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Original article

Aggravation of absence seizure related to levetiracetam

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ABSTRACT

Recent data have reported the effectiveness of levetiracetam (LVT) on generalized seizures. Among them, it seems that LVT can be successfully used to treat absence seizures. Many antiepileptic drugs (AEDs) have been occasionally reported to paradoxically aggravate some seizures. We retrospectively identified patients with aggravation of absence seizures using LVT from the databases of 2 pediatric neurology departments (Robert-Debré, Paris and Amiens; France). We also used the prospective data from an open-label clinical trial performed in a third pediatric neurology department (Necker, Paris; France). We included 6 patients: $n = 2$ childhood absence epilepsy, $n = 3$ juvenile absence epilepsy and $n = 1$ epilepsy with myoclonic absences. All of them have had an aggravation of the absences with a causal and temporal relationship between introduction of the drug and the detrimental effect. The aggravation disappeared when LVT was decreased or was withdrawn. This report highlights that LVT may aggravate epilepsy with absence seizures.

Levetiracetam (LVT) is an antiepileptic drug (AED) with a novel mechanism of action primarily involving an interaction with the synaptic vesicle protein 2A (SV2A). Binding affinity for SV2A is strongly correlated with antiepileptic potency in animal models of partial and generalized epilepsy, supporting the concept that SV2A is an important broad-spectrum anticonvulsant target.[4] LVT has been shown to be effective in controlling partial-onset seizures as adjunctive therapy in adults, children and in infants and as initial monotherapy in adults with newly diagnosed epilepsy. Moreover, two multicenter, double-blind, placebo-controlled, randomized clinical trials have shown adjunctive LVT to be effective in controlling myoclonic seizures[6] and generalized tonic clonic seizure (GTCS)[2] in patients with idiopathic generalized epilepsy (IGE).

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A supplementary analysis of data from these two double-blind trials has been conducted to assess the efficacy and tolerability of adjunctive LVT by specific IGE syndrome. In juvenile absence epilepsy, the responder rate (≥50%) was significantly higher for LVT versus placebo (53.3% vs. 25.0%; $p = 0.004$).[7] Moreover, a multicentre, prospective, long-term, open-label study reported the use of LVT as a first monotherapy in absence epilepsy. At the 6-month evaluation, out of 21 patients enrolled, 11 were seizure free and one showed 'decreased' seizures (more than 50% reduction in seizures).[10]

Many antiepileptic drugs have been described to aggravate seizures in IGE. It has been notably reported with carbamazepine in absence seizures and lamotrigine that aggravates myoclonic seizure in juvenile myoclonic epilepsy.[3] LVT has been also reported to increase seizure frequency in 7 patients of 30 included in a prospective uncontrolled, open study using LVT on patients with refractory epilepsy. All of them were adults and presented complex partial seizures with long duration of epilepsy.[8] Here, we report six pediatric patients with absence epilepsies who had exacerbation of absence seizures related to the use of LVT.

1. Methods

We included patients from three pediatric neurology departments in France. The study was retrospective in two departments (Robert-Debré Paris and Amiens) that used their own database (November 2008–May2010 in Robert-Debré Paris and October 2006–May2010 in Amiens). The data from Necker-Paris were collected prospectively. These data are coming from an open labeled add-on trial (LVT in adjunctive treatment in pediatric refractory epilepsy, 103 included patients over 2-year period; Chhun S et al. In preparation). We included in this report the patients that have experienced an exacerbation of the seizure while taking LVT for absence seizures. Seizure frequency was based on diaries analysis.

Aggravation was diagnosed if the number of seizure was increased by more than 50% of the usual seizure frequency after start of new antiepileptic drugs or if generalized tonic-clonic occurred without irregular intake of medication, overdosage or inappropriate lifestyle.

We considered the following data for each patient: epileptic syndrome, age at diagnosis, type(s) of seizures, age at start of LVT, comedication, description of the aggravation and dose of LVT at aggravation and follow-up.

2. Results

We identified 6 patients (2 from each university epilepsy center). The patients were treated for the following epilepsies: $n = 2$ childhood absence epilepsy, $n = 3$ juvenile absence epilepsy and $n = 1$ epilepsy with myoclonic absences. The Table 1 report the data collected in our patients.

Table 1 – Description patient with absence seizure worsening related to levetiracetam. ESM: Ethosuximide; GTCS: generalized tonic clonic seizure; LTG: lamotrigine; VPA: valproate; Sz: seizure.

Patient	Age at diagnosis	Epileptic syndrome	Type(s) of seizure observed	Age at start of LVT	Comedication	LVT at aggravation	Description of the aggravation	Evolution
1	4y	Childhood Absence Epilepsy	Typical absences	11y	ESM (17 mg/kg/d)	500 mg (17 mg/kg/d)	• Increase of daily number of absence • Increase of duration of Absence • Cluster of GTCS	Recovers previous condition after stopping LVT
2	3y6m	Childhood Absence Epilepsy	Typical absences	4y	VPA (30 mg/kg/d)	750 mg (43 mg/kg/d)	• Increase of daily number of absence	Recovers previous condition after stopping LVT
3	12y	Juvenile Absence Epilepsy	Typical Absence 1 GTCS	12y	Switch from LTG due to rash	2000 mg (50 mg/kg/j)	• Increase of daily number of absence • Increase of duration of Absence	Recovers previous condition after stopping LVT; then seizure free with VPA
4	8y	Juvenile Absence Epilepsy	Typical Absence 1 GTCS	13y	LTG (7 mg/kg/d)	1750 mg (57 mg/kg/d) No effect on Sz frequency until 40 mg/kg/d	• Increase of daily number of absence • Increase of duration of Absence	Decrease of duration and frequency according to the decrease of the Amount of LVT until recovery of the previous condition when LVT was totally withdrawn Then seizure free on VPA + LTG
5	13y	Juvenile Absence Epilepsy	Typical absences	14y	VPA (20 mg/kg/d) ESM (15 mg/kg/d)	2000 mg (30 mg/kg/d)	• Increase of daily number of absence • Increase of duration of Absence	Recovers previous condition after stopping LVT
6	2y6m	Myoclonic Absences	Myoclonic absences	3y6m	VPA (29 mg/kg/d)	300 mg (18 mg/kg/d)	• Increase of daily number of absence	Recovers previous condition after stopping LVT