Valproate-Induced Hyperammonemonic Encephalopathy: A Case Report and Brief Review of the Literature

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Almost 50 years after its discovery, valproic acid remains a mainstay in the treatment of epilepsy, both alone and in combination with other anticonvulsants. It is also associated with a hyperammonemic encephalopathy, when used in combination with other drugs. We present a case of valproate-induced hyperammonemic encephalopathy in a patient on multiple anticonvulsant and psychotropic medications. The patient presented with altered mental status and became progressively more obtunded and finally began to experience seizures. Her symptoms resolved with the discontinuation of valproic acid and with supportive care.

Keywords: valproic acid, encephalopathy, hyperammonemia, carnitine, VHE, side effects

INTRODUCTION

Since its licensure in 1967, valproic acid (VPA) has become the mainstay in the treatment of seizure disorders and has become the most widely prescribed antiepileptic medication worldwide, and is being used in the treatment of various mood disorders, and for migraine prophylaxis. It is usually well tolerated and has fewer common nonneurological side effects than do other anticonvulsants. Neurological side effects tend to be transient, including valproate-associated hyperammonmonic encephalopathy. We present a patient with known psychiatric disorders and a history of remote seizures in which a high index of suspicion led to the final diagnosis of valproate-associated hyperammonemic encephalopathy.

CASE

A 52-year-old female with a medical history significant for schizoaffective disorder and remote seizures was admitted to the psychiatric ward with deteriorating mental status changes, suicidal ideation, low-grade temperature, and worsening seizures. Medications on admission included risperidone, divalproex, and phenytoin. She had also been started on haloperidol and lorazepam recently. She was started on ciprofloxacin for presumptive infection, without improvement in symptoms. Her divalproex dose was increased without any effect on seizure control and with a concomitant obtundation. In view of her fever, declining mental status, and new seizure activity, she was transferred to the general medical unit for further work-up.

On physical examination, the patient had a temperature of 100.2°F and blood pressure of 134/73 mm Hg. She was lethargic but arousable. She was anicteric but had perseveration and asterixis. She did not make eye contact or follow commands. The patient was able to move all extremities, and strength and deep tendon
reflexes were preserved bilaterally and meningeal signs were negative. Physical examination was otherwise unremarkable.

Initial laboratory findings showed mildly elevated alanine transaminase and aspartate transaminase. Her alkaline phosphatase, total bilirubin, total protein, white blood cell count, hemoglobin, coagulation times, thyroid-stimulating hormone, urinalysis values, and chest film results were all normal. Serum potassium of 3.3 mEq/L (normal: 3.5–5.1 mEq/L) was the only electrolyte abnormality. Her serum ammonia level was 218 μmol/L. Serum VPA level was 81 μg/mL. Electroencephalograph (EEG) during drowsy state showed a marked diffused background slowing intermixed with 2–2.5 Hz of high-amplitude slow waves, which occurred synchronously over both hemispheres without any epileptiform activity (Fig. 1). Relevant laboratory investigations excluded any metabolic cause of encephalopathy. The lack of response to intravenous diazepam excluded nonconvulsive status epilepticus leading us to believe the condition to be a generalized encephalopathy. The patient was taken off lorazepam, risperidone, divalproex, and phenytoin and started on lactulose. Her ammonia levels and liver functions rapidly improved after the discontinuation of her medications. Her mental status also returned to baseline, along with normalization of her EEG. After being afebrile for 48 hours, she was serially challenged with lorazepam, risperidone, divalproex, and phenytoin and started on lactulose. Her ammonia levels and liver functions rapidly improved after the discontinuation of her medications. Her mental status also returned to baseline, along with normalization of her EEG. After being afebrile for 48 hours, she was serially challenged with lorazepam, risperidone, and phenytoin. Her laboratory examination values remained normal and she continued to be afebrile. Her mental status also remained stable despite the resumption of the medications. This, along with the temporal relation of VPA initiation in the form of divalproex, led us to the final diagnosis of VHE.

**DISCUSSION**

VPA potentiates γ-aminobutyric acid (GABA) functions by increasing both GABA synthesis and release. It reduces the release of GABA, attenuates neuronal excitation induced by N-methyl-d-aspartate and also alters dopaminergic and serotonergic neurotransmissions. 2–4 VPA has a half life ranging from 9 to 16 hours, but shorter half lives of 5–12 hours can occur in patients taking enzymes inducing comedication such as phenytoin as in the case of our patient. 5–8 Conversely, peak plasma concentrations may be markedly delayed after acute overdose, up to 30 hours. 9 VPA is significantly bound to plasma proteins depending on the drug concentration, but the percentage decreases at higher VPA levels. 9, 10 This results in a nonlinear relation between the dose administered and the total serum levels at any given time.11 VPA has fewer, and milder, common side effects than do other anticonvulsants, which can often be minimized by initiating the drug slowly3; more serious adverse reactions include hepatotoxicity, encephalopathy, coagulation disorders, pancreatitis, and bone marrow suppression.3, 12 Although they probably do not contribute to its anticonvulsant effects, some of the metabolites are involved in the toxic effects of VPA.

Hyperammonaemia occurs in nearly 50% of patients on chronic therapy, but this remains asymptomatic in almost 50% of cases.3, 13 VHE is rare during monotherapy. It may occur after both acute on chronic overdosage and regular chronic use of VPA. 5, 9, 12, 14 The typical signs of VHE include an acute onset of impaired consciousness with confusion and lethargy, focal or bilateral neurologic symptoms or signs, and increased seizure activity.15 EEG changes consist of pronounced

![FIGURE 1. EEG shows an irregular, continuous, and diffuse slowing, consistent with diffuse cerebral dysfunction.](image-url)
generalized slowing and an increase in epileptiform discharges.16 Multiple authors have reported on the magnetic resonance imaging findings in VHE, but these have not been able to define a specific localized defect.17–19

Although the exact pathogenesis of VHE is still incompletely understood, several mechanisms have been put forward. The direct drug effect on neurotransmitters is considered to be the main mechanism of VHE.20 Certain drugs such as topiramate have been shown to have an increased risk of encephalopathy when combined with VPA.15,21 VHE also seems to be more prevalent in individuals with carnitine deficiency and congenital urea cycle defects.3,16,22–24 VPA reduces hepatic citrullinogenesis through inhibition of hepatic carbamyl phosphate synthetase activity, acting as an urea cycle inhibitor.23,25 VPA may also cause neuronal toxicity and cerebral edema by causing an increased intracellular concentration of glutamate and ammonium in astrocytes.3,16,21

In conclusion, we have presented a case where the diagnosis of VHE could have been misdiagnosed as an exacerbation of our patients’ psychiatric disorder or history of seizures. Unfortunately, VHE may not have any correlation with the valproate dosage or serum concentration. Therefore, a very high index of suspicion must be maintained when a patient on VPA presents with encephalopathy. Early recognition and prompt intervention are imperative.

REFERENCES