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Original article

# Efficacy and tolerability of levetiracetam for pediatric refractory epilepsy

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**Abstract**

*Introduction:* Levetiracetam has a high tolerability and is effective against various seizure types and epilepsy syndromes. However, no study has specifically evaluated the efficacy of levetiracetam in children with refractory epilepsy based on magnetic resonance imaging (MRI) findings and the presence of intellectual disability (ID).

*Methods:* We retrospectively evaluated levetiracetam efficacy and safety in 49 pediatric patients who met the following inclusion criteria: (1) diagnosis of refractory epilepsy with first-line antiepileptic (AED) treatment $\geqslant$2 years, (2) younger than 20 years old, and (3) received oral levetiracetam treatment for $\geqslant$6 months. We assessed the relationships of these outcomes with MRI findings and ID status.

*Results:* Eighteen (37%) patients achieved a $\geqslant$50% reduction in seizure frequency, and the majority (78%) had no remarkable side effects. Twenty-two (45%) patients had previously been treated with more than seven antiepileptic drugs prior to levetiracetam. Among 18 patients who achieved a $\geqslant$50% reduction in seizure frequency, 13 and 5 had negative and positive MRI findings, and 9 and 9 had and did not have ID, respectively.

*Conclusions:* Our findings suggest that even for intractable pediatric cases with symptomatic etiology (i.e., MRI lesion and ID), levetiracetam has favorable efficacy for refractory epilepsy with tolerable adverse effects.


*Keywords:* Refractory epilepsy; MRI lesion; Intellectual disability; Levetiracetam

## 1. Introduction

Levetiracetam is a relatively new antiepileptic drug with high tolerability and efficacy against various seizure types and epilepsy syndromes [1–6]. It was approved as an adjunctive therapy to treat intractable partial seizures for adults in the U.S., EU, and Japan in 1999, 2000, and 2010, respectively.

A recent study that assessed the efficacy, safety, and tolerability of levetiracetam monotherapy reported a $\geqslant$50% reduction in seizures in newly diagnosed patients with child absence epilepsy (CAE) [7]. Another report

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concluded that levetiracetam is potential candidate therapy for patients with continuous spikes and waves during sleep (CSWS) [8].

Levetiracetam's mechanisms of action are presumed to be related to modulation of synaptic vesicle protein 2A, which is ubiquitously expressed in the central nervous system [9]. The pharmacokinetics of levetiracetam remain unclear, but its favorable safety profile, minimal drug-to-drug interactions, high bioavailability, high tolerability, and linear pharmacokinetics [10], make levetiracetam an attractive candidate for both pediatric and adult patients.

In a review of four well-controlled clinical studies, the most general adverse reactions related to levetiracetam in combination with other anti-epileptic drugs (AEDs) were somnolence, asthenia, infection (usually common colds), and dizziness [11]. Behavioral symptoms such as agitation, anxiety, apathy, hostility, depression, and emotional lability were recognized in 13.3% of levetiracetam-treated patients, and 15% of patients experienced an adverse event that led to discontinuation or reduction of the levetiracetam dosage. Somnolence (14.8%), asthenia (14.7%), headache (13.7%), infection (13.4%), and dizziness (8.8%) were more commonly recognized as adverse effects of levetiracetam [11]. Conversely, we have no clinical information about the efficacy of levetiracetam in patients with magnetic resonance imaging (MRI) lesions and intellectual disability (ID), which are relatively common in subjects with refractory epilepsy.

This study aimed to evaluate the efficacy and safety of levetiracetam in pediatric patients with refractory epilepsy, specifically with regard to brain MRI lesions and ID.

## 2. Subjects and methods

This retrospective open-label study assessed 420 patients treated between January 1, 2012, and November 30, 2014, who were recruited from epilepsy outpatients of Gunma University hospital and three related hospitals. The inclusion criteria were (1) diagnosis of refractory epilepsy with treatment $\geqslant$2 years and first-line AED, (2) younger than 20 years old, (3) received oral levetiracetam treatment for $\geqslant$6 months. We assessed clinical characteristics, disease pathogenesis, efficacy, and safety in 49 levetiracetam-treated patients. Surgical procedures had already been performed in three patients before they enrolled in the study. Levetiracetam is typically administered as a daily dose of 10 mg/kg in two divided doses (5 mg/kg twice daily) and increased by 60 mg/kg every 1–2 weeks. Some cases received increases more than 60 mg/kg; however, the maximum dosage was limited to 3000 mg/day. The exclusion criteria were poor compliance, progressive adverse effects, secondary epilepsy with progressive neurodegenerative disease, and previous use of levetiracetam, but no patient met any of these criteria. We also examined the relationships between levetiracetam efficacy, and the presence of MRI abnormalities and/or ID. ID was defined as an intelligent quotient (IQ) <70 if patients performed any intelligence test; for those who were not tested, ID was noted if they exhibited impairment while performing daily school activities. The patients were classified into four groups: MRI lesions and ID (MRI (+)/ID (+)), MRI lesions and no ID (MRI (+)/ID (−)), no MRI lesions and ID (MRI (−) / ID (+)), and no MRI lesions and no ID (MRI (−)/ID (−)). All patients were evaluated by MRI to evaluate the presence of lesions with T1- and T2-weighted intensity and fluid-attenuated inversion recovery (FLAIR) modes. Fisher's exact tests were performed to compare the efficacy of levetiracetam in subjects with and without MRI lesions or ID; all statistical analyses were carried out with IBM SPSS Statistics 23.

Ethical approval for this study was obtained from the Gunma University Graduate School of Medicine committee on the ethics of human clinical research (No. 15-49).

We obtained oral caregiver consent for oral levetiracetam treatment for all patients with generalized epilepsy because the Japanese government did not allow its use in pediatric patients before 2015.

### 2.1. Clinical evaluation

Seizure type and frequency were recorded by parents or caregivers. Efficacy variables included the responder rate for all seizures and a reduction in frequency (i.e., mean number per week or month). A favorable responder rate was defined as a $\geqslant$50% reduction. Aggravation was defined as a $\geqslant$50% increase in seizure frequency after initiating a new AED.

## 3. Results

We assessed 49 levetiracetam-treated patients (mean age: $10.6 \pm 5.0$ years old). Eighteen (37%) patients achieved $\geqslant$50% seizure reduction, 13 (27%) patients became seizure free, and 9 (18%) had a <50% reduction in seizure frequency. Twenty (41%) patients showed no response, and 2 (4%) patients showed seizure aggravation (Fig. 1A).

Most patients experienced more than one seizure type; complex partial seizures, simple partial seizures, secondary generalized seizures, tonic seizures, and atonic seizures were observed in 32, 9, 8, 7, and 2 patients, respectively. Forty (82%) patients are categorized into localization-related epilepsy, and 37 (93%) patients of this group were symptomatic or cryptogenic. Forty (82%) patients had paroxysmal abnormalities on electroencephalography (EEG). Seven (14%) patients had