Recurrent Stupor Associated with Chronic Valproic Acid Therapy and Hyperammonemia

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Valproic acid (VPA) and its derivatives, valproate and divalproex, are anticonvulsant and mood-stabilizing drugs used in the treatment of epilepsy and acute mania as well as for prophylaxis of migraine headaches. Although VPA is generally considered a safe and well-tolerated drug, rare but serious complications may occur in some patients, such as hepatic failure, pancreatitis, thrombocytopenia, and hyperammonemic encephalopathy.[1,2] Although symptoms of VPA–induced hyperammonemic encephalopathy may be mild, this condition can progress to stupor and coma and may be fatal without appropriate management. However, VPA–induced hyperammonemic encephalopathy can be easily reversed once VPA is discontinued, particularly if diagnosis occurs in a timely manner.[3,4] This article reports the case of a 45-year-old man diagnosed with schizophrenia and epilepsy who experienced a recurrent stuporous state and hyperammonemia associated with chronic VPA treatment. A review of the underlying mechanisms, clinical features, diagnosis, and management of VPA–induced hyperammonemic encephalopathy is also provided.

CASE PRESENTATION

Presentation and History

A 45-year-old man diagnosed with schizophrenia was transferred from a residential nursing home to a hospital psychiatric service for evaluation of inappropriate behavior (initially irritability, agitation, and refusal to eat) and excessive somnolence, which began a few days before admission. The patient's past medical history was significant for well-controlled epilepsy associated with generalized tonic-clonic seizures; the patient had no witnessed seizure activity in years. His medication regimen, which had been unchanged for 2 years, consisted of phenytoin 400 mg/day, VPA 1500 mg/day, ziprasidone 40 mg/day, and lorazepam 2 mg as needed for agitation. Prior to symptom onset, he was able to ambulate and perform all the activities of daily living without assistance. The patient's history was also notable for 3 prior hospitalizations with similar symptoms, with the first episode occurring 6 months ago and the most recent occurring 2 weeks prior to the current presentation. In each instance, the patient was admitted to the psychiatric service, and he became progressively more lethargic and did not eat or take his medications. After 2 or 3 days, the patient slowly recovered and was discharged on his prior medication regimen. A diagnosis of possible catatonic state was made for these episodes.

Initial Management

At the current admission on the psychiatric service, he received intramuscular lorazepam (2 mg every 6 hours for 4 doses while admitted to the psychiatric service) for presumed catatonia; the rest of the medications were taken intermittently by the patient. Laboratory studies (including complete blood count, electrolyte panel, glucose levels, serum blood urea nitrogen, and creatinine) were within normal limits. After 2 days without improvement, the patient was transferred to the medical service for further testing and intravenous hydration. A nasogastric tube was inserted for feeding and medication administration and phenytoin, ziprasidone, and VPA were restarted.

Clinical Evaluation

On physical examination, the patient's vitals signs were normal, pupils were equal and sluggish reactive, and signs of jaundice or stigmata of chronic liver disease were absent. The patient was in a stuporous state. Specifically, he was not responsive to verbal stimuli and was briefly arousable only by deep stimulation. Deep tendon reflexes were symmetric, with extensor plantar

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responses bilaterally. The remainder of the physical examination was normal.

Results of initial laboratory investigations including complete blood count, electrolyte panel, glucose levels, serum creatinine, liver function test, coagulation profile, albumin, and thyroid function test were normal. In addition, the serum level of phenytoin was 10.5 mg/dL (therapeutic level, 10–20 mg/dL) and the level of VPA was 75 mg/dL (therapeutic level, 50–100 mg/dL). Chest radiograph, electrocardiogram, and noncontrast head computed tomography (CT) were unremarkable. An electroencephalogram (EEG) was interpreted as diffuse abnormal consistent with metabolic encephalopathy. The lack of diagnosis for the stuporous state prompted neurologic consultation.

A neurology consultant ordered measurement of the patient's ammonia level, which was found to be 3 times the upper limit of normal (venous ammonia level, 87 μmol/L [normal, 10–30 μmol/L]). As assessment of carnitine status is recommended in patients with suspected VPA–induced hyperammonemic encephalopathy or hepatotoxicity,[5] total and free carnitine levels were checked and found to be low: total carnitine, 8 μmol/L (normal, 42–81 μmol/L) and free carnitine, 31 μmol/L (normal, 35–67 μmol/L). The patient was diagnosed with VPA–induced hyperammonemic encephalopathy on hospital day 3.

Treatment

VPA was tapered off, and the patient was administered L-carnitine 330 mg twice daily by nasogastric tube and was placed on a low protein diet. Over the next 2 days, the patient became progressively more alert. On hospital day 5, the patient's ammonia level was normal (20 μmol/L), and his mental status returned to baseline. He was transferred to the psychiatric unit for management of his medication regimen. VPA was not restarted, but he was continued on the rest of his medications. The patient recovered entirely but had retrograde amnesia of the event. The patient did not experience any similar episodes of stupor over the following months, and he remained seizure free.

VPA–INDUCED HYPERAMMONEMIC ENCEPHALOPATHY

Although the exact incidence of hyperammonemic encephalopathy due to VPA therapy is unknown, hyperammonemia is common in patients who take VPA. In 1 series of 55 outpatients who were taking VPA, 53% had ammonia concentrations elevated above normal range.[6] Elevated ammonia levels without hepatic dysfunction have also been described previously in patients with VPA.[4,7]

Mechanisms of VPA-Induced Hyperammonemia

Several possible mechanisms for the development of hyperammonemia in patients taking VPA who do not have underlying hepatic dysfunction have been proposed. VPA metabolism occurs primarily in the liver and produces propionate, which impairs the urea cycle (the process that primarily metabolizes ammonia) via inhibition of carbamyl phosphate synthetase (the enzyme that initiates the urea cycle). With sufficient enzyme inhibition, ammonia levels may accumulate and result in encephalopathy.[2,8]

Development of VPA-induced hyperammonemia may also be attributed in part to preexisting or VPA–induced carnitine deficiency.[2,5,8,9] Multiple studies suggest that epileptic patients treated with VPA have low total and free carnitine levels;[5] a similar decrease in total and free carnitine levels was also found in psychiatric patients treated with VPA.[9] Chung et al[10] showed significantly lower levels of total and free carnitine in patients treated with VPA monotherapy or polytherapy, with an inverse correlation between the carnitine level and the duration of VPA therapy. Insufficient carnitine can impair the urea cycle by reducing mitochondrial long-chain fatty acid metabolism, resulting in low levels of acyl-CoA that inhibit production of N-acetyl glutamic acid, a cofactor for carbamyl phosphate synthetase. Carnitine deficiency also increases production of metabolites such as propionate, which impairs the urea cycle as previously described.[2] As a result, chronic therapy with VPA or an acute overdose of VPA can cause hyperammonemia. However, it should be noted that not all cases of VPA–induced hyperammonemic encephalopathy have demonstrated carnitine deficiency.[9]

Increased renal glutaminase activity is another proposed mechanism by which VPA may cause hyperammonemia without hepatic dysfunction.[2,3] Underlying urea cycle disorders also can predispose patients to severe hyperammonemic encephalopathy that is sometimes fatal.[2,7] VPA is contraindicated in patients with known urea cycle disorders.[1] Finally, some studies suggest that simultaneous treatment with phenobarbital, phenytoin, carbamazepine, or topiramate may exacerbate VPA–related hyperammonemic encephalopathy.[3,6,11–14] Of note, the case patient was concomitantly taking phenytoin.

Once hyperammonemia occurs, encephalopathy may develop. Hyperammonemia most likely increases glutamine synthetase activity, which increases glutamine production in the astrocytes and provokes neuronal injury and cerebral edema that leads to encephalopathy.[2,4,12]

Clinical Features

The literature describes only a few cases of symptomatic hyperammonemia in patients receiving a chronic,

stable dose of VPA,[7,15] but there are reports of different acute or subacute neurologic symptoms related to VPA–induced hyperammonemic encephalopathy that rapidly resolve after VPA is discontinued.[16] In general, the initial presenting symptoms of hyperammonemic encephalopathy due to VPA include impaired consciousness (eg, drowsiness, lethargy), confusion, and increased seizure frequency in some patients with epilepsy. Rarely, focal neurologic symptoms can be present in patients with epilepsy.[14] Patients may progress to ataxia, stupor, and coma.[2,12,16] The diagnosis of hyperammonemia may be delayed if a patient's increasing lethargy is interpreted as a medication side effect or worsening of psychiatric or neurologic disease.[15,16] Unless specifically sought, hyperammonemia may be overlooked as a cause of change in mental status.

Laboratory studies of patients with hyperammonemic encephalopathy due to VPA therapy reveal either normal or high levels of VPA. Hyperammonemia occurs either due to an acute overdose with elevated VPA levels or due to chronic VPA treatment with VPA levels in therapeutic range,[17] as was seen in the case patient. Obtaining a blood ammonia level in all patients (including psychiatric patients or patients with epilepsy) presenting with altered mental status and receiving VPA is indicated.[7,9,15,16] When interpreting the ammonia level result, physicians should keep in mind the limitations of the test and sources of errors: phlebotomy technique, analysis on ice, and concomitant presence of chronic kidney disease.[18] Usually, arterial ammonia is measured because the venous value can change depending on the amount of time that the tourniquet is around the arm. An ammonia level is not useful as an isolated test but must be correlated with the clinical findings. It should be noted that there is no correlation between the VPA level and the ammonia level.[4,11] The presence of other laboratory abnormalities depends on the underlying cause (eg, elevated serum aminotransferases may be present in cases with hepatic dysfunction).

In conjunction with elevated ammonia levels, VPA–induced hyperammonemic encephalopathy can be diagnosed with EEG. Changes on EEG usually consist of diffuse slowing of background activity, consistent with metabolic encephalopathy.[3] Head CT is frequently performed in a patient with acute change in mental status, especially when focal neurologic symptoms are present, to rule out other neurologic causes such as hemorrhagic stroke or subdural hematoma.[3,7]

Differential Diagnosis

Hyperammonemic encephalopathy is among the possible causes of stuporous state in patients who have a normal head CT scan (**Table 1**). In many cases, standard laboratory studies can narrow the differential diagnosis. Hepatic failure is typically the suspected cause of hyperammonemic encephalopathy in adults, but multiple nonhepatic factors can produce hyperammonemia (**Table 2**). Common causes of hyperammonemia include urea cycle defects, organic acidemias, hepatic dysfunction, and medications.

Table 1. Differential Diagnosis of Stuporous State in Patients with Normal Computed Tomography Scan of the Head

Toxic or metabolic disorders
Electrolyte disturbances
Hypercalcemia or hypocalcemia
Hypernatremia or hyponatremia
Glycemic control disturbances
Diabetic ketoacidosis
Hyperosmolar nonketotic hyperglycemia
Hypoglycemia
Hyperthyroid and hypothyroid states
Hyperammonemic encephalopathy
Hepatic encephalopathy
Uremic encephalopathy
Anoxic encephalopathy
Hypercapnic encephalopathy
Drug intoxication
Postseizure state, status epilepticus
Infections
Encephalitis
Meningitis
Psychogenic unresponsiveness
Brainstem infarct

In the case patient, VPA had been prescribed for 3 years, and he had multiple episodes of confusion and lethargy with complete recovery between episodes, which makes the differentiation between postictal state and encephalopathy difficult. However, the patient resided in a nursing home and had no witnessed epileptic episode in years. Since the ammonia level was not tested, it is possible that his past episodes of stupor were erroneously diagnosed as catatonic states. At the final stuporous episode, the patient improved rapidly after VPA was discontinued, and this recovery correlated with the normalization of the ammonia level. EEG performed when the patient was unresponsive ruled out subclinical seizures. Furthermore, the patient's recovery from the previous lethargic episodes occurred after 2 to 3 days of not eating and not taking his medications. We

Table 2. Causes of Hyperammonemia

Urea cycle disorders	Hepatic encephalopathy (acute or chronic)
Arginase deficiency	Drugs
Argininosuccinate lyase deficiency	Asparaginase
Argininosuccinate synthetase deficiency	5-Fluorouracil
Carbamyl phosphate synthetase I deficiency	Salicylate
Ornithine transcarbamylase deficiency	Valproic acid
N-acetyl glutamate synthetase	Other
Organic acidemia	Parenteral nutrition
Isovaleric acidemia	Portosystemic shunt
Methylmalonic acidemia	Reye's syndrome
Multiple carboxyl acidemia	Urinary tract infections due to urease producing organisms
Propionic acidemia	
Transient hyperammonemia of newborn	

Data from Alqahtani S, Federico P, Myers RP. A case of valproate-induced hyperammonemic encephalopathy: look beyond the liver. CMAJ 2007;177:568–9; *and* Segura-Bruna N, Rodriguez-Campello A, Puente V, Roquer J. Valproate-induced hyperammonemic encephalopathy. Acta Neurol Scand 2006;114:1–7.

hypothesize that he improved in all of these episodes because VPA was stopped. It is unclear why he developed intermittent stupor. A possible explanation is fluctuation of carnitine levels, with symptomatic hyperammonemia developing when the carnitine level was low. Fluctuating concentrations of ammonia, glutamine, and other cytotoxic amino acids resulting in a chronic or episodically recurring encephalopathy was reported in females with ornithine transcarbamylase deficiency.[13,19]

Of note, we did not perform the specific testing to determine whether the patient had urea cycle enzymopathy; however, clinical manifestations of hyperammonemic encephalopathy are more severe in hemizygous males, who typically present in the neonatal period.[18] It is recommended that patients who develop VPA–induced hyperammonemic encephalopathy undergo evaluation for underlying urea cycle disorders.[1]

Management

The management of VPA–induced hyperammonemic encephalopathy consists of supportive measures and discontinuation of VPA. Carnitine supplementation has been shown to correct hypocarnitinemia[5] and improve hyperammonemia, which may lead to faster recovery;[7,20,21] however, the evidence is inconclusive.[2,5,8,9] To date, there are no randomized trials comparing outcomes of patients with VPA–induced hyperammonemic encephalopathy who had VPA discontinued and received carnitine and those who only had VPA discontinued. Additionally, carnitine deficiency is not found in all patients with VPA-induced hyperammonemia.[9] The main dilemma regarding carnitine is whether asymptomatic low carnitine levels should be treated with carnitine supplementation to prevent complications and whether carnitine levels should be checked in patients at higher risk of developing VPA-induced hyperammonemia.[2,5,8,9] The case patient had low total and free carnitine levels, and carnitine supplementation together with VPA withdrawal resulted in a significant improvement.

CONCLUSION

Hyperammonemic encephalopathy with or without hepatic dysfunction is a rare but serious adverse effect of VPA therapy. Unless specifically sought, hyperammonemia is overlooked as a cause of changes in mental status in both psychiatric patients and patients with epilepsy. Ammonia levels should be checked in patients taking VPA who develop new neurologic symptoms. VPA–induced hyperammonemic encephalopathy is managed by discontinuation of VPA and supportive therapy; carnitine supplementation can be useful. **HP**

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