Int J Clin Exp Med 2016;9(6):9612-9619
www.ijcem.com /ISSN:1940-5901/IJCEM0017255

Case Report

Retrospective study on treatment of subclinical epileptiform discharges in attention deficit hyperactivity disorder using atomoxetine combined with sodium valproate

Min-Jian Wang[1], Li Jiang[2], Xiao-Ju Tang[3]

[1]Department of Psychology, Children's Hospital of Chongqing Medical University, Chongqing; Ministry of Education Key Laboratory of Child Development and Disorders; Key Laboratory of Pediatrics in Chongqing; Chongqing International Science and Technology Cooperation Center for Child Development and Disorders, China; [2]Department of Neurology, Children's Hospital of Chongqing Medical University, Chongqing, Ministry of Education Key Laboratory of Child Development and Disorders; Key Laboratory of Pediatrics in Chongqing, Chongqing International Science and Technology Cooperation Center for Child Development and Disorders, China; [3]Department of Neurology, Children's Hospital of Chongqing Medical University, Chongqing, China

Received July 19, 2015; Accepted March 15, 2016; Epub June 15, 2016; Published June 30, 2016

Abstract: Objective: To observe the efficacy of atomoxetine combined with sodium valproate for subclinical epileptiform discharges (SED) in attention deficit hyperactivity disorder (ADHD). Method: A retrospective analysis was performed on 26 cases with comorbidity of ADHD and SED. All patients received 24-hour electroencephalography (EEG) before treatment and 12 months after treatment to detect SED. Cognitive abilities were evaluated using Wechsler Intelligence Scales. Moreover, SNAP-IV scale, Connors Parent Symptom Questionnaire and integrated visual and auditory continuous performance test were adopted in conjunction to evaluate ADHD symptoms. χ^2 test was used to compare the normal rate of EEG. The improvement of cognitive abilities and ADHD symptoms of the two groups was determined by repeated measures analysis of variance. Results: All 26 cases were male, without significant differences in average age and composition of ADHD types between the two groups. There were no significant differences in the results of tests with Wechsler Intelligence Scales, Connors Parent Symptom Questionnaire or integrated visual and auditory continuous performance test. Conclusion: Atomoxetine combined with sodium valproate did not improve EEG results in children with comorbidity of ADHD and SED or affect the cognitive abilities. The efficacy of the combined medication was comparable to that of atomoxetine alone.

Keywords: Attention deficit hyperactivity disorder (ADHD), subclinical epileptiform discharges (SED), atomoxetine (ATX), sodium valproate (VPA), retrospective study

Introduction

Attention deficit hyperactivity disorder (ADHD) is a common neuropsychiatric disorder featured by attention deficit, hyperactivity and inability to control impulses. The core symptoms may persist into adulthood and severely affect the social functions of patients [1]. Subclinical epileptiform discharges (SED) refer to epileptiform discharge on EEG without clinical onset of symptoms [2]. The incidence of SED comorbid with ADHD can reach 5.6%-30.1% [3]. The existing studies have shown that SED interferes with the normal cognitive abilities. It is still a controversy whether antiepileptics should be given in SED comorbid with ADHD and which drug is the most appropriate.

We retrospectively reviewed the medical records of 26 cases with comorbidity of ADHD and SED and discussed the efficacy and safety of antiepileptics in these cases.

Subjects and methods

Subjects

From January 2011 to December 2013, 26 cases confirmed as ADHD with comorbid SED at the Affiliated Children's Hospital of Chongqing

Medical University satisfied the inclusion criteria. Among them 11 cases were treated by atomoxetine (ATX) combined with sodium valproate (VPA), and the remaining 15 cases by ATX alone.

Inclusion criteria: (1) Comorbidity of ADHD and SED. ADHD was diagnosed by physicians in child psychiatry department according to DSM-IV Criteria; SED was diagnosed by physicians in child psychiatry department upon discovery of epileptiform discharges on 24-hour EEG, with the absence of clinical onset of symptoms; (2) Follow-up for at least 1 year.

Exclusion criteria: Autism spectrum disorder, intellectual disability, epilepsy, severe heart, liver and kidney diseases.

Methods

Medications

At present, ATX and methylphenidate are the only two choices available for treating ADHD in China. Some scholars believe that methylphenidate lowers convulsive threshold, thereby increasing epilepsy. Therefore, ATX is the preferred choice for children with comorbidity of ADHD and SED. Since there is a lack of guidelines for choosing antiepileptics, VPA is usually used as the classical broad-spectrum antiepileptics with high safety in children. Therefore, all collected cases were treated by VPA.

Evaluation method

Before treatment, all cases were evaluated for cognitive abilities using Chinese Wechsler Intelligence Scale for Children (C-WISC); ADHD symptoms were evaluated with integrated visual and auditory continuous performance test (IVA-CPT) in conjunction with SNAP-IV (Swanson, Nolan, and Pelham Rating Scale (Version IV)) and Conners Parent Symptom Questionnaire (PSQ). Twelve months after treatment, EEG and tests with C-WISC, SNAP-IV, PSQ and IVA-CPT were performed again. All scales and questionnaire in Chinese versions were of high reliability and validity. Tests with C-WISC and IVA-CPT were administered by trained specialists. SNAP-IV was administered by physicians in child psychiatry department, with issuing of PSQ instructions. Double-blinded method was adopted for all tests.

Routine blood and urine tests, liver and kidney function tests and ECG were performed before treatment, 6 months and 12 months after treatment. Blood concentration of VPA was measured 1 month, 6 months and 12 months after treatment.

Evaluation tools

C-WISC is the most commonly used intelligence test that reflects the cognitive abilities of subjects [6] using full intelligence quotient (FIQ), verbal intelligence quotient (VIQ) and performance intelligence quotient (PIQ).

SNAP-IV consists of 26 items, each rated from 0 to 3: 0, completely no; 1, a little bit; 2, fairly; 3, very much. The observation indicators include attention, hyperactivity-impulse and oppositional defiance.

PSQ is generally used to evaluate behavioral problems of children aged 3-17 years, which is especially suitable for ADHD [8]. The scale consists of 48 items, which are filled by father or mother on a 0-3 rating (as in SNAP-IV). The observation indicators include ADHD-related behaviors and conduct, hyperactivity-impulse and hyperactivity index.

IVA-CPT applies to children aged above 6 years. Using repeated auditory and visual stimuli, sustained attention and response control ability of children is detected [9, 10]. The observation indicators are full scale response control quotient (FRCR), full scale attention quotient (FAQ) and hyperactivity (HYP). The test equipment was manufactured by Guangzhou Rainjet Medical Devices Co., Ltd.

Statistical analysis

SPSS11.7 was used for all statistical analyses. Count data were analyzed with χ^2 test. Measurement data were expressed as X±s, and t test and repeated measures analysis of variance were adopted. $P<0.05$ was considered as statistically significant.

Results

Demographic data

All the 26 patients included in the study were males. The mean age was 9.5±2.1 and 10.2±1.6 years for the patients in the control

Table 1. General data of patients in the 2 groups

No/group	Age (years)	ADHD type	Major complication
No: 1/control group	7	Mixed	Learning disorder
No: 2/control group	6	Mixed	Oppositional defiant disorder
No: 3/control group	12	Predominantly inattentive presentation	Others (sleep disorder)
No: 4/control group	10	Predominantly hyperactive/impulsive presentation	Tic disorder
No: 5/control group	9	Mixed	None
No: 6/control group	9	Mixed	Oppositional defiant disorder
No: 7/control group	8	Predominantly hyperactive/impulsive presentation	Others (enuresis)
No: 8/control group	12	Predominantly hyperactive/impulsive presentation	Oppositional defiant disorder
No: 9/control group	10	Mixed	Oppositional defiant disorder
No: 10/control group	12	Mixed	Tic disorder
No: 11/control group	12	Predominantly hyperactive/impulsive presentation	Tic disorder
No: 12/control group	10	Predominantly hyperactive/impulsive presentation	Learning disorder
No: 13/control group	9	Predominantly inattentive presentation	Learning disorder
No: 14/control group	10	Mixed	Learning disorder
No: 15/control group	6	Mixed	Learning disorder
No: 1/treatment group	12	Mixed	Others (sleep disorder)
No: 2/treatment group	12	Mixed	Tic disorder
No: 3/treatment group	9	Predominantly hyperactive/impulsive presentation	Learning disorder
No: 4/treatment group	12	Predominantly hyperactive/impulsive presentation	Learning disorder
No: 5/treatment group	9	Mixed	None
No: 6/treatment group	10	Mixed	Oppositional defiant disorder
No: 7/treatment group	9	Predominantly hyperactive/impulsive presentation	Oppositional defiant disorder
No: 8/treatment group	11	Predominantly hyperactive/impulsive presentation	Tic disorder
No: 9/treatment group	7	Mixed	Oppositional defiant disorder
No: 10/treatment group	10	Predominantly inattentive presentation	Learning disorder
No: 11/treatment group	11	Mixed	Learning disorder

Note: The mean age was 9.5±2.1 and 10.2±1.6 years for the patients in the control and treatment groups, respectively. The mean age was not significantly different between the 2 groups (t=0.924, P=0.365). The distributions of different ADHD types (χ^2=0.119, P=0.942) and major complications (including learning disorder, oppositional defiant disorder, and tic disorder) were also not significantly different between the 2 groups (χ^2=0.040, P=0.998).

and treatment groups, respectively. The mean age was not significantly different between the 2 groups (t=0.924, P=0.365). The distributions of different ADHD types (χ^2=0.119, P=0.942) and major complications (including learning disorder, oppositional defiant disorder, and tic disorder) were also not significantly different between the 2 groups (χ^2=0.040, P=0.998). No antipsychotic drug was used for the 5 patients with the symptoms of mild tic disorder (**Table 1**).

Results of EEG

Four patients each in the control group and the treatment group were with normal EEG at the end of the 1-year follow up. Fisher's exact test was performed no significant difference was found in the normal rate of EEG at the end of the 1-year follow up (P=0.6828) (**Table 2**).

Comparison of C-WISC results between the 2 groups

Two-way repeated-measures ANOVA showed that the FIQ (F=0.27, P=0.6110), VIQ (F=0.32, P=0.5746), and PIQ (F=0.11, P=0.7486) were not statistically different between the 2 groups. FIQ and PIQ were significantly different at 12th months after the treatment as compared to the levels before the treatment (P<0.05), VIQ before and after the treatments were not significantly different in either groups (P=0.0560) (**Table 3**).

Comparison of SNAP-IV results between the 2 groups

Two-way repeated-measures ANOVA showed that the attention score (F=0.17, P=0.6819), hyperactivity/impulsivity score (F=0.47, P=

Table 2. General data of the EEG of patients in the 2 groups

No/group	Pre-treatment	12-month post-treatment
No: 1/control group	Diffused spike/spike slow wave	Diffused spike/spike slow wave
No: 2/control group	Left parietal sharp/sharp and slow wave	Left parietal sharp and slow wave
No: 3/control group	Left parietal, middle and posterior temporal area sharp and slow wave	Left middle and posterior temporal area sharp and slow wave
No: 4/control group	Occipital spike and sharp wave	Normal
No: 5/control group	spike/spike-sharp and slow wave paroxysmal activity	Normal
No: 6/control group	Right frontal-middle temporal area sharp/sharp and slow wave	Right frontal-middle temporal area sharp/sharp and slow wave
No: 7/control group	Frontal spike and sharp wave paroxysmal activity	Normal
No: 8/control group	Right posterior temporal sharp/sharp and slow wave	Right posterior temporal sharp/sharp and slow wave
No: 9/control group	Temporal spike and sharp wave paroxysmal activity	Temporal spike and sharp wave paroxysmal activity
No: 10/control group	Right posterior temporal sharp/sharp and slow wave	Right posterior temporal sharp/sharp and slow wave
No: 11/control group	Frontal spike and sharp wave	Frontal spike and sharp wave
No: 12/control group	Multifocal (Frontal and temproral) sharp/sharp and slow wave	Multifocal (Frontal and temproral) sharp/sharp and slow wave
No: 13/control group	Left temproral spike/spike and slow wave	Normal
No: 14/control group	Left temproral spike and slow wave	Left temproral spike and slow wave
No: 15/control group	parietal-occipital area sharp and slow wave	parietal-occipital area sharp and slow wave
No: 1/treatment group	Temproral spike and slow wave paroxysmal activity	Temproral spike and slow wave paroxysmal activity
No: 2/treatment group	Right anterior frontal sharp/sharp and slow wave spread	Right anterior frontal sharp/sharp and slow wave spread
No: 3/treatment group	Diffuse sharp and slow wave	Normal
No: 4/treatment group	Right frontal spike sharp wave paroxysmal activity	Right frontal spike sharp wave paroxysmal activity
No: 5/treatment group	Occipital sharp and slow wave paroxysmal activity	Normal
No: 6/treatment group	Anterior frontal sharp and slow wave	Anterior frontal sharp and slow wave
No: 7/treatment group	Temproral sharp and slow wave	Temproral sharp and slow wave
No: 8/treatment group	Middle temproral spike and slow wave	Normal
No: 9/treatment group	Occipital spike and slow wave paroxysmal activity	Occipital spike and slow wave paroxysmal activity
No: 10/treatment group	Right frontal spike wave	Normal
No: 11/treatment group	Middle and posterior temporal sharp and slow wave paroxysmal activity	Middle and posterior temporal sharp and slow wave paroxysmal activity

Note: Fisher's exact test was performed no significant difference was found in the normal rate of EEG at the end of the 1-year follow up (P=0.6828).

Table 3. General data of the WISC-R of patients in the 2 groups

Group	Variable	Pre-treatment	12-month post-treatment
Control group (N=15)	FIQ	93.20±10.45	102.87±9.52*
	VIQ	95.13±9.60	98.67±8.91
	PIQ	88.53±10.48	106.07±10.75*
Treatment group (N=11)	FIQ	92.73±8.64	99.64±7.67*
	VIQ	94.82±9.52	98.09±8.17
	PIQ	89.45±8.90	102.54±8.94*

Note: Compared to pre-treatment, *P<0.05.

Table 4. General data of the SNAP-IV of patients in the 2 groups

Group	Variable	Pre-treatment	12-month post-treatment
Control (N=15)	Attention	2.02±0.33	0.97±0.30*
	Hyperactivity/impulsivity	1.81±0.41	0.80±0.16*
	Opposition	0.93±0.28	0.76±0.24*
Treatment (N=11)	Attention	2.17±0.42	1.01±0.27*
	Hyperactivity/impulsivity	1.90±0.36	0.87±0.19*
	Opposition	0.98±0.25	0.63±0.15*

Note: Compared to pre-treatment, *P<0.05.

Table 5. General data of the PSQ of the patients in the 2 groups

Group	Variable	Pre-treatment	12-month post-treatment
Control (N=15)	Conduct problem	2.04±0.61	1.32±0.16*
	Hyperactivity/impulsivity	2.50±0.88	1.06±0.38*
	Hyperactivity index	2.81±0.45	1.09±0.24*
Treatment (N=11)	Conduct problem	2.16±0.73	1.13±0.37*
	Hyperactivity/impulsivity	2.39±0.74	1.24±0.44*
	Hyperactivity index	2.75±0.56	1.27±0.33*

Note: Compared to pre-treatment, *P<0.05.

0.5008), and opposition score (F=0.00, P=0.9553) were not significantly different between the 2 groups. Significant improvement was found within each group after treatment compared with that at admission (P<0.05) (**Table 4**).

Comparison of the PSQ scores between the 2 groups

Two-way repeated-measures ANOVA showed that the conduct problem score (F=0.00, P=0.9932), hyperactivity/impulsivity score (F=0.28, P=0.6037), and hyperactivity index score (F=0.01, P=0.9215) were not significantly different between the 2 groups. Significant improvement was found within each group after treatment compared with that at admission (P<0.05) (**Table 5**).

Comparison of the IVA-CPT results between the 2 groups

Two-way repeated-measures ANOVA showed that the FRCQ score (F=0.02, P=0.8880), FAQ score (F=0.21, P=0.6542), and HYP score (F=0.04, P=0.8475) were not significantly different between the 2 groups. Significant improvement was found within each group after treatment compared with that at admission (P<0.05) (**Table 6**).

Comparisons of the drug doses and adverse reactions between the 2 groups

The mean ATX dose was 28.13±10.96 mg/d and 30.00±8.94 mg/d for the control and treatment groups, respectively; the ATX dose was not significantly different between the 2 groups (t=0.463, P=0.647).

The blood concentration of VPA was measured at 1st, 6th, and 12th months after the treatment, and the results were (71.05±7.17) ug/ml, (65.88±8.36) ug/ml and (69.46±7.96) ug/ml. The results showed that the blood concentrations of the VPA were all within the effective treatment range.

The major side effects in the control group were gastrointestinal reaction which mainly occurred at the early stages of the treatment. One patient in the treatment group was found with difficulty in sleeping, which disappeared after reducing the dose of the drug. While in the treatment group, the major side effects were gastrointestinal reaction and mild sedative effect. Two

Table 6. General data of the IVA-CPT of the patients in the 2 groups

Group	Variable	Pre-treatment	12-month post-treatment
Control (N=15)	FRCQ	75.23±21.78	85.22±12.39*
	FAQ	80.65±19.50	86.17±10.62*
	HYP	78.20±15.84	86.45±12.97*
Treatment (N=11)	FRCQ	77.96±22.53	85.75±14.36*
	FAQ	78.22±18.15	79.43±13.61*
	HYP	76.39±17.47	86.93±11.07*

Note: Compared to pre-treatment, *P<0.05.

patients were noticed with having vomiting in the early stages of the treatment, which disappeared without specific treatment. The blood routine, urine routine, liver function, renal function, and ECG of the patients were re-examined at 1st, 6th, and 12th months after the treatment, and revealed no clinically significant abnormalities.

Discussion

Comorbidity of ADHD and SED is rare. We performed a retrospective analysis of 26 cases presenting with comorbidity of ADHD and SED. Clinically, the incidence of ADHD among males is greater than that among females. Thus we only collected male cases in the present study. The rate of normal EEG in treatment group one year after treatment was not significantly different from that in control group in terms of SED over a period of 24 hours. This indicated VPA did not effectively reduce the occurrence of SED. However, the small sample size may be another reason, and SED may happen in a non-persistent manner. False negative result may appear with 24-hour EEG. It is unclear whether normal EEG in 4 control cases one year later indicated a false negative result or disappearance of SED. The two groups did not differ significantly in the results of C-WISC. Thus VPA caused no obvious impact on cognitive abilities. Inter-group comparison suggested significant differences in FIQ and PIQ between the two groups before and after treatment. This was because PIQ was correlated with attention and the improvement of ADHD would lead to an obvious increase of PIQ. For all cases, ADHD symptoms were evaluated using SNAP-IV, PSQ and IVA-CPT. The two groups did not show significant differences in scores of each quotient in SNAP-IV, PSQ and IVA-CPT, and intra-group comparison revealed a significant difference before and after treatment for each quotient. ATX combined with VPA and ATX alone could both improve ADHD symptoms, to a similar extent. Based on our results, VPA was not of great benefits in SED comorbid with ADHD.

Gibbs et al. first reported SED in 1936. It was found afterwards that the probability of SED progressing into epilepsy was less than 5%, and SED disappeared for most cases during follow-up periods in some researches. SED did not attract enough attention for a very long time [1]. In the 1980s, Aarts et al. detected EEG, verbal response and auditory-visual spatial judgment simultaneously and found that 50% of the subjects showed delay in response or misjudgment. On this basis, transient cognitive impairment (TCI) caused by SED was proposed [11]. More and more researches have confirmed that SED does induce TCI [12], from which the dispute over the need to use antiepileptics for SED arises.

Many studies concerning the use of antiepileptics for SED are small-sample-size trials or case studies. For example, Henriksen O et al. found that the cognitive abilities of SED patients were improved after VPA treatment and the improvement degree was proportional to the reduction of frequency of SED [13]. Kevin Gordo et al. carried out a follow-up on a 7-year-old patient with comorbidity of SED and learning disability. Using Wechsler Intelligence Scales, Connors Parent and Teacher Questionnaire, the patient was significantly improved after VPA treatment for 4 weeks with a better performance in handwriting neatness; there was an obvious reduction in the number of sharp and spike waves on EEG per unit time [14]. Pressler RM found that lamotrigine improved cognitive abilities by reducing SED [15]. Bakke KA reported that levetiracetam inhibited SED and improved cognitive abilities [16]. However, some scholars believed that VPA did not reduce SED, nor did it improve he cognitive abilities. Chez MG et al. showed that there was no obvious correlation between improvement of EEG results and cognitive and behavioral improvements after antiepileptics therapy for SED comorbid with autism [17]. Spencer SS believed that VPA

could not reduce the frequency of SED [18], and D'Antuono M also proved the failure of VPA to control SED below convulsive threshold through animal experiment [19]. Although there was no existing study on the treatment of SED comorbid with ADHD by ATX combined with VPA, we found that VPA did not improve SED. This agreed with the results by Spencer SS and D'Antuono M.

The mechanism of comorbidity of ADHD and SED is not clear [14, 15]. We do not know whether there is a pathophysiological basis behind it or whether it is pure coincidence. Other problems remaining unknown include the influence of SED on the symptoms and prognosis of ADHD, the degree of influence, and whether the influence of SED varies for different types of ADHD. Another question is whether SED in different brain areas has a different influence on ADHD (eg. whether frontotemporal SED has a greater influence on ADHD).

To conclude, ATX combined with VPA did not significantly improve EEG results in SED comorbid with ADHD, nor did it improve the cognitive abilities. Similar efficacy was achieved for ATX with or without VPA. However, the present study had the limitations of small sample size and short follow-up duration. To confirm the findings, it is necessary to combine with quantitative EEG and to carry out multi-center, large-sample-size and long-follow-up trials.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Li Jiang, Department of Neurology, Children's Hospital of Chongqing Medical University, Chongqing; Ministry of Education Key Laboratory of Child Development and Disorders; Key Laboratory of Pediatrics in Chongqing, Chongqing International Science and Technology Cooperation Center for Child Development and Disorders, Chongqing, China. Tel: +86-02363622984; Fax: +8602363620593; E-mail: jiangli0755@163.com

References

[1] Connor DF, Ford JD. Comorbid symptom severity in attention-deficit/hyperactivity disorder: a clinical study. J Clin Psychiatry 2012; 73: 711-717.

[2] So EL. Interictal epileptiform discharges in persons without a history of seizures: what do they mean? J Clin Neurophysiol 2010; 27: 229-238.

[3] Millichap JG, Millichap JJ, Stack CV. Utility of the electroencephalogram in attention deficit hyperactivity disorder. Clin EEG Neurosci 2011; 42: 180-184.

[4] García-Peñas JJ. Interictal epileptiform discharges and cognitive impairment in children. Rev Neurol 2011; 52 Suppl 1: S43-52.

[5] Mulas F, Roca P, Ros-Cervera G, Gandía-Benetó R, Ortiz-Sánchez P. Pharmacological management of attention deficit hyperactivity disorder with methylphenidate and atomoxetine within a context of epilepsy. Rev Neurol 2014; 58 Suppl 1: S43-49.

[6] Fujikawa DG, Licht EA, Jacobsen RH. Chronic epileptic encephalopathy in adult patients with bilaterally synchronous frequent and/or prolonged subclinical epileptiform discharges. Epilepsy Behav 2012; 25: 442-8.

[7] Alda JA, Serrano-Troncoso E. Attention-deficit hyperactivity disorder: agreement between clinical impression and the SNAP-IV screening tool. Actas Esp Psiquiatr 2013; 41: 76-83.

[8] Yılmaz S, Bilgiç A, Hergüner S. Effect of OROS methylphenidate on encopresis in children with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol 2014; 24: 158-160.

[9] Tinius TP. The Integrated Visual and Auditory Continuous Performance Test as a neuropsychological measure. Arch Clin Neuropsychol 2003; 18: 439-454.

[10] Kim J, Lee Y, Han D, Min K, Kim D, Lee C. The utility of quantitative electroencephalography and Integrated Visual and Auditory Continuous Performance Test as auxiliary tools for the Attention Deficit. Clin Neurophysiol 2015; 126: 532-40.

[11] Aarts JH, Binnie CD, Smit AM, Wilkins AJ. Selective cognitive impairment during focal and generalized epileptiform EEG activity. Brain 1984; 107: 293-308.

[12] Holmes GL, Lenck-Santini PP. Role of interictal epileptiform abnormalities in cognitive impairment. Epilepsy Behav 2006; 8: 504-515.

[13] Henriksen O. Education and epilepsy: assessment and remediation. Epilepsia 1990; 31 Suppl 4: S21-25.

[14] Gordon K, Bawden H, Camfield P, Mann S, Orlik P. Valproic acid treatment of learning disorder and severely epileptiform EEG without clinical seizures. J Child Neurol 1996; 11: 41-43.

[15] Pressler RM, Robinson RO, Wilson GA, Binnie CD. Treatment of interictal epileptiform discharges can improve behavior in children with

behavioral problems and epilepsy. J Pediatr 2005; 146: 112-117.
[16] Bakke KA, Larsson PG, Eriksson AS, Eeg-Olofsson O. Levetiracetam reduces the frequency of interictal epileptiform discharges during NREM sleep in children with ADHD. Eur J Paediatr Neurol 2011; 15: 532-538.
[17] Chez MG, Chang M, Krasne V, Coughlan C, Kominsky M, Schwartz A. Frequency of epileptiform EEG abnormalities in a sequential screening of autistic patients with no known clinical epilepsy from 1996 to 2005. Epilepsy Behav 2006; 8: 267-271.
[18] Spencer SS, Goncharova II, Duckrow RB, Novotny EJ, Zaveri HP. Interictal spikes on intracranial recording: behavior, physiology, and implications. Epilepsia 2008; 49: 1881-1892.
[19] D'Antuono M, Köhling R, Ricalzone S, Gotman J, Biagini G, Avoli M. Antiepileptic drugs abolish ictal but not interictal epileptiform discharges in vitro. Epilepsia 2010; 51: 423-431.
[20] Pineda E, Jentsch JD, Shin D, Griesbach G, Sankar R, Mazarati A. Behavioral impairments in rats with chronic epilepsy suggest comorbidity between epilepsy and attention deficit/hyperactivity disorder. Epilepsy Behav 2014; 31: 267-275.
[21] Kaufmann R, Goldberg-Stern H, Shuper A. Attention-deficit disorders and epilepsy in childhood: incidence, causative relations and treatment possibilities. J Child Neurol 2009; 24: 727-733.