VALPROATE INDUCED HYPERAMMONEMIA WITH DERANGED LIVER FUNCTION

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ABSTRACT

Valproate is one of the most prescribed anti-epileptic drugs. It could cause a rise in serum ammonia level in patients, especially children and young adults. This presents with altered orientation, lethargy, focal neurological deficit, etc. If this condition is not treated, then it can be fatal. There is a good correlation between fall of ammonia level and clinical improvement. We, here, present a case of valproate induced hyperammonemia and deranged liver function in a child of 1-year age admitted to a tertiary care hospital.

Keywords: Hyperammonemia, Hyperammonemic encephalopathy, Valproate.

INTRODUCTION

Valproate is an effective anti-epileptic drug also prescribed for psychiatric conditions such as bipolar disorder, schizoaffective disorder, phobia, etc. This is also used for prophylaxis of migraine. Most studies in children have shown that it has got the tendency to cause hyperammonemia and encephalopathy, which presents with cognitive impairment, focal neurological deficit, lethargy, drowsiness, etc. [1,2]. Valproate may also reduce the seizure threshold [3]. Etiopathogenesis is not completely understood, although the increase in serum ammonia level is due to several mechanisms, the most important one appearing to be the inhibition of carbamoyl phosphate synthetase-I, the enzyme that begins the urea cycle. It is important that all patients with hyperammonemia should avoid valproic acid as it can cause a rise in blood ammonia level in healthy subjects also. Literatures have shown that serum valproate level is within the normal range [4]. All these patients require dietary restriction of protein [5]. We are presenting one case report of valproate induced hyperammonemia with deranged liver function admitted in a tertiary care hospital. The patient was of 1-year age and recovered after stoppage of valproate.

CASE REPORT

A 1-year-old female child presented with cough and cold for 12 days, fever for 6 days, convulsion (multiple episodes) for 1 day. She developed fever 6 days back which was high grade, continuous in nature, not associated with chills and rigor. On the day of hospitalization, the patient developed convulsion multiple episodes, generalized tonic-clonic type of seizures, each lasting for 3-5 minutes followed by loss of consciousness for a brief period. She was admitted multiple times to the hospital due to convulsion occurring while the onset of fever. Patient was a known case of birth asphyxia and was on phenobarbitone from birth and was changed to valproic acid at 3 months of age. At 4 months of age, the baby developed convulsion lasting for 5-10 minutes within 24 hrs of fever. Patient was admitted to the local hospital; no specific cause was found out, discharged with calcium and valproic acid. Patient developed similar episodes of convulsions with fever multiple times. Admitted multiple times for such complaints. Serum electrolytes, cerebrospinal fluid (CSF) studies, and neuroimaging (magnetic resonance imaging [MRI]) of the brain were normal. Patient was being treated with calcium, vitamin D3, and valproic acid. Taking history, we found that the baby achieved social smile at the age of 5 months, was not able to hold her neck nor was sitting with support nor having palmer grasp at the time of hospitalization. There was no history of contact with tuberculosis. Immunization status of the baby is as per date. Last immunization was measles at the age of 9 months. Patient received valproic acid at a dose of 20 mg per kg from 3 months of age till date along with calcium, vitamin D3, and multivitamins supplements.

On examination, we found the baby to be sick looking, lethargic, febrile (Fig. 1). Pulse was 140/minute; blood pressure was 90/60 mmhg. There was no pallor, no icterus, chest and abdomen were normal in contour, no clubbing, no cyanosis or lymphadenopathy. Child was lethargic, not interested in surroundings, and no neck holding cranial nerves were intact. Hypotonic plantar reflex, deep tendon reflex, (knee, ankle, bicep, tricep) were diminished. On abdominal examination, we found liver palpated 5 cm (span-12 cm) and spleen 3 cm below the costal margin.

According to laboratory investigations, hemoglobin count - 9.6 g/dl. Liver function tests were disarranged with aspartate aminotransferase 6428UI/L, alanine aminotransferase 4123UI/L. Serum sodium - 139 mmol/lt, potassium - 5.05 mmol/lt. CSF study-clear, nil cells, no organism, sugar - 62 mg/dl, protein - 36 mg/dl, no growth on culture, 6428UI/L, alanine aminotransferase 41230UI/L. Serum sodium - 139 mmol/lt, potassium - 5.05 mmol/lt. CSF study-clear, nil cells, no organism, sugar - 62 mg/dl, protein - 36 mg/dl, no growth on culture, serum ammonia - 150 μg/dl.

We could not reach a definite diagnosis depending on the clinical examination and laboratory findings. Investigations were showing
gross derangements in LFT and a raised level of serum ammonia. As convulsion was ongoing and the general condition of the child was deteriorating, we decided to change the anti-convulsant from valproic acid to phenobarbitone and managed symptomatically. To our utter surprise, there was a marked level of improvement in the general condition of the baby, serum ammonia level, and the liver dysfunction after 15 days (Table 1). Impression - valproate induced hyperammonemia with deranged liver function recovered after stoppage of valproate.

**DISCUSSION**

Valproate is a commonly used drug for epileptic condition as well as in psychiatric disorders. However, one unusual side effect of valproate is hyperammonemic encephalopathy, which may lead to death. This condition presents with decreased level of consciousness, drowsiness, lethargy, disorientation or focal neurological deficit. It may also reduce the seizure threshold. Patient can be cured of the condition by stoppage of valproate and if necessary other treatments are given. Hyperammonemia is more common in children, and it develops within days to weeks of treatment [6].

Our case of valproate induced hyperammonemia also presented with deranged liver function test (serum aspartate aminotransferase - 6428 IU/L, serum alanine aminotransferase - 4123 IU/L). This finding correlates with other literatures [7,8]. Serum ammonia along with liver enzymes should be measured regularly in epileptic patients on valproate medication and those showing features of valproate toxicity. One thing we observed in this case is that the child had recurrent intermittent attacks of seizure as well as features of hyperammonemia when on treatment with valproate as evidenced from the history. Some literatures have shown the intermittent nature of valproate induced hyperammonemia [9]. In our case, we observed complete remission of symptoms as suggested from the data given in the table after stoppage of valproate. Both serum ammonia and deranged liver function tests came to normal value.

One most important part of any adverse drug reaction is causality assessment. Causality assessment is the process of knowing the strength of the relationship between the culprit drug and the adverse reaction. In our case, we did causality assessment by using both Naranjo [10] and WHO-UMC [11] scales. According to WHO-UMC scale, this case can be categorized in the probable category since dechallenge is positive (reaction abated after stoppage of culprit drug). According to Naranjo scale, the culprit drug valproate categorized in the probable category (points-5). Rechallenge could not be done for ethical issues since this adverse reaction is a serious one.

### Table 1: Improvement in laboratory parameters after withdrawal of valproate

<table>
<thead>
<tr>
<th>Parameters</th>
<th>On valproic acid</th>
<th>On withdrawal of valproic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>6.7 kg</td>
<td>7.5 kilograms</td>
</tr>
<tr>
<td>Serum ammonia</td>
<td>150 µg/dl</td>
<td>56 µg/dl</td>
</tr>
<tr>
<td>Serum aspartate aminotransferase</td>
<td>6428 IU/L</td>
<td>38.7 IU/L</td>
</tr>
<tr>
<td>Serum alanine aminotransferase</td>
<td>4123 IU/L</td>
<td>27.7 IU/L</td>
</tr>
</tbody>
</table>

**CONCLUSION**

Any patient, especially children on treatment with valproate, showing features of cognitive impairment, focal neurological deficit, drowsiness, must be evaluated for hyperammonemia and also liver function test so that early diagnosis could be done, and prompt withdrawal of sodium valproate will lead to clinical improvement.

**REFERENCES**