

Letters

Original letter subject to peer review

Electrical Status Epilepticus of Sleep in Association with Topiramate

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To the Editor:

Most studies suggest that the majority of children taking antiepileptic drugs (AEDs) do not experience clinically relevant cognitive or behavioral adverse events from these medications (1). However, there are a few instances in which the AED may induce serious cognitive decline. We report the occurrence of electrical status epilepticus of sleep (ESES) induced by topiramate (TPM) in a 5-year-old boy with refractory epilepsy.

This 5-year-old boy is the first child of unrelated parents, born after an uneventful pregnancy. Developmental milestones were delayed, and he had refractory epilepsy since age 18 months. At age 5 years, he had several drop attacks and myoclonic and tonic seizures, daily. EEG showed multifocal spikes, and generalized spike-and-wave complexes, <85%. He was using lamotrigine (LTG), 100 mg/day, and clobazam (CLB), 10 mg/day, when TPM was introduced gradually until 200 mg/day. Seizures improved markedly, but he still had one or two myoclonic seizures a week. Despite that, the family stopped giving him LTG abruptly, without medical advice.

Symptoms started gradually, and 11 months after the introduction of TPM, his family reported that he was more somnolent, and 1 month later, it was clear that there was a compromise of previously acquired abilities.

Neurologic examination showed only diffuse hypotonia and wide-based gait. Complete blood count (CBC), platelets, Na⁺, K⁺, glucose, blood urea nitrogen (BUN), liver enzymes, evoked potential (visual and brainstem), amino acids, and organic acid chromatography were normal. There were no signs of metabolic acidosis. Magnetic resonance imaging (MRI) was normal. At this time, the EEG showed very frequent, almost continuous, generalized spike-and-wave complexes during >90% of slow sleep (Fig. 1). TPM was discontinued, and when the drug was being tapered off, he already started to improve. One month after drug discontinuation, he recov-

ered completely and returned to his previous neurologic background. Two months after complete drug discontinuation, EEG showed marked improvement, although there was still some slowing and epileptiform activity (Fig. 2). He is currently taking CLB and has weekly tonic and myoclonic seizures.

ESES results from the association of various seizure types. The characteristic EEG pattern consists of continuous (>85%) spikes and slow waves during non-rapid eye movement (REM) sleep, and the abnormality is substantially less frequent during the awake state and REM sleep. This condition is associated with neuropsycholog-

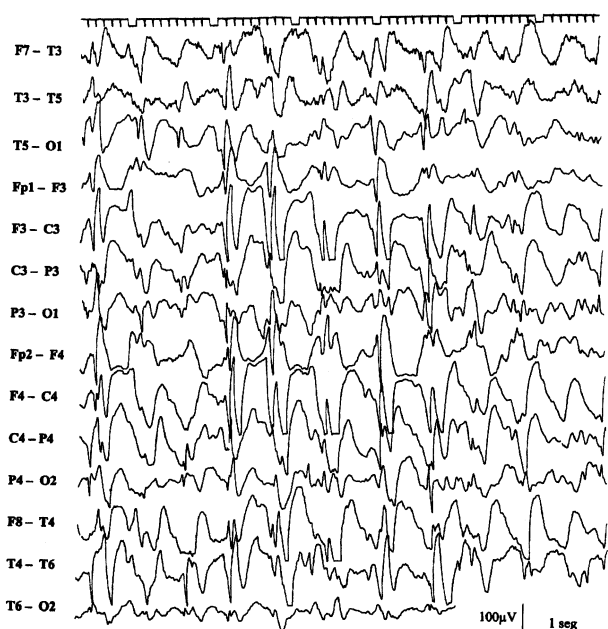


FIG. 1. Sleep EEG showing very frequent generalized spike-and-wave complexes, more pronounced at the frontocentral regions of the brain. This sample was recorded when the patient was taking topiramate and showed cognitive impairment and compromise of previously acquired abilities.

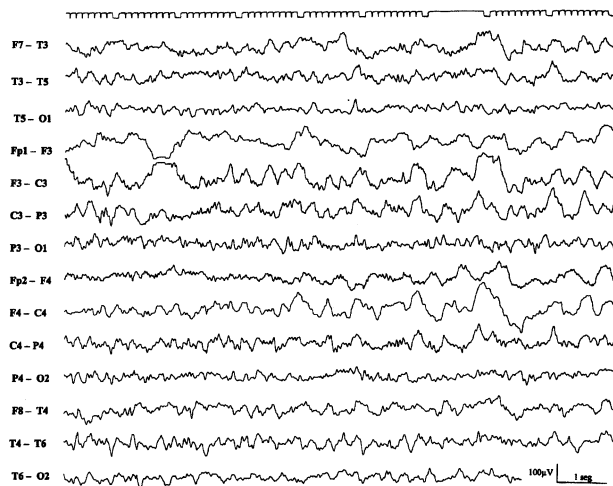


FIG. 2. Sleep EEG showing marked improvement of epileptiform abnormalities. This sample was recorded 2 months after complete cessation of topiramate.

ical deterioration, and although there is improvement in adolescence, some residual neuropsychological dysfunction may occur (2–4).

When assessing cognitive impairment in patients with epilepsy, it is always difficult to establish whether the neuropsychological abnormality is related to the etiology of epilepsy, seizure frequency, or neurobehavioral effect of the AED.

Our patient had a secondary generalized epilepsy, most likely Lennox–Gastaut syndrome. After TPM introduction, he had improvement in seizure frequency and no more tonic seizures. There also was a change in the EEG pattern characterized by continuous spikes and waves during slow sleep (>90%), without bursts of fast rhythms at sleep. Although sometimes the differential diagnosis between Lennox–Gastaut syndrome and ESES is difficult to establish, it is clear that after 12 months of TPM use, there was a change in seizure and EEG patterns. At this time, the clinical and EEG findings were consistent with ESES, according to the International League Against Epilepsy (2): (a) benign presentation of seizures, without tonic seizures; (b) neuropsychological deterioration; and (c) continuous spikes and waves during slow sleep (>85%).

It is known that epilepsy can be aggravated by AEDs. Few studies provide details about the type of epileptic syndrome and seizure aggravation by AED. Most of the time, seizure worsening is not associated with cognitive impairment/encephalopathy. AED-induced encephalopathy without seizure worsening is unusual (5,6).

ESES induced by AEDs has been reported in children with benign rolandic epilepsy. In these children, carbamazepine (CBZ) was associated with an increase in seizure frequency characterized by atypical absences and falls. EEG showed continuous spike-and-wave dis-

charges during sleep, and the condition improved after drug discontinuation (5,7).

We conclude that although it is difficult to confirm the causal relation between TPM and ESES, the response to TPM discontinuation was impressive. We believe that in this case, the occurrence of ESES may have been induced by TPM. Patients receiving TPM should be carefully monitored for cognitive and behavioral abnormalities. In case of neuropsychological deterioration, a sleep EEG should be performed to rule out ESES.

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Midline Spikes in Children and Clinical Correlations

To the Editor:

Kutluay et al. (1) highlighted midline spikes and associated seizure semiology, a subject that has previously received little attention, as reviewed elsewhere (2). Midline spikes alone were found in 35 (0.2%) of 20,000 EEGs. These commonly occurred in children and were significantly associated with heterogeneous types of focal and generalized seizures of idiopathic (16 cases), symptomatic (13), or undetermined cause (6). Onset of seizures was mainly between ages 1 and 6 years (21 of 35 cases) (1). Midline spikes were facilitated by sleep or occasionally seen only during sleep (1).

We supplement these observations with our results from an ongoing prospective study from 1998 (3,4). At the end of the first 3 years, we had recorded 424 EEGs in 308 children aged 1–14 years; 228 (74%) had one or more epileptic seizures. All EEGs were recorded digitally, which allows optimal study of midline and other spike

locations; in old paper EEGs, midline spikes are not detected in montages that do not include midline electrodes. Of 228 patients with seizures, 21 (9.2%) had at least one EEG with midline spikes alone (six, or 2.6%) or together with spikes in other, usually multiple, locations (15, or 6.6%). Midline spikes were frequently of high

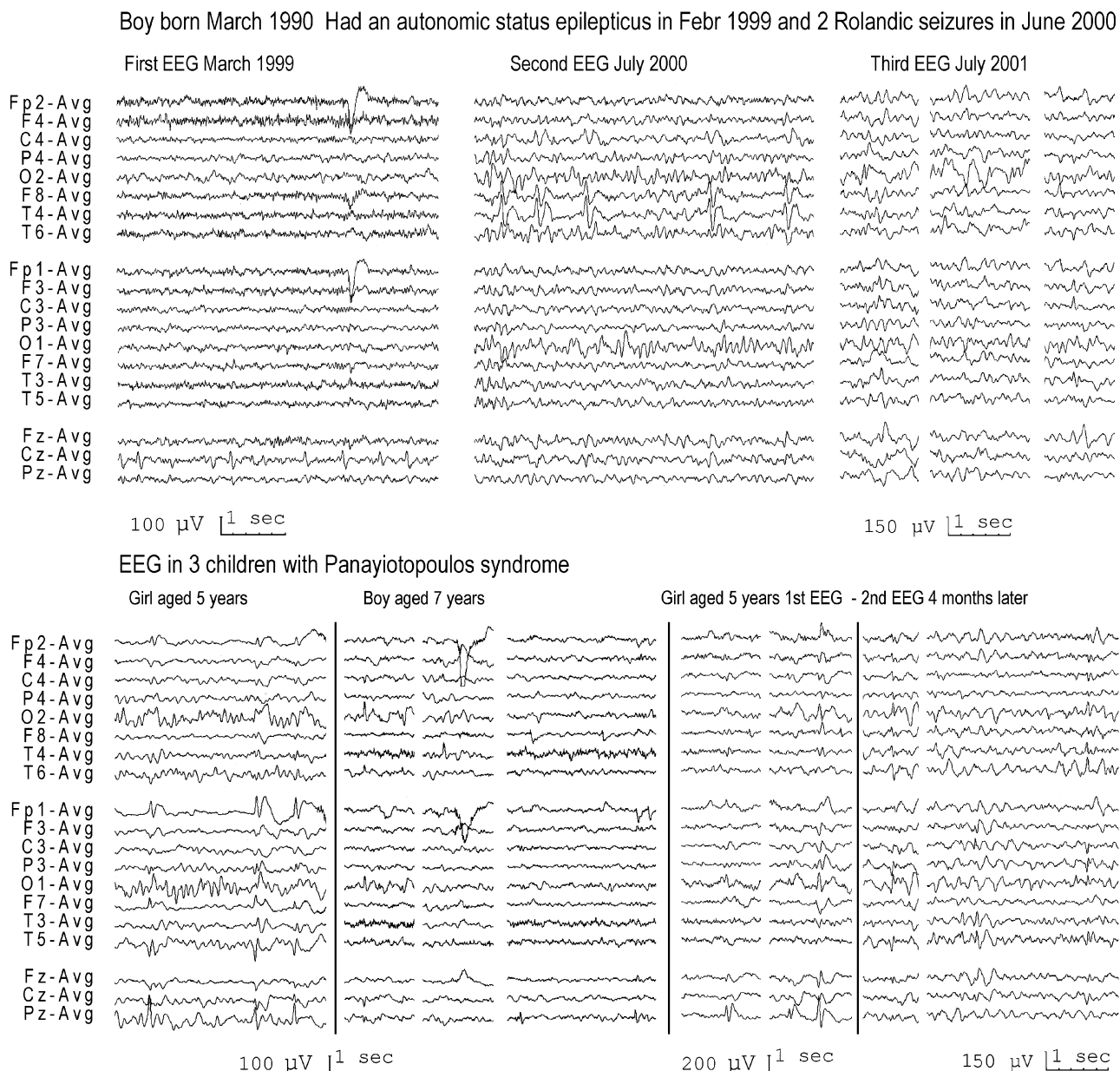


FIG. 1. Top: EEGs of a child with Panayiotopoulos syndrome. At age 9 years, he had pure autonomic status epilepticus that lasted for 4 h. He felt tired, complained of headache, became agitated, and was very pale. Within 5 min, he started banging his head on the wall and soon became unresponsive and floppy “like a rag doll.” He was doubly incontinent, his eyes were widely open, and pupils were markedly dilated. At this stage, he vomited vigorously. Recovery without convulsions started 4 h from onset. He did not convulse at any stage. One day a year later, he had two left-sided rolandic seizures of unilateral facial twitching, each lasting 5–10 min. The first EEG had only midline spikes at Cz electrode, occasionally forming an ill-defined dipole with F4 positivity. The second EEG had centrotemporal spikes forming a dipole with midline positivity. There were no midline spikes. Occasionally a positive occipital spike also was recorded. The third EEG had infrequent and scattered small spikes mainly at O2 and C3 electrodes. **Bottom:** Interictal EEGs of three children with typical seizures of Panayiotopoulos syndrome. **Left:** Repetitive multifocal spike–wave complexes with midline spikes. **Middle:** Independent multifocal spikes at various locations including midline spikes. **Right:** First EEG had predominantly midline spikes alone or synchronous with other spikes, but the second EEG 4 months later had multifocal spikes in other than midline locations.

amplitude and in clusters but could also be small, singular, and sparse (Fig. 1). For comparison, occipital spikes alone or with other, including midline, spikes were found in 36 (16%) cases. Centrottemporal spikes alone or with other, including midline, spikes were found in 48 (21%) cases.

Five of the six patients with at least one EEG having midline spikes only had normal development. These had febrile seizures (one case), rolandic epilepsy (one), Panayiotopoulos syndrome (one), occipital and a single complex partial seizure (one), and brief seizures with loss of consciousness only (one). The only symptomatic case had generalised convulsions. In follow-up EEGs of these 6 children, none of them had only midline spikes alone (fig). Instead, midline spikes occurred together with centrottemporal, occipital or other spikes in various combinations (3 patients), disappeared but spikes were seen in other locations (1) or EEGs were normalised (2).

Significantly, of the 21 patients with midline spikes alone or in combination with other spikes, six had definite Panayiotopoulos syndrome (another four were possible cases of the same syndrome) manifesting with single or infrequent autonomic seizures, autonomic status epilepticus, or both (4,5). Conversely, midline spikes were present in 15% of patients with this syndrome (4).

Our results are generally in agreement with those of Kutluay et al. (1), but it appears that midline spikes (a) are much more frequent than previously appreciated (which is attributed to improved detection with digital EEGs); (b) usually occur together with spikes in other locations; more rarely, they occur alone, but this is not a consistent localisation in serial EEGs of the same patient; and (c) are significantly associated with benign childhood focal seizures and particularly with Panayiotopoulos syndrome.

From a practical point of view, an EEG with midline and multifocal spikes in a normal child with a single or a few seizures should raise the possibility of benign childhood seizures and particularly of Panayiotopoulos syndrome of autonomic seizures and autonomic status epilepticus (2,4,5).

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Response

To the Editor:

We read with interest the report of Sanders et al. on the results of their ongoing prospective study. In their study, the authors found isolated midline spikes in six (2.6%) of 228 patients, compared with a frequency of 0.2% in our study (1). They postulate that the higher frequency in their study is due to an improved detection with digital EEG. Although the latter might indeed help to detect cases otherwise missed with paper EEG, especially when midline electrodes are not used, a number of differences between the two studies also could explain this discrepancy. For instance, in our study, we included in the denominator all EEGs performed in our laboratories, including those of neonatal, pediatric, and adult patients. In the study by Sanders et al., only children ranging in age from 1 to 14 years were included. In addition, the majority (74%) of patients included in their study had seizures, whereas the percentage of patients referred to our laboratories for a seizure disorder is substantially lower. Finally, in our study, the denominator included all EEGs performed over a 10-year period, whereas the denominator in the study by Sanders et al. consisted of the number of patients, many of whom had sequential EEGs.

Based on our findings, we have to disagree with the conclusion of the Sanders et al. stating that midline spikes are significantly associated with benign childhood focal seizures and particularly with the Panayiotopoulos syndrome. None of our patients with isolated midline spikes had seizure semiology that was consistent with either of those two electroclinical syndromes, despite a careful characterization of the semiologies based on a review of the medical records and telephone interviews with patients or their parents when needed.

We strongly believe that to start defining the electroclinical syndrome of midline spikes, it is imperative to exclude patients with any other additional epileptiform discharges. Midline spikes can be associated with focal epileptiform discharges at other locations in various epilepsy syndromes, including patients with benign epilepsy of childhood with centrottemporal sharp waves (2). In our study, all patients had isolated midline spikes, and all patients displayed the epileptiform activity during wake-

fulness. Only with the application of strict criteria will we be able to characterize better the clinical features, semiology, and neuroimaging abnormalities associated with this syndrome.

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