Pediatric Neurology 50 (2014) 243–249

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

Efficacy of Levetiracetam in Electrical Status Epilepticus During Sleep of Children: A Multicenter Experience

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ABSTRACT

BACKGROUND: Electrical status epilepticus during sleep is characterized by epilepsy, a specific electroencephalographic pattern, and neuropsychological impairment. This study aims to evaluate the efficacy and safety of levetiracetam in treating children with electrical status epilepticus during sleep. **METHODS:** A multicenter, retrospective, open-label study enrolled 73 children (mean age: 8 years) affected by electrical status epilepticus during sleep. The efficacy was rated according to the seizure frequency and electroencephalography response. **RESULTS:** After a mean treatment period of 19 months (range: 6 to 24 months), 33 (63.5%) of 52 patients became seizure-free or had experienced remarkable reduction in seizures. The electrical status epilepticus of 41 (56.2%) of 73 patients disappeared off their electroencephalography. The electroencephalography efficacy of levetiracetam treatment was noted in the monotherapy (61.9%) and add-on (53.9%) groups. The clinical (67.7%) and electroencephalography (64.3%) response rates of the idiopathic group were better than those of the symptomatic group (57.1% and 45.2%, respectively). No patient discontinued the trial because of intolerability of side effects. **CONCLUSIONS:** Levetiracetam is effective in individuals with electrical status epilepticus during sleep with tolerable side effects.

Keywords: electrical status epilepticus during sleep, levetiracetam, children, idiopathic, symptomatic, treatment

Pediatr Neurol 2014; 50: 243-249

Introduction

Electrical status epilepticus during sleep (ESES) is an electroencephalography (EEG) phenomenon that was first described by Patry in 1971.[1] Tassinari et al. subsequently reported similar patients and introduced the term ESES. In these patients, the term "continuous spikes and waves during slow sleep" (CSWS) was considered synonymous to ESES.[2] The International League Against Epilepsy suggested that epileptic encephalopathy with status epilepticus during sleep is an age-related and self-limited disorder. It is characterized by epilepsy with different seizure types, neuropsychological impairment, and a specific electroencephalographic pattern of continuous spikes and waves during nonrapid eye movement sleep.[3] The characteristic EEG pattern consists of continuous and diffused spike waves mainly at 1.5 Hz to 2.5 Hz during slow sleep.[2] Spike–wave index (SWI) has a central function in the diagnostic criteria of ESES/CSWS. However, various criteria have been used, including an SWI of at least 90%, 85%, 60%, 50%, and 25%.[4] The International League Against Epilepsy did not

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Article History:
Received August 2, 2013; Accepted in final form October 28, 2013

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0887-8994/$ - see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pediatrneurol.2013.10.015

provide an exact cutoff value and merely reported a strong activation of epileptiform activity during sleep.[5] Clinical variants associated with an EEG pattern of ESES/CSWS are encephalopathy with CSWS/ESES, Landau-Kleffner syndrome, and atypical benign childhood epilepsy with centrotemporal spikes.[6]

The clinical manifestations and epileptiform discharges of ESES, as an age-related and self-limited disorder, will improve or even disappear with advancement in age. However, epileptic disturbances during the maturation of the cortical network may result in permanent impairment of the network. A study on the cognitive impairment of patients with ESES has demonstrated that good cognitive recovery after disappearance of ESES occurs in only one of 10 children, and partial recovery in four.[7] Urgent treatment is needed to prevent neuropsychological and motor impairment. Currently, a systematic therapeutic strategy for ESES and its related syndromes has not been established. Available treatment options primarily include antiepileptic drugs, corticosteroids,[8] adrenocorticotropic hormone,[9] intravenous immunoglobulins,[10] ketogenic diet,[11] and surgeries.[12] For antiepileptic drugs, benzodiazepines,[13] valproate combined with ethosuximide,[9] and levetiracetam have all been used to treat ESES. Sulthiame was also reported to be effective for ESES.[14]

Levetiracetam is a second-generation antiepileptic drug that is considered beneficial in the treatment of childhood epilepsy because of its favorable tolerability, little interaction with other antiepileptic drugs, and neuroprotective ability.[15,16] After its approval for use in partial-onset seizures in adults and children aged ≥4 years,[17] some studies have shown that adjunctive levetiracetam is efficacious and well-tolerated for partial-onset seizures in infants and young children.[18] Unlike traditional antiepileptic drugs, levetiracetam has a unique mechanism of action. The binding site of levetiracetam was identified as synaptic vesicle protein 2A, which inhibits calcium release from intraneuronal stores. Thus, it opposes the activity of negative modulators of gamma-aminobutyric acid and glycin-gated currents.[19] It lacks cytochrome P450 isoenzyme–inducing potential.[19] Approximately 66% of the drug is excreted unchanged in urine.[16] Some reports that studied a limited number of patients have suggested that levetiracetam is effective for ESES.[20,21] In addition, one study has found that CSWS is a definite target of levetiracetam.[22] The current study investigated the efficacy of levetiracetam in improving the clinical manifestations and EEG pattern of 73 children with ESES.

Materials and Methods

Study design

This research was designed as a multicenter, retrospective, open-label study. Between 2009 and 2013, 73 patients were diagnosed with ESES at seven pediatric centers in China. The trial was conducted in accordance with the international rules of good clinical practice and was by the Ethical Committee of the Chinese PLA General Hospital. Informed consent was obtained from each patient's parents before the initiation of the trial-related procedures. The first month before the patients' arrival at the research clinics was considered the baseline period. After being diagnosed with ESES, all patients underwent video-EEG, cerebral magnetic resonance imaging, urine analysis, complete blood count, and biochemical tests. The ESES of the patients who had received other antiepileptic drugs before inclusion in this study was not prevented or controlled. Levetiracetam was then administered to all patients either as monotherapy or add-on therapy. Levetiracetam therapy was started at a dosage of 20 mg/kg per day. The dosage was increased by 10 mg/kg per day increments every week, and the subsequent dosage ranged from 30 to 60 mg/kg per day. During the treatment and evaluation period, the patients were evaluated at 1 and 3 months after levetiracetam administration and then every 3 months thereafter. The follow-up duration for each patient was no less than 6 months. School performance was evaluated according to clinical judgment. All-night video-EEG was performed at least three times at every evaluation visit. The international 10/20 electrode placement system was used. The open–closed eye test and hyperventilation were involved in every video-EEG test.

The patients were divided into idiopathic and symptomatic groups according to etiology. The new International League Against Epilepsy report proposes to replace the terms "idiopathic," "symptomatic," and "cryptogenic" with "genetic," "structural–metabolic," and "unknown," respectively. In this study, the previous terms were maintained. The efficacy of levetiracetam in the monotherapy and add-on therapy groups was also observed in this study. Patients in the monotherapy group were treated using levetiracetam as an independent drug, whereas those in the add-on therapy group were treated by adding levetiracetam to the antiepileptic drugs that the patients previously received.

Patients

All patients met the following inclusion criteria: (1) onset of focal seizures or focal EEG discharges; (2) further occurrence of new clinical manifestations, such as atypical absences, atonic, myoclonic, and negative myoclonic seizures; and (3) characterized epileptic activity of ESES according to video-EEG; during nonrapid eye movement, the focal or diffuse spikes and waves became continuous with SWI ≥50%. The SWI was confirmed by two physicians trained in electrophysiological images. The exclusion criteria were as follows: (1) Lennox-Gastaut syndrome and West syndrome that do not fulfill the criteria for ESES and (2) patients who had previously received levetiracetam.

Assessment

Throughout the study, the patients' parents or legal caregivers kept diaries to record seizure types and frequencies. The efficacy of levetiracetam was measured by seizure frequency and the reduction in SWI that were compared with data gathered during the baseline period. Clinical response to therapy was graded as seizure-free, significant reduction in seizures, and no change or increase in seizures. EEG response to therapy was divided into three categories: ≥50% reduction in SWI, <50% reduction in SWI, and with no change or increase in SWI.

Statistical analysis

Mann-Whitney U test was used to compare the efficacy between the idiopathic and symptomatic groups with a 0.05 two-sided significance level.

Results

Demographics and baseline clinical characteristics

The clinical and EEG outcomes of 73 patients with ESES were analyzed in this study. The median follow-up duration was 19 months (range: 6 to 24 months). The 73 patients comprised 45 males and 28 females. All urine analysis, complete blood count, and biochemical test results were normal during the follow-up period. The median age of the patients was 8 years. The age at onset of focal epilepsy was 4 months to 10 years and 3 months, with a median age of 2 years. The age at onset of ESES was 1 year and 1 month to 11 years and 8 months, with a median age