountered and a rather nonspecific interictal EEG. However, as in our case, careful history taking will reveal a characteristic, three-phase course of epilepsy. After an initial period lasting from a few days to months with relatively rare seizures that frequently have a motor component, seizure frequency dramatically increases and ictal semiology becomes highly polymorphous. At this stage, numerous daily seizures are observed that remain therapy-refractory in most cases and tend to occur in clusters. In many patients, seizures become less frequent after several months, reflecting a "burnt-out" stage of the

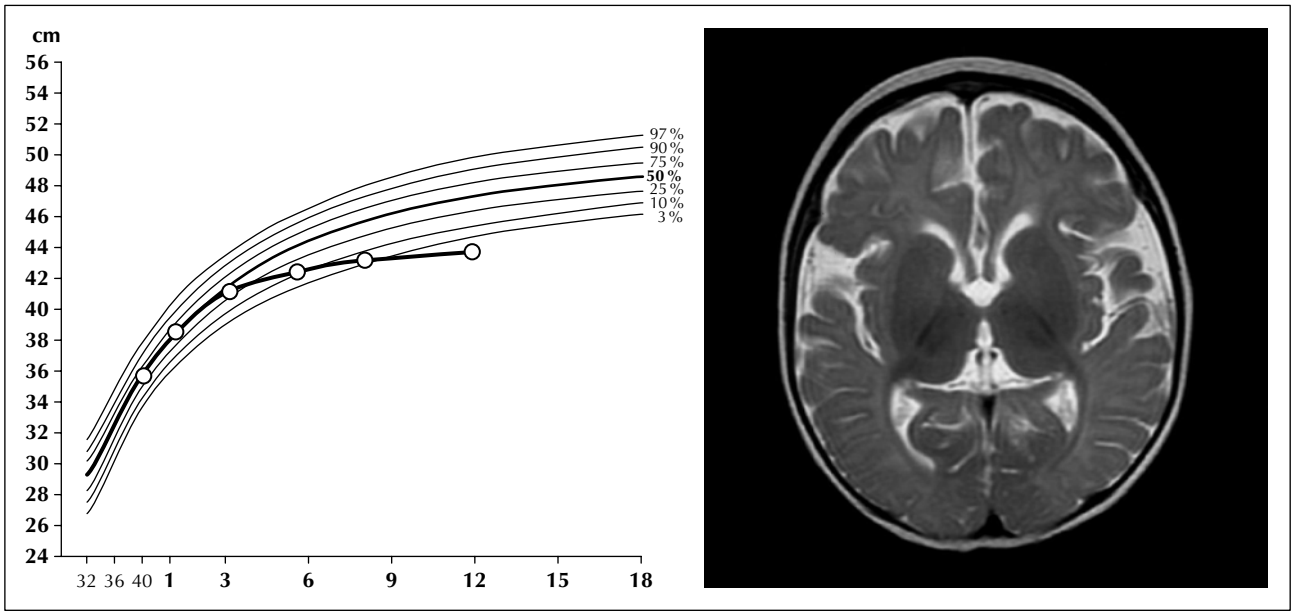

Figure 1. Head circumference in relation to age disclosing secondary microcephaly and T2-weighted MRI at age 8 months demonstrating fronto-temporal accentuated cerebral atrophy.

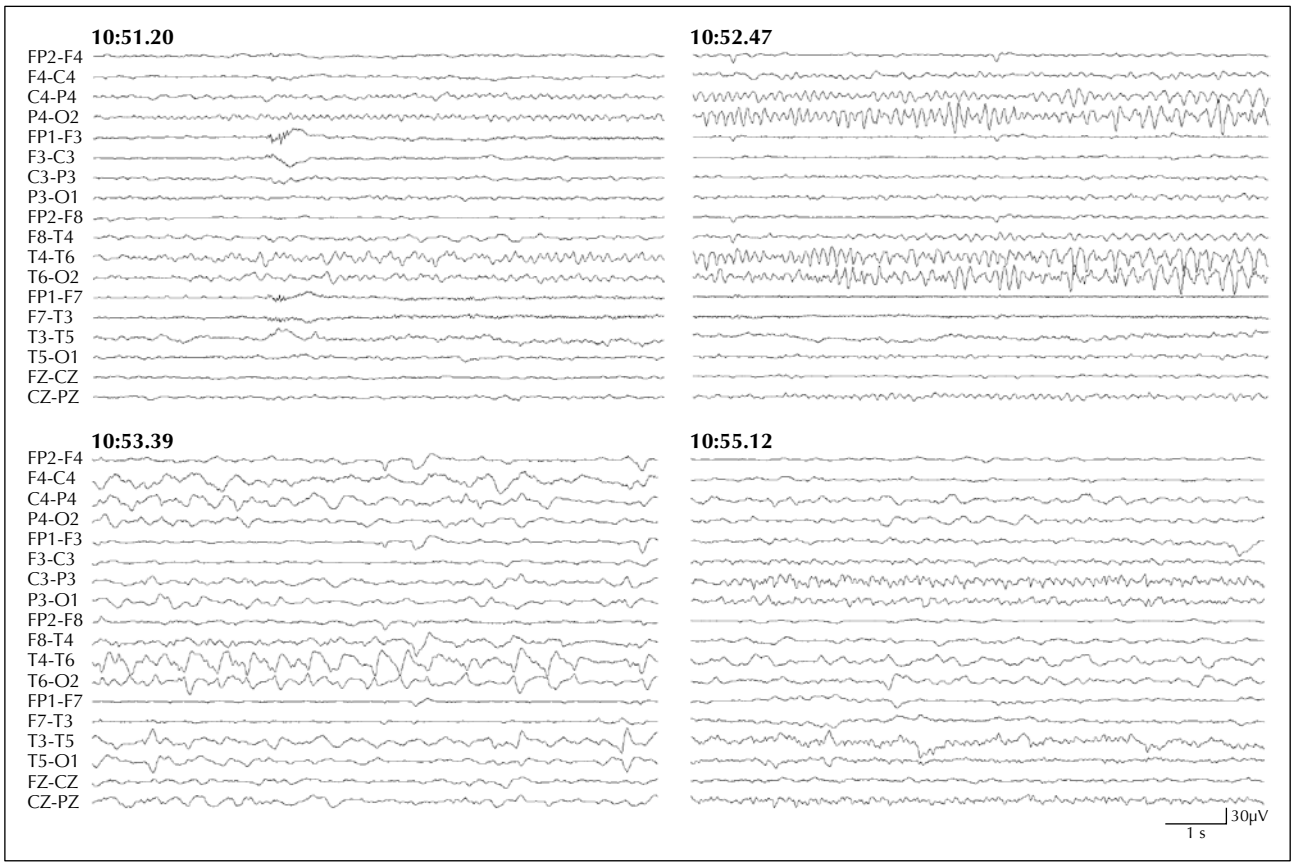

Figure 2. Ictal EEG of the patient at age 61/2 months. At 10.51, a monomorphic 8/s-activity arises from the right temporo-occipital region that increases in amplitude and slightly declines in frequency while propagating to adjacent areas (10.52). The seizure ends with slow rhythmic delta-discharges at 10.53. At 10.55, a further seizure begins, now originating from the left centro-temporal region.

epileptic encephalopathy rather than a response to pharmacotherapy (Coppola *et al.* 1995, Dulac 2002). Some patients die by the end of the first year whereas the survivors are left with severe neuro-mental deficits (Dulac 2002).

As in our patient, video-EEG-recordings display seizures with variable ictal symptomatology originating from different cortical regions. Typically, a rhythmic theta or slow alpha activity is recorded that progressively involves adjacent areas and may spread about both hemispheres while the frequency of discharges becomes slightly slower. During periods of high seizure frequency, consecutive seizures may overlap, with ictal discharges arising from another region or hemisphere even before the end of the previous one. Notably, there is a correlation between localization of ictal discharges and seizure symptomatology (*e.g.* occipital discharges and oculoclonias or head deviation, temporal discharges and mastication or staring, and frontal discharges and limb hypertonia) (Dulac 2002). These electroclinical features should allow us to distinguish MMPSI from other epilepsy syndromes manifesting in the neonatal period or during infancy, in particular neonatal epileptic encephalopathy with suppression-burst and West-syndrome (Dulac 2002, Wilmshurst *et al.* 2000).

Seizure control could be reached in two subjects with a combination of stiripentol and high doses of clobazam (Coppola *et al.* 1995, Dulac 2002), and with bromides in two additional infants (Okuda *et al.* 2000), whereas these medicines have failed in others (Gross-Tsur *et al.* 2004, Hmaimess *et al.* 2006, Veneselli *et al.* 2001, Wilmshurst *et al.* 2000). Recently, a good response to levetiracetam has been claimed in a case with neonatal onset (Hmaimess *et al.* 2006), but this drug was without effect in our patient. Although some progress in psychomotor development has been noticed in patients responding to antiepileptic treatment, even seizure control does not significantly modify clinical outcome (Okuda *et al.* 2000, Dulac 2002, Marsh *et al.* 2005, Hmaimess *et al.* 2006).

No neurometabolic anomaly and no cortical malformation have been identified in any patient with MMPSI reported so far. Moreover, no mutations have been found in genes encoding for potassium (KCNQ2, KCNQ3), sodium (SCN1A, SCN2A), and chloride (CLCN2) ion channels (Coppola *et al.* 2006). *Postmortem* studies were per-

formed in three patients. Hippocampal gliosis was the only abnormal finding in two of them (Coppola *et al.* 1995, Dulac 2002), whereas no anomaly was noticed in the third case (Wilmshurst *et al.* 2000). Magnetic resonance spectroscopy was performed in one subject and revealed reduction of N-acetyl-aspartate in basal ganglia and frontal cortex (Gross-Tsur *et al.* 2004).

As in our patient, tonic seizures, sometimes occurring in series, are a characteristic feature of MMPSI, whereas epileptic spasms are consistently absent. This phenomenon remains unexplained. However, in MMPSI, seizures begin later than in neonatal encephalopathy with suppression-burst, and earlier than in West syndrome. The electroclinical findings in MMPSI suggest that the whole cortex is prone to generate tonic activities migrating from one cortical area to the other, whereas it is assumed by most authors that subcortical structures are involved in the generation of epileptic spasms (Dulac 2002, Dulac and Tuxhorn 2002). Thus, it has been postulated that a diffuse, maturation-related, predominantly cortical hyperexcitability plays an important role in the pathophysiology of MMPSI (Dulac 2002).

Coppola reported microcephaly in 11 out of 14 patients at age 12 months in an initial series and in all three subjects reported subsequently (Coppola *et al.* 1995, 2006). Wilmshurst and colleagues (Wilmshurst *et al.* 2000) observed a decline of head circumference in the first and mild cerebral atrophy in the second patient described by them. Progressive brain atrophy was also noticed in the two patients reported by Gross-Tsur and co-workers (Gross-Tsur *et al.* 2004) and in three out of six subjects described by Marsh (Marsh *et al.* 2005). No specifications about head circumference or brain atrophy were made in the case reported by Hmaimess and colleagues (Hmaimess *et al.* 2006), in the two patients added by Okuda (Okuda *et al.* 2000), and in the three subjects appended by Veneselli (Veneselli *et al.* 2001). Overall, microcephaly, decline of head circumference or cortical atrophy evolved during the course of the disease in 21 out of 27 subjects in whom this issue was addressed. In our patient, an almost complete arrest of head growth with onset of seizures was a striking feature, underscoring the malignant nature of this epileptic encephalopathy. Taken together, these observations suggest that secondary microcephaly is a further characteristic feature of MMPSI.

Recently, Marsh and colleagues (Marsh *et al.* 2005) expanded the clinical phenotype of MMPSI by reporting six patients who had passed some early psychomotor milestones. Two of them had even learned to walk and had developed some degree of spoken language. It can be hypothesized that these subjects correspond to the less severe end of the clinical spectrum, whereas those with virtual complete arrest of brain growth and only mimimal psychomotor progress reflect the most severe form of the disease. □

Legend for video sequence

The video shows a tonic seizure lasting 21/2 minutes. At 11:48.55, a monomorphous alpha-activity occurs in the right temporo-occipital region while the patient is asleep. After a few seconds, the boy starts sucking and opens his eyes. There is tonic deviation of the eyeballs upwards and to the right, accompanied by a slow turning of the head to this side. Epileptic discharges gradually propagate to adjacent areas and spread about both hemispheres while slightly declining in frequency and increasing in amplitude. At 11:50.15, there is tonic stretching of both legs and arms reflecting involvement of the frontal cortex. The increased muscle tone slowly resolves and the boy seems to partly regain consciousness while ictal discharges slowly run out as higher-amplitude theta-activity.

References

Coppola G, Plouin P, Chiron C, *et al.* Migrating partial seizures in infancy: a malignant disorder with developmental arrest. *Epilepsia* 1995; 36: 1017-24.

Coppola G, Veggiotti P, Del Giudice EM, *et al.* Mutational scanning of potassium, sodium, and chloride channels in malignant migrating partial seizures in infancy. *Brain Dev* 2006; 28: 76-9.

Dulac O. Malignant migrating partial seizures in infancy. In: Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P, eds. *Epileptic syndromes in infancy, childhood and adolescence (3rd edition).* London: John Libbey & Company Ltd., 2002: 65-8.

Dulac O, Tuxhorn I. Infantile spasms and West syndrome. In: Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P, eds. *Epileptic syndromes in infancy, childhood and adolescence (3rd edition).* London: John Libbey & Company Ltd., 2002: 47-63.

Gross-Tsur V, Ben-Zeev B, Shalev RS. Malignant migrating partial seizures in infancy. *Pediatr Neurol* 2004; 31: 287-90.

Hmaimess G, Kadhim H, Nassogne MC, *et al.* Levetiracetam in a neonate with malignant migrating partial seizures. *Pediatr Neurol* 2006; 34: 55-9.

Marsh E, Melamed SE, Barron T, *et al.* Migrating partial seizures in infancy: expanding the phenotype of a rare seizure syndrome. *Epilepsia* 2005; 46: 568-72.

Okuda K, Yasuhara A, Kamei A, *et al.* Successful control with bromide of two patients with malignant migratine partial seizures in infancy. *Brain Dev* 2000; 22: 56-9.

Veneselli E, Perrone MV, DiRocco M, *et al.* Malignant migrating partial seizures in infancy. *Epilepsy Res* 2001; 46: 27-32.

Wilmshurst JM, Appleton DB, Grattan-Smith PJ. Migrating partial seizures in infancy: two new cases. *J Child Neurol* 2000; 15: 17-722.