



## Research Article

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# Investigation of The Frequency and Risk Factors of Hyponatremia in Patients Receiving Levetiracetam Treatment

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## Abstracts

**Background:** Levetiracetam (LEV) is a widely used antiepileptic drug (AED) in the treatment of various type of seizures. The side effects of LEV are somnolence, asthenia, dizziness, mood changes, kidney dysfunction, rhabdomyolysis, minor infections, and thrombocytopenia. Recently, hyponatremia due to LEV therapy has been reported.

**The Aim:** The goal of the study was to evaluate frequency and risk factors associated with hyponatremia in LEV administration.

**Method:** One hundred and fiftytwo children were enrolled. The risk factors were analysed.

**Results:** Among the 152 patients, 79 (52.0%) were boys and 73 (48.0%) were girls, and the mean age was  $90.37 \pm 46.43$  months (24-188 months). Of the 152 patients, 64 (42.1%) were treated monotherapy, and 88 (57.9%) polytherapy. We detected hyponatremia in one patient (0.7%). The serum sodium level was 130 mmol/l. The patient was asymptomatic, and LEV dose was 25 mg/kg. To investigate the etiology of hyponatremia in the patient, syndrome of inappropriate antidiuretic hormone secretion tests were performed and found normal. There were no significant differences in the hyponatremia between the patients treated with LEV.

**Conclusion:** We detected that LEV may cause hyponatremia. When treating patients with LEV, clinicians should closely monitor serum sodium level. To the best of our knowledge, this is the first study of hyponatremia associated with LEV therapy in children.

**Keywords:** Levetiracetam; Hyponatremia; Children

**Abbreviations:** AEDs: Antiepileptic Drugs; LEV: Levetiracetam; GABA: Gammaaminobutyric Acid; ILAE: International League Against Epilepsy; CT: Cerebral computed tomography; SIADH: Antidiuretic Hormone Secretion

## Background

Epilepsy is one of the common chronic illnesses of childhood. Antiepileptic drugs (AEDs) are used for its long-term treatment. This therapy may be associated with several side effects. Levetiracetam (LEV) is a new broad spectrum antiepileptic agent with favourable efficacy and low profile of toxicity in epilepsy treatment. LEV does not bind to plasma proteins, and is eliminated by the kidneys [1]. It

has been argued that LEV can act on the N-type  $Ca_2$  channel and can reverse the gammaaminobutyric acid (GABA) and glycine-gated currents [2].

Side effects include somnolence, asthenia, dizziness, mood changes, minor infections, skin rashes, thrombocytopenia, interstitial nephritis and rhabdomyolysis [1-5]. Recently,

hyponatremia has been recognized to be one of the adverse effects of LEV [6-10]. It is known that hyponatremia is caused by the use of AEDs such as carbamazepine and oxcarbazepine [11]. To our knowledge, there are a few case reports of LEV associated hyponatremia in the literature [6,7,9,10]. However, there are no studies of LEV associated hyponatremia. Therefore, we planned a study designed to identify the frequency and risk factors associated with hyponatremia during LEV therapy in children with epilepsy.

## Methods

This retrospective study was performed in the pediatric neurology department of our hospital between January 2016 and January 2018. Patients with symptoms and signs of illnesses other than epilepsy (eg, kidney, liver, gastrointestinal, endocrine, and metabolic). In addition, patients who received carbamazepine, oxcarbazepine and other medication (such as diuretics), which can cause hyponatremia, were not included in the study. The patients were divided into two groups according to their therapy. Group 1 consisted of 64 patients who treated with only LEV, group 2 consisted of 88 patients treated with add on LEV. Group 1 has a history of new-onset epilepsy and treated monotherapy with LEV. Group 2 was treated add-on LEV included patients with more treatment refractory epilepsy, who were taking 1-3 AEDs, and had been diagnosed with intractable epilepsy. The institutional ethics committee approved the study protocol. Possible risk factors that may have a role in the hyponatremia prognosis such as age, sex, number of the antiepileptic drugs (mono or polytherapy), dosage of LEV, intellectual disability, neurological abnormality, neuroimaging findings, and etiology were investigated. We classified seizures according to the International League Against Epilepsy (ILAE) criteria. According to the guidelines of ILAE, seizures were divided partial, generalized, and mixed seizures. Aetiologies of the epilepsies were divided into 3 groups as symptomatic, idiopathic, and cryptogenic. Cerebral computed tomography (CT) and/or magnetic resonance imaging (MRI) studies were performed in all patients. Considering the related neuroradiologic studies, the patients were divided into 2 groups: normal and abnormal. The tests used to determine the degree of mental retardation of the patients were the Wechsler Intelligence Scale for Children (standardized for Turkish children) in patients aged 6 to 16 years and the Stanford Binet (American format) for patients aged 2 to 6 years. Levetiracetam was initially administered in a twice daily administration with a starting dose of 10 mg/kg per day. Further doses were titrated until patients were seizure-free. Patients who were started at the beginning of the study and followed for at least 12 months were included in the study. Serum concentration of LEV could not do in our hospital. Retrospectively, patients whose serum sodium levels were examined before the start of treatment and 3 and 12 months after treatment were recorded. A sodium level lower than and equal to 134 mEq/L was defined as hyponatremia.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 21.0 (IBM SPSS Corp.; Armonk, NY, USA). Descriptive statistical methods (mean, median) as well as qualitative data were compared using the chi-square test.  $P < .05$  was considered as a significance level.

## Result

One hundred fiftytwo children, mean age  $90.37 \pm 46.43$  months (24-188 months), were included in this study. Among the 152 patients, 79 (52.0%) were boys and 73 (48.0%) were girls. Of the 152 patients, 64 (42.1%) were treated monotherapy, and 88 (57.9%) polytherapy. Hyponatremia was detected only in 1 (0.7%) patient. The patient was a 5-year-old girl and she had mild intellectual disability. She was only receiving LEV therapy. The serum sodium level measured at 3 months of treatment was 130 mmol/l (normal range; 135-145 mmol/l) and. The patient was asymptomatic, and LEV dose was 25 mg/kg. To investigate the etiology of hyponatremia in the patient, syndrome of inappropriate antidiuretic hormone secretion (SIADH) tests were performed and found normal. We thought that hyponatremia may be due to LEV therapy. LEV treatment was discontinued, and the serum sodium level normalized after 3 days.

**Table 1:** Summary of demographics data and risk factors for hyponatremia in study.

Parameters		n	%	P value
Age	<10 years	102	67.1	0.691
	≥10 years	50	32.9	
Sex	Girl	73	48	0.48
	Boy	79	52	
Number of the AEDs	Monotherapy	64	42.1	0.421
	Polytherapy	88	57.9	
Dose of LEV	<30 mg/kg	54	35.5	0.355
	≥30 mg/kg	98	64.5	
Neurologic deficits	Yes	96	63.2	0.632
	No	56	36.8	
Intellectual disability	Yes	54	35.5	0.645
	No	98	64.5	
Neuroimaging findings	Normal	61	40.1	0.599
	Abnormal	91	59.9	
Aetiology	Symptomatic	81	53.5	0.631
	Cryptogenic	22	14.5	
	Idiopathic	49	32.2	
Hyponatremia	Yes	1	0.7	
	No	151	99.3	

AEDs: Antiepileptic drugs; LEV: Levetiracetam

There was no correlation between hyponatremia and age, sex, number of the AEDs, LEV dose, intellectual disability, neurological

abnormality, abnormal cerebral magnetic resonance findings, and aetiology. Table 1 shows demographics data and the associations between hyponatremia and risk factors (Table 1).

## Discussion

Levetiracetam is an AED, used for the treatment of epilepsy, either monotherapy or add-on therapy. LEV has a favorable pharmacological profile, with almost complete absorption after oral administration, linear pharmacokinetics, and a low extent of metabolism. Levetiracetam is unlikely to interact with other AEDs, because it has a low protein binding [1,2]. Comparison with the other AEDs, LEV use is gradually increasing due to its favourable pharmacokinetics and safety.

The most frequently observed adverse effects were somnolence and behavioural. However, LEV induced thrombocytopenia, interstitial nephritis, rhabdomyolysis, fulminant liver failure, and rise of gamma glutamyl transferase have been reported in patients in literature [1,2,5]. Recently, a few cases have been reported hyponatremia due to LEV treatment [6,8,10]. In previously reports, hyponatremia was reported to occur with the use of antiepileptic drugs (AEDs) such as carbamazepine, oxcarbazepine, valproate, lamotrigine, and lacosamide [11-14]. In the recent a report, Rosca et al. [10] reported a 73-year-old man with epilepsy in whom hyponatremia was induced by only LEV. Nasrallah et al. [6] described hyponatremia due to LEV therapy in a 65-year patient. The patient was receiving LEV and pantoprazole. Belcastro et al. [8] observed a patient developing hyponatremia with LEV monotherapy. The other case was described by Cordoba Lopez et al. [7]. Ari et al. [9] reported a 74-year-old man with hyponatremia induced only LEV therapy. In the literature, to our knowledge, this is the first report of hyponatremia due to LEV therapy in the children.

Since epilepsy is a common disease requiring long-term treatment with AEDs, adverse effects such as hyponatremia can be a major problem [11,12,14]. Especially carbamazepine and oxcarbazepine were associated with a vastly increased risk [11,15]. Both carbamazepine and oxcarbazepine are known to cause hyponatremia with an occurrence of 4.8-31.3% and 0.14-73.3%, respectively [11,16]. Although not fully elucidated, SIADH is believed to be the major contributor of AEDs-induced hyponatremia [16,17]. However, some studies have demonstrated that AEDs-induced hyponatremia can occur without ADH levels being affected [18,19]. Some antiepileptic drugs may have a direct effect on renal tubules and/or increase the tubular response to ADH [16]. Of the previously published cases with LEV-induced hyponatremia, four had a predisposition to SIADH [6-10]. Similar to the case of Belcastro et al. [8], we could not detect SIADH as the cause of hyponatremia. Hyponatremia due to lev therapy develops rarely and generally progresses asymptotically. Similar to the cases reported in the literature [6,8,10] in our case it was asymptomatic.

No clinical studies of hyponatremia have been reported with its use in the literature. Therefore, we conducted a study designed to identify the frequency and risk factors associated with hyponatremia during LEV therapy in children with epilepsy. We detected, one of 152 patients (0.7%) had hyponatremia during LEV therapy. So far, to our knowledge, this is the first study of hyponatremia secondary to LEV treatment in the literature. We detected no significant difference between the risk factors and hyponatremia during LEV therapy.

## Conclusion

In conclusion, we found a case with hyponatremia due to LEV treatment, and the patient was asymptomatic. Thus, patients taking LEV and presenting these risk factors should be particularly monitored for laboratory evidence of hyponatremia. Future studies are needed to determine the frequency and risk factors of this side effect, as well as to determine whether hyponatremia is due to SIADH or an alternative mechanism.

## Ethics Approval and Consent to Participate

An ethical approval was granted by the Institutional Ethics Committee of Cukurova University.

## Conflict of Interest

No conflict of interest noted by the authors

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## Author's Contribution

Both the authors both authors contributed at every stage of the article.

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