Case Report

Pregabalin Neurotoxicity Associated with Triphasic Waves on Electroencephalogram. Conservative Management or Hemodialysis?

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Introduction:
Pregabalin is a lipophilic analogue of γ-aminobutyric acid. It is approved for the treatment of neuropathic pain, anxiety disorder, fibromyalgia, and as an adjunctive therapy for partial seizures (Calandre EP, Rico-Villademoros F, Slim, 2016; National Center for Biotechnology Information, 2021; Derry, Bell, Straube, Wiffen, Aldington, & Moore, 2019). Lately, pregabalin is also being prescribed for uremic pruritis (Khan, Wu, Goh, Lee, Alhafez, & Syed Sulaiman, 2016). Significant pregabalin toxicity associated with therapeutic use has been reported in chronic kidney disease (CKD) patients (Olaizola, Ellger, Young, Bosebeck, Evers, & Kellinghaus, 2006; Braga & Chidley, 2007; Huppertz, Feuerstein, & Schulze-Bonhage, 2001). Here, we report a case of pregabalin neurotoxicity presenting as acute severe encephalopathy, and facial myoclonus manifesting as triphasic waves on electroencephalogram (EEG) in a CKD IIIb-IV patient.
Case narration:
A 69-year-old woman was admitted to the intensive care unit with acute encephalopathy. Her medical history included HFrEF, CKD IIIb-IV, depression, and post traumatic distress disorder. Her psychotropic medications included pregabalin, quetiapine, and venlafaxine. Her family reported that she had become progressively short of breath for ten days leading up to her admission; therefore, her diuretic dose was increased. On presentation, she was arousable only to noxious stimulation. She had altered sensorium, unable to follow commands, and frequently falling asleep during the exam. Corneal reflexes and horizontal oculocephalic reflexes were present bilaterally. The pupils were equal, round, and reactive to light, and the pharyngeal reflex was present. There was spontaneous continuous myoclonus of the face. Muscle tone was normal. Plantar reflexes were equivocal bilaterally, and no clonus was observed on examination. The neck was supple.

Laboratory studies revealed an elevated serum creatinine of 3.86 mg/dL from a baseline creatinine of 2.3 mg/dL (normal: 0.60–1.30 mg/dL). Complete blood count and comprehensive metabolic panel at baseline. Her arterial blood gas showed a pH 7.49, pCO2 49 mmHg, bicarbonate 30 mmol/L. Additional laboratory studies showed blood ethanol level < 3 mg/dl, and blood ammonia level 19 umol/L. The urine toxicology screen was negative. Acetaminophen and salicylate were undetectable.

CT head revealed no acute abnormalities. Her EEG is shown here (Figure 1) and revealed continuous moderate generalized slowing of the background and abundant intermittent bi-anterior predominant, bi-synchronous triphasic waves that often occurred over several second runs at 1.5-2.2 Hz. Given the patient’s worsening renal function associated with oliguria, there was a concern about pregabalin and venlafaxine toxicity. She was treated with intravenous fluids for the next 24 hours without any clinical improvement. The patient was then hemodialyzed for 3 hours leading to complete resolution of encephalopathy, facial myoclonic, and triphasic waves on EEG.

Discussion:
Pregabalin is an anti-epileptic, anxiolytic, and analgesic medication often used for neuropathic pain. Pregabalin binds selectively to the alpha2delta (A2D) subunits of presynaptic calcium channels in the central nervous system (Calandre EP, Rico-Villademoros F, Slim, 2016). This binding prevents calcium influx and blocks the calcium-dependent release of neurotransmitters, including serotonin, dopamine, norepinephrine, glutamate, and substance P (National Center for Biotechnology Information, 2021). This reduced excitability has efficacy in treating neuropathic pain (Derry, Bell, Straube, Wiffen, Aldington, & Moore, 2019). The most common adverse effects include dizziness, somnolence, myoclonus, blurred vision, peripheral edema, tremor, visual field loss, and rhabdomyolysis (Toth, 2014; Gunathilake, Boyce, &Knight, 2013).

Pregabalin is well absorbed orally and has a bioavailability of >90%. It is excreted almost entirely unchanged in the urine (90%) and does not have any hepatic metabolism. To achieve comparable plasma drug concentrations in patients with creatinine clearance (CL\text{cr}) values of < 60 ml/min, it is usually recommended that pregabalin doses be decreased by ∼50% for each 50% decline in CL\text{cr}.
In individuals with normal kidney function, the drug has a serum half-life of 9 hours which increases to 49 hours when CL\textsubscript{cr} drops below 15 ml/min. Hence, when CL\textsubscript{cr} drops below 60 mL/min, reduced frequency of pregabalin administration should be considered (Randinitis, Posvar, Alvey, Sedman, Cook, & Bockbrader, 2003). In our patient, a significant decrease in her CL\textsubscript{cr} and continued 75 mg twice daily dosing increased her serum level of pregabalin to induce acute encephalopathy, facial myoclonus, and triphasic EEG waves. The pharmacokinetics of pregabalin makes it a dialyzable drug. It has a low volume of distribution, low molecular weight and is not protein bound. Hemodialysis reduces the half-life to 4 hours (Lee, Lee, Kim, Chang, & Park, 2011). Yoo et al. described a case of a hemodialysis-dependent end-stage renal failure patient who developed myoclonus that was thought to be related to pregabalin accumulation following an increase in the prescribed dose. Hemodialysis resulted in improvement of the clinical symptoms (Yoo, Matalon, Hoffman, & Goldfarb, 2009). Our patient was becoming progressively unresponsive. We favored hemodialysis over the potential risks of intubation. Immediately after dialysis patient’s encephalopathy and myoclonus resolved completely. Fast recovery after dialysis supports pregabalin toxicity and argues against the venlafaxine toxicity as it is non-dialysable (Yeh et al., 2014).

Triphasic morphology EEG discharge waveforms have three principal phases: a positive, sharp transient preceded and followed by negative waves of relatively lower amplitude (Figure 1). These discharges are bilaterally synchronous, occurring at a frequency of 1.5 to 2.2 Hz and only rare reports have shown an association between these discharges and pregabalin toxicity (Anand & Kaplan, 2018). When triphasic waves are present in an individual with acute encephalopathy, it often indicates a more significant impairment, prolonged hospital course, and increased odds of mortality (Emmady & Murr, 2021). Triphasic waves resemble certain EEG patterns associated with nonconvulsive status epilepticus. However, unlike nonconvulsive status epilepticus, the encephalopathy associated with triphasic waves does not improve or resolve with the administration of benzodiazepines (Fountain & Waldman, 2001). In our patient, the marked improvement in her EEG after dialysis suggests that her triphasic waves were related to pregabalin toxicity. Although serotonin syndrome has been described in association with triphasic waves, our patient had no hyperthermia, ankle clonus, dilated pupils, diaphoresis, or diarrhea to suggest this diagnosis.

After one week, pregabalin level was reported to be supratherapeutic at 12.3 mg/L (normal therapeutic 0.15 - 8 mg/L) (May, Rambeck, Neb, & Jürgens, 2007). Naranjo Score was 5, indicating a probable adverse drug reaction. This was not a definite case because we did not rechallenge her. Our patient had experienced a progressive decline in her CL\textsubscript{cr} in the year prior to admission; however, her pregabalin dose had not been reduced. This case highlights that in patients with CKD, it is important to reduce dose and frequency of administration when further decline of creatinine clearance occurs. Additionally, this case underscores the potential role of dialysis in pregabalin toxicity to facilitate reversal of encephalopathy.
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**Abbreviations:**

AKI: Acute Kidney Injury.

CKD: Chronic Kidney Disease.

CL_{cr}: Creatinine Clearance.
Figure legend

Figure 1 showing intermittent bi-anterior predominant, bi-synchronous triphasic waves running at runs at 1.5-2.2 Hz.

Figure 2 showing resolution of triphasic waves post HD.