Original article with video sequences

Epileptic Disord 2011; 13 (1): 22-6

The efficacy of bromides, stiripentol and levetiracetam in two patients with malignant migrating partial seizures in infancy

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Received April 18, 2010; Accepted November 28, 2010

ABSTRACT – The syndrome of malignant migrating partial seizures in infancy is a devastating, age-specific, epileptic encephalopathy, which still presents an aetiological, pathophysiological and therapeutic problem. In this study, we present two patients who were diagnosed with the disease, based on electroclinical symptoms. The patients were treated with a combination of sodium bromide, stiripentol and levetiracetam. The first patient unequivocally responded, following a course of ineffective conventional drugs, and the second, who was diagnosed and treated immediately, showed a more significant therapeutic response. Antiepileptic drugs, previously reported to be beneficial in case reports, when given concomitantly, may substantially reduce the number and severity of seizures, without influence on psychomotor development. *[Published with video sequences]*

Key words: migrating partial seizures, bromide, stiripentol, levetiracetam, therapeutic effect, refractory epilepsy

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The syndrome of malignant migrating partial seizures in infancy (MMPSI) is a rare, age-specific epileptic encephalopathy with severe prognosis and unknown aetiology. MMPSI was first described in 1995 (Coppola *et al*., 1995) and approximately 50 patients have been reported to date (Coppola, 2009). Epilepsy is resistant to various combinations of AEDs. Reports of seizure control with potassium bromide (Okuda *et al*., 2000; Coppola *et al*., 2007), stiripentol with clonazepam (Perez *et al*., 1999) and levetiracetam (Hmaimess *et al*., 2006) have been previously published. Here, we report the efficacy of these drugs given in combination to two patients affected with this type of epilepsy.

doi:10.1684/epd.2011.0402

Patient 1

The first patient was the second child after an uneventful pregnancy (birth weight 2,720 g, length 51 cm). Her mother noticed eyelid twitches and blushing of the face in the first days of life. On admission she was two months old, irritable and without eye contact. Head circumference was 37.5 cm (45th percentile). Head lag was present and tone of the extremities was increased. She had many daily seizures, manifesting as lateral eye deviation, blinking, chewing, drooling, and flushing, as well as 4-20 seizures with elevation of one arm, clonic jerks of the arm and leg, and cyanosis. Routine haematological, biochemical and blood gas analyses, as well as metabolic screening of urine, amino acids in serum, very long chain fatty acids in serum and organic acids in urine were normal. Ocular funduscopic findings and brain magnetic resonance imaging (MRI) were normal. During the first month, several conventional inter-ictal EEGs showed basic theta activity and multifocal spikes. She was weaned off valproate and vigabatrin, and given vitamin B6 i.v., ACTH, nitrazepam, clobazam, carbamazepine, lamotrigine and zonisamide in various combinations, without evident therapeutic effect. Continuous infusion of midazolam was started in the intensive care unit. After a month, we became aware of the pattern of ictal discharges which originated successively from one area of the brain to another *(figure 1)*. She had 11-18 seizures at that time, with arm jerks and many discreet daily seizures. The diagnosis of MMPSI was considered, and sodium bromide was introduced (up to 80 mg/kg, in 10 mg/kg week increments). After three weeks, she had three to six seizures a day with arm jerks, and fewer discreet seizures. At the age of four months, stiripentol was added and raised to 100 mg/kg. After 15 days, seizures with jerks were reduced to one per day. She had transient worse episodes during intercurrent infections. At the age of 6.5 months, levetiracetam was administered at a dose of up to 60 mg/kg. With this combination of AEDs she had no seizures with arm jerk or tonic elevation, but had about 6-30 eye or head deviations per day. She was discharged from the hospital and was hypotonic and without psychomotor progress at the age of seven months.

Between 12 and 15 months of age, her mother reported three to four discreet focal seizures daily. She had progressive microcephaly at that time, and head circumference was in the 5th percentile. Her body weight and height were in the 50th and 25th percentile, respectively. During the periods of seizure worsening, she was given midazolam, lorazepam and phenobarbitone through an i.v. drip, and Chloraldurat as add-on therapy. Mechanical ventilation was used when needed, and she was fed by nasogastric tube. The girl died at the age of 20 months, affected by pneumonia and acute respiratory distress syndrome.

Patient 2

The second patient was a four-month-old female infant who was treated for a series of multifocal seizures from her third month of life with phenobarbitone, valproate, vitamin B6 and clonazepam. She was the second child to non-consanguineous parents. Pregnancy and delivery were uneventful (birth weight 3,000 g, length 51 cm). Her mother recalled jerks of extremities and lateral eye deviation from the second month.

When admitted she was calm, with rare spontaneous movements, without dysmorphic features and eye contact. Head circumference was 40 cm (40th percentile). She had pronounced head lag, hypertonia of the extremities, brisk tendon reflexes and positive ankle clonus. Extensive investigations revealed no neurometabolic aetiology. MRI of the brain showed slightly wider subarachnoid space on convexities of hemispheres.

From the first day, the seizures were almost continuous, manifesting as lateral deviation of the eyes and head, lateral eye jerks, tonic elevation of one or both extremities on one side, flushing, drooling or cyanosis. The first three minutes of the first EEG were indicative of MMPSI, showing focal discharges from various areas of both hemispheres *(see video sequence)*. During the first month of stay, four AEDs were consecutively introduced; first i.v. followed by oral levetiracetam, clobazam instead of clonazepam, sodium bromide and stiripentol. Her EEG improved with irregular basic activity and dominance of theta band (6Hz) and multifocal sharp waves. At six months of age, she had three to six clinically mild observable seizures per day. However, at follow-up her head circumference was 1 cm below the 5th percentile at the age of 15 months. She had no eye contact, blinked when exposed to bright light and was hypotonic with rare spontaneous movements. Tendon reflexes were brisk.

Discussion

This report documents the efficacy of bromides, stiripentol and levetiracetam in two children with clinical and electroencephalographic features of malignant migrating partial seizures in infancy, as described by Coppola in 1995 (Coppola *et al*., 1995). The epilepsy in this condition is highly refractory to old and new antiepileptic drugs. In some reports, seizures were controlled or significantly reduced with potassium bromide at a maximal dosage of 80 mg/kg per day without adverse effects (Okuda *et al*., 2000; Coppola *et al*., 2007) and two patients were also reported to respond well at unusually high doses of 124-600 mg/kg daily (Caraballo *et al*., 2008).

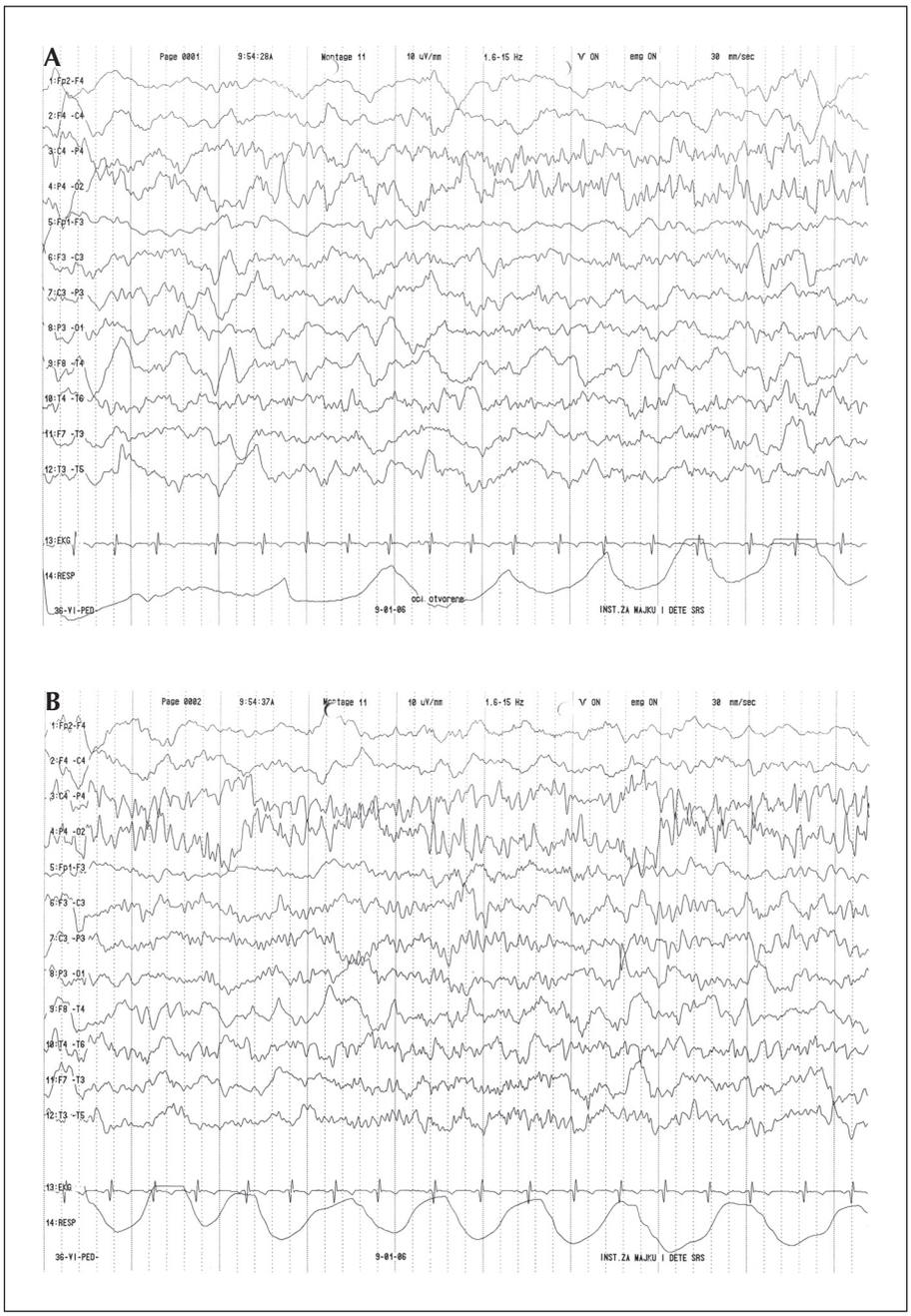

Figure 1. Ictal EEG of Patient one.
A) Onset of sharp alpha and theta discharge over the right centro-parietal region (time: 09:54:28).
B) Onset of rhythmic beta discharge from the fronto-centro-parietal left region, and simultaneous involvement of two different areas with discharges of different frequencies (time: 09:54:37).

We administered sodium bromide to the first patient at the age of three months. Relative therapeutic effect was evident after two to three weeks, although the seizures did not stop. The second patient was administered sodium bromide on day 15 after admission according to the same schedule with levetiracetam and clobazam as concomitant therapy, and after two weeks, the number of seizures was halved.

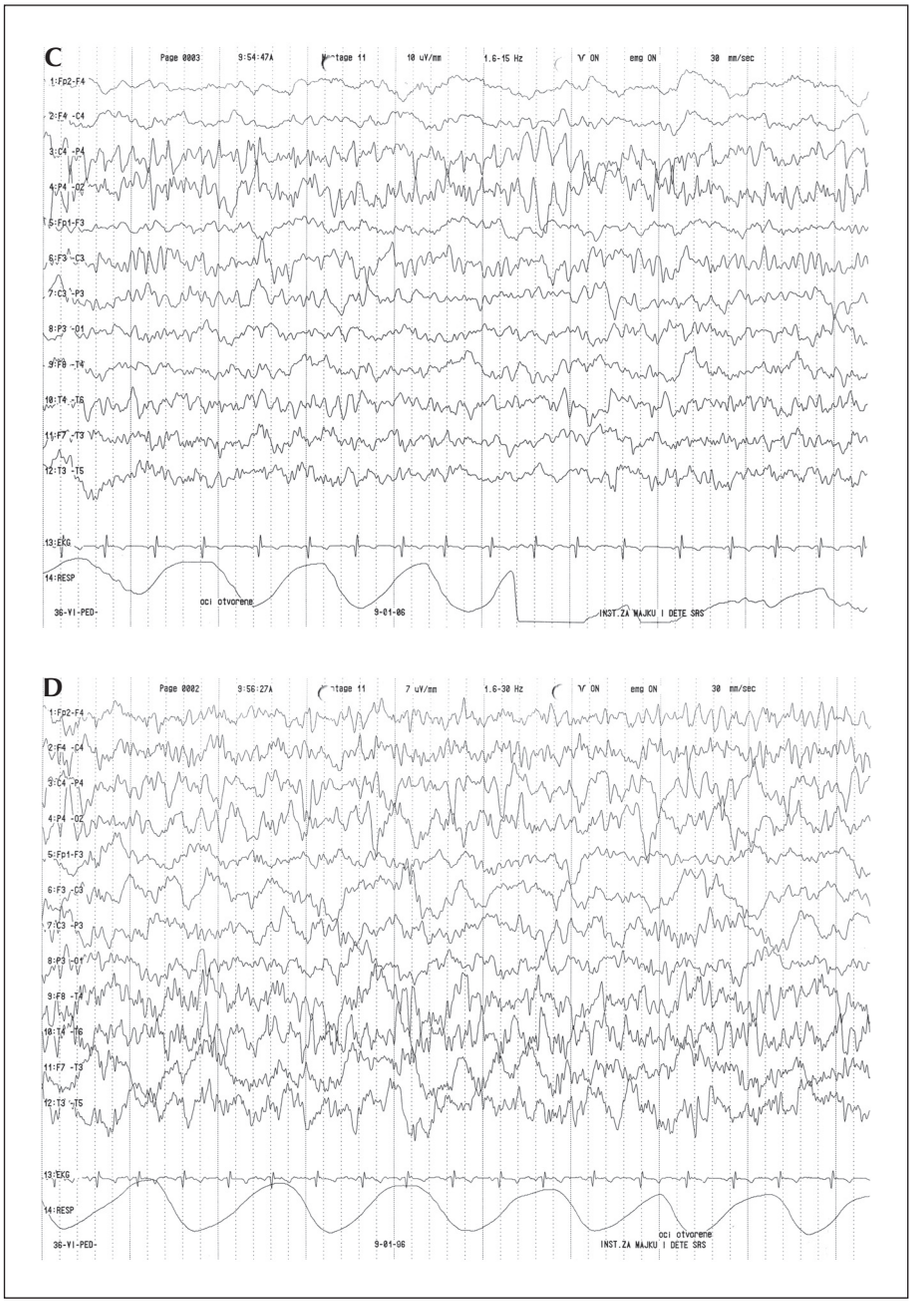

Figure 1. **C**) Frequency of discharges slows down (time: 09:54:47).
D) Rhythmic beta and alpha discharge from the right fronto-centro-temporal region with simultaneous rhythmic beta from the fronto-temporal left region (time: 09:56:27).

Stiripentol, a new allylic alcohol compound, is considered to exert its antiepileptic properties by increasing cerebral γ-aminobutyric acid (GABA) concentrations and also by inhibiting cytochrome P-450 which increases the levels and effect of other AEDs. The favourable response to stiripentol, in combination with clonazepam, was reported in two patients with MMPSI by Coppola (Coppola *et al*., 1995) and in

nine of 12 patients by Perez (Perez *et al*., 1999). In a controlled trial of severe myoclonic epilepsy in infancy, the authors found higher blood levels of clobazam and norclobazam after adding stiripentol. They concluded that stiripentol inhibits hydroxylation of the active metabolite norclobazam to hydroxynorclobazam, which could potentiate antiepileptic activity (Chiron *et al*., 2000).

Our first patient was given stiripentol at the age of four months. Its efficacy was evident in the first month of treatment, although the seizure clusters during intercurrent infections were not suppressed. The second patient received stiripentol as the last AED in the first month of stay, thus any efficacy could not be separated from that of levetiracetam or bromides. However, the average number of clinically recordable seizures was reduced by more than 50% after one month.

A beneficial effect of levetiracetam was previously reported in one patient with a reduction of seizures from 186 to 66 per day, on the eighth day of therapy (Hmaimess *et al*., 2006). We introduced levetiracetam to the first patient at 6.5 months, which was followed by a disappearance of "bigger seizures". The second patient received levetiracetam i.v. in a loading dose of 60 mg/kg, but without any immediate effect and a subsequent AED was given after several days. Although the effect of any individual AED could not be assessed, the frequency of seizures dropped after two months.

In conclusion, the two cases reported here fulfil the diagnostic criteria for malignant migrating partial seizures in infancy. The patients were treated with all AEDs previously reported to be beneficial. One patient had an unequivocal response and the other a more significant improvement, but without complete seizure control. Early introduction of potentially efficacious AEDs did not prevent psychomotor arrest. Further investigation of MMPSI and identification of the specific pathophysiological processes is necessary before efficacious management of these patients becomes possible. □

Disclosure.
None of the authors has any conflict of interest or financial support to disclose

Legend for video sequence

Mixed theta, delta, and alpha basic activity and multifocal sharp-slow wave complexes.
Left temporal-occipital alpha (11 Hz) discharge (8 seconds) with concomitant right temporal-occipital discharge (6 seconds) and high voltage sharp waves were followed by slight attenuation of activity over both hemispheres (time: 19:01:08).
The first clinical seizure manifestations were eye opening and blinking (time: 19:01:16). Right alpha-beta discharge (14 seconds) was followed by sharp-slow wave complexes with discreet blinking at the end of the discharge (time: 19:01:24).
Subclinical rhythmic alpha discharge over the right hemisphere lasted 11 seconds (time: 19:02:07). Left parieto-temporo-occipital alpha, theta discharge (14 seconds) (time: 19:02:24) and right temporo-occipital discharge intermixed with high voltage waves (time: 19:02:36) was then recorded with ensuing attenuation of basic activity and slow waves and fluctuating asymmetry.
Seizure manifested with tonic elevation of the left arm and, to a slightly lesser extent, the leg, eye opening and turning of head and eyes from right to left. This was followed by axial tonic contraction and (during attenuation) slow blinking and mastication movements (time: 19:02:40).

References

Caraballo RH, Fontana E, Darra F, *et al*. Migrating focal seizures in infancy: analysis of the electroclinical patterns in 17 patients. *J Child Neurol* 2008; 23: 497-506.

Chiron C, Marchand MC, Tran A, *et al*. Stiripentol in severe myoclonic epilepsy in infancy: a randomized placebo-controlled syndrome-dedicated trial. STILCO study group. *Lancet* 2000; 356: 1638-42.

Coppola G. Malignant migrating partial seizures in infancy: an epilepsy syndrome of unknown etiology. *Epilepsia* 2009; 50(Suppl. 5): 49-51.

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

Coppola G, Operto FF, Auricchio G, D'Amico A, Fortunato D, Pascotto A. Temporal lobe dual pathology in malignant migrating partial seizures in infancy. *Epileptic Disord* 2007; 9: 145-8.

Hmaimess G, Kadhim H, Nassogne MC, Bonnier C, van Rijckevorsel K. Levetiracetam in a neonate with malignant migrating partial seizures. *Pediatr Neurol* 2006; 34: 55-9.

Okuda K, Yasuhara A, Kamei A, Araki A, Kitamura N, Kobayashi Y. Successful control with bromide of two patients with malignant migrating partial seizures in infancy. *Brain Dev* 2000; 22: 56-9.

Perez J, Chiron C, Musial C, *et al*. Stiripentol: efficacy and tolerability in children with epilepsy. *Epilepsia* 1999; 40: 1618-26.