CASE REPORT

Acute Hypoxic Respiratory Failure /Hyperammonemic Encephalopathy in the Setting of Concurrent Use of Valproic Acid and Topiramate

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Abstract

Valproic acid (VPA) is widely used for the treatment of epilepsy, migraine, and a variety of psychiatric symptoms, including bipolar disorder, borderline personality disorder, and alcohol withdrawal. Valproate is associated with severe idiosyncratic adverse effects, the most notable being valproate-induced hyperammonemic encephalopathy (VHE). Topiramate is also a broad-spectrum anticonvulsant that is also extensively used for migraine prophylaxis, as a mood stabilizer, and for alcohol dependency. There is increased occurrence of VHE when valproate is used with other medications like phenytoin, phenobarbital, and topiramate. We report a young patient who was on valproic acid and topiramate and developed metabolic encephalopathy with hypoxic respiratory failure with review of the causes and management of the hyperammonemic encephalopathy. We believe that clinicians should be aware of possible hyperammonemic encephalopathy in any patient who is taking valproic acid and presenting with impaired consciousness and cognitive decline. We also underline the importance of early recognition and high index of suspicion of encephalopathy related to hyperammonemia.

Case presentation:

A 21-year-old female patient with past medical history of medically refractory epilepsy, hypothyroidism and mood disorder came with altered mental status and respiratory distress. She started to have seizure disorder from early childhood. She underwent vagal nerve stimulation procedure for her epilepsy and she was on Levetiracetam, Valproic acid and topiramate. In the emergency room, she was found to be tachycardic and hypoxic with a On physical examination, BP 124/86, HR 107 /m, RR was 19 /m and T 99.2. Scattered crepitations in the lower posterior chest bilaterally with no cardiac murmurs or gallop or leg edema. On neurologic examination, she was alert, with no focal deficits or meningeal irritation signs. ABGs showed PH of 7.37, PCO2 of 39 and PO2 of 56 CT chest showed bilateral lung infiltrates suggestive of pneumonia. Procalcitonin and lactic acid levels were found to be with in normal range. Respiratory viral /atypical panel was negative and blood and sputum culture were negative.

She was started on broad spectrum antibiotics. Her antiepileptic medications were also restarted at the same dose that she was getting at home.. Antibiotics were deescalated accordingly. On the next day of admission, patient was still having mild confusion and ammonia level was elevated at 102 μg/deciliter (mcg/dl). Valproic acid level was 77 mcg/dl (normal 50–125 mcg/dl). TSH level was within the normal limit. At this point, metabolic encephalopathy due to hyperammonemia was considered and she was started on L-carnitine and Lactulose.

Ammonia level increased to 126 mcg/dl. EEG showed intermittent generalized slowing consistent with a mild encephalopathy but there were no electroencephalographic seizures or any interictal epileptiform activity. The cause of the hyperammonemia was thought to be related to valproic acid.

Neurology evaluation suggested decreasing the dose of topiramate as it was a relatively new medication. Her topiramate dose was halved and she was kept on L- Carnitine and lactulose but her confusion stayed the same and her ammonia level on the next day increased to 162. Due to lack of significant response, valproic acid was stopped resulting in gradual improvement in her clinical status and decline in Ammonia level towards normal value. No further seizures noted after she was changed to Levetiracetam and lacosamide.

Introduction:

Metabolic encephalopathy represents a serious problem that needs to be addressed in a multidisciplinary approach since this might lead to respiratory and CNS complications. Serum ammonia level is a useful test to guide in diagnosing VHE but it is very important to realize that level as such does not correlate with the severity of VHE. Increased familiarity with the diagnosis and appropriate treatment of VHE is also essential. Resolution or prevention of hyperammonemia may be enhanced with the administration of intravenous L-carnitine as the oral form has low bioavailability.

Valproic acid is a broad-spectrum antiepileptic drug that inhibits degradation, and promotes postsynaptic

transmission of gamma-aminobutyric acid (GABA). Valproic acid (VPA) is widely used for the treatment of epilepsy, migraine, and a variety of psychiatric symptoms, including bipolar disorder, borderline personality disorder, and alcohol withdrawal. VPA has been used effectively to reduce agitation and aggression in both acute and post-acute traumatic brain injury patients, as well as a variety of other neuropsychiatric syndromes, including dementia and mental retardation. Valproate is associated with severe idiosyncratic adverse effects, the most notable being valproate-induced hyperammonemic encephalopathy (VHE), which is seen in up to 0.9% of patients taking valproate [5]. Topiramate is also a broad-spectrum anticonvulsant that is also extensively used for migraine prophylaxis, as a mood stabilizer, and for alcohol dependency. There are studies in the literature which has shown an increased occurrence of VHE when valproate is used with other medications like phenytoin, phenobarbital, and topiramate.

The combined antiepileptic valproate and topiramate therapy causes reduction of topiramate metabolism through cytochrome P 450 pathway and topiramate decreases levels of valproate by increasing its metabolism.

VHE causes metabolic encephalopathy which is defined as a diffuse cerebral dysfunction, typically manifesting as changes in cortical functions and as disorders of consciousness, ranging from confusion to coma.

Recognition of VHE requires a high level of clinical suspicion, as clinical presentation is nonspecific and correlates poorly with dosage, blood levels, or duration of treatment.

The development of hyperammonemia, the consequences of which are difficult to differentiate from the pathology itself and that can be misdiagnosed as therapeutic failure instead of an adverse drug reaction related to the use of VPA.

This case report illustrates the importance high clinical suspicion and early recognition of VHE and its management.

Literature review: In one report, it is estimated that up to 50% of patients taking valproate develop hyperammonemia. Most of these patients have elevations of ammonia with normal liver function and are asymptomatic. There is also no clear correlation between blood ammonia levels and the severity of encephalopathy, suggesting that mechanisms other than those involving ammonia contribute to the neurological dysfunction. Approximately 0.9% of patients using valproate develop hyperammonemic encephalopathy. This number could be higher if patients are taking sedatives and other antiepileptic medications like lamotrigine, topiramate and risperidone.

Carnitine deficiency and urea cycle enzyme abnormalities also expose patients for valproate and topiramate induced hyperammonemic encephalopathy. Our patient was on topiramate in addition to the valproic acid but she was not checked for carnitine deficiency or urea cycle enzyme defect. Topiramate was originally synthesized as a potential hypoglycemic agent even if it was found not to have that effect and it was later found out that it is an important medication for seizure,

migraine prophylaxis and mood disorder due to its effect in the CNS and sodium and calcium channels. The presence of pneumonia in our patient might be responsible for her deterioration and presentation to us but her clinical response with the decrease in the level of the ammonia supports the fact that the hyperammonemia is responsible for her deterioration.

The mechanism by which valproate causes hyperammonemia is not clear but hepatic and renal metabolic pathways have been proposed. Propionate, a metabolite of valproate reduces hepatic N-acetylglutamate concentration, which is an obligatory activator of carbamoyl phosphate synthetase 1 (CPS-1), the first enzyme of the urea cycle. Decline in CPS-1 activity results in defective ammonia utilization and accumulation of ammonia. Another mechanism thought to play a role is reduction of hepatic carnitine levels by valproate. This results in decreased beta-oxidation of fatty acids, which in turn results in reduced levels of Acetyl Co-A. This decrease in Acetyl Co-A ultimately disrupts the urea cycle resulting in ammonia accumulation. The less common mechanism is that valproic acid stimulates kidney tubule glutaminase that subsequently enhances glutamine uptake into renal cortical cell mitochondria. The conversion of glutamine ultimately leads to increased ammonia production. The cytosolic ammonia accumulated within astrocytes and neuronal cells which is conjugated with glutamine by glutamine synthetase is responsible for the oxidative stress and subsequently leads to mitochondrial swelling and cytosolic edema. Availability of electroencephalogram recordings may help improve diagnostic validity, but it is unlikely to facilitate differentiation of VPA from other causes of encephalopathy.

We have EEG recordings done in our patient which showed intermittent generalized slowing consistent with a mild encephalopathy but there were no electroencephalographic seizures or any interictal epileptiform activity. Our patient could possibly have a non-convulsive seizure due to drug withdrawal with subsequent deterioration since she was not taking her medications for 3 days before presentation. This is very difficult to prove as we only have EEG 2 days after her presentation.

The mainstay of VHE treatment is discontinuation of VPA, which leads to complete recovery in most patients. We decreased the dose of both valproate and topiramate in our patient but patient's clinical condition didn't improve. So, both medications were stopped and she was started on L-carnitine. Persistence of VHE despite reduction or discontinuation of VPA is an indication for additional ammonia-depleting agents such as lactulose, charcoal, neomycin, rifaximin, or L-carnitine. We have used L-carnitine and lactulose in our patient since discontinuation of the medications didn't completely improve her clinical condition. L-carnitine is an amino acid derivative and important nutrient involved in fat metabolism. Up to 75% of L-carnitine is provided by diet, particularly red meat and dairy products. It is also biosynthesized endogenously from dietary amino acids (methionine, lysine), especially in the liver and in the kidneys. Carnitine is responsible for 2 metabolic functions. It eases the fatty acyl-group transport into

mitochondria and it also preserves the ratio of acyl-CoA to free CoA in the mitochondria. As VPA-induced hyperammonemia and VHE could be mediated at least in part by carnitine deficiency, it has been hypothesized that L-carnitine supplementation may prevent, correct, or attenuate these adverse effects [. L-carnitine should be given intravenously because of the low bioavailability of enteral L-carnitine. There is also a literature on the use of arginine supplementation for treatment of hyperammonemic encephalopathy even if we haven't used it in our patient. Arginine supplementation tends to normalize elevated plasma ammonia concentrations. Arginine plays a critical role in ammonia detoxification, as ammonia is detoxified via its metabolism into urea. On the one hand, it has been accepted that arginine is an activator of N-acetyl glutamate synthetase (NAGS) via agmatine; on the other hand, arginine entering the liver via the portal vein is metabolized to provide ornithine for citrulline and aspartate synthesis and for the priming of the urea cycle. The clinical response of our patient was correlated with the decrease in the serum ammonia level but literature has shown that serum levels of ammonium do not correlate with the severity of valproate-induced encephalopathy and there is no conclusive evidence of a major causative role of hyperammonemia on encephalopathy in human clinical studies. Because of that it is suggested to follow patients clinically rather than monitor the level of serum ammonia once the diagnosis of hyperammonemic encephalopathy was made and the right treatment started. The valproic acid level of our patient stayed in the normal range the whole time in our patient but still there is no concordance with respect to a direct relationship between the development of VHE and serum valproic acid levels.

Conclusion:

Metabolic encephalopathy is a rare but serious complication of valproic acid (VPA) therapy that usually presents with impaired consciousness. Major drug interactions that are life-threatening are not common, but are of serious concern. Topiramate increases the risk of valproic acid-induced encephalopathy. It should be carefully used in patients receiving VPA treatment.
Respiratory distress and hypoxic respiratory failure might also develop within this clinical setting

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