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Temporal lobe dual pathology in malignant migrating partial seizures in infancy

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ABSTRACT – A child had the characteristic clinical and EEG pattern of migrating partial seizures in infancy with left temporal lobe atrophy, hippocampal sclerosis and cortical-subcortical blurring.Seizures were drug-resistant, with recurring episodes of status epilepticus. The child developed microcephaly with arrest of psychomotor development. Focal brain lesions, in the context of migrating partial seizures, have not been previously reported.
[Published with video sequences]

Key words: migrating partial seizures in infancy, temporal lobe dual pathology, hippocampal sclerosis, microcephaly

Malignant migrating partial seizures in infancy (MMPSI) are unusual, and is an often overlooked epilepsy syndrome that was first described in 1995 (Coppola *et al.* 1995). Since the proposal for the revision of the ILAE classification of epilepsy syndromes (Engel *et al.* 2001) labelled MMPSI as a developmental syndrome, and included it among the symptomatic and probably symptomatic focal epilepsies, it has been reported in many countries (Coppola *et al.* 2006, Gerard *et al.* 1999, Gross-Tsur *et al.* 2004, Hamaimess *et al.* 2006, Marsh 2005, Okuda *et al.* 2000, Veneselli *et al.* 2001, Wilmshurst *et al.* 2000).
The main features include normal development before seizure-onset, first seizures appearing generally in the first semester of life, nearly continuous electro-clinical focal seizures starting from different lobes and shifting from one hemisphere to the other, and progressive deterioration or arrest of psychomotor development. To date, this syndrome has no clear-cut structural or metabolic aetiology.
Post-mortem studies in three patients revealed hippocampal gliosis in two of them (Coppola *et al.* 1995), whereas no anomaly was noticed in the third case (Wilmshurst *et al.* 2000). However, no focal neocortical lesions were disclosed on neuroradiological examination or neuropathology, and no other aetiology was identified. Magnetic resonance spectroscopy was performed in one subject that showed decreased N-acetyl-aspartate in basal ganglia and frontal cortex, a probable consequence of neuronal death (Gross-Tsur *et al.* 2004).
Nonetheless, the hypothesis of a genetic etiology has not been supported so far by familial cases, and a mutational scanning of a number of genes coding for KCNQ2, KCNQ3, SCN1A, SCN2A

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and CLCN2 ion channels in three children with MMPSI did not disclose any mutation (Coppola *et al.* 2006).
We report a child who developed the typical electroclinical pattern of migrating partial seizures in infancy, associated with MRI findings of left temporal pole atrophy and hippocampal sclerosis.

Case report

I.C. is the only child of healthy, non-consanguineous parents. She was born at term, by Caesarean section because of suspected gestosis. Birth weight was 3,250 g, length 50 cm and occipital-frontal-circumference (OFC) 33.5 cm. Apgar scores were normal. Developmental milestones were reported as normal until the age of four months, when daily brief episodes of flushing of the face, drooling and lachrymation associated with fixed gaze were noted. Such episodes lasted 20-30 seconds. An initial video-EEG recording showed discharges of rhythmic theta waves, not always associated with clinical symptoms, over the left temporal and occipital leads *(see video sequence 1)*.
A week later, epileptic discharges shifted to the opposite temporal lobe and, progressively, started migrating to frontal and/or occipital leads. Clinical seizures became polymorphous, involving the face and limbs. They consisted of clusters of rhythmic ocular jerks, facial erythrosis, lateral deviation of the eyes to the left, upper limb jerks mainly on the right side, salivation, tachycardia and cyanosis. In many instances, close observation of the child showed immobility or absent gaze as the only manifestations that EEG recording showed to be ictal *(see video sequence 2)*.
Neurometabolic and genetic evaluations (serum amino acids, oligotests, VLCFA, lysosomal enzymes, lactate, pyruvate and serum ammonia, organic aciduria, skin biopsy and caryotype) were normal. MRI scans at five months showed no volume or signal abnormalities of the temporal lobes or the hippocampal regions.
Visual- and auditory-evoked potentials disclosed no abnormal findings. Various antiepileptic drugs as monotherapy and in combination, were ineffective, including valproic acid, phenobarbital, phenytoin, clonazepam, topiramate, vitamin B6 and hydrocortisone. Long-lasting, video-EEG recordings at five and half months and six months, respectively, showed seizures that clearly started from various areas of both hemispheres *(see video sequences 3 and 4)*. The diagnosis of migrating partial seizures was then considered.
With the occurrence of almost continuous, polymorphous, migrating seizures, the child became poorly responsive, losing visual contact and the ability to grasp objects, and was unable to turn around.
At the age of seven months, potassium bromide was added to the baseline therapy and titrated up to a daily dose of 80 mg/kg, leading to seizure control and significant EEG improvement within about three weeks. Later, phenobarbitone was tapered off, and the child received combination therapy of bromide, topiramate and clonazepam.
At the age of eight months, mild acquisition of neuropsychomotor milestones was recorded, consisting of inconsistent visual pursuit, grasping movements and vocal sounds, but without independent sitting. At the age of nine months, TPM was discontinued, with no further seizures. Interictal EEG recordings showed independent temporal-occipital sharp waves over both hemispheres with increasing synchronous and asynchronous spindles during slow sleep stages.
The child was moderately hypotonic in the absence of pyramidal signs. Head circumference was 43 cm (< 2 SD).
At 19 months of age, the child was able to sit alone. Because of the recurrence of daily, polymorphous seizures with repeated episodes of epileptic status lasting over 2 hours, carbamazepine was added to the baseline combination therapy of bromide and clonazepam. Concomitantly, psychomotor development significantly worsened.
At the age of three years, the child showed major axial and limb hypotonia, and no speech. MRI scans showed a decreased volume of the left temporal pole together with an abnormal signal from the temporal white matter. There was also a poor differentiation between the cortex and white matter that was hyperintense on T2-weighted images *(figure 1)*.
Over the following two years, convulsive status recurred two to three times a year, consisting of frequent, complex partial seizures, mostly during sleep. A third MRI study at the age of five years confirmed the previous findings *(figure 2A, B)*. At this age, the child was severely mentally retarded, with frequent, stereotyped movements and no speech.

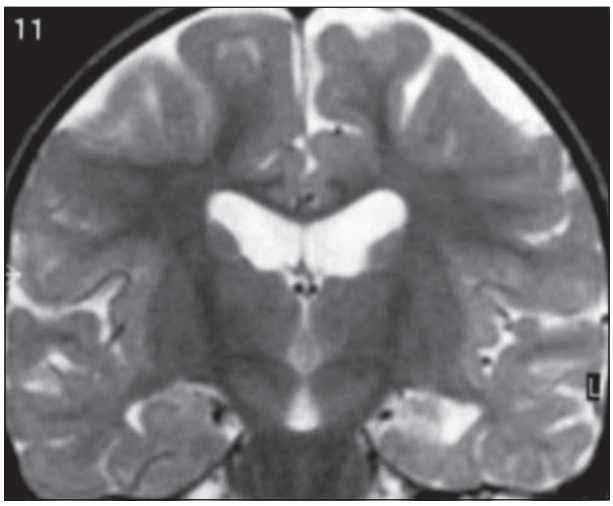

Figure 1. Coronal TSE T2-weighted image at three years of age shows increased signal of the left hippocampus and greater left temporal horn dilatation.

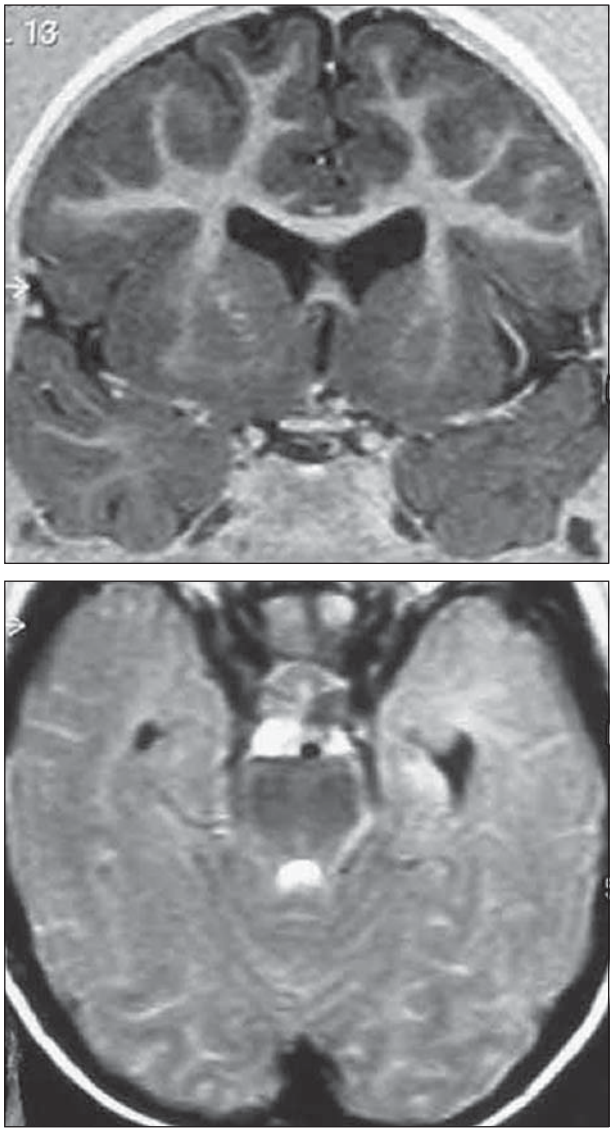

Figure 2. Coronal IR T1-weighted image (**A**), shows decreased signal in the left temporal white matter and temporal lobe atrophy. Axial T2-weighted image (**B**) confirms a markedly increased signal from the left hippocampus, and temporal horn dilatation.

Discussion

The present report describes the clinical history of a child who developed the typical clinical and EEG pattern of MMPSI, associated with a clear-cut, focal brain lesion in the left temporal lobe.

This lesion, consisting of a dual pathology of the temporal lobe, developed probably in the prenatal period. It is, in fact, less likely that such a lesion was caused by epileptic seizures alone, or by anoxic-ischemic damage, as it was unilateral and involved both the hippocampus and the neocortex.

Nonetheless, such a focal lesion may be associated with West syndrome (Asanuma *et al.* 1995, Cusmai *et al.* 1998, Chugani *et al.* 1990), leading to age-dependent, cortical hyperexcitability. The same mechanism may apply to the present case of MMPSI.

Indeed, this is not the clinical pattern of symptomatic temporal lobe epilepsy, in which seizures originate from the same brain region, although they might spread across different pathways.

Temporal lobe seizures starting between two and 24 months of age, tend to show no change with age (Acharya *et al.* 1997), and typical semiology includes symmetric motor phenomena of the limbs, postures similar to those seen in frontal lobe seizures in adults, and head nodding as in infantile spasms (Brockhaus and Elger, 1995), or hypomotor seizures, eyes opening or psychomotor arrest, with oroalimentary automatisms (Rathgeb *et al.* 1998). In our patient, hypomotor seizures with flushing of the face were quickly followed by occipital, rolandic or frontal discharges, migrating from one hemisphere to the other.

In addition, the well-known mesio-temporal lobe epilepsy syndrome is characterised by an initial event consisting of an usually prolonged febrile seizure in early childhood, followed by a silent interval (Cendes *et al.* 1993), or a period where seizures are well controlled with low/average doses of anticonvulsant medication. Temporal lobe seizures occur in late childhood and then remain relatively stereotyped, often becoming medically intractable. Hippocampal sclerosis is therefore unlikely to contribute to the pattern of migrating partial seizures in the present case.

Since the first description of MMPSI (Coppola *et al.* 1995), patients with very early seizure-onset (within the first day of life) (Hamaimess *et al.* 2006), others with congenital microcephaly (Gross-Tsur *et al.* 2004), and still others with slightly better outcomes (Marsh *et al.* 2005), have been reported. This raises the possibility of a wider clinical spectrum for this syndrome (Korff and Nordli, 2006) than was initially considered.

Our case adds new data, including a clear-cut, focal brain lesion that most likely preceded the onset of the disease. This raises the issue as to whether early surgical intervention could have changed the course of the disease. However, the migrating character of the electroclinical discharges and the well known difficulty in demonstrating neuroradiological focal brain abnormalities in the first year of life, did not suggest any surgical treatment, and, indeed at onset, MMPSI may consist of misleading, monofocal seizures (Gérard *et al.* 1999).

In conclusion, the case reported here fulfils the diagnostic criteria for migrating partial seizures in infancy associated with microcephaly and arrest of psychomotor milestones, independent of the temporal lobe lesion. □

Legends for video sequences

Video sequence 1 (four months old):
Prolonged left temporal discharge of rhythmic theta activity with no apparent clinical component. This seizure was overlooked by her mother. The child had a great number of seizures of this type over a 24-hour recording period.

Video sequence 2 (four months and seven days old):
Prolonged left temporal discharge during which a concomitant prolonged discharge of rhythmic theta waves over the right occipital region appears. The child is sleeping with no obvious clinical signs. The child continued to show this EEG pattern over several days.

Video sequence 3 (five and half months old): rhythmic theta discharges recorded over both hemispheres ending with left partial monomorphic theta and alpha activity. The child shows irregular breathing, increased salivation, and is poorly responsive.

Video sequence 4 (six months old):
Prolonged right occipital discharge associated with left facial and eyelid clonic jerks.

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