소아뇌전증에서 Levetiracetam 부가요법에 따른 경련 증가: 단일 기관 경험

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Seizure Aggravation Following Adjunctive Levetiracetam Therapy in Children with Epilepsy: a Single Tertiary Center Experience

Purpose: The aim of this study is to evaluate the prevalence and risk factors of seizure aggravation of adjunctive levetiracetam therapy in children with epilepsy.

Methods: We retrospectively identified 125 children (0.3-18 years) with epilepsy who were newly treated with adjunctive levetiracetam therapy from November 2008 to July 2014 in Pusan National University Hospital, and 44 patients were excluded according to the exclusion criteria. Aggravation was diagnosed if the seizure frequency increased by more than 50% of baseline or there were new types of seizures after 1 month of adjunctive levetiracetam therapy.

Results: Eighty-one patients (male:female, 44:37) were enrolled, including 27 (33.5%) with generalized seizures and 54 (66.7%) with focal seizures. Twelve patients (14.8%) exhibited seizure aggravation and 69 patients (85.2%) had improvement or no change after 1 month of levetiracetam therapy. Eleven patients (91.7%) in seizure aggravation group and 16 patients (23.2%) in non-seizure aggravation group had generalized seizures, with aggravation significantly more frequent in patients with generalized seizures ($P < 0.001$). Other factors such as age at diagnosis, age at adding levetiracetam, sex, baseline seizure frequency, etiology, electroencephalography and magnetic resonance imaging abnormalities, and concomitant drug use were not identified as risk factors.

Conclusion: Although levetiracetam is an effective antiepileptic drug in children with epilepsy, adjunctive levetiracetam therapy was associated with worsening of seizures in 14.8 % of included patients, especially those with generalized seizures. Careful monitoring for increased seizure frequency or the onset of a new type of seizures is advised for patients prescribed levetiracetam add-on treatment.

Key Words: levetiracetam; anticonvulsants; seizures; generalized epilepsy; adverse effects

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Introduction

Levetiracetam (LEV) is a second-generation antiepileptic drug (AED) that has been marketed in the U.S. since 1999. In the initial stage, LEV use was restricted

to adjunctive therapy for focal seizures, but a recent clinical trial demonstrated the effectiveness of LEV to treat various types of seizures. In pediatric epilepsy, LEV has been approved for focal seizures in patients older than 1 month with epilepsy¹⁾, myoclonic seizures in patients 12 years or older with juvenile myoclonic epilepsy²⁾, and primary generalized tonic-clonic seizures in those 6 years and older with idiopathic generalized epilepsy³⁾. The exact action mechanism of LEV is not fully understood, but it does not involve the well-known targets of other AEDs, such as gamma-aminobutyric acid (GABA) facilitation, sodium channel inhibition, or modulation of low-voltage activated calcium (Ca^{2+}) channels. Synaptic vesicle protein 2A (SV2A) is thought to be involved in Ca^{2+} -dependent exocytosis of synaptic vesicles, and this protein has been identified as a putative LEV target⁴⁾.

An increase in the frequency, severity, and/or duration of seizures is a general feature of AED-induced seizure aggravation. Aggravation can also manifest as the appearance of a new seizure type or worsening of electroencephalography (EEG) findings⁵⁾. It is not always clear that seizure aggravation is due to AEDs, but clinical improvement after dose reduction is highly suggestive of the drug leading to seizure aggravation.

While LEV has come into general use, there are only a few case reports linking it to seizure aggravation⁶⁻¹⁰⁾. To date, the studies regarding the prevalence and risk factors of seizure aggravation caused by LEV have been rare. This retrospective investigation was designed to determine the prevalence and factors associated with seizure worsening by LEV add-on therapy in pediatric patients with different types of epilepsy.

Materials and methods

1. Patients

We identified 125 patients who received oral adjunctive LEV therapy for epilepsy in Pusan National University Hospital between November 2008 and July 2014. Their ages were between 3 months and 18 years (mean age; 8.58 ± 5.25 years). The diagnosis of epilepsy was based on the international Classification of Epilepsies¹¹⁾. Forty-four patients of the 125 patients were excluded because they met the following exclusion criteria: (a) adjunctive LEV therapy initiated in other hospitals ($n=21$), (b) changed to another medication before the effect of LEV was evaluated due to noncompliance and adverse events (irritability, sedation, aggression, and violent behaviors) ($n=19$), and (c) LEV prescribed to control a disease other than epilepsy (e.g., prophylactic use after head trauma or

neurosurgery) ($n=4$). Ultimately, 81 patients were enrolled in the present study for analysis (Fig. 1).

2. Methods

We retrospectively reviewed medical records of patients for the following information: sex, age at onset of epilepsy, age at LEV add-on, baseline seizure frequency at LEV add-on, seizure type, etiology, comorbidity of intellectual disability or developmental delay, magnetic resonance imaging (MRI) findings, EEG findings, and other medications. We also collected information associated with LEV add-on therapy including the initial and maximum doses of LEV, alteration of seizure frequency after LEV add-on or dose modification, and adverse events associated with LEV.

We defined seizure aggravation as (a) seizure frequency increased $\geq 50\%$ compared to baseline or new types of seizures or status epilepticus after adjunctive LEV therapy which repeated after the onset, and (b) no concomitant medication having adverse interaction with LEV. We divided our subjects into two groups based on the presence of seizure aggravation and performed a comparative analysis to identify risk factors of seizure aggravation. The dosage of LEV was titrated gradually depending on the seizure frequency, compliance, and adverse events.

The Institutional Review Boards of Pusan National University Hospital approved this study (PNUHIRB E-2015021), and written informed consents were obtained from the patients' parents.

3. Statistical analysis

SPSS statistics version 22.0 (IBM Corporation, Armonk, NY, USA) was used for statistical analysis. Mann-Whitney U tests

Fig. 1. Patient disposition and seizure outcomes in patients with adjunctive levetiracetam therapy.

were performed to analyze continuous variables (e.g., age, numbers of AEDs), and Pearson chi-square test and Fisher's exact tests were used to analyze categorical data. Two-tailed *P* values <0.05 were considered statistically significant.

Results

1. Demographic data

The patients' baseline clinical characteristics are summarized in Table 1. We assessed 44 males and 37 females. Twenty-seven (33.3%) had generalized seizures and 54 (56.7%) had focal seizures. The mean age at epilepsy diagnosis and adjunctive LEV therapy were 3.84 ± 4.32 years (1 month-17 years) and 8.58 ± 5.25 years (3 months-18 years), respectively. The etiology of epilepsy was idiopathic in 26 patients (32.5%) and cryptogenic or symptomatic in 54 (67.5%). Seventy-five patients (92.6%) exhibited EEG abnormalities including abnormal background activities in 29 patients (35.8%) and the presence of interictal epileptiform discharges in 46 (57.5%). Forty-one patients (50.6%) had abnormal brain MRI.

2. Seizure aggravation

The patients were divided into two groups based on seizure

aggravation status: 12 patients (14.8%) with seizure aggravation (group A) and 69 patients (85.2%) without seizure aggravation (group B) (Fig.1). Clinical characteristics of patients with seizure aggravation following adjunctive LEV therapy are summarized in Table 2. In group B, the seizure frequency declined from 2.15 ± 3.14 (range 0.03-100) to 1.72 ± 2.59 (0-12) per day after 1 month of adjunctive LEV therapy. In group A, the seizure frequency increased from 1.82 ± 2.60 (0.03-13) to 3.15 ± 2.30 (0.07-27) per day. In 11 patients (91.6%) in group A, seizure frequency increased >50% of the baseline frequency. Just one patient experienced aggravation in the form of a new seizure type. No patient had status epilepticus. All patients in group A discontinued LEV due to seizure aggravation and the onset of a new seizure type.

3. Risk factors

We analyzed diverse factors that might be related to seizure aggravation, including age at seizure onset, age at LEV initiation, sex, baseline seizure frequency, comorbid developmental delay or intellectual disability, presence of underlying cause, EEG abnormality, MRI lesion, and numbers of concomitantly used drugs. Most of the analyzed factors showed no significance as a risk factor except for epilepsy type (Table 1).

Only seizure type influenced seizure aggravation in subjects

Table 1. Demographic Profiles and Clinical Characteristics of Patients with Levetiracetam Add-on Therapy

	Total	Group A	Group B	<i>P</i> value
Number, %	81	12 (14.8)	69 (85.2)	
Age at diagnosis, years	3.84 ± 4.32	3.35 ± 4.94	3.95 ± 4.23	0.659
Age at LEV therapy, years	8.58 ± 5.25	9.95 ± 4.94	8.34 ± 5.30	0.331
Boys/girls, %	44 (54.3)/37 (45.7)	5 (41.7)/7 (58.3)	39 (56.5)/30 (43.5)	0.366
Generalized/focal seizures, %	27 (33.3)/54 (66.7)	11 (91.7)/1 (8.3)	16 (23.2)/53 (76.8)	<0.001
Epilepsy etiology, %				0.002
Structural	21 (25.9)	5 (41.6)	16 (23.2)	
Genetic	1 (1.2)	0 (0)	1 (1.4)	
Infectious	5 (6.2)	0 (0)	5 (7.2)	
Metabolic	2 (2.5)	2 (16.7)	0 (0)	
Immune	0 (0)	0 (0)	0 (0)	
Unknown	52 (64.2)	5 (41.6)	47 (68.1)	
With developmental delay or ID, %	35 (43.2)	6 (50)	29 (44.6)	0.754
EEG finding				
Epileptiform discharge, %	74 (91.4)	10 (83.3)	50 (72.4)	0.845
Abnormal background activity, %	29 (35.8)	4 (33.3)	14 (20.3)	0.450
MRI finding				
Abnormal, %	41 (50.6)	7 (58.3)	34 (49.3)	0.756
Baseline seizure frequency (/day)	2.08 ± 3.06	1.82 ± 2.60	2.15 ± 3.14	0.557
Seizure frequency at 1month of LEV treatment	2.01 ± 2.60	3.15 ± 2.30	1.72 ± 2.59	0.015
Starting LEV dose (mg/kg/day)	19.87 ± 1.53	19.90 ± 1.08	19.86 ± 1.60	0.935
Max LEV dose (mg/kg/day)	29.90 ± 4.90	28.36 ± 4.04	30.18 ± 5.01	0.238
Comedication	2.01 ± 1.24	1.93 ± 1.252	2.50 ± 1.09	0.141

LEV, levetiracetam; ID, intellectual disability; EEG, electroencephalography; MRI, magnetic resonance image.

on adjunctive LEV therapy. In group A, eleven patients (91.7%) had generalized seizures, and one patient (8.3%) had focal seizures. In group B, sixteen patients (23.2%) had generalized seizures, and 53 patients (76.8%) had focal seizures. Seizure aggravation was significantly more frequent in patients with generalized seizures than those with focal seizures ($P<0.001$).

4. Adverse events

Ten patients (12.3%) experienced adverse events of LEV other than seizure aggravation. These included fatigue ($n=3$, 3.7%), headache ($n=2$, 2.5%), ataxia ($n=2$, 2.5%), personality change including violent behavior ($n=1$, 1.2%), hyperactivity ($n=1$, 1.2%) and weight gain ($n=1$, 1.2%).

Discussion

Our results show that LEV can worsen seizures with a prevalence

of 14.8%. This was higher than other reports. Chhun et al, reported no seizure aggravation after LEV therapy for 102 pediatric epilepsy patients¹²⁾, Aivazian et al, determined that 5.7% of 192 patients experienced seizure aggravation¹³⁾, and Auriel et al, described a prevalence rate of 8% in 49 adults with refractory epilepsy¹⁴⁾.

There have been many reports of AED-associated seizure worsening in recent decades^{5-10,15-21)}. Unfortunately, they provided limited information about seizure aggravation because most were anecdotal case reports or series. Nevertheless, there is cumulative knowledge about the mechanisms of seizure aggravation, the definitions of seizure aggravation, and their relationship with AED use. The circumstances of seizure aggravation include paradoxical intoxication, paradoxical reaction, drug-induced encephalopathy, and sedative effects or inappropriate choice of drug for patients with certain types of epilepsy^{5,15,19)}. Paradoxical intoxication is when seizure aggravation occurs in the context of a toxic level or above the therapeutic level of the AED. Drugs that can have this effect include phenytoin (PHT) and phenobarbital (PB). Worsening

Table 2. Description of Patients with Seizure Aggravation Related to Levetiracetam Add-on Therapy

Patient	Sex	Age at beginning LEV	Comedication	Starting LEV dose (mg/kg/day)	Max LEV dose (mg/kg/day)	Type of seizure	Brain MRI	Intellectual disability /developmental delay
1	M	13.0	VPA	21.0	30.0	GTC	Normal	No
2	F	13.0	VPA, TPM, LTG	19.0	25.0	GT	Lissencephaly	Yes
3	F	14.0	CLB, VPA, OXC	18.0	34.0	Myoclonic	Cerebral atrophy, Ventriculomegaly	Yes
4	F	2.0	VPA, VGB, ZSM	19.8	31.0	GTC, GT	Normal	Yes
5	M	18.0	GPN	21.0	32.0	GTC, GT	Bilateral hyperintensity of putamen in T2, partial agenesis of corpus callosum	No
6	M	9.5	CLB, VPA, LTG	20.0	24.5	GTCS, GAS	Normal	No
7	F	6.4	VPA, LTG, VGB	21.0	20.3	GT	Mildly enlarged ventricle	Yes
8	F	9.3	CLB, CLZ, TPM, OXC	20.0	30.0	GT, atonic	Cerebral atrophy	No
9	M	3.7	CBZ, CLB, PB, VGB	21.0	24.0	GES	Normal	Yes
10	F	10.0	PB, OXC	20.0	30.0	GTC	Cortical dysplasia	No
11	M	5.5	CLB, TPM, VGB	20.0	29.8	FIAS	Venous angioma	Yes
12	F	14.0	VPA	18.0	34.0	GTC, GT	normal	No

LEV, levetiracetam; MRI, magnetic resonance image; VPA, valproic acid; TPM, topiramate; LTG, lamotrigine; CLB, clobazam; VGB, vigabatrin; ZSM, zonisamide; GPN, gabapentin; OXC, oxcarbazepine; CBZ, carbamazepine; PB, phenobarbital; GTCS, generalized tonic-clonic seizure; GT, generalized tonic; GAS, Generalized absence seizure; GES, Generalized epileptic spasms; FIAS, focal impaired awareness seizure; This finding is compatible with Wilson's disease.

Table 3. Overview of Reports of Seizure Aggravation Associated with Levetiracetam

Reference	Year	Patients – number (%)	Concomitant medication	Manifestation, specific condition, seizure types
Nakken, et al. ⁹⁾	2003	Adults - 14 (18%)	Various	Refractory epilepsy
Auriel et al. ¹⁴⁾	2007	Adults – 4 (8%)	Various	Refractory epilepsy, add-on therapy
Szűcs, et al. ¹⁰⁾	2008	Adults – 31 (14%)	Various	Intellectual disability
Caraballo, et al. ⁷⁾	2010	Children - 2	LTG, PB	CSWSS
Auvin, et al. ⁶⁾	2011	Children - 6	ESM, VPA, LTG	Absence seizures
Aivazian, et al. ¹³⁾	2011	Children – 11 (5.7%)	Various	Add-on therapy
Liu, et al. ²³⁾	2012	Children - 3	None	Myoclonic seizures
Makke, et al. ⁸⁾	2015	Children - 2	None	Myoclonic-astatic seizures
This study	2016	Children – 12 (14.8%)	Various	Add-on therapy

PB, phenobarbital; CSWSS, continuous spikes and waves during slow sleep; ESM, ethosuximide; VPA, valproic acid; LTG, lamotrigine.

generalized seizures according to high serum concentrations have also been reported with carbamazepine (CBZ), tiagabine (TGB), vigabatrin (VGB), lamotrigine (LTG), and gabapentin (GBP)¹⁹. Paradoxical reactions can be described by paradoxical pharmacodynamic effects at nontoxic serum levels: that is, the drug aggravates rather than reduces seizures²¹. Patients with generalized epilepsy seem to be more predisposed to paradoxical reactions than those with focal epilepsy¹⁵. CBZ is the most common example of paradoxical reaction^{5,15}. Other AEDs, such as CBZ, oxcarbazepine (OXC), LTG, PHT, benzodiazepines, VGB, TGB, topiramate (TPM), pregabalin (PGB) and LEV can also induce seizure aggravation, presumably via paradoxical reaction^{5,19}. Drug-induced encephalopathy can occur in patients treated with valproic acid (VPA). VPA encephalopathy is commonly reported with liver failure and hyperammonemia, but it can also affect patients without liver dysfunction^{20,22}. Sometimes, other AEDs like PB, CBZ, VGB, TGB, LTG, and zonisamide (ZNS) induce seizure aggravation with encephalopathy, but this is rare^{15,19}. The sedative effects of AEDs such as benzodiazepines and PB are considered to influence seizure aggravation because drowsiness and sleep can lower the seizure threshold. However, some authors regard sedative effects as paradoxical intoxication or reactions¹⁹.

Inappropriate drug choice can aggravate seizures, especially in patients with specific seizure types. Therefore, there is always a need to reconsider the diagnosis and classification when seizures worsen or a new type manifests. For instance, blockade of voltage-gated sodium channels by CBZ, OXC, PB, PHT, and LTG may be counterproductive in patients with absence or myoclonic seizures^{18,23,24}.

Based on the existing literature, LEV seems to cause seizure aggravation via paradoxical reaction. None of patients with seizure aggravation (group A) showed evidence of drug-associated encephalopathy or intoxication. LEV-associated seizure aggravation was also reported in other studies (Table 3)⁶⁻¹⁰. Seizure aggravation associated with LEV has been reported in patients with absence seizures⁶, continuous spikes and waves during slow sleep⁷, myoclonic seizures¹⁷, myoclonic-astatic seizures⁸, and refractory epilepsy⁹. To date, there is insufficient evidence that LEV induces seizure aggravation in patients with certain seizure types or syndromes.

There are some accepted mechanisms for determining whether seizure aggravation is due to AED use. The most famous mechanism is Na⁺ channel-induced seizure aggravation as for CBZ; GABA signaling within the reticular nucleus and ventrobasal complex of the thalamus is associated the aggravation of absence seizures by CBZ²⁰. This mechanism was investigated in the transgenic model of generalized absence epilepsy rats from Strasbourg (GAERS). The

authors found that CBZ produced a dose-dependent potentiation of the GABA current and specifically affected the ventrobasal thalamus²³. Similar with CBZ, OXC potentiates activation of GABA (A) receptors and aggravates absence seizures²⁵. Some other Na⁺ channel-blocking drugs are PHT, CBZ, OXC, PB, and LTG, which have similar tendencies to aggravate absence or myoclonic seizures, especially in patients with idiopathic generalized epilepsy^{19,25}.

LEV has a different mechanism of action than other AEDs. Lynch et al. reported that it exerts its effects by binding to the synaptic vesicle protein SV2A²⁶. Yang et al. described a decrease in vesicle rate after LEV binding to SV2A²⁷. The overall effects are reversal of the inhibition of neuronal GABA- and glycine-gated currents²⁸ and focal depression of the Ca²⁺ current²⁵. This suggests that there are other mechanisms underlying LEV-induced seizure aggravation, and further investigations would be needed.

In general, there are known risk factors associated with seizure aggravation including AED polytherapy, epileptic encephalopathy, cognitive impairment, refractory epilepsy, and high seizure frequency⁵. In our study, the only one risk factor for seizure aggravation by LEV add-on therapy was generalized seizure type. Unlike Na⁺ channel-blocking agents, LEV is an effective drug for generalized and focal seizures, a so-called broad spectrum AED. Therefore, it is not an appropriate choice for patients with generalized seizure. The results of present study highlight the need to monitor seizure aggravation in generalized seizures. Szűcs et al. reported that the risk of worsening epilepsy increased when initiating LEV treatment in epileptic patients with intellectual disability¹⁰. In our study, group A showed more cryptogenic or symptomatic etiologies, developmental delay or intellectual disability, abnormal EEG background activities, and abnormal MRI compared to patients in group B; however, the differences were not significant.

Seizure aggravation is difficult to define. Because of the unpredictability of seizures, aggravation is frequently and easily overestimated. Seizure fluctuation can be observed in patients receiving a placebo, and it probably represents a spontaneous change in seizure frequency^{19,20}. Thus, it is important to be cautious in determine if seizure aggravation is due to AEDs as there are many reasons other possible reasons (e.g., general illness, therapy noncompliance, use of alcohol and other recreational drugs, natural course of the epilepsy, and sleep deprivation). A fluctuation in seizure frequency does not mean it is due to an AED.

This study has a retrospective study design and assessed a relatively small number of subjects. In addition, the patients were enrolled in a tertiary care center and had been transferred from other hospitals. Focal to bilateral tonic-clonic seizures can be

misdiagnosed as generalized onset seizures. Types of seizures are determined based on the description of seizure by parents of patients. More detailed history taking and close observation of seizures are needed to classify seizures accurately. Recruitment bias could have resulted in a higher prevalence of seizure aggravation by LEV. Although LEV is used as a mono- or polytherapy, the present study only included patients receiving LEV as adjunctive treatment. This increases the possibility of overestimation of seizure worsening by LEV therapy. Further investigations of seizure aggravation after LEV mono-/polytherapy would provide more information about the factors associated with seizure exacerbation. A review of follow-up EEG after seizure aggravation was not performed in the present study, but EEG monitoring would be helpful to clarify AED-mediated seizure aggravation²²⁾. Rechallenging could not be done due to the ethical issues and the refusal to reuse levetiracetam by patients and their parents.

LEV adjunctive therapy may induce seizure aggravation, especially in patients with generalized seizures. Physicians should carefully monitor seizure exacerbation following the addition of LEV. Besides generalized seizure type, we did not identify any risk factors for increased seizure frequency with adjunctive LEV. Given the limitations of this study, further multicentric, prospective investigations are needed to clarify the factors associated with seizure aggravation after LEV therapy.

요약

목적: 본 연구는 소아 뇌전증에서 levetiracetam 부가요법에 따른 경련의 증가를 평가하고 위험인자를 확인하고자 하였다.

방법: 2008년 11월부터 2014년 7월까지 부산대학병원에서 levetiracetam 부가요법으로 치료받은 125명(0.3-18세) 소아를 후향적으로 확인하였다. 44명은 제외 기준에 따라 타 병원에서 치료를 시작하거나, 짧은 치료기간, 뇌전증 외의 치료 용도로 사용되어 포함하지 않았다. 경련의 증가는 levetiracetam 부가 요법을 시작하고 1달 이상 경과한 후 기저 경련 빈도의 50% 이상 증가하거나 새로운 형태의 경련이 발생하는 경우로 정의하였다.

결과: 81명(남:여 44:37)이 연구에 포함되었고, 이중 27명(33.5%)가 전신성 경련, 54명(66.7%)가 국소성 경련을 보였다. Levetiracetam 부가요법을 시작한 지 1달 후 경련의 증가를 보인 Group A 12명(14.8%)과 경련의 감소 혹은 변화가 없는 Group B 69명(85.2%)을 비교하였다. Group A 중 11명(91.7%)과 group B 중 16명(23.2%)는 전신성 경련을 보였고, 경련의 증가는 전신성 경련을 보인 환자에서 더 흔히 관찰되었다($P<0.001$). 그 외 진단 시 연령, levetiracetam 추가한 연령, 성별, 기저 경련 빈도, 병인, 뇌파 소견, 뇌 MRI 소견, 동시 복용 중인 약제 등은 경련 증가와 관련이 없었다.

결론: Levetiracetam은 소아뇌전증의 효과적인 항경련제이나, 본

연구에서는 14.8%에서 경련 증가를 보였고 전신성 경련에서 더 흔히 관찰되었다. Levetiracetam 부가요법을 시행하는 경우에는 경련의 증가나 새로운 형태의 경련이 발생하는지 면밀한 관찰이 필요하다.

References

- 1) Glauser TA, Ayala R, Elterman RD, Mitchell WG, Van Orman CB, Gauer LJ, et al. Double-blind placebo-controlled trial of adjunctive levetiracetam in pediatric partial seizures. *Neurology* 2006;66:1654-60.
- 2) Noachtar S, Andermann E, Meyvisch P, Andermann F, Gough WB, Schieman-Delgado J. Levetiracetam for the treatment of idiopathic generalized epilepsy with myoclonic seizures. *Neurology* 2008;70:607-16.
- 3) Berkovic SF, Knowlton RC, Leroy RF, Schieman J, Falter U; Levetiracetam N01057 Study Group. Placebo-controlled study of levetiracetam in idiopathic generalized epilepsy. *Neurology* 2007;69:1751-60.
- 4) Deshpande LS, Delorenzo RJ. Mechanisms of levetiracetam in the control of status epilepticus and epilepsy. *Front Neurol* 2014;5:11.
- 5) Gayatri NA, Livingston JH. Aggravation of epilepsy by anti-epileptic drugs. *Dev Med Child Neurol* 2006;48:394-8.
- 6) Auvin S, Chhun S, Berquin P, Ponchel E, Delanoë C, Chiron C. Aggravation of absence seizure related to levetiracetam. *Eur J Paediatr Neurol* 2011;15:508-11.
- 7) Caraballo RH, Cersósimo R, De los Santos C. Levetiracetam-induced seizure aggravation associated with continuous spikes and waves during slow sleep in children with refractory epilepsies. *Epileptic Disord* 2010;12:146-50.
- 8) Makke Y, Hmaimess G, Nasreddine W, Fawaz A, Beydoun A. Paradoxical exacerbation of myoclonic-astatic seizures by levetiracetam in myoclonic astatic epilepsy. *BMC pediatr* 2015;15:6.
- 9) Nakken KO, Eriksson AS, Lossius R, Johannessen SI. A paradoxical effect of levetiracetam may be seen in both children and adults with refractory epilepsy. *Seizure* 2003;12:42-6.
- 10) Szucs A, Clemens Z, Jakus R, Rásonyi G, Fabó D, Holló A, et al. The risk of paradoxical levetiracetam effect is increased in mentally retarded patients. *Epilepsia* 2008;49:1174-9.
- 11) Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia* 2010;51:676-85.
- 12) Chhun S, Troude P, Villeneuve N, Soufflet C, Napuri S, Motte J, et al. A prospective open-labeled trial with levetiracetam in pediatric epilepsy syndromes: continuous spikes and waves during sleep is definitely a target. *Seizure* 2011;20:320-5.
- 13) Aivazian SO, Shiriaev IuS. [The retrospective study of efficacy

- and safety of levetiracetam as an add-on treatment of epilepsy in children]. *Zh Nevrol Psikhiatr Im SS Korsakova* 2011;111:33-8.
- 14) Auriel E, Chistik V, Blatt I, Margolin N, Neufeld M. [Efficacy and safety of levetiracetam (keppra) add-on treatment in adult patients with refractory epilepsy in two tertiary centers]. *Harefuah* 2007;146:269-71, 318.
- 15) Chaves J, Sander JW. Seizure aggravation in idiopathic generalized epilepsies. *Epilepsia* 2005;46 Suppl 9:133-9.
- 16) Gelisse P, Genton P, Kuate C, Pesenti A, Baldy-Moulinier M, Crespel A. Worsening of seizures by oxcarbazepine in juvenile idiopathic generalized epilepsies. *Epilepsia* 2004;45:1282-6.
- 17) Liu YH, Wang XL, Deng YC, Zhao G. Levetiracetam-associated aggravation of myoclonic seizure in children. *Seizure* 2012;21:807-9.
- 18) Somerville E. Assessment of seizure aggravation. *CNS drugs* 2004;18:403-4.
- 19) Somerville ER. Aggravation of partial seizures by antiepileptic drugs: is there evidence from clinical trials? *Neurology* 2002;59:79-83.
- 20) Somerville ER. Some treatments cause seizure aggravation in idiopathic epilepsies (especially absence epilepsy). *Epilepsia* 2009;50 Suppl 8:31-6.
- 21) Hirsch E, Genton P. Antiepileptic drug-induced pharmacodynamic aggravation of seizures: does valproate have a lower potential? *CNS drugs* 2003;17:633-40.
- 22) Vendrame M, Khurana DS, Cruz M, Melvin J, Valencia I, Legido A, et al. Aggravation of seizures and/or EEG features in children treated with oxcarbazepine monotherapy. *Epilepsia* 2007;48:2116-20.
- 23) Liu L, Zheng T, Morris MJ, Wallengren C, Clarke AL, Reid CA, et al. The mechanism of carbamazepine aggravation of absence seizures. *J Pharmacol Exp Ther* 2006;319:790-8.
- 24) Sazgar M, Bourgeois BF. Aggravation of epilepsy by antiepileptic drugs. *Pediatr Neurol* 2005;33:227-34.
- 25) Zheng T, Clarke AL, Morris MJ, Reid CA, Petrou S, O'Brien TJ. Oxcarbazepine, not its active metabolite, potentiates GABAA activation and aggravates absence seizures. *Epilepsia* 2009;50:83-7.
- 26) Lynch BA, Lambeng N, Nocka K, Kensel-Hammes P, Bajjalieh SM, Matagne A, et al. The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. *Proc Natl Acad Sci USA* 2004;101:9861-6.
- 27) Yang XF, Weisenfeld A, Rothman SM. Prolonged exposure to levetiracetam reveals a presynaptic effect on neurotransmission. *Epilepsia* 2007;48:1861-9.
- 28) Rigo JM, Hans G, Nguyen L, Rocher V, Belachew S, Malgrange B, et al. The anti-epileptic drug levetiracetam reverses the inhibition by negative allosteric modulators of neuronal GABA- and glycine-gated currents. *Br J Pharmacol* 2002;136:659-72.