



# **Levetiracetam Induced Hyperkalemia – A Rare Side Effect in Elderly with Pre-Existing Subclinical Renal Insufficiency Presenting with Bradyarrhythmia**

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## **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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**Case Study**

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## **ABSTRACT**

Levetiracetam is a commonly used drug in today's world for long term management of partial as well as generalized seizures mainly due its major advantage that is has so few and non-threatening side effects[1].In the following case scenario, we show how a 70 years old male presented with severe hyperkalemia and after no other common culprits were seen, it was thought to be a side effect therapy with levetiracetam and after discontinuing it and managing hyperkalemia, the patient's condition improved from a very critical state. We also show a rare form ECG presentation of severe hyperkalemia in the form of bradyarrhythmia with absent P waves. Our experience shows that unpredictable and rare side effects of new anti-epileptic drugs should be given attention and such cases often go undiagnosed.

**Keywords:** *Levetiracetam; epilepsy; hyperkalemia; bradyarrhythmia.*

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## ABBREVIATIONS

SA node - Sinoatrial node  
ECG - Electrocardiogram  
AV - Atrioventricular  
CT - Computed tomography  
LVEF - Left ventricular ejection fraction

## 1. INTRODUCTION

Levetiracetam is one of the most commonly used anti-epileptics in current scenario as both an adjunctive or as a single drug therapy with acceptable side effects that mainly include irritability, asthenia, somnolence and behavioral problems[2]. Generally, no major systemic complications have occurred however, according to Kathleen A. Hurwitz, interstitial nephritis and renal failure are underrecognized cause of impairment of renal functions in children[2]. Levetiracetam may also cause transcellular shift of  $K^+$  as it occurs with other drugs leading to hypokalemia[1]. It was suggested by Aksoy et al that hypokalemia may be a sign that patient has developed a renal dysfunction in patients who are on levetiracetam therapy[1]. Here we have thought of a similar theory by which our patient had presented with paraparesis owing to severe hyperkalemia and levetiracetam has been suggested as the culprit owing to transcellular shift of potassium ions. Similar case has been reported by Mahta et al where they have described interstitial nephritis and renal failure as a rare complication of levetiracetam and such a rare possibility should always be kept in mind in such cases[3]. Our case had a deranged renal function test and presented with severe hyperkalemia and an episode of life threatening pulseless ventricular tachycardia from which he was revived after administration of DC shock of 200 J. Secondly, we will also be presenting a rare form of ECG abnormality seen in hyperkalemia. There is no clear margin as to when the ECG changes occur when the potassium levels rise but 80% of the patients show ECG changes after the serum potassium level crosses 6.8 mEq/dl[4]. The most common and widely acknowledged sign of hyperkalemia is tall and peaked "tented" T waves but this not considered the significant if there are no signs and symptoms or risk factors for hyperkalemia present[5]. With further rise in serum potassium levels, there is silence of the sinoatrial and atrioventricular conduction (sinoatrial conduction delay manifests first as atrial tissue is considered to be more sensitive to extracellular potassium than ventricular tissue)

which presents as flattening or absence of P waves and combined with AV blocks and often escape beats happen[6]. As the levels aggravate and the clinical pictures becomes more severe, T waves convert from tall and tented to broadened which often fuse with the QRS complex which is noticed as wide and bizarre and this presentation is typically termed as "sine wave appearance"[5,7]. We will be showing ECG of severe hyperkalemia presenting as bradyarrhythmia with absent P waves.

## 2. PRESENTATION OF CASE

A 70 years old male presented in the emergency department with complaints of sudden onset bilateral lower limb loss of power since the last 2 hours with no associated signs of symptoms. The patient was known case of seizure disorder for 25 years for which he was on tablet levetiracetam 500 mg twice daily. He was also a known diabetic for the last 40 years on oral hypoglycemic drugs and a known case of systemic hypertension since last 40 years on irregular medications. Patient was on tablet Gepride m2 (glimepiride 2 mg + metformin 500 mg) twice daily for diabetes and tablet amlodipine 5 mg twice daily for systemic hypertension since last 40 years. There was no history of intake of any diuretics anytime in the past. There was no history of any past renal or hepatic disorders. All the common probable causes were ruled out and his CT thoracolumbar spine scan was suggestive of no obvious abnormality. CT brain showed periventricular ischemic changes and generalized age-related cerebral atrophy. 2D echo was suggestive of normal study with no valvular disease and normal LVEF OF 60%. His blood investigation reports revealed severe hyperkalemia with serum potassium of 14 mEq/dl and his serum creatinine was 2.0 mg/dl, other electrolytes were within normal. Serum cortisol and thyroid profile reports were all within normal range. There was no evidence of peripheral neuropathy due to diabetes mellitus. Sensations were intact, there was history of tingling or numbness over peripheries and his blood sugar levels were well controlled over the years. Hba1c was 5.8. The serum potassium levels were repeated to be sure and the blood sample tested was non-hemolyzed. Also, there was no evidence of any active hemolysis and rhabdomyolysis.

Levetiracetam was thought to be the culprit for hyperkalemia and it was stopped. Patient also developed 1 episode of pulseless ventricular tachycardia during the hospital stay for which he

was revived with 1 delivery of DC shock of 200 J and the patient was immediately intubated and shifted on mechanical ventilation. He was given iv glucose-insulin continuously with iv calcium gluconate. But as there was no clinical improvement in the patient's clinical condition, he was subjected to 2 cycles of hemodialysis with potassium free fluid with no ultra-filtrate removal

for 4 hours each and with a blood flow of 250ml/min under intensive cardiac and blood pressure monitoring.

With this the patient's serum potassium levels normalized and he improved symptomatically. He was later extubated and was managed conservatively.

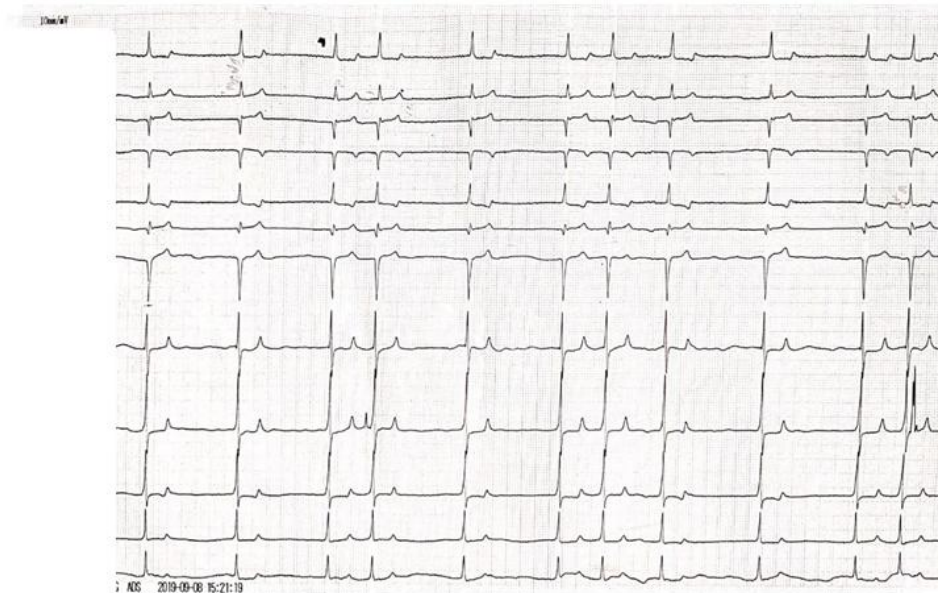


Fig 1. ECG of the patient on admission

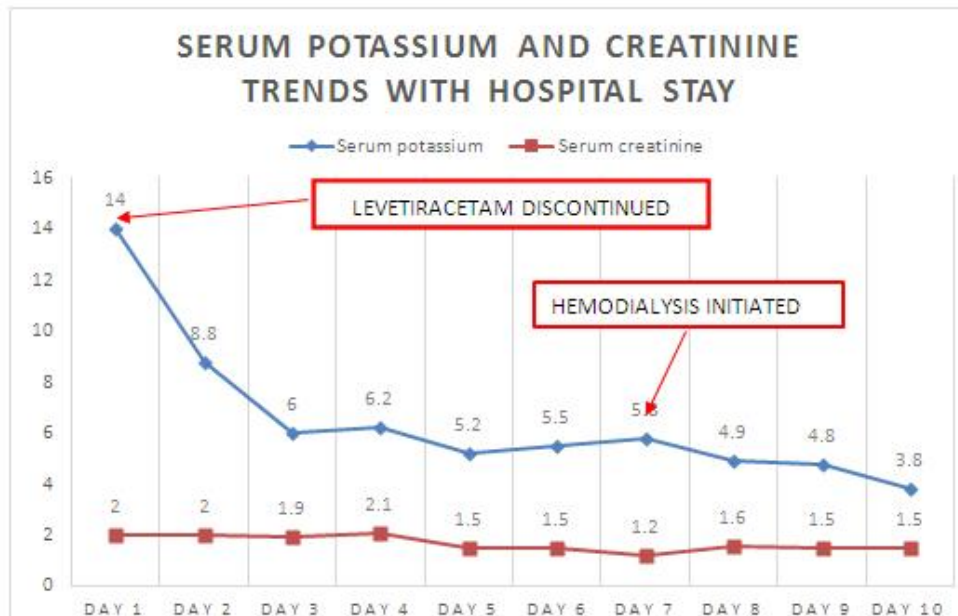


Fig. 2. Serum potassium and creatinine levels during the hospital stay

Fig. 1 shows the ECG recorded during the admission. It depicts absent p waves with bradyarrhythmia (atrial p waves are not visible as they are flattened which is seen in severe hyperkalemia)[6].

Fig.2 shows the turn of events that happened as the patient's potassium levels subsequently normalized and it also depicts the consistent deranged creatinine levels which are suggestive of subclinical renal dysfunction.

We had diagnosed this patient as a case of severe hyperkalemia due to levetiracetam which is also the agent causing renal dysfunction. The patient recovered completely and was discharged 1 month later with regular follow up.

### 3. DISCUSSION

In our case, there was no history of tingling and numbness over the lower limbs and the symptoms were acute in onset, thus diabetic peripheral neuropathy was ruled out. Also, he has good control over his blood sugar levels.

Levetiracetam is mainly excreted through renal mode of excretion in its unchanged form and only about 27% is metabolized[8]. The lack of liver involvement in its pharmacokinetics and lack of protein binding ability are important in understanding why it has so little or practically no pharmacokinetic interactions with other drugs like anti-coagulants, digitalis, oral contraceptive pills and so on[8]. However, the dose has to be adjusted in patients with renal failure[8]. There have been few case reports reported until now where levetiracetam has been shown to cause hypokalemia and hypomagnesemia as per Vallianou et al and Aksoy et al[1,9]. However, hyperkalemia has not been previously reported. But we do know that it can cause interstitial nephritis and requires dose alterations in cases with renal dysfunction. Therefore, we think that as suggested by Aksoy et al, transcellular shift of  $K^+$  ions induced by levetiracetam can also present as hyperkalemia as in our case. This case reports shows that such side effects with such a commonly used anti-epileptic should be given enough importance in literature as they might be more common than what we actually might have thought.

We think this effect will be more common in aged individuals (more than 60 years) as it is a well-known fact that many subjects exhibit

progressive decreases in glomerular filtration rate (GFR) and renal blood flow (RBF), with wide variability among individuals. These hemodynamic changes occur in concert with structural changes, including loss of renal mass; hyalinization of afferent arterioles and in some cases, development of glomerular arterioles; an increase in the percentage of sclerotic glomeruli; and tubulointerstitial fibrosis[10]. Extremities of age can cause alterations in clearance of LEV. Clearance in almost half in people with more than 65 years of age and is increased by about 30-40% in pediatric age group patients[11].

However, it is important to understand that chronic use of levetiracetam is associated with renal dysfunction and its immediate use will not affect renal function as such. A study was carried in which 3980 levetiracetam users were matched to 7960 nonusers and levetiracetam use was not significantly associated with a higher risk of AKI within 30 days. Similarly, there was no significant association with AKI within 180 days. The change in the concentration of serum creatinine did not significantly differ between levetiracetam users and nonusers [12].

Now to the second part, hyperkalemia is one of the most life threatening metabolic condition that can lead to cardiac arrest and it is also a reversible peri-arrest condition[13,14]. However, potassium levels often go above their normal values unnoticed and cardiac arrhythmias can occur without any sign or symptom that might give us a clue to it[13]. ECG is therefore a widely and commonly used modality to sense such dangerous conditions but its correlation with the potassium levels in serum has been disputed[13]. As sodium is the main extracellular cation, potassium is main intracellular cation its serum levels are maintained between the two compartments (extracellular and intracellular) by  $Na^+/K^+$  ATPase pump, beta adrenergic agents, passive shift and mineralocorticoids[6]. A long term potassium homeostasis is achieved by gastrointestinal uptake and renal excretion[7]. The common ECG abnormalities seen in hyperkalemia are peaked or "tented" P waves, PR segment prolongation, flattening of P waves followed by its subsequent disappearance, "wide and bizarre" QRS complexes, conduction blocks, sine-wave pattern, ventricular tachycardia/systole and finally asystole[6]. Our ECG showed absence of P waves. This explained by the fact that sinoatrial node or the SA node is not as much responsive to high potassium levels as the atrial myocardial fibers are[15]. So as the

potassium levels rise, atrial conduction is present but its contractility is lost as evident by absent P waves. In simple words as stated by Kirat et al, the SA node directly triggers the AV node without causing an atrial contraction (P wave) and such a rhythm is known as sinoventricular rhythm[16]. It is noteworthy that the rhythm can still be considered a sinus rhythm as it still is originating for the SA node. This ECG is often misinterpreted as a junctional rhythm. But as the potassium levels rise further the SA node is affected and there can actually be sinus pause or arrest with ventricular escape rhythm. So, to determine whether the ECG is an SA nodal block with junctional idioventricular rhythm or an atrial fibrillation with absent P waves, electrophysiological study of the conduction system is essential. Lastly, a third possibility has been raised of a second-degree SA nodal block that is constantly varying along with loss of P waves seen in hyperkalemia. A case study published by Yu et al shows such an ECG with P waves present but slow ventricular rhythm in our ECG can be justified with this theory.[15].

#### 4. CONCLUSION

Choosing an anti-epileptic drug should be done after thorough check up of the patient along with his all-routine bloodwork and his cardiac monitoring should be done on follow up basis for now such side effects have been reported in recent times with newly emerging anti-epileptics. Also, changing the line of management like altering the dose of anti-epileptic along with regular renal function monitoring seems to be a sensible option. According to a study carried out in 2014, anti-epileptics can be classified in to 3 groups: (a) Ones which are excreted by renal route without any changes in structure, (b) Ones that are exclusively excreted by the liver metabolism, and (c) Ones that eliminated by a mixture of renal and non-renal excretion. Gabapentin, pregabalin, vigabatrin, and topiramate belong in the first group. They mostly avoided in renal dysfunction or as modified cautiously. Phenytoin, valproate, carbamazepine, tiagabine, and rufinamide belong in the second group. Their toxicity can develop in hepatic failure. Levetiracetam, lacosamide, zonisamide, primidone, phenobarbital, ezogabine/retigabine, oxcarbazepine, eslicarbazepine, ethosuximide, and felbamate are from the third group. These drugs can be used cautiously in patients with either renal or liver failure.[17] However dose adjustment is required even with these drugs. Owing to the complexities in their mechanisms of

action, mode of transport and excretion routes, anti-epileptic drug therapy requires special attention in subjects with chronic kidney disease or end stage renal diseases. Toxicities can occur even in therapeutic level dosage due impaired clearance and these symptoms manifest later. In our case, due to subclinical renal disease, hyperkalemia resulted due to effective supra-therapeutic levels of levetiracetam.[18] About 66% of the parent LEV dose is excreted by the kidneys in unchanged form. Therefore in renal dysfunction, accumulation will take place leading to toxicity. This has also been documented in the older population due to an age-related decline in renal function. Even very mild renal can lead to a 35% decrease of LEV CL[19].

#### DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

#### CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

#### ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

#### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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