Original article

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Clinical experience with levetiracetam in idiopathic generalized epilepsy according to different syndrome subtypes

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ABSTRACT – Clinical experience in open-label studies and anectodal reports suggest that levetiracetam is effective in generalized epilepsy. In this open-label prospective study, 19 patients (3 men, 16 women) affected by idiopathic generalized epilepsy were followed for at least 6 months following the introduction of levetiracetam. Patients were categorized according to syndrome subtype: juvenile myoclonic epilepsy (8), juvenile absence epilepsy (5), childhood absence epilepsy (4), and eyelid myoclonia with absences (2). Eleven patients received levetiracetam as monotherapy, eight as add-on therapy. Effectiveness was demonstrated in 18 patients: 13 became seizure-free (five juvenile myoclonic epilepsy, five juvenile absence epilepsy, three childhood absence epilepsy), and five achieved significant reductions in seizure frequency (three juvenile myoclonic epilepsy, one childhood absence epilepsy, one eyelid myoclonia with absences). Only one patient experienced no change in seizure frequency (eyelid myoclonia with absences). Clinical improvement was accompanied by EEG abnormality suppression or reduction. Levetiracetam was well tolerated; no patient reported side-effects.

Key words: idiopathic generalized epilepsy, juvenile myoclonic epilepsy, levetiracetam, monotherapy, add-on therapy

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Levetiracetam is an antiepileptic drug (AED) with a proven efficacy in patients with partial seizures. To date, no double-blind, randomized, controlled trials have evaluated this drug in patients with generalized seizures. A double-blind, placebo-controlled study in partial epilepsy included some patients with generalized seizures (Betts *et al.* 2000). However, animal models support the use of levetiracetam in primary generalized epilepsy, as do open-label studies and case reports (Krauss *et al.* 2001, Greenhill *et al.* 2002, Krauss *et al.* 2003, Kasteleijn-Nolst Trenité and

Hirsch 2003, Kumar and Smith 2004). We report the effects of levetiracetam in 19 patients with idiopathic generalized epilepsy (IGE).

Patients and methods

We selected and prospectively followed 19 patients (3 males, 16 females, mean age 30 years) with primary generalized epilepsy. The diagnosis of IGE was defined according to the following criteria: 1) age at seizure onset, 8-20 years, 2) seizure type consisting of typical absence, generalized tonic-clonic seizures, and myoclonic seizures or the association of two or more of these seizure types, 3) interictal or ictal electroencephalogram (EEG) characterized by generalized spike-and-wave discharges, generalized polyspike-and-wave discharges, photoparoxysmal response, or the association of two or more of these items, and 4) normal neurological examination and neuroimaging. A positive family history for epilepsy was considered significant but not indispensable. After a preliminary evaluation, patient subgroups were identified according to the diagnostic criteria reported in Panayiotopoulos' proposal (Panayiotopoulos 1997); we considered this subdivision more detailed and clinically oriented than the classification accepted by the *ad hoc* Commission of ILAE (Commission 1989). Eight patients had juvenile myoclonic epilepsy, 4 had childhood absence epilepsy, 5 had juvenile absence epilepsy, and 2 had eyelid myoclonia with absences.

Before administering levetiracetam, we performed a basal assessment by definition of seizure frequency (the three months prior was considered as the baseline period), a standard EEG with photic stimulation, an ambulatory EEG aimed at verifying abnormalities and their relationship to the sleep-awake cycle.

Levetiracetam was introduced at a starting daily dose of 500mg. The mean daily dose was 2,300mg/day (range 1,500-3,000mg/day). Patients were followed for 6-10 months (mean duration of exposure, 8 months). Duration of follow-up was based on clinical and EEG evaluations. Seizure frequency and tolerability of levetiracetam were estimated according to the patients' diaries; neurophysiological evaluation, including two standard EEGs (at the second and the fourth month), and an ambulatory EEG (at the sixth month).

Before starting levetiracetam, patients were informed about the lack of any indications for this drug in generalized epilepsy. All patients gave informed consent, and the study was approved by the local ethics committee.

Results

General characteristics of the patient population are summarized in *table 1*. Levetiracetam was administered as monotherapy to 11 patients (6 were *de novo*) and as add-on therapy to 8 patients. Concomitant AED therapy included valproate, lamotrigine, valproate plus lamotrigine, valproate plus phenobarbital, valproate plus ethosuximide and clonazepam (one patient on each regimen) and phenobarbital (3 patients). The effectiveness of levetiracetam was demonstrated in 18 patients: 13 became seizure-free, and 5 achieved a 50-75% reduction in seizure frequency. No change in seizure frequency was observed in 1 patient.

Outcome according to syndrome subtype

All 5 patients with juvenile absence epilepsy and 3 out of 4 with childhood absence epilepsy were seizure-free after therapy with levetiracetam *(figure 1)*. The fourth patient with childhood absence epilepsy partially responded to levetiracetam. Five of the 8 patients with juvenile myoclonic epilepsy became seizure-free, and 3 experienced a 50-75% reduction in seizure frequency (myoclonic jerks on awakening were occasionally reported). Almost all (6) of the patients with juvenile myoclonic epilepsy received levetiracetam as add-on therapy. One patient with eyelid myoclonia with absences responded only partially to levetiracetam, whereas no response was observed in our second patient.

EEG features after levetiracetam therapy

Clinical improvement was accompanied by a reduction in or disappearance of ictal/interictal EEG abnormalities. In particular, generalized spike-and-wave discharges were reduced in patients with absence epilepsy, and photoparoxysmal response was suppressed or reduced in patients with myoclonic epilepsy.

When considered as a whole, the results of our study show that the standard EEG was normal at the 4-month evaluation in 10 cases, while a 50-75% reduction in abnormalities was observed in a further 8 cases (the number of generalized spike-and-wave/polyspike-and-wave discharges was calculated by EEG inspection). In all but one of the patients with absences, seizures were fully controlled and normal EEGs achieved. In most of the cases with myoclonic seizures, we observed a suppression of the photoparoxysmal response and a disappearance of the related clinical manifestations; in some cases a residual, asymptomatic photoparoxysmal response persisted at high frequency stimulation only. In 3 patients with incompletely controlled juvenile myoclonic epilepsy, the photoparoxysmal response was markedly reduced, though accompanied by slight clinical phenomena at high frequency stimulation. In 2 patients with eyelid myoclonia with absences, an interictal/ictal EEG and photoparoxysmal response partial reduction was observed, but was considered clinically relevant in only one of these cases.

Table 1. Patient characteristics and follow-up data.

Pt	Sex	Age	Age at seizure onset	Epilepsy*	Seizure type	Seizure frequency	EEG	Previous therapy	Current therapy	LEV daily dose mg	Follow-up duration	LEV onset of action / current seizure frequency
1	F	42	13	JME	Absence – myoclonic - GTC	Monthly	GSWD	VPA + LTG	VPA + LTG + LEV	1500	6 months	2 months/50-75% reduction
2	M	11	11	JAE	Absence	Daily	GSWD; PSWD	-	LEV	3000	7 months	1 week/seizure-free
3	F	18	5	EMA	Eyelid myoclonia with absence	Daily	GSWD; IPS (+)	-	LEV	3000	10 months	No response/unchanged
4	F	18	15	JAE	Absence - GTC	Daily	GSWD	-	LEV	2000	8 months	1 week/seizure-free
5	F	35	6	CAE	Absence	Sporadic	GSWD	CNZ	LEV	2000	6 months	2 months/seizure-free
6	M	21	10	JME	Myoclonic	Daily	IPS (+)	-	LEV	2000	10 months	1 week/seizure-free
7	F	29	8	CAE	Absence	Sporadic	GSWD	VPA	LEV	2000	8 months	2 months/seizure-free
8	F	40	14	JAE	Absence	Sporadic	GSWD; IPS (+)	VPA	LEV	2000	10 months	2 months/seizure-free
9	F	39	12	JME	Absence - myoclonic - GTC	Monthly	GSWD	VPA + LTG + PB	VPA + PB + LEV	1500	7 months	2 months/50-75% reduction
10	F	24	13	JAE	Absence - GTC	Sporadic	GSWD; PSWD; IPS (+)	VPA	LEV	2000	9 months	2 months/seizure-free
11	M	39	13	JME	Myoclonic - GTC	Daily	GSWD; PSWD	PB + OXC + CNZ	LEV + PB	2000	6 months	1 week/seizure-free
12	F	13	10	JAE	Absence	Monthly	GSWD; IPS (+)	-	LEV	2000	8 months	2 months/seizure-free
13	F	31	12	JME	Absence – myoclonic	Monthly	GSWD	PB	PB + LEV	3000	10 months	2 months/50-75% reduction
14	F	36	8	JME	Absence - myoclonic - GTC	Monthly	GSWD; PSWD	VPA	VPA + LEV	3000	7 months	2 months/seziure-free
15	F	26	9	EMA	Eyelid myoclonia with absence	Weekly	GSWD; PSWD; IPS (+)	PB	PB + LEV	3000	6 months	2 weeks/50-75% reduction
16	F	36	4	CAE	Absence - GTC	Daily	GSWD; PSWD	ETS + VPA + CNZ	ETS + VPA + CNZ + LEV	3000	7 months	1 week/50-75% reduction
17	F	26	21	JME	Myoclonic - GTC	Monthly	IPS (+)	LTG	LTG + LEV	2000	9 months	2 months/seizure-free
18	F	8	6	CAE	Absence – GTC	Monthly	GSWD; IPS (+)	-	LEV	2000	8 months	2 months/seizure-free
19	F	16	15	JME	Absence – myoclonic	Sporadic	GSWD	LTG	LEV	2000	10 months	2 months/seizure-free

Syndrome classification according to Panayiotopoulos's proposal (Panayiotopoulos 1997). **CAE** = childhood absence epilepsy; **CNZ** = clonazepam; **EMA** = eyelid myoclonia with absences; **ETS** = ethosuxamide; **GSWD** = generalized spike-and-wave discharge; **GTC** = generalized tonic-clonic; **IPS (+)** = photoparoxysmal response; **JAE** = juvenile absence epilepsy; **JME** = juvenile myoclonic epilepsy; **LEV** = levetiracetam; **LTG** = lamotrigine; **OXC** = oxcarbazepine; **PB** = phenobarbital; **PSWD** = polyspike-and-wave discharge; **VPA** = valproate.

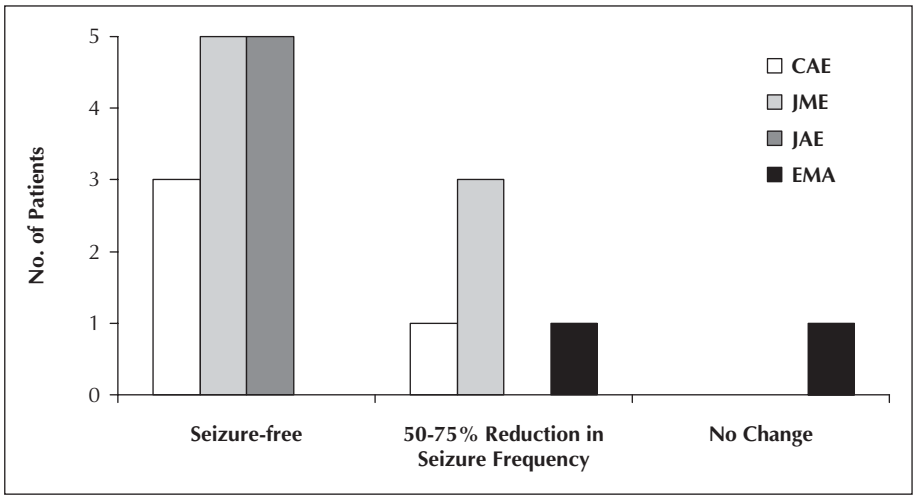

Figure 1. Response to levetiracetam treatment according to syndrome subtype. **JME** = juvenile myoclonic epilepsy; **JAE** = juvenile absence epilepsy; **CAE** = childhood absence epilepsy; **EMA** = eyelid myoclonia with absences.

After 6 months of levetiracetam therapy, ambulatory EEG evaluations assessing the number of discharges over 24 hours showed a significant improvement, with an average reduction in discharges of 60% when compared with the baseline value. In none of the patients were sleep-wave cycle alterations documented.

Tolerability of levetiracetam

In all the patients, levetiracetam was well tolerated, no major side-effects were reported. In just 3 cases was a slight sedation during the titration phase mentioned.

Discussion

Clinical experience in open-label studies and anecdotal case reports suggest that levetiracetam is effective in treating several forms of generalized seizures in adults and children, including myoclonic, absence, and primarily generalized seizures (Krauss *et al.* 2001, Greenhill *et al.* 2002, Krauss *et al.* 2003, Kasteleijn-Nolst Trenité and Hirsch 2003, Weber and Beran 2004). A multicenter, double-blind, randomized study (Betts *et al.* 2000) in patients with various types of refractory epilepsies seemed to confirm these data, but its results were not significant because of the small number of patients with idiopathic generalized epilepsy. Nevertheless, results obtained in patients affected by childhood absence epilepsy, juvenile absence epilepsy, and juvenile myoclonic epilepsy are convincing (Greenhill *et al.* 2002, Krauss *et al.* 2001, Krauss *et al.* 2003, Kasteleijn-Nolst Trenité and Hirsch 2003, Cohen 2003, Kumar and Smith 2004). In our study, in the first two syndromes, levetiracetam was as effective as monotherapy, whereas the last syndrome almost always required polytherapy because of drug-resistant myoclonic seizures. These results agree with data published by Smith *et al.* (2000) confirming the effectiveness of levetiracetam in drug-resistant juvenile myoclonic epilepsy.

The two patients with eyelid myoclonia with absences did not benefit from levetiracetam; the poor response to therapy of this syndrome has also been reported by others (Kasteleijn-Nolst Trenité and Hirsch 2003). We observed, in almost all the cases, a marked suppression of or reduction in interictal/ictal generalized spike-and-wave discharges, generalized polyspike-and-wave discharges, and the photoparoxysmal response, confirming the effect of levetiracetam on the EEG (Kasteleijn-Nolst Trenité *et al.* 1996, Kasteleijn-Nolst Trenité and Hirsch 2003, Gallagher *et al.* 2004). According to published data, the most significant effect on the EEG was observed in patients with absence seizures, whereas complete suppression of photoparoxysmal response was not always achieved in patients with myoclonic seizures (Kasteleijn-Nolst Trenité and Hirsch 2003).

In conclusion, our results confirm the effectiveness of levetiracetam in patients with generalized seizures as a manifestation of idiopathic generalized epilepsy. The small number of patients and the methodological limitations of an open-label study do not allow us to identify any specific "syndrome target" of this drug in the spectrum of IGE. Additional controlled studies are required to confirm the large spectrum of levetiracetam and its efficacy in idiopathic generalized epilepsies. □

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