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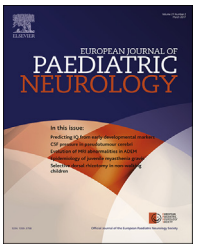

Original article

Topiramate in childhood epileptic encephalopathy with continuous spike-waves during sleep: A retrospective study of 21 cases

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ABSTRACT

Objective: Encephalopathy with continuous spike-wave during sleep (CSWS) is a particularly difficult-to-treat childhood epileptic syndrome. This study sought to present the EEG improvement and clinical efficacy of topiramate (TPM), a broad spectrum antiepileptic drug (AED), in a series of 21 children with CSWS encephalopathy.

Methods: We retrospectively reviewed the EEG results and clinical data of children with CSWS followed-up in our institution and treated with TPM. Sleep EEGs were performed 0–3 months prior to TPM introduction and then at 3 and 12 months. The exclusion criteria were (1) introduction of another AED and (2) withdrawal of a potentially aggravating AED during the first 3 months of treatment. In addition to spike index (SI), the severity of EEG abnormalities was rated using an original scale that also considered the spatial extent of interictal epileptiform discharges.

Results: 21 patients were included (18 males, 4-14y, three symptomatic cases). At 3 months, sleep EEG was improved in 14 and normalized in four (TPM doses: 2–5.5 mg/kg/day). Among these 18 patients, 16 manifested cognitive or behavioural improvement. In a subgroup of seven patients with frequent seizures, five became seizure-free and one had over 75% decrease in seizure frequency. At the one-year follow-up, 20 children were still on TPM and 10 exhibited persistent EEG improvement without any other AED being introduced, most of them with clinical benefits.

Conclusion: TPM can decrease EEG abnormalities in epileptic encephalopathy with CSWS, achieving clinical improvement in the majority of patients. However, relapse may occur in the long-term in nearly half of cases. Otherwise, TPM has proven particularly useful in reducing seizure frequency in refractory cases.

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1. Introduction

Encephalopathy with continuous spike waves during sleep (CSWS) is an epileptic syndrome affecting children, characterized by cognitive or behavioural degradation associated with a particular age-dependant electroencephalography (EEG) pattern, with or without clinical seizures. There is currently no consensus on the definition of this EEG pattern.[1] Classically, diagnosis requires observation of diffuse epileptiform discharges with a spike index (SI) superior to 85% during sleep.[2] Yet this definition is probably too restrictive, potentially reflecting only the "tip of the iceberg".[3] Several authors have, in fact, widened their definition to include an SI inferior to 85%, and no SI cut-off has so far been specified in the International League Against Epilepsy (ILAE) definition of 1989.[4,5] The causes of encephalopathy with CSWS include early structural lesions in about 40% of cases and genetic factors, most frequently GRIN2A mutation, though the aetiology remains undetermined for a significant proportion of patients.[6,7] Decreases in interictal epileptiform discharges (IED) have been linked to clinical improvement.[8]

In the absence of any randomized controlled trial (RCT) data, there are currently no evidence-based therapeutic guidelines available. The treatments usually considered are: (1) standard antiepileptic drugs (AEDs) like valproate (VPA), levetiracetam (LEV), sulthiame (STM); (2) benzodiazepines; (3) corticosteroids.[9] Nevertheless, many children are drug-resistant. There is also no methodological consensus on EEG abnormality quantification and treatment efficacy evaluation.

Topiramate (TPM) is a "broad spectrum" AED with multiple mechanisms of action, including carbonic anhydrase inhibition, sodium channel blockage, GABAergic activity, and decrease in glutamate-mediated excitation via the AMPA/kainate receptor.[10] TPM has been proven effective in RCTs as add-on therapy in the following epileptic syndromes of childhood: symptomatic focal epilepsy, idiopathic generalized epilepsy with tonic-clonic seizures, and Lennox-Gastaut syndrome.[10] Open studies have also suggested TPM efficacy in West syndrome and Dravet syndrome.[11,12] Until now, the efficacy of TPM has never been specifically studied in CSWS encephalopathy. Positive results have been suggested in some large case series of refractory childhood epilepsies.[11,13]

This retrospective study sought to evaluate, over the long and short term, EEG findings and clinical response to TPM in a series of 21 children with CSWS encephalopathy.

2. Methods

We retrospectively reviewed EEG and clinical data from children with epileptic encephalopathy associated with CSWS followed-up in our institution and treated with TPM. The following inclusion criteria applied: (1) cognitive or behavioural degradation in relation with abundant epileptic activity on sleep EEG; (2) bilateral IED significantly increased during sleep, with an SI of at least 50%; (3) sleep EEG performed 0–3 months before TPM initiation, and then at 3 and 12 months; (4) availability of clinical history, brain magnetic resonance imaging (MRI), and IQ scores. The exclusion criteria were: (1) introduction of another AED and (2) withdrawal of a potentially aggravating AED, such as carbamazepine (CBZ) or oxcarbazepine (OXC), during the first 3 months of TPM treatment. The dosages and titration of the TPM varied depending on the clinician's choice.

SI was defined as the percentage of 1-second periods of EEG containing at least one spike-wave, as described by Aeby et al.[14] Overnight EEG was monitored during the first hour of sleep by three neurologists (VdB, FL, and PV). In addition to SI, the severity of EEG abnormalities was rated a posteriori using an original gradation scale, also taking into account the spatial extent of the IEDs, as described in Fig. 1. This scale was based on a score resulting from two numbers between 0 and 4 multiplied together, the first being the SI, the second reflecting the spatial distribution of IEDs. The scale included six grades, from 0 (no EEG abnormality) to 5 (continuous generalized IEDs during more than 80% of sleep). Some examples of sleep EEG recordings with their corresponding grade are shown in Supplementary Materials. EEG improvement was defined as a decrease by at least one grade.

All children were hospitalized in our institution during topiramate treatment. They benefitted from multidisciplinary care with speech therapy, occupational therapy, education and for some of them neuropsychological and psychomotor therapy. IQ was performed 1–11 months before TPM introduction (mean 2,7 months). IQ scales used were WISC-III, Hiskey Nebraska or KABC.

Clinical evaluation was based on neuropsychological, psychological, and speech therapist qualitative reports and/or quantitative assessments, as well as remarks from the family and clinicians taken from the medical files. The clinical data was reviewed independently by a neuropsychologist (PM) and paediatric neurologist (CB), neither of whom were directly involved in the children's treatment, both blinded to the EEG results. At 3 months, the cognitive and behavioural aspects were considered separately. At 1 year, only the clinical global tendency was considered. Clinical outcome was defined as improvement, no significant change, or aggravation. Evolution was considered positive if majority of therapists described improvement, stable if only a slight progress was noted or quantified evaluation showed no change, and negative if therapists described no improvement or regression, or quantified evaluation showed degradation.

The number of seizures was taken from family and nursing reports.

3. Results

3.1. *Patients (Table 1)*

From 1999 onwards, 32 children had been treated with TPM in our institution for CSWS and cognitive or behavioural disturbance. We did not include 11 as they did not fulfil inclusion criteria, primarily due to lack of EEG data. Data from 21 patients was analysed, which included 18 boys aged 4y4m to 14y with global IQs of between 44 and 121. MRI was normal in all but three children. GRIN2A mutation was found in one case.