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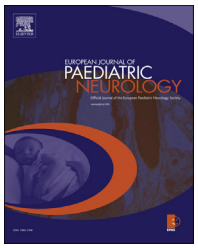

Original article

Effect of levetiracetam on behavioral problems in pervasive developmental disorder children with epilepsy

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ABSTRACT

Aims: We investigated the relationship between behavioral problems, location of electroencephalogram (EEG) paroxysmal abnormalities (PA), and treatment with levetiracetam in children with pervasive developmental disorder (PDD) and epilepsy.

Methods: Twelve PDD children with epilepsy were included in the study. All patients had EEG PA (frontal spikes, 8; rolandic, 3; generalized, 1). After a 3-month baseline period, patients were given levetiracetam with an initial dose of 10 mg/kg/day for the first week, followed by increments of 5 mg/kg/day every week. Levetiracetam dosage was then adjusted up to a maximum of 60 mg/kg/day. EEG recordings were performed every 3 months, focusing on PA frequency. We counted the frequency of seizures and EEG PA, and scored instances of panic/aggressive behaviors.

Results: Eight (66.7%) of the 12 patients were considered to be responders to clinical seizures and EEG findings (≥50% reduction in both seizures and PA frequency). Six (75%) of these eight patients were considered to be responders for behavioral problems (≥50% reduction in panic/aggressive behavior). These six patients had frontal EEG paroxysms, whereas the remaining two patients without behavioral responses had rolandic EEG paroxysms. Patients with frontal PA showed a significantly higher correlation between EEG/clinical seizures and behavioral improvements ($p < 0.05$).

Conclusion: The present data indicated the usefulness of LEV in reducing behavioral problems related to the reduction of seizures and frontal spikes in PDD for some but not all of the patients. Thus, levetiracetam represents an important addition to treatment for PDD children with epilepsy presenting with frontal EEG paroxysms.

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1. Introduction

Levetiracetam (LEV), one of several new antiepileptic drugs (AEDs), has become widely used in the treatment of various types of epilepsy in adults and children.[1] LEV is an effective adjunctive treatment for medication-resistant partial seizures with or without secondary generalization.[2] Studies published on the use of LEV in epileptic children have shown excellent pharmacokinetic and tolerability profiles, with few deleterious effects on cognitive function and no known pharmacokinetic interactions.[3] Furthermore, a recent study showed a good response in refractory childhood epilepsy with a broad spectrum as well as good safety profiles.[2]

Pervasive developmental disorder (PDD) is one of the most common neuropsychiatric disorders in children with epilepsy.[4] The high occurrence of epilepsy in children with PDD is a clear indication that PDD may have a neurobiological basis. Epilepsy is more common in people with PDD than in the general population,[5] and PDD is more common in people with epilepsy than in those without.[6] Thus, there appears to be a strong association between PDD and seizure disorders, which warrants further investigation.[7]

For partial epilepsies, the relationship between interictal epileptiform discharges on electroencephalogram (EEG) and behavioral abnormalities is controversial, but some interictal epileptiform activities have subtle clinical manifestations. The relationship between epilepsy and cognitive/behavioral disturbances is influenced by several factors, including etiology, age at onset, type of epilepsy, and treatment.[8] On the other hand, in patients with PDD, EEG paroxysmal abnormalities (PA) are frequently recorded. A recent study has reported that the majority of PA at the time of epilepsy onset appeared in the frontal areas of the brain.[9] Frontal lobe dysfunction is associated with seizure onset in 58% of cases based on EEG findings.[10] Accordingly, the presence of frontal paroxysms may indicate a higher risk of epilepsy and cognitive/behavioral impairments in PDD.[11]

Recently, reports have indicated that LEV may cause neuropsychiatric manifestations such as aggressiveness. Therefore, it has been recommended that special consideration should be given when using LEV in PDD patients. Nevertheless, LEV reduces the incidence of seizures[1] and interictal epileptiform discharges[12] in adult patients with localization-related epilepsy. A recent study showed that treatment with LEV reduced interictal epileptiform discharges in children with attention deficit hyperactivity disorder (ADHD).[13] Another recent study showed decreased hyperactivity and impulsivity after LEV administration in children with epilepsy presenting with secondary bilateral synchrony on EEG.[14] However, little is known about the safety and efficacy of LEV for PDD children with epilepsy.

The present study aimed to determine the relationship between behavioral problems, location of PA, and treatment with LEV in PDD children with epilepsy.

2. Methods

2.1. Participants

The patients were recruited from among epilepsy with PDD outpatients of authors' hospital and five related hospitals between May 1, 2011 and April 30, 2012, and selected according to the criteria as below. Twelve (7 males, 5 females) PDD patients with refractory epilepsy, aged between 8.6 years and 14.2 years (with a mean age of 10.3 years) at enrollment, were included in the present study. The diagnosis of PDD was made according to DSM IV criteria (299.00 Autistic Disorder), such as qualitative impairment in social interaction, qualitative impairment in communication, and restrictive, repetitive, and stereotypic pattern of behavior, interests, and activities.[15] The following criteria had to be fulfilled: 1) seizures refractory to at least two first-line AEDs (appropriate AED for each seizure type or epileptic syndrome, with therapeutic concentrations of AEDs); 2) at least four seizures a month during the 3 months before LEV administration; 3) neuropsychological impairments such as impulsivity and aggressiveness, as referred to in the DSM-IV[15]; and 4) at least 12 months of follow-up. Age at onset of epilepsy ranged from 5.9 years to 11.8 years (mean, 7.2 years). The mean duration of epilepsy history was 3.1 years (range, 1.9–4.3 years). All patients were affected by localization-related epilepsy. In 11 patients, partial seizures evolved to secondary generalization. Participants in the present study were taking a stable regimen of two or three concomitant AEDs, such as carbamazepine, valproate sodium, zonisamide, phenytoin, or clobazam. The mean number of AEDs taken before introducing LEV treatment was 4.3 (range, 2-6 AEDs).

The study was carried out in accordance with the Declaration of Helsinki. Informed consent was obtained from the parents of each patient following a full explanation of the procedures to be undertaken.

2.2. Strategy for LEV administration

After a 3-month baseline period, patients with epilepsy were given LEV at an initial dose of 10 mg/kg/day twice daily, followed by increments of 5 mg/kg/day every week. The dosage was increased to 15 mg/kg/day after 1 week, and then subsequently increased to 20 mg/kg/day after another week. During this period, LEV dosage could be increased up to 60 mg/kg/day (or 3000 mg/day), according to the clinician's judgment. The goal of treatment in this protocol was to obtain a seizure response ($\geq$50% seizure reduction) without adverse effects. The LEV dose was not increased in cases of complete seizure control and could be decreased in cases of adverse effects. The final dose regimen that was reached was maintained unchanged during the first 3 months of the evaluation period and could be adjusted for the following 3 months in cases of inadequate seizure control or adverse effects. The comedication remained unchanged from baseline to the end of the 12-month evaluation period.

Before entering the trial, children were tested for intellectual achievement, using a variety of well-established methods such as the Wechsler Intelligence Scale for Children, third edition (WISC-III). Complete blood count, platelet count, liver enzyme levels, and blood concentrations of AEDs prior to LEV administration were recorded at baseline for all children.

2.3. EEG analyses

EEGs were performed using a 12- or 16-channel machine every 3 months. The duration of tracings was at least 20 min. For