Case Report

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Valproate-Induced Hyperammonemic Encephalopathy in a patient with Ischemic Stroke

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ABSTRACT:

Valproate-induced hyperammonemic encephalopathy in a patient with ischemic stroke

Hyperammonemic encephalopathy is a rare, life threatening complication of valproate therapy. We describe an adult male with manic disorder and alcohol dependence who developed encephalopathy within two weeks of therapy with valproate. Risperidone and lorazepam were the concomitant medications. His serum ammonia was found to be elevated. There was complete resolution of symptoms after valproate was stopped. The patient's clinical picture was further complicated by imaging findings of ischemic changes and infarcts in the brain. Our report highlights the importance of considering hyperammonemic encephalopathy in any patients who develops acute changes in mental state while receiving valproate.

Keywords: hyperammonemia, encephalopathy, valproate

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INTRODUCTION

Asymptomatic hyperammonemia is frequently seen with valproate therapy but hyperammonemic encephalopathy due to valproate is a rare complication and most of the cases have been described in pediatric neurology literature. The first report of valproate induced symptomatic hyperammonemia in a psychiatric setting was reported by Settle in 1995[1]. A review of 14 cases of valproate induced hyperammonemic encephalopathy in psychiatric settings found an equal incidence in both sexes and onset ranging from soon after initiation of therapy to months or years of usage. Clinical features include lethargy, vomiting, cognitive slowing, focal neurological deficits and impairment of consciousness[2]. The severity of clinical symptoms was found to be unrelated to the blood ammonia levels[3]. Even though the incidence and severity of hyperammonemic encephalopathy are not related to the dosage, duration of treatment or serum level of valproate, and encephalopathy can occur with normal hepatic function, cases of

valproate induced hyperammonemia with supratherapeutic valproate levels have been described[2,4,5,6]. A review of 30 cases of hyperammonemic encephalopathy in psychiatric patients led to the identification of the following risk factors: valproate- drug interactions, mental retardation, urea cycle disorders and carnitine deficiency. The primary treatment of hyperammonemic encephalopathy is discontinuation of valproate. Lactulose, L carnitine and neomycin have been found to be useful adjuvants[2]. We report an adult patient with mania who developed encephalopathy following valproate therapy and whose clinical picture was further complicated by findings on neuroimaging.

THE CASE

Our patient was a 48 year old male, who presented with ten days history of an acute onset of a manic syndrome characterized by elated mood, increased speech and goal directed activity, grandiose delusions, physical assaultiveness towards family members, decreased sleep, and significant socio-occupational impairment. Precipitating factor was a financial stressor. There was also history of alcohol dependence for the past five years. There was no past history of mood disorder or complicated alcohol withdrawal state. There was no history of any medical illnesses in the past. There was a family history of alcohol dependence in his father, three brothers and history of suicide in brother following a stroke. General physical and neurological examination was normal at the time of presentation. Hematological tests, liver function tests, blood sugars, electrolytes, and renal function tests were within normal range.

Patient was admitted with a diagnosis of mania with psychotic symptoms. Secondary mania was not considered because history, physical examination, and laboratory examinations did not suggest any medical morbidity. He was started on valproate 500 mg which was gradually increased over six days to 1500 mg at night. He was also started on risperidone up to 5 mg for control of agitation. Lorazepam 2 mg was given thrice a day for detoxification and it was gradually tapered and stopped on the eighth day of hospital stay. Soon after admission his blood pressure was found to be high and he was started on antihypertensives. Serum valproate level was measured and found to be 100 µg/ ml. On the 12th day of in-patient stay, patient developed lethargy, ataxia, disorientation to time and place, visual hallucinations, irrelevant speech, increased motor activity, and disturbance of the sleep wake cycle. There was impairment in attention, immediate and recent memory. There were no focal neurological deficits. A diagnosis of delirium was made. Laboratory studies including urea, creatinine, electrolytes, liver function tests, total and differential counts were repeated and found to be normal. A CT scan was also performed the following day to examine the delirium further.

In view of acute onset of changes in the mental state following valproate therapy, the possibility of valproate-induced hyperammonemic encephalopathy was considered. Serum ammonia was found to be three times the upper limit of normal [113 µmol/ l (normal 11 to 35 µmol/ l)]. Valproate was stopped immediately and patient was started on syrup lactulose 30 ml thrice a day (3.335 gm of lactulose per ml) and rifaximin 400 mg thrice a day. After 48 hours patient's cognition and sleep became normal. Serum ammonia test was repeated and found to be within normal limits (18 µmol/ l).

Incidentally the CT scan revealed lacunar infarcts in the left external capsule, hyperdense cortical vein in the left parietal lobe and diffuse cerebral atrophy. MRI with MRA and MRV was ordered by the neurologist and it showed acute ischemic infarct in the left putamen, bilateral small vessel ischemic changes, bilateral chronic lacunar infarcts in the basal ganglia, and a venous angioma in the left parieto-occipital region. Patient was started on antiplatelet agents. The antipsychotic was changed to haloperidol due to hypertension and above-mentioned findings on the brain imaging and patient's manic symptoms improved. He was not rechallenged with valproate.

DISCUSSION

Asymptomatic hyperammonemia is a frequent complication of valproate therapy and an incidence of 51.2% was found in a prospective study on psychiatric patients receiving valproate[7]. However valproate–induced hyperammonemic encephalopathy is a rare, potentially life threatening complication of valproate therapy. It is seen more frequently in patients with carnitine deficiency and congenital urea cycle enzyme defects[8]. Therapy is quite rewarding if the condition is recognized early and treated accordingly.

The proposed mechanism for valproate induced accumulation of ammonia is reduction of free carnitine and co-enzyme A in the hepatic mitochondria. This leads to depletion of N-acetyl glutamate which is an activator of carbamoyl phosphate synthetase I, the initial enzyme in the urea cycle[8,9]. Increased ammonia results in higher production of glutamine within the astrocytes in the brain. This leads to cerebral edema and astrocyte dysfunction[10]. Valproate also increases the renal uptake of glutamine[11].

Polypharmacy is a frequently described risk factor for valproate-induced hyperammonemic encephalopathy, especially the combination of valproate with other anti-epileptics such as phenytoin, phenobarbital, and topiramate. The proposed mechanism is synergistic action on the urea cycle[12,13]. Hyperammonemic encephalopathy has also been described in children and adults who received a combination of valproate and risperidone. Competition for protein binding sites leading to increase in free valproate levels was considered as a possible mechanism[14,15]. An interaction between valproate and lorazepam was implicated in another case of hyperammonemic encephalopathy[16]. Valproate reduces the elimination of lorazepam since both drugs are metabolized through glucuronidation. A case of coma probably due the above combination has been described[17].

Our patient developed signs and symptoms of encephalopathy within two weeks of initiation of valproate therapy. An elevated serum ammonia level of more than thrice the upper limit of normal led us to consider the possibility of hyperammonemic encephalopathy due to valproate. However the clinical picture of our patient was further complicated with history of alcohol dependence, and imaging findings of acute and chronic infarcts in the brain. Hepatic encephalopathy was not considered because liver function tests were normal. The acute infarct in the left putamen was also considered unlikely to play a major role in the patient's delirium because of the brain region involved. Patient did not have dystonia or dysphasia seen with infarcts in the putamen. The complete resolution of delirium following stoppage of valproate and return of serum ammonia level to normal further confirmed our clinical suspicion of valproate induced hyperammonemic encephalopathy and helped rule out other causes. The important risk factor in our patient was the concomitant administration of risperidone and lorazepam with valproate. Previously published case reports enabled us to consider the possibility of valproate-induced hyperammonemic encephalopathy in our patient despite the findings on neuroimaging.

Our case report highlights the importance of considering hyperammonemic encephalopathy in any patient treated with valproate who develops acute changes in the mental state despite having other predisposing and precipitating factors for delirium. The presence of polypharmacy should be considered as a definite risk factor for the same. This will enable clinicians to detect this rare but life threatening complication early and institute appropriate management, which involves stopping valproate and initiate supportive care.

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