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Topiramate efficacy in an infant with partial seizures refractory to conventional antiepileptic drugs

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Many studies showed that Topiramate (TPM) may be a useful drug in a wide spectrum of childhood epilepsies. We report a 3-month-old female with stormy onset of secondarily generalized partial seizures. She showed a high seizure frequency and a progressive worsening electroencephalogram (EEG), despite standard antiepileptic drugs administration. TPM succeeded in controlling seizures, even after the other drugs were discontinued. This case suggests that TPM may represent a good choice for the treatment of partial seizures refractory to conventional drugs in infants.

Key words: topiramate; efficacy; infancy; partial seizures; drug-resistant.

INTRODUCTION

Topiramate (TPM) is a sulfamate-substituted monosaccharide that modulates the voltage-gated sodium and calcium channels, blocks the kainate/AMPA type of glutamate receptors and increases the GABAergic inhibition at a unique site on the GABA receptor[1,2].

Experience in children have been limited, but TPM has been demonstrated to be effective in children with refractory partial seizures[3,4], Lennox–Gastaut syndrome[5,6] and refractory infantile spasms[7] as well as severe myoclonic epilepsy in infancy[8].

Here we report the experience of TPM treatment in a 3-month-old infant with refractory seizures.

CASE REPORT

A 15-month-old female was admitted at the age of 3 months to our Department because of new onset of partial seizures. They were characterized by paleness, stertorous breathing, staring, sometimes conjugate tonic deviation of eyes without a preferential side, that often progressed to a generalized stiffness and jerks at the forelimbs. The episodes were frequent (5–10 daily) and had an average duration of 1–2 minutes. The family history was unremarkable. The perinatal period was normal. At first seizure onset, she was treated with Phenobarbitone, obtaining only a transitory improvement; Diazepam at first, then Clonazepam were been added-on. Moreover, Pyridoxine 100 mg a day over 7 days was given, without any response. At the time of the first admission to our Department, she was drowsy and poorly reactive to stimuli with poor spontaneous motility. Seizures were frequent and presented the same clinical features. Some episodes were recorded, which corresponded to depression of EEG activity (sometimes starting from the left hemisphere, sometimes from the right) followed by rapid generalization of the abnormalities. We introduced Valproic Acid (VPA) and continued administrating Pyridoxine, Phenobarbitone and Clonazepam. The Griffiths Developmental Scale for Children was low, documenting a Development Quotient (DQ) of 37 (see Fig. 1). The brain MRI was normal. A polygraphic video-EEG recorded during sleep revealed quite good organization with sporadic focal epileptic abnormalities, not activated by sleep. Over the next days, seizures became more frequent (up to 20 episodes daily), even when the VPA dosage was progressively increased

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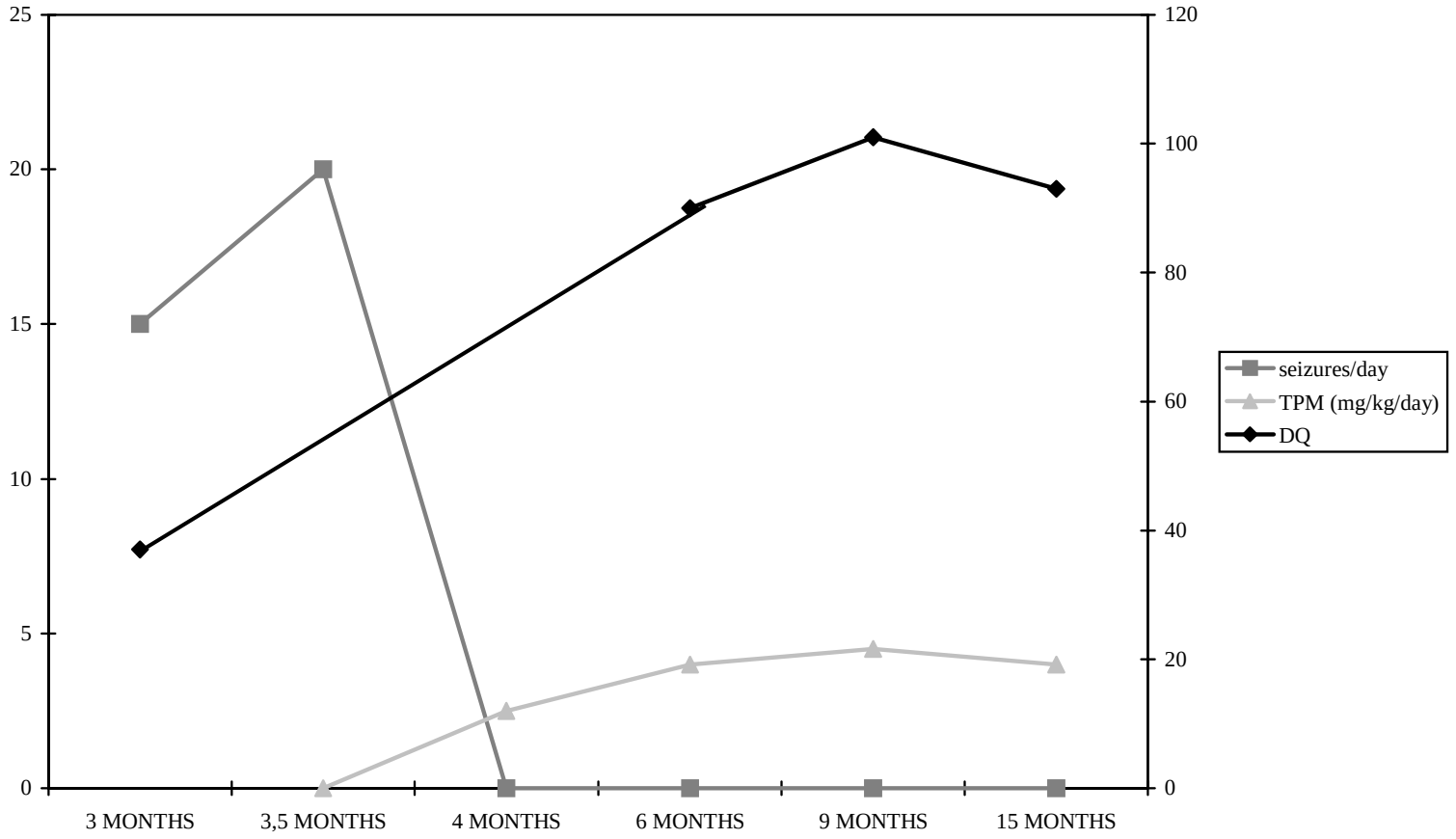

Fig. 1: Clinical and psycomotor course.

(to 37 mg/kg/day). Moreover, the subsequent two video-EEG recordings (1 and 2 weeks after seizure onset) showed a progressive loss of organization with multifocal abnormalities, very similar to a modified hypsarhythmia. At the same time, we recorded infrequent spasms which corresponded to diffuse high amplitude slow-waves. Considering the progressive clinical and EEG worsening, we decided to reduce the VPA dosage and to introduce TPM starting at 1.3 mg/kg/day, with daily increases of 0.3 mg/kg. This choice allowed a quick reduction of seizure frequency with a complete remission when she was administered 2.5 mg/kg/day of TPM. A second admission was arranged when she was 6 months old. She was seizure free and still receiving Phenobarbitone at a low dosage, and TPM (4 mg/kg/day). The EEG was normal. A neurological examination showed improved responsiveness, and the DQ was 90 (see Fig. 1).

Now, at the age of 15 months, she is still receiving TPM in monotherapy (4 mg/kg/day) and is seizure free; neurological examination and EEG are normal and she has a DQ of 90 (see Fig. 1).

DISCUSSION

As regards the diagnosis, the early seizure onset, at 3 months of age, and the patient's poor condition suggested a symptomatic epilepsy. Nevertheless, the neuroimaging was normal, metabolic disease was investigated and excluded. Pyridoxine-dependent epilepsy was a possible diagnosis from a clinical and EEG point of view[9], but our patient was not responsive to the Pyridoxine administration. The multifocal interictal abnormalities and the variability of the epileptogenic focus (from both hemispheres) led us to consider migrating partial seizures of infancy[10]. Moreover, we observed no seizures simultaneously affecting different areas of the cortex, and a favourable outcome followed, excluding this diagnosis. We considered the hypothesis of an idiopathic partial epilepsy, similar to those described by Watanabe and Okumura[11] since the perinatal history was unremarkable and the psychomotor development was normal before seizure onset; however, the high seizure frequency, the occurrence of epileptic spasms and the progressive interictal EEG worsening with modified hypsarhythmia ruled those out. As regards the therapy, our patient was unresponsive to conventional antiepileptic drugs: Phenobarbitone (up to 9 mg/kg/day) and VPA (up to 37 mg/kg/day), Clonazepam (up to 0.24 mg/kg/day) and Diazepam (up to 0.6 mg/kg/day) were ineffective. We chose TPM given its effectiveness in controlling both partial and generalized seizures and spasms and given its good safety profile. TPM efficacy in infancy has not been described in literature. TPM started to be effective at only 2.5 mg/kg/day and we increased the dose to 4 mg/kg/day. After 1 year of treatment with TPM in monotherapy, the patient was still seizure free and we observed no adverse effects, such as irritability, weight loss, anhydrosis or cognitive deterioration. We know that a single case does not prove TPM efficacy in infants, but we think that further clinical reports and controlled studies of TPM administration in infancy are needed in order to gain better knowledge of this drug in this age group.

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