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Levetiracetam efficacy in children with epilepsy with electrical status epilepticus in sleep

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ABSTRACT

Purpose: Epilepsy with electrical status epilepticus in sleep (ESES) is a devastating disease, and we sought to evaluate the efficacy of levetiracetam (LEV) for the treatment of patients with this epileptic encephalopathy in China.
Methods: Clinical data from all patients with ESES who received LEV therapy at our pediatric neurology outpatient clinic between 2007 and 2014 (n = 71) were retrospectively analyzed. The LEV dosage was 30–50 mg/kg/day. Electroencephalography recordings and neuropsychological evaluations were performed repeatedly for 3–75 months after the start of LEV therapy.
Results: Thirty-five (70%) of 50 patients who had seizures at the start of LEV therapy had a >50% reduction in seizure frequency. Positive response on EEG was found during the first 3–4 months of LEV therapy in 32 (45%) of 71 patients, with normalization of EEG in 5 patients. Relapse occurred in 8 (25%) of the initial electrical responders. Hence, 47 patients (66%) still suffered from ESES and only 13 patients regained their baseline level of function at the last follow-up. The response to LEV was significantly associated with ESES duration, age at onset of ESES, and etiology of epilepsy. Although fatigue and anorexia were the primary adverse events, LEV was well-tolerated by all patients.
Conclusions: Levetiracetam is safe and may be efficient when used to treat ESES syndrome; however, the efficacy EEG neuropsychological outcomes is limited on the whole.

1. Introduction

Electrical status epilepticus in sleep or continuous spikes and waves during slow-wave sleep (ESES or CSWS) is defined as a typical electroencephalography (EEG) pattern of continuous and diffuse epileptiform during sleep, occupying more than 85% of nonrapid eye movement (NREM) sleep with descriptions of diffuse, bilateral, and recently, also unilateral or focal localization [1,2]. The EEG pattern combined with functional deterioration within an age range constitutes the ESES syndrome, which is ESES syndrome (ESESS) [3–6]. This syndrome is considered an epileptic encephalopathy, "a condition in which the epileptiform abnormalities themselves contribute to the progressive disturbance in cerebral function" [5,7,8].

The ESES syndrome (or The epileptic sydrome with electrical status epilepticus in sleep) is a potentially serious disorder in childhood. Although epilepsy resolves over time in most cases, many children have significant residual cognitive, language, or other functional impairments. The goal of treatment is not only to control clinical seizures but also to eliminate the EEG pattern of ESES and prevent potential functional deterioration. However, agreement about the optimal treatment for this condition is lacking [9], and response to treatment with AEDs has usually been disappointing. Valproate may be helpful in reducing seizures, but it often does not eliminate the ESES pattern on EEG and recent reports indicated a lack of significant improvement in cognitive and communication skills [9,10]. Short-term intravenous injection of a BDZ can be valuable; however, because of a lack of sustained long-term benefit, this treatment must be repeated after any relapse [9,11]. Steroids seem to offer better efficacy and longer lasting effect than conventional AEDs but are limited by side effects and a high relapse rate [10–12].

Levetiracetam is a newer AED that has good pharmacokinetics and tolerability in children [13] and may have valuable efficacy for treating ESES. However, the existing studies of LEV efficacy in children suffering from ESES have evaluated only a small number of children and reach different conclusions [14–17]. Levetiracetam entered the Chinese market in 2007; therefore, we conducted a large retrospective study to evaluate the efficacy and safety of LEV in treating children with ESES and report the results herein since 2007.

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2. Methods

2.1. Patients and methods

This was a retrospective observational study and was approved by the Ethical Committee of Chongqing Medical University and was conducted according to the guidelines of the Declaration of Helsinki. Data were obtained from the medical records of children who were treated for epilepsy with ESES syndrome at the outpatient clinic of the Children's Hospital of Chongqing Medical University between October 1, 2007 and October 31, 2014. Inclusion criteria were as follows: (1) presence of the ESES EEG pattern with continuous and diffuse epileptiform activity indicated by the spike–wave index (SWI) for at least 85% of NREM sleep according to video-EEG, ambulatory 24-h EEG, or a prolonged nap EEG recording including at least one sleep cycle. Various criteria are used for determining SWI, and in this study, SWI was visually calculated using the percentage of SWI during the first non-REM sleep cycle by two authors; (2) functional deterioration that occurred in temporal relation with the ESES pattern; and (3) treatment with LEV for ESES starting before October 31, 2013 to guarantee at least 12 months of follow-up. Patients with continuous epileptic activity during sleep diagnosed with autistic epileptiform regression, Lennox–Gastaut syndrome, myoclonic–astatic epilepsy, or Doose syndrome were excluded [5,18].

The clinical presentation, seizure type and frequency, etiology of epilepsy, psychomotor development and schooling, neuropsychological and behavioral evaluations, drugs used before LEV, and response and tolerance to LEV were obtained from medical records. Information regarding neuropsychological and other functional deteriorations or improvements before and during the treatment period was obtained from psychological tests that evaluated global intelligence and special cognitive ability adapted to the patient's age, a questionnaire completed by parents and teachers, and school examination results.

Levetiracetam therapy was started with a twice-daily oral regimen of 10 mg/kg/day and was gradually increased to the target dosage of 30–50 mg/kg/day within 4–6 weeks according to clinical efficacy and tolerability. All patients were evaluated by clinical and EEG assessments at 3–4 months after the start of LEV therapy. Clinical seizure response was classified as seizure-free, >50% decrease in seizure frequency, or inefficient (<50% decrease in seizure frequency). Neuropsychological response was assessed according to the neuropsychological evaluations and other symptoms observed during the ESES period and was classified as complete reversal, improvement by >50%, or inefficient (improvement < 50%). Electrical response was assessed according to the presence ESES on EEG and classified as complete normalization of the record, >75% improvement in SWI, >50% improvement in SWI, or no response (<50% improvement in SWI). A relapse of ESES on EEG was defined as a re-increase of SWI to half or more of what it was before LEV therapy.

2.2. Statistical analysis

The relation between response to LEV and the following factors was statistically evaluated using *t*-tests: age at ESES onset, ESES duration, and the number of AEDs before LEV. The association between response to LEV and etiology was examined using Fisher's exact test. For the analysis, SPSS for Windows version 13.0 was used, and significance was set at $p < 0.05$.

3. Results

3.1. Patient characteristics

The study sample consisted of 71 patients. Patient characteristics are summarized in Table 1. All children had experienced seizures before the evolution of ESES. Twenty-three patients (32%) experienced an increase in seizure severity during the ESES phase. Neuroimaging abnormalities were present in 20 patients and included developmental as well as destructive lesions (atelencephalia or atrophy, gray matter heterotopia and leukomalacia, white matter changes, abnormal/delayed myelination, and brain cysts).

Table 1
Patient characteristics.

	Patients (n = 71)
Sex	
Male	40 (56%)
Female	31 (44%)
Age (years, months)	
Age at seizure onset	4 years (6 months–10 years, 7 months)
Age when ESES was detected	7.8 years (1 year, 2 months–13 years, 2 months)
ESES duration before LEV treatment	12.5 months (2–60 months)
Seizure types (the five most common)	
Focal seizures without secondary generalization	36 (51%)
Generalized tonic–clonic seizures	35 (49%)
Focal seizures with secondary generalization	19 (27%)
Myoclonic seizures	15 (21%)
Atypical absence	10 (14%)
Etiology	
Idiopathic	28 (39%)
Cryptogenic	23 (32%)
Symptomatic	20 (28%)

Before the onset of ESES, 31 patients (44%) had normal development, 28 (39%) had mental retardation, and 22 (31%) had motor deficits. After the onset of ESES, intellectual deterioration was present in 39 patients (55%), language deterioration in 12 patients (17%), memory deficits in 11 patients (15%), and attention-deficit hyperactivity disorder in 12 patients (17%). Behavioral abnormalities, mainly aggressiveness, were present in twenty patients (28%), and new motor deficits were present in seven patients (10%), including two patients with spastic diplegia and athetosis who became immobile.

3.2. Characteristics of LEV therapy

Before LEV therapy, 66 patients (93%) had received at least one antiepileptic treatment (Table 2). Twenty-two patients (31%) had received steroid treatment, including seven who had a poor response to steroids and 15 who became steroid-dependent and had a relapse when steroid treatment was reduced or stopped.

Table 2
Antiepileptic treatment (including steroids) tried before LEV.

	Patients (n = 71)
Number of treatments	
0	5 (7%)
1	19 (27%)
2	25 (35%)
3	15 (21%)
4	3 (4%)
≥5	10 (14%)
Types	
VPA	55 (77%)
TPM	26 (37%)
LTG	20 (28%)
OXC	17 (24%)
CBZ	16 (23%)
BZDs	16 (23%)
CNP	8 (11%)
NP	8 (11%)
PB	2 (3%)
PHT	2 (3%)
Steroids	22 (31%)

VPA, valproate; LTG, lamotrigine; TPM, topiramate; OXC, oxcarbazepine; CBZ, carbamazepine; BZDs, benzodiazepines; CNP, clonazepam; NP, nitrazepam; PB, phenobarbital; PHT, phenytoin.