Available online at www.sciencedirect.com
SCIENCE DIRECT®
Epilepsy & Behavior 6 (2005) 260–263
Epilepsy & Behavior
www.elsevier.com/locate/yebeh

Brief Communication

Add-on therapy with topiramate in progressive myoclonic epilepsy

Ebru Aykutlu[a], Betül Baykan[a,*], Candan Gürses[a], Nerses Bebek[a], Nesimi Büyükbabani[b], Ayşen Gökyiğit[a]

[a] Department of Neurology, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey
[b] Department of Pathology, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey

Received 30 September 2004; revised 23 November 2004; accepted 23 November 2004

Abstract

We evaluated the clinical responses to add-on therapy with topiramate in eight patients with progressive myoclonic epilepsy (PME). Severe myoclonic seizures disturbing daily activities were persistent despite adequate trials of various combinations of antiepileptic drugs in all patients. After the initiation of topiramate therapy, five patients had a marked decrease in myoclonic seizure frequency, prominent improvement of daily functioning, and recovery from previous drug-related side effects such as weight gain and irregularities of menstruation due to polycystic ovary syndrome. However, we had to discontinue topiramate in three patients because of side effects. Topiramate seems to be a useful alternative agent in the treatment of PME. The antimyoclonic effect provides some independence in daily activities and decreases the side effects related to other antiepileptic drugs, which are clear benefits for this grave disease, although having a short-term effect in some patients.

Keywords: Myoclonus; Progressive myoclonus epilepsy; Topiramate

1. Introduction

Progressive myoclonic epilepsy (PME) comprises a group of heterogeneous syndromes, often associated with intractable myoclonic seizures, ataxia, and dementia [1]. Although PME syndromes have many causes, the most common are: Unverricht–Lundborg disease (ULD), Lafora disease (LD), mitochondrial encephalomyopathies, neuronal ceroid lipofuscinoses, and sialidosis [2]. Generally, the onset is in late childhood and adolescence, with deterioration often leading to a fatal outcome in early adulthood [3].

Medical treatment of PME is mainly symptomatic against myoclonus and other epileptic seizures. Because of the limited options, treatment is the most important problem for clinicians. Unfortunately, it is known that some of the major antiepileptic drugs (AEDs), such as carbamazepine, gabapentin, vigabatrin, and phenytoin, have aggravating effects on myoclonus in PME patients [1]. Older drugs like phenobarbital (PB) and especially primidone (PMD), as well as combination therapy with valproate (VPA) and clonazepam (CLZ), may be useful. The generalized convulsive seizures are often abated with these classic AEDs except clonazepam; however, myoclonus, the main symptom that affects daily activities, is refractory to these conventional treatments [1]. Although one of the most effective agents for myoclonus is piracetam (PIR), its dose-related efficacy makes adherence to treatment difficult (30–40 g/day) [4]. Prolonged treatment with PIR remains effective over 10 years, even if efficacy decreases slightly [5,6]. Among the new AEDs, levetiracetam (LEV) and zonisamide have been reported to be beneficial with respect to myoclonus in small series of patients with ULD and LD [6–9]. Magaudda et al. [7] concluded that high-dose PIR is not always well tolerated and a combination of a

* Corresponding author. Fax: +90 212 533 43 93.
E-mail addresses: draykutlu@hotmail.com (E. Aykutlu), baykanb@istanbul.edu.tr (B. Baykan).

1525-5050/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.yebeh.2004.11.014

lower dose of PIR and LEV, which is a more potent form of PIR, appeared to be a practical solution in ULD patients. In anecdotal case reports, the effectiveness of topiramate (TPM) was also noted in patients with ULD [10].

Our aim was to report the beneficial effects of TPM in a heterogeneous PME group consisting of eight patients whose myoclonus was poorly controlled despite all previous efforts.

2. Cases and methods

Diagnosis of PME was based on both clinical and laboratory findings in eight patients (Table 1). At the end of the diagnostic evaluation, we determined that five patients had LD with typical clinical, EEG, and axillary skin biopsy findings. Evaluation of the remaining three patients with unknown etiology included cranial MRI, cerebrospinal fluid studies, axillary skin biopsy, muscle biopsy, back-averaging and somatosensory evoked potential studies, as well as blood chemistry and urine studies, in addition to EEG follow-ups. All patients were regularly followed at our epilepsy outpatient clinic with control intervals of 1 to 3 months. Written informed consent was obtained from all study subjects. This investigator-initiated study was done without any specific funding and without the involvement of any pharmaceutical company.

Severe myoclonic seizures were persistent before the introduction of TPM despite adequate trials of various combinations of AEDs including VPA, CLZ, PB, and lamotrigine (LTG) in all patients (Table 1). Two patients (cases 7 and 8) were also treated with high-dose PIR. Two patients with LD (cases 1 and 5) had a recent history of status epilepticus episodes (Table 1). Polycystic ovary syndrome established by clinical and ultrasonographical data (case 1) and excessive weight gain (cases 1 and 2) were noted as side effects of VPA therapy. TPM was started at 25 mg/day and progressively increased by 25 mg weekly, according to each patient's need, with a mean dosage of 200 mg/day. During this period, patients continued taking the AEDs they had used previously, concomitantly with TPM. After establishment of the effectiveness of TPM, other AEDs with disturbing side effects were gradually tapered and could be discontinued in some patients (Table 2).

For the purposes of the current study, we developed the following motor disability score from myoclonus frequency, intensity, and effects on daily activities: a score of 0 represents no myoclonus and no effects on daily activity; a score of 1, mild and rare myoclonus (>3 minor episodes/day) with independence in daily activity; a score of 2, moderate or frequent ($\leqslant$3 and $\geqslant$6 episodes of myoclonus and some dependence in daily activity; and a score of 3, very frequent episodes (>6) or severe myoclonus with total dependence in daily activities such as walking and eating.

Severity of other neurological symptoms such as ataxia and cognitive impairment was also scored semiquantitatively for convenience. Ataxia was scored as 0 for no ataxia; score 1 for mild to moderate ataxia with minor effects on daily activity (using walking aids or assistance in some occasions); and 2 for moderate to severe ataxia with dependence in daily activity such as walking and eating. Cognitive impairment was scored

Table 1
Clinical and EEG characteristics of PME patients and their initial scores of disability[a]

Case/sex/age/disease duration (years)	PME subtype	Seizures				Ataxia	Cognitive impairment	EEG findings	
		Myoclonus	GCS[b]	CPS	Status epilepticus			Slowing of background activity	Generalized spike–waves
1/M/19/6	LD[b]	2	+	+	+	1	1–2	+	+
2/F/18/4	LD[c]	2	+	–	–	1	1–2	+	+
3/F/18/4	LD[c]	3	+	–	–	2	2	+	+
4/M/29/8	LD	1–2	+	–	–	1	1–2	+	+
5/M/31/14	LD[c]	1–2	+	–	+	1	1–2	+	+
6/M/31/3	Unknown[d] (AD pedigree)	1–2	+	–	–	1	2	+	+
7/F/32/14	Unknown[e,f] (associated with CD)	3	+	+	–	2	0–1	–	–
8/F/26/9	Unknown[e,g]	3	+	–	–	2	0–1	+	–

[a] Severity of neurological symptoms such as myoclonus, ataxia, and cognitive impairment was scored as described under Cases and methods.
[b] AD, autosomal dominant; CD, celiac disease; CPS, complex partial seizures; GCS, generalized convulsive seizures; LD, Lafora disease; PME, progressive myoclonus epilepsy; MERRF, myoclonic epilepsy with ragged-red fibres.
[c] Genetic analysis also confirmed the diagnosis of LD.
[d] Genetic analysis excluded Huntington's disease.
[e] Genetic analysis excluded ULD.
[f] Cortical origin of myoclonus was shown by back-averaging study in case 7.
[g] Muscle biopsy was repeated twice and genetic studies were done to exclude MERRF.