

Levetiracetam is associated with decrease in subclinical epileptiform discharges and improved cognitive functions in pediatric patients with autism spectrum disorder

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Objective: Subclinical epileptiform discharges (SEDs) are common in pediatric patients with autism spectrum disorder (ASD), but the effect of antiepileptic drugs on SEDs in ASD remains inconclusive. This physician-blinded, prospective, randomized controlled trial investigated an association between the anticonvulsant drug levetiracetam and SEDs in children with ASD.

Methods: A total of 70 children with ASD (4–6 years) and SEDs identified by electroencephalogram were randomly divided into two equal groups to receive either levetiracetam and educational training (treatment group) or educational training only (control). At baseline and after 6 months treatment, the following scales were used to assess each individual's behavioral and cognitive functions: the Chinese version of the Psychoeducational Profile – third edition (PEP-3), Childhood Autism Rating Scale (CARS), and Autism Behavior Checklist (ABC). A 24-hour electroencephalogram was recorded on admission (baseline) and at follow-up. The degree of satisfaction of each patient was also evaluated.

Results: Relative to baseline, at the 6-month follow-up, the PEP-3, CARS, and ABC scores were significantly improved in both the treatment and control groups. At the 6-month follow-up, the PEP-3 scores of the treatment group were significantly higher than those of the control, whereas the CARS and ABC scores were significantly lower, and the rate of electroencephalographic normalization was significantly higher in the treatment group.

Conclusion: Levetiracetam appears to be effective for controlling SEDs in pediatric patients with ASD and was also associated with improved behavioral and cognitive functions.

Keywords: autism spectrum disorder, subclinical epileptiform discharges, levetiracetam, behavioral function, cognitive function, randomized controlled trial

Introduction

Autism spectrum disorder (ASD) is a common neurodevelopmental disability that is characterized by impaired social communication and interaction, restricted interests, repetitive and stereotyped behaviors, and abnormal sensory response.¹⁻³ Early onset of ASD is detectable in children aged 12 to 18 months. As awareness of this disease has improved, the rates of early recognition and diagnosis have significantly increased.^{4,5}

ASD is also associated with epilepsy and epileptiform discharges on electroencephalogram (EEG). Approximately one-third of children with ASD develop epilepsy, although the definitive prevalence is inconclusive because the data have varied considerably.⁶ Subclinical epileptiform discharges (SEDs) are commonly detected

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on EEG in 4%–61% of patients without clinical seizures, depending on the method of sampling.⁶ Clinical evidence indicates that in children with ASD, SEDs may be associated with impaired cognitive and behavioral functions,^{7,8} and suppressing SEDs in these patients may lessen the symptoms of ASD and improve social functions.^{9,10} Recently, antiepileptic drugs have been investigated for managing SEDs in children with ASD, but the efficacy of such treatment remains controversial.¹¹

Levetiracetam is an anticonvulsant agent used to treat epilepsy. It may selectively prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity by binding to synaptic vesicle glycoprotein 2A (SV2A) protein. Levetiracetam is considered to regulate the release of neurotransmitters and impulse conduction across synapses.^{12,13} Previous clinical studies have suggested that levetiracetam modulates EEG background frequency and improves cognitive functions in patients with epilepsy.¹⁴ Nevertheless, there are also studies that have associated levetiracetam with negative results for managing ASD patients.^{15–17}

This study investigated the efficacy of levetiracetam for controlling SEDs in children with ASD and an association between levetiracetam treatment and changes in cognitive and behavioral functions.

Methods

The institutional review board and ethics committee of Children's Hospital of Chongqing Medical University approved this physician-blinded prospective randomized controlled trial. All guardians of the children provided written informed consent.

Patients

The study population consisted of 70 consecutive pediatric inpatients of Children's Hospital of Chongqing Medical University between January 2014 and May 2016. Pediatric psychiatrists conducted all the diagnoses of ASD using the diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*.¹ Patients with any of the following were excluded from the study: disorders of mental development, comprehensive developmental delays, cerebral palsy, or previous history of epileptic seizures. Epileptiform discharges were identified on a 24-hour EEG, and the results were reassessed by two pediatric neurologists independently.

Grouping and treatment

The 70 patients were randomly and equally apportioned to either a treatment or control group using a random number table.

The treatment group (n=35) received levetiracetam and educational training. The control group (n=35) received educational training only. The physician-investigators were blinded to the study group assignment.

Patients in the treatment group were given levetiracetam at a dosage of 60 mg/kg/day; plasma concentrations of levetiracetam were measured at 1 and 6 months after the beginning of treatment. The educational training included the Treatment and Education of Autistic and Communication Handicapped Children program, verbal behavior training, the Relationship Development Intervention program, and the Developmental, Individual-Differences, Relationship-Based (DIR/Floortime) model. Follow-up data were obtained by telephone interviews. No other antipsychotic medications were used during the study period.

Psychological assessment

Before treatment (baseline) and at the 6-month follow-up, individual behavioral and cognitive functions were assessed using the following: Psychoeducational Profile – third edition (PEP-3; Chinese version), Childhood Autism Rating Scale (CARS), and Autism Behavior Checklist (ABC). The PEP-3 scale that was used to assess children's language levels in this study was the revised Chinese version adopted in Hong Kong.¹⁸ The sections that are closely related to the development of cognitive function were used, including the cognitive verbal/preverbal (CVP) function, expressive language, and receptive language. The communication composite score combined the CVP, expressive language, and receptive language raw scores. The physical and behavioral sections of the PEP-3 scale were not included in this study. The PEP-3 tests were performed by a staff who was trained and qualified for special education assessment.

The CARS is a reliable scoring system for diagnosing ASD and evaluating its severity; a score ≥ 30 points supports a diagnosis of ASD.^{19,20} CARS scores were evaluated by pediatric psychiatrists.

The ABC scale²¹ was recorded by caregivers. The 57 items regarding behavioral functions were organized into five groups: social and self-help, language, body and object use, sensory, and relating. A score ≥ 67 points supports a diagnosis of ASD. ABC examinations were finished by individual parents under the guidance of pediatric psychiatrists.

EEG and satisfaction investigation

A 24-hour EEG was recorded on admission and during the follow-up, and the results were reassessed independently by two neurologists blinded to the study group. The guardians'

satisfaction was investigated using a 10-point questionnaire (poor, 1–4; fair, 5–7; good, 8–10).

Statistical analysis

All statistical analyses were performed using SPSS software (version 23.0; IBM Corporation, Armonk, NY, USA). Data are expressed as mean \pm standard deviation. The variables in the two groups were compared using the chi-squared test or Student's *t*-test. A *P*-value <0.05 was considered as statistically significant.

Results

Demographic characteristics

In the treatment group, three children were withdrawn from the study since they did not take levetiracetam as required, and thus, a total of 32 patients were included (Table 1).

Table 1 Demographic and clinical characteristics of the treatment and control groups

Characteristics	Treatment	Control	P-value
Demographics			
Subjects	32	35	
Gender, M/F	28/4	29/6	0.594
Age, months	61.6 \pm 13.8	63.1 \pm 12.7	0.645
Clinical characteristics			
PEP-3			
CVP function			
Baseline	19.14 \pm 9.47	20.85 \pm 11.06	0.501
6 months	38.60 \pm 11.26	0.19 \pm 12.38	0.005 ^a
EL			
Baseline	8.89 \pm 5.13	7.56 \pm 4.72	0.273
6 months	20.35 \pm 8.24	15.78 \pm 6.29	0.013 ^a
RL			
Baseline	13.13 \pm 7.82	12.02 \pm 6.54	0.530
6 months	25.00 \pm 8.64	18.46 \pm 6.99	0.001 ^a
CCS			
Baseline	31.23 \pm 3.45	30.00 \pm 3.19	0.134
6 months	38.07 \pm 3.12	34.94 \pm 2.85	0.000 ^a
CARS score			
Baseline	46.35 \pm 9.72	45.01 \pm 8.91	0.552
6 months	33.14 \pm 5.75	36.24 \pm 5.73	0.031 ^a
ABC score			
Baseline	90.31 \pm 22.75	89.88 \pm 20.45	0.935
6 months	66.12 \pm 18.06	76.53 \pm 19.00	0.025 ^a
EEG			
SEDs remained	8 (25.0%)	25 (71.4%)	0.000 ^a
SEDs disappeared	24 (75.0%)	10 (28.6%)	
Satisfaction ^b			
Good	19 (59.4%)	25 (71.4%)	0.5445
Fair	10 (31.3%)	7 (20.0%)	
Poor	3 (9.3%)	3 (8.6%)	

Notes: Data are shown as n, n/n, n (%) or mean \pm SD. ^aStatistically significant. ^bChi-squared value = 1.2157.

Abbreviations: ABC, Autism Behavior Checklist; CARS, Childhood Autism Rating Scale; CCS, communication composite score; CVP, cognitive verbal/preverbal; EEG, electroencephalogram; EL, expressive language; F, female; M, male; PEP-3, Psychoeducational Profile – third edition; RL, receptive language; SED, subclinical epileptiform discharge.

There were no significant differences in the male-to-female ratios or the average ages of the treatment and control groups ($P>0.05$).

Levetiracetam treatment and adverse effects

The average plasma levetiracetam concentrations at 1 and 6 months after treatment were 30.9 and 34.4 μ g/mL, respectively. During the treatment, one child developed fatigue and somnolence during titration and one child exhibited irritability. These symptoms were relieved after the dosage of levetiracetam was reduced. One child experienced anorexia, which resolved spontaneously. Laboratory examinations (including complete blood count, urinalysis, electrocardiogram, and hepatorenal functions) showed no significant abnormality before or after the treatment.

PEP-3 evaluation

The baseline PEP-3 scores of the treatment and control groups were statistically comparable ($P>0.05$; Table 1). In each group, the following scores at the 6-month follow-up were significantly higher compared with the corresponding baseline scores: CVP, expressive language, receptive language, and communication composite score ($P<0.05$). However, these 6-month follow-up scores were all significantly higher in the treatment group compared with the control ($P<0.05$).

CARS assessment

Prior to the start of treatment, the baseline CARS scores of the treatment and control groups were statistically similar ($P>0.05$; Table 1). In each group, the CARS scores at the 6-month follow-up were significantly lower than the corresponding baseline scores ($P<0.05$), but the 6-month CARS scores of the treatment group were significantly lower than those of the control group ($P<0.05$).

ABC evaluation

Before the treatment, the baseline ABC scores of the treatment and control groups were not significantly different ($P>0.05$; Table 1). In each group, the ABC scores at the 6-month follow-up were significantly lower than the corresponding baseline levels ($P<0.05$). The 6-month ABC scores of the treatment group were significantly lower than those of the control group ($P<0.05$).

EEG examination and individual satisfaction

Before the treatment, SEDs were identified in each patient (Table 1). At the 6-month follow-up, SEDs were absent in

24 of the 32 patients (75.0%) in the treatment group and 5 of the 35 patients (14.3%) in the control group. The chi-squared test showed a significant difference in the electroencephalographic normalization rate of the two groups ($P < 0.05$). There was no significant difference in individual satisfaction between the two groups ($P > 0.05$).

Discussion

Autism was originally described by Kanner in 1943,²² and the umbrella term “autism spectrum disorder (ASD)” was introduced in the DSM-5 to define a continuum of autistic symptoms. In recent years, extensive studies have documented the clinical manifestation, etiology, and treatment of ASD.^{21,23,24} The core symptoms of ASD include deficits in social communication and interaction and restricted or repetitive patterns of behavior, interests, or activities; in addition, pediatric patients with ASD may also have concurrent intellectual and/or language deficiencies and/or comorbid diseases (such as epilepsy).²⁵ Although there has been no specific treatment for ASD, a diverse range of psychosocial, behavioral, and educational interventions have been attempted to alleviate various core symptoms of ASD.^{26,27} Seida et al²⁷ performed an umbrella systematic review of psychosocial interventions for ASD and proposed that some forms of psychosocial interventions were associated with positive outcomes. This indicated that these treatments may be favorable compared with no treatment. Nevertheless, they also emphasized that there was little evidence for the relative effectiveness of these psychosocial interventions.²⁷ Subsequently, some scholars conducted systematic reviews of psychosocial interventions for patients with ASD and found that the effects of psychosocial treatment in adult ASD were largely positive.^{26,28,29} However, the quantity and quality of these studies have been limited. Further high-quality randomized controlled trials are warranted to evaluate the definitive effectiveness of psychosocial treatment for ASD. Moreover, the current psychosocial intervention approaches all target the core symptoms and behavioral disorders of ASD but provide no benefit for comorbid diseases such as epilepsy.

Epilepsy and epileptiform EEGs are closely associated with ASD. As previously reported, ASD patients had a high rate of developing epilepsy with an estimated prevalence ranging from 5% to 46%. The rate of ASD is also high in epilepsy populations, with as much as 32% meeting the diagnostic criteria.⁶ Extensive studies have noted that SEDs are commonly detected in patients with ASD.^{6,30} Some scholars assumed that SEDs in childhood can cause

behavioral or cognitive deterioration by disturbing the formation of synapses.⁷ As early as 1993, Binnie¹⁰ noted that the presence of SEDs was associated with impaired behavioral and cognitive functions in children. Kanemura et al³¹ after long-term observation found that ASD children with SEDs can develop epileptic seizures. Hollander et al⁹ performed an open trial and found that divalproex sodium can suppress EEG abnormalities, alleviate ASD symptoms, and improve individual social functions.

However, it is not known whether levetiracetam may control SEDs or improve the behavioral and cognitive functions of patients with ASD. In the current study, we demonstrated that levetiracetam, combined with educational intervention, can effectively control SEDs and improve the behavioral and cognitive functions of children with ASD. After a 6-month treatment period, both the treatment and control groups showed significant improvements in their behavioral and cognitive functions, confirmed by the cognitive evaluation scales PEP-3, CARS, and ABC. Moreover, functional improvement in the treatment group was much more remarkable than in the control, which suggests that levetiracetam can facilitate cognitive rehabilitation. In previous studies, Rugino and Samsok³² also noted consistent results that indicated the nootropic bioactivity of levetiracetam.

According to the EEG examination results, after 6 months of treatment, SEDs were significantly better controlled in the treatment group compared with the control, evidenced by a remarkably higher electroencephalographic normalization rate. This suggests that levetiracetam may be an effective agent for controlling SEDs in patients with ASD. A previous study has reported safe and effective dosages of levetiracetam ranging from 70 to 275 mg/kg/day (mean 146 mg/kg/day).³³ Because of individual differences in response to antiepileptic drugs, underlying developmental defects, and electroencephalographic patterns, individualized levetiracetam regimens are recommended.¹⁵ In the present study, the association between electroencephalographic normalization rate and improvements in behavioral and cognitive functions warrants much longer follow-up studies involving a larger sample size.

Based on the present findings, we speculate that early use of antiepileptic drugs can help suppress SEDs and further improve behavioral, cognitive, and language skills in children with ASD. According to previous studies, antiepileptic drugs such as sodium valproate, levetiracetam, lamotrigine, and others ameliorate significantly the clinical symptoms of SEDs that accompany ASD and also help control irritability, impulsiveness, and other emotional symptoms.

Chez et al²³ found that the prevalence of SEDs in patients with ASD was ~60.7%. Among 176 ASD patients with SEDs, 80 experienced electroencephalographic normalization after administration of sodium valproate and 30 showed significant clinical improvement. In a meta-analysis of seven relevant studies, Hirota et al³⁴ found that SEDs were frequently detected in children with ASD. However, antiepileptic drugs seemed to be ineffective for improving the clinical symptoms of ASD. These results require further verification due to the limited sample size.

The efficacy of antiepileptic drugs for improving behavioral symptoms of ASD (eg, irritability and compulsivity) is also controversial. Hollander et al^{24,35} found that sodium valproate can effectively ameliorate impulsive and irritable behaviors. However, Hellings et al³⁶ reported that the effect of sodium valproate was similar to a placebo for controlling aggressive behaviors. In the current study, we found that levetiracetam treatment was associated with an improvement in behavioral defects in children with ASD.

Levetiracetam is not generally considered to be a mood stabilizer. Studies regarding the administration of levetiracetam and evaluation of behavioral and cognitive functions in pediatric patients with ASD are sparse. Rugino and Samsock³² followed 10 ASD patients (aged 4–10 years) and reported that a 4-week treatment with levetiracetam effectively reduced symptoms of hyperactivity, impulsivity, emotional instability, and regression, but there were no significant nootropic effects.

In addition, some scholars have observed negative results when managing ASD patients with antiepileptic drugs. Wasserman et al¹⁷ administered levetiracetam for 10 weeks to 20 ASD children (aged 5–17 years), and no improvement in behavioral abnormalities was noted. Rajapakse and Pringsheim¹⁶ found that levetiracetam was ineffective for controlling stereotyped movements in patients with ASD. Moreover, Camacho et al¹⁵ even reported a 6-year-old girl who developed stereotypies and severely deteriorated social and communicative dysfunction after administration of levetiracetam, suggesting that levetiracetam may provoke unusual behavioral adverse effects. In the current study, we did not note significant levetiracetam-related complications or cognitive deterioration. However, a conclusion regarding the definitive safety of long-term use of levetiracetam still requires much longer observation.

Conclusion

In this physician-blinded, prospective, randomized controlled trial, we found that levetiracetam is a safe and effective

agent for controlling SEDs in pediatric patients with ASD and may improve behavioral and cognitive functions. We recommend a dosage of 60 mg/kg/day and a therapeutic course of 6 months.

Disclosure

The authors report no conflicts of interest in this work.

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