Seizure (2006) **15**, 649—652

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CASE REPORT

Topiramate treatment for nocturnal frontal lobe epilepsy

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Received 24 January 2006; received in revised form 5 July 2006; accepted 14 July 2006

KEYWORDS
Sleep;
NFLE;
Topiramate

Summary

Purpose: Aim of this study was to evaluate the efficacy and tolerability of the antiepileptic drug topiramate (TPM) in a sample of patients with nocturnal frontal lobe epilepsy (NFLE).
Methods: A 24 patients with video-polysomnographically confirmed NFLE received topiramate as single or add-on therapy. They all completed diaries concerning the seizures frequency and complexity and underwent to periodic follow-up visits. We classified the patients as: seizure-free, responders or non-responders.
Results: 15 M; 9 F; mean age 29.3 ± 10.4 years. The video-polysomnographic recordings showed a wide spectrum of seizures, ranging from repeated stereotypic brief motor attacks to prolonged attacks, with complex and bizarre behaviour; the recorded episodes occurred during non-REM sleep, both stage 2 and stage 3—4. The EEG during wakefulness was normal in all the patients, while seven of them showed epileptiform abnormalities during polysomnography. TPM was administered as single or add-on therapy from 50 to 300 mg daily at bedtime. The follow-up duration ranged from 6 months to 6 years. The patients were classified as: seizure-free = 6 (25%); responders (reduction of at least 50% of seizures) = 15 (62.5%); non-responders = 3 (12.5%). The adverse events were: weight loss (6 pts, 25%); paresthesias (3 pts, 12.5%); speech dysfunction (2 pts, 8.3%). All the adverse events disappeared within 3 months.
Conclusions: In our experience, TPM seems to be effective in about 90% of patients with NFLE. Few of them experienced transitory adverse events. TPM could be included in the options for patients with this form of epilepsy.

Introduction

In the last years, a distinct form of clear-cut seizures arising from epileptic foci located within the frontal

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1059-1311/$ — see front matter
doi:10.1016/j.seizure.2006.07.002

lobe (in particular in mesial and orbital cortices) and emerging almost exclusively from sleep has been described with the term of nocturnal frontal lobe epilepsy (NFLE).[1–4] Seizures are characterized by a wide spectrum of clinical features: assumption of postures, rhythmic and repetitive movements of arms and legs, rapid uncoordinated movements, with dystonic or dyskinetic components, complex motor activities (deambulation, wandering, pelvic thrusting), sudden elevation of the trunk and head associated with expression of fear and vocalization.

Provini et al.[4] in a series of 100 consecutive patients with NFLE emphasized the usefulness of a clinical distinction of motor manifestations into three subgroups—(a) paroxysmal arousals: brief (<20 s) episodes characterized by sudden eye opening, head raising or sitting up in bed, often with a frightened expression and sometimes vocalization; (b) nocturnal paroxysmal dystonia: episodes of intermediate duration (20 s—2 min) characterized by wide, often ballistic movements, dystonic posturing or choreoathetoid movements of head, trunk and limbs and vocalization[3]; episodic nocturnal wandering: episodes of longest duration (1—3 min) with stereotyped, paroxysmal ambulation, accompanied by screaming and bizarre, dystonic movements. All three types of seizures frequently occur in the same patients.

Ictal and interictal standard EEG are often usually normal or not interpretable because of the presence of muscular artefacts.[3,4] Only sphenoidal and intracerebral EEG recordings can help to identify ictal and/or interictal discharges.[1,5] In some cases, the electro-clinical analysis of the ictal episodes suggests an extra-frontal origin of the attacks. In the literature, and also in our sample, with the term of NFLE are likely included some patients with complex nocturnal motor automatisms of extra-frontal origin.[6]

In about two-third of patients carbamazepine (CBZ) is reported to greatly reduce nocturnal seizures in frequency and complexity.[1,4,7] In this kind of epilepsy, seizures are almost exclusively during sleep and the patients are often unaware of the presence, complexity and frequency of attacks. Probably due to this difficulty in monitoring the seizures frequency, extensive data about the pharmacological treatment of NFLE are still lacking.

Aim of this study is to evaluate the efficacy and tolerability of the antiepileptic drug topiramate (TPM) in a sample of patients with NFLE.

Patients and methods

Twenty-four consecutive patients admitted to our Sleep Disorders Center from 1998 to 2003 for nocturnal paroxysmal episodes suggestive of NFLE underwent: neurological examination; detailed sleep interview with parents or bed partner; electroencephalographic studies during wakefulness; cerebral magnetic resonance imaging; full night video-polysomnography (after an adaptation night to the laboratory) including EEG monitoring (standard bipolar leads positioned according to the International 10—20 System), electrooculogram, submental electromyography, EKG and, in most cases, electromyography of arms and legs and abdominal and/or thoracic respiratory movements.

We analysed all the video-polysomnographic recordings and selected all the pathological motor events. We examined the EEG tracing and compared the seizures semeiology with the EEG patterns. Sleep was scored according to international criteria.[8] According to literature data,[4] the diagnosis of NFLE was straightforward when patients displayed one or more motor episodes, of any kind of intensity and duration, associated with clear-cut ictal epileptiform activity during polysomnography. When ictal EEG was uninformative, we required the recording of two or more seizures with a stereotypic motor pattern.

In order to record and describe the seizure pattern, the antiepileptic therapy was gradually reduced by 50% within 1 week before polysomnography, in three patients already under treatment (CBZ 800 mg/d in one case and 1000 mg/d in the other two cases). All these patients were non-responders to CBZ treatment. None of our 24 patients was taking psychoactive medications in the month before the visit. They all received TPM as single or add-on therapy. The initial dose of TPM was of 25 mg/d at 9 p.m., and it was increased every 7 days by 25 mg/d until a satisfactory control of symptoms was reported or until side effects began to appear.

They all completed, with the aid of parents or the bed partner, detailed diaries concerning the seizures frequency and complexity. All the patients underwent periodic (every 6 months) follow-up visits (with the presence of parents or bed partner). Eight of them underwent a second nocturnal video-polysomnography. We classified the patients as: seizure-free (disappearance of seizures since starting TPM); responders (reduction of at least 50% of seizures); non-responders (reduction of less than 50% of seizures).

Results

The patients were 15 males and 9 females, with a mean age of 29.3 ± 10.4 years; the seizures began in

Table 1

Age/sex	TPM daily dose	Seizures I	Seizures II	EEG I	EEG II	Seizures log	Seizures PSG
M 36	100	5 PA	2 PA	—	—	SF	R
M 26	200	2 NPD	—	—	—	SF	SF
M 27	100	4 PA	—	P (R; L)	P (R; L)	SF	SF
M 28	200	5 PA	1 PA	—	—	R	R
M 25	150	5 NPD	—	—	—	SF	SF
F 24	100	2 NPD	—	T (L)	T (L)	R	SF
F 33	150	3 PA	—	FT (L)	FT (L)	NR	SF
M 28	200	3 PA	—	—	—	R	SF

Seizures I: seizures during the diagnostic polysomnography; Seizures II: seizures during the second polysomnography; EEG I: EEG abnormalities during the diagnostic polysomnography; EEG II: EEG abnormalities during the second polysomnography; P: parietal; T: temporal; FT: fronto-temporal; R: right; L: left; Seizures log: subjective report of seizures during the last month; Seizures PSG: seizures during the second polysomnography; SF: seizure free; R: responders; NR: non-responders.

childhood (the age at onset ranged from 4 to 40 years; mean 14.6 ± 10.5 years) and persisted throughout adult life. Nine of them reported similar nocturnal seizures in other family relatives, with a pedigree consistent with an autosomal dominant pattern of inheritance (i.e. ADNFLE). Three patients presented daytime focal seizures with possible secondary generalization.

The video-polysomnographic recordings showed a wide spectrum of seizures, ranging from repeated stereotypic brief motor attacks (paroxysmal arousals) to prolonged attacks, with complex and bizarre behaviour, assumption of abnormal posture, dystonic bipedal and/or bimanual movements, shouting and/or unintelligible mumbling (nocturnal paroxysmal dystonia and nocturnal wandering).

The recorded episodes occurred during non-rapid eye movements sleep, both stage 2 and stage 3—4. The EEG during wakefulness was normal in all the patients, while seven of them showed epileptiform abnormalities during polysomnography. Only one patient showed neuroradiological abnormalities (focal frontal pachigyria).

At the first visit, three patients were treated by CBZ: in these cases, TPM was administered as add-on therapy. Twenty-one patients were drug-free and have never been treated before by antiepileptic drugs: in these cases, TPM was administered as monotherapy, ranging from 50 to 300 mg daily at bedtime (mean 132.3 ± 55.4 mg). The follow-up duration ranged from 6 months to 6 years (mean 2.3 ± 1.4 years).

On the basis of the analysis of the seizure logs, the patients were classified as: seizure-free = 6 (25%); responders = 15 (62.5%); non-responders = 3 (12.5%). The response to TPM was assessed by comparing the absolute number of attacks over the 3 months before starting TPM treatment to the 1 of the 3 months which preceded the clinical follow-up. In the 21 responders patients (including 6 seizure-free patients), the mean dosage of TPM was 102.2 ± 24.4 mg, while in the 3 non-responders it was 233.0 (range 150—300).

We recorded the following adverse events: weight loss (mean 3.8 ± 2.3 kg) in 6 pts (25%) at the first 6 months clinical follow-up; paresthesias in 3 pts (12.5%) and speech dysfunction in phonematic verbal fluency in 2 pts (8.3%). All the adverse events disappeared spontaneously within 3 months. No patients reduced or withdrew TPM due to adverse events.

We compared the data of the seizures logs with the polysomnographical data of the second night for the eight patients available: in six cases (75%) there was an agreement between the data (Table 1).

Discussion

NFLE has been described as sporadic and familial form. Autosomal dominant NFLE (ADNFLE) was first described by Scheffer et al.[9] in 1994: the authors collected six families with 39 affected individuals in Australia, United Kingdom and Canada and were able to demonstrate monogenic inheritance with an autosomal dominant transmission pattern. Afterwards further families, most of them of Caucasian origin, have been described.[7,10,11]

Up to 40% of patients affected by NFLE reported parasomniac behaviour (sleep-talking; sleep-walking; sleep terrors; primary enuresis; bruxism) in at least one of their first degree relatives. The coexistence between parasomnia and NFLE, together with the typical NFLE clinical and EEG profile, could generate diagnostic difficulties in differentiating the two conditions.

The EEG studies in NFLE during wakefulness (and often also during sleep) are usually normal. Moreover, the patients are often unaware of the

presence, complexity and frequency of attacks. For these reasons, there are relatively few data about the clinical, video-polysomnographical and, particularly, pharmacological profiles of NFLE.

CBZ is reported to greatly reduce nocturnal seizures in frequency and complexity in about two-third of patients.[1,4,7] Varadkar et al.[12] reported three members of a family with ADNFLE that responded to acetazolamide (ACZ) as add-on therapy to CBZ. As ADNFLE is suspected to be a channelopathy, the authors hypothesized that ACZ may be exerting its therapeutic effect through this action, rather than by potentiating CBZ.

The antiepileptic drug topiramate is known to be effective in new-onset partial epilepsies[13] as well as in refractory partial and generalized epilepsies.[14] The most common adverse events include somnolence, anorexia, weigh loss, paresthesias and psychomotor slowing. In our case series, topiramate seems to be effective in NFLE: about 90% of patients had a good response to a low dose of the drug. Probably due to the low dose (mean 132 mg at bedtime), few of them experienced (transitory) adverse events. The efficacy of TPM in new-onset partial epilepsies and refractory partial and generalized epilepsies is sustained by several class I studies (prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population).[13,14] There are insufficient data to make recomendation for the syndromes individually, including NFLE. According to the results of genetic investigations, mutations in alpha 4 beta 2 subunit of the nicotinic acetylcholine receptor could play a role in the NFLE pathogenesis. Since among the proposed sites of TPM action (voltage-activated Na^+ channels; $GABA_A$ receptor; glutamate receptor; Ca^{2+} channel; carbonic anhydrase) the acetylcholine receptor is not included, a clear molecular explanation for these results is actually not available and should be further investigated.[15,16]

On the basis of the present case series (class IV study) we cannot make specific recomendation for NFLE, but we could include topiramate in the options for patients with NFLE. Considering the possible extra-frontal origin of complex nocturnal motor seizures,[5,6] the effectiveness of TPM could be widen to patients with sleep-related epileptic attacks with complex motor behaviours (i.e. focal epilepsy with sleep-related seizures).

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