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Case Report

Valproate enduced encephalopathy in a psychiatric patient with normal liver function tests

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ABSTRACT

Sodium valproate is a broad spectrum antiepileptic drug (AED) and is being widely used in various neuro-psychiatric conditions. It can cause hyper-ammonemic encephalopathy (HE) especially when used with other anti-epileptics like topiramate, phenobarbitone, phenytoin etc. Here we describe such a patient who was taking valproate for bipolar disorder with no other AEDs and earlier misdiagnosed as viral encephalitis, which on further evaluation was found to be suffering from HE. The patient was managed accordingly and recovered completely.

1. Introduction

The use of valproic acid frequently results in elevated plasma ammonia.[1] In some people, it may be clinically significant, resulting in hyperammonemic encephalopathy (HE), which may be severe. Valproic acid-induced hyperammonemic encephalopathy may occur in people with normal liver function, despite normal doses and serum levels of valproic acid (VPA). Physicians should be aware of this potential complication of VPA and check ammonia levels in patients taking VPA who present with alterations in mental status. A high index of suspicion is required to diagnose valproate-induced HE. Behavioral changes may be ascribed to post-ictal state or nonconvulsive status epilepticus. Seizure exacerbation may prompt the clinician either to increase the dose of existing anti-epileptic drugs (AEDs) or to add more AEDs. Considerable overlap exists in the EEG findings between HE and nonconvulsive status epilepticus. Since serum ammonia level may at times be normal, amelioration of encephalopathic features on withdrawal of valproate may be the only way to clinch the diagnosis. Because of these reasons, valproate induced HE may be a grossly underdiagnosed entity. Treatment with L-carnitine may be beneficial in reducing ammonia levels.[1]

2. Case Report

A left handed non-hypertensive, non-diabetic, non-alcoholic, non-smoker elderly male patient presented to us with history of insidious onset and gradually progressive drowsiness of twelve days duration. The patient developed generalized tonic-clonic seizures after two days of drowsiness, with a total of six episodes over next two days followed by persistent deranged sensorium since then. There was no asymmetry in movements of the limbs, vomiting, headache or any history suggestive of cranial nerve deficit, history of fever or head injury, or any past history of tuberculosis or other systemic illness. The patient was a known case of bipolar disorder, with an attack of psychosis 2 years back and depression since then, he had been on regular treatment with sodium valproate 500 mg twice a day, amitriptyline 10 mg at bed time and sertraline 25 mg. On examination, the patient was drowsy with normal vitals. He was disoriented to time and place, and partially oriented to person. Rest of Central Nervous

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System examination didn't reveal any focal abnormality, and plantar response was extensor bilaterally. Investigations revealed hemoglobin of 14.1gm/dL, total White Blood Cell (WBC) count 7610/mm^3, 83%neutrophils, 12% lymphocytes and an Erythrocyte Sedimentation Rate of 26 mm in 1st hour. Blood sugar was 82mg%, urea 24mg%, creatinine 0.96mg%, ALT-27 IU/L, AST- 32 IU/L, Serum Na^+ 137mEq/L, Serum K^+ 3.47mEq/L. Cerebrospinal spinal fluid(CSF) analysis was normal (CSF sugar 61mg% with matching blood sugar 87mg%, CSF protein 48mg%, WBC- 02, 100% lymphocytes, ADA-1.0; Gram, Acid Fast Bacilli and India ink stain negative). CSF herpes simplex virus (HSV) polymerase chain reaction (PCR) was negative. Electroencephalogram (EEG) showed frequent slowing but didn't show any epileptic discharges. Magnetic resonance imaging of brain showed non-specific bilateral symmetrical altered signals in basal ganglia, suggestive of either metabolic encephalopathy, hypoxic ischemic encephalopathy or encephalitis. The patient was given a trail of acyclovir till results of CSF HSV PCR were obtained, but failed to show any positive response. In view of the seizures, valproate was continued and levetiracetam added. However, patient failed to show any response. After a negative HSV PCR report, valproate induced encephalopathy was considered. Serum ammonia levels were 132 (normal range 10-70), after which a final diagnosis of valproate induced hyperammonemic encephalopathy was made. Valproate was then omitted after which patient improved within the next few days. At the time of discharge, the patient was completely asymptomatic and well.

3. Pathophysiology

Valproate increases ammonia levels through both hepatic (due to decreased hepatic urea production through valproate induced inhibition of liver carbamoyl phosphate synthetaseI) and renal (due to stimulation by valproate of glutaminase activity in the renal cortex) mechanisms. Topiramate facilitates hyperammonemia probably through inhibition of carbonic anhydrase (which increases ammonia due to decrease in the mitochondrial urea synthesis in liver) and cerebral glutamate synthetase (which detoxifies cerebral ammonia). The metabolism of ammonia occurs primarily through the urea cycle. Ammonia is a by-product of the conversion of amino acids to α-ketoacids. In the liver, ammonia is converted to urea, which is then excreted in the urine. VPA inhibits the activity of carbamoyl phosphate synthetase I, the first enzymatic reaction in the urea cycle, thereby hindering the excretion of ammonia and raising plasma ammonia levels.[2]

The mental status change associated with hyperammonaemia is not fully understood. However, a likely mechanism is that hyperammonaemia stimulates increased glutamine synthetase activity, causing increased production of glutamine in astrocytes. CSF and blood levels of glutamine may be elevated in conjunction with hyperammonaemia. Glutamine in astrocytes causes an osmotic shift of fluid into the astrocytes, producing astrocyte swelling and cerebral edema.[2]

Our experience with this patient with valproate induced HE without hepatic failure tell us that valproate-induced HE may not be uncommon. Even subtle clinical features such as excessive somnolence, seizure exacerbation, and behavioral disturbance in a patient receiving valproate, especially in combination with other AEDs, should alert the clinician about HE, and since this complication more often occurs when valproate is used along with other AEDs, unnecessary AED polytherapy should be avoided. There are currently no specific recommendations for screening people for asymptomatic hyperammonaemia, nor are there any known consequences. In previous case reports the patients were also taking some other drugs like topiramate[3] and herbal ayurvedic medicines from Neeraj clinic which may be a confounding factor.[4]

At present we take a clinical examination based decision as at times we do not have access to serum ammonia level and we get positive results. Use of lactulose and discontinuation of valproate along with protein restriction and glucose supplementation lake as in hepatic encephalopathy is the ultimate answer.[1,5]

4. Conclusion

VHE is a potentially serious consequence of the use of VPA; physicians should consider this possible cause of changes in mental status in patients treated with VPA. Mental status changes in patients, with the addition of a second anticonvulsant (especially topiramate), which is considered a rational combination because of weight maintenance, should prompt consideration of hyperammonaemia. Patients with VPA-induced hyperammonaemia may be asymptomatic, may have behavioural changes, or may have marked deteriorations in their level of consciousness. Deaths have been reported. The primary therapy is withdrawal of VPA; L-carnitine supplementation may decrease ammonia levels and improve symptoms. Levetiracetam and carbamazepine should be considered in an appropriate setting so as to avoid this complication.

5. Conflicts of Interest

All contributing authors declare no conflicts of interest.

6. Source of Funding

None.

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