

Levetiracetam-Induced Urination and Urinary Frequency in Pediatrics. A Case Report

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ABSTRACT

Objectives: Levetiracetam (LEV) is a broad-spectrum antiepileptic drug used in children and adults. The use of LEV is associated with behavioral abnormalities as adverse drug reactions. However, it might increase the frequency of urination as an adverse effect, which has not been observed or reported previously in Saudi Arabia. It is a description of the unusual side effects of levetiracetam. **Methodology:** A case report of three patients aged 6, 5 and 6 years, respectively. They were diagnosed with epilepsy and treated with levetiracetam. After LEV treatment, all three cases experienced increased urinary frequency and incontinence. **Results:** The Naranjo Adverse Drug Reaction Probability Scale was applied on the three cases and was found to be possibly related in two cases to LEV therapy and probably related in one. We reduced the dose in one patient, and the side effects improved to half. Moreover, it was resolved after discontinuation of the medication. In the other two cases, the side effect resolved on its own. It was reported in the literature that 2 cases had urinary frequency after starting on levetiracetam and improved after reducing the dose and switching to other medication. **Conclusion:** LEV might induce an increase in the frequency of urination. It was an under-reported issue and should be addressed as a transient adverse drug reaction effect. However, it can strongly affect compliance with medication. Therefore, clinicians should be attentive and look exclusively for this symptom to educate the families during follow-up visits.

Keywords: Levetiracetam, Urinary frequency, Urgency, Daytime incontinence, Adverse drug reaction.

INTRODUCTION

Levetiracetam (LEV) is a broad-spectrum antiepileptic drug. It works effectively as monotherapy against newly diagnosed seizures and is adjunctive in refractory partial onset seizures, idiopathic generalized tonic-clonic, or myoclonic seizures. It does its action through binding to vesicle 2A at Synapses (SV2A) to inhibit the neurotransmitter release. Adverse drug reactions to levetiracetam use include asthenia, somnolence, infection, and dizziness in adults. In the pediatric age group, side effects were somnolence, accidental injury, hostility, nervousness, and asthenia. LEV's major excretion pathway is through the renal system.¹ The frequency of urination and daytime enuresis with LEV therapy is an under-reported problem. This is the second paper to report LEV-induced urinary frequency and daytime urge incontinence cases.

PATIENT INFORMATION

Case One

A 6 years old boy, normally developed, was diagnosed with epilepsy after multiple unprovoked tonic-clonic seizures. He was started on levetiracetam, titrated to 26 mg/kg/day. After seven months of being on LEV, the family reported that the patient exhibited an increase in the frequency of urination, sometimes leading to daytime incontinence. It was occurring multiple times every hour daily. Physical exam laboratory tests were unrevealing. There was no record of urinary incontinence before LEV administration. Upon a follow-up clinic visit, the urinary frequency and incontinence stopped independently after one month from onset.

Case Two

A 5-and-a-half-year-old boy with no medical history was put on levetiracetam after two seizures. The dose increased gradually to 28 mg/kg/day. Six months after initiating LEV, his parents noticed an increase in the frequency of urination with the subsequent urge to wet his clothes in the daytime. It was noted to be approximately daily. Physical exam and laboratory tests were unremarkable for positive findings. At the follow-up clinic, parents mentioned the frequency, and enuresis resolved one month after the symptom started.

Case Three

A 6 years old girl with occipital lobe epilepsy was treated with levetiracetam. The dose was titrated gradually until it reached 30 mg/kg/day. One week later, her parents noticed an increase in the urinary frequency to almost every half an hour, causing daytime urge urinary incontinence. A complete physical exam and laboratory exam were normal. After reducing the LEV dose to 15 mg/kg/day, the urinary incontinence frequency declined to once per day and wholly resolved when parents discontinued LEV.

DISCUSSION

Urinary incontinence is involuntary leakage or uncontrollable passage of urine. It can be primary or secondary. If a child has only enuresis with no other lower urinary tract symptoms, he is said to have Monosymptomatic Enuresis (MNE). If a child develops daytime or with other lower urinary tract symptoms, for example, frequency, urgency, or dysuria, it is termed Non-Monosymptomatic Enuresis (NMNE). Urge incontinence is the loss of urine and leakage from urgency.² It is either

Table 1: Demographics and clinical characteristics of the patients on levetiracetam.

	Case 1	Case 2	Case 3
Age	6 years	6 years	5 years
Gender	Male	Male	Female
Toilet Trained	Yes	Yes	Yes
Physical / Neurological exam	Normal	Normal	Normal
Constipation or fecal incontinence	Null	Null	Null
Urine analysis	Color Yellow Appearance Clear WBC 0 RBC 0 Epithelial cells Nil Cast. Nil Yeast. Nil	Color Yellow Appearance Clear WBC 0 RBC 0 Epithelial cells Nil Cast. Nil Yeast. Nil	Color Yellow Appearance Clear WBC 0 RBC 0 Epithelial cells Nil Cast. Nil Yeast. Nil
Urine culture	Negative for bacteria	Negative for bacteria	Negative for bacteria
Kidney Function Test	Na 139 mmol/L (normal range: 136-145) K 4.9 mmol/L (normal range: 3.5-5.1) Ca 2.43 mmol/L (normal range: 2.1-2.5) Creatinine 23 umol/L (normal range: 71-115) BUN 2.8 mmol/L (normal range: 2.5-6.4)	Na 139 mmol/L (normal range: 136-145) K 4.3 mmol/L (normal range: 3.5-5.1) Ca 2.34 mmol/L (normal range: 2.1-2.5) Creatinine 31.5 umol/L (normal range: 71-115) BUN 3.59 mmol/L (normal range: 2.5-6.4)	Na 139 mmol/L (normal range: 136-145) K 3.8 mmol/L (normal range: 3.5-5.1) Ca 2.38 mmol/L (normal range: 2.1-2.5) Creatinine. 34 umol/L (normal range: 71-115) BUN. 3.4 mmol/L (normal range: 2.5-6.4)
Seizure during LEV therapy	Null	Null	Null
Time of starting LEV and appearance urinary frequency	7 months	6 months	Second week
Occurrence of urinary frequency during the day	Hourly	Hourly	Hourly
Disappearance of urinary frequency	After 3 weeks	After 6 weeks	After stopping medication by parents

LEV: Levetiracetam; **Na:** Sodium; **K:** Potassium; **Ca:** Calcium; **Mg:** Magnesium; **BUN:** Blood urea nitrogen.

due to anatomical problems like ectopic ureter, neurological causes such as myelodysplasia, or functional causes that occur without structural or neurological reasons. Causes are rarely due to anatomical or neurological problems and primarily because of functional causes. E.g., urinary tract infection, fecal incontinence, constipation, psychiatric problems, and behavioral disorders.³ For our patients, these factors were assessed and were not present. The Naranjo Adverse Drug Reaction Probability Scale in cases 1, 2 and 3 was found to be 4, 4 and 5, respectively, which indicates a possible adverse drug reaction to LEV in case 1 and 2, and probable adverse drug reaction in case 3. Moreover, in one of our patients, urinary incontinence eased after reducing the dose of levetiracetam and resolved when discontinuing the medication. Ju *et al.* reported two cases, one of a 6-year-old boy who was given LEV for an unprovoked seizure. From the third day of initiating LEV, the child experiences up to 20 times daily urinary frequency, sometimes urge incontinence. When the LEV dose is cut to half, the urinary frequency is reduced to 10 times daily. It was resolved after LEV changed to lamotrigine. A second case of a 13 years old girl started on LEV for convulsion and had frequent urgency, leading to 7-8 times daytime incontinence. When LEV dosage decreased, the urinary frequency reduced by 60%.⁵ On the other hand, enuresis was observed frequently with other antiepileptic drugs before. Malik *et al.* observed daytime incontinence in one patient in his mid-twenties who was diagnosed with epilepsy and was on Valproic acid. On the follow-up, he complained of daytime urinary incontinence while awake and alert.

He improved by reducing the valproic acid dose and resolved symptoms when switching to another antiepileptic drug.⁶ Prolonged carbamazepine therapy caused urinary overflow incontinence, as reported by Andres *et al.*⁷ A 36 years old male diagnosed with schizophrenia and put on topiramate who developed urinary incontinence while asleep and subsided when topiramate was discontinued and replaced by another drug.⁸ The pathway responsible for incontinence varies, while it is thought it could be related to the depth of sleep as in valproate-induced enuresis,⁹ and over-relaxation to striatal muscle in benzodiazepine and gabapentine.^{9,10} Although levetiracetam was suggested by its psychiatric effect,⁵ the mechanism by which LEV can cause urinary frequency is not fully understood, and further evaluation is needed. Renal function tests could be affected in the case of urinary incontinence; however, it was normal in our patients. We did not have a follow-up to the renal profile to ensure no changes happened after resolving the symptoms. Moreover, levetiracetam level was not tested during the symptoms as the kit was unavailable. We suggest closely monitoring the renal profile during and after disappearance of symptoms. As well as to measure levetiracetam level if possible.

Urinary frequency and incontinence after LEV therapy can stop independently, as seen in the two case studies we reported. However, it can strongly affect compliance with medication. Therefore, clinicians should be attentive and look exclusively for this symptom to educate the families.

CONCLUSION

Based on the observations in the three case reports (post-marketing experience), LEV may cause a transient increase in the frequency of urination and a diurnal effect in children. Except for some case reports, it has not been documented as a known adverse effect.

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CONSENT FOR PUBLICATIONS

Written informed consent was obtained from the patient's legal guardian to publish this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

ETHICAL APPROVAL

The Institutional Review Board approved the IRB registration number with KACST, KSA. (H-01-R-012) (IRB approval number: 21-443E).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FUNDING

The authors declare that no financial support was received for the submitted work.

ABBREVIATIONS

LEV: Levetiracetam; **MNE:** Mono-symptomatic enuresis; **NMNE:** Non Mono-symptomatic enuresis.

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