# Valproate-induced hyperammonemic encephalopathy in a child without hepatic failure: A case report

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## ABSTRACT

Sodium valproate or valproic acid (VPA) is an effective antiepileptic drug that is commonly used for epilepsy in children because of its broad-spectrum activity. The use of VPA frequently results in elevated plasma levels of ammonia with or without raised transaminases. This condition usually happens when VPA with polypharmacy or underlying metabolic disorders like urea cycle defects. We are reporting a case of valproate-induced hyperammonemic encephalopathy in a child which is rare in children. Health professionals should be aware of this potential complication, and it is highly recommended to check ammonia levels in patients taking VPA who present with a change in mental status. If identified early, it can treat with appropriate measures and it can reversible.

**Key words:** *Ammonia, Encephalopathy, Valproate*

Sodium valproate or valproic acid (VPA) is an effective antiepileptic drug (AED) that is commonly used for childhood epilepsy because of its broad-spectrum of activity [1]. The frequent use of VPA results in elevated plasma levels of ammonia with or without raised transaminases [2]. This condition usually happens when VPA interacts with other drugs [3,4] or underlying metabolic disorders such as urea cycle defects or carnitine deficiency [5]. We are reporting a case of VPA-induced hyperammonemic encephalopathy (VHE) in a child on VPA monotherapy, which is rare in children.

## CASE REPORT

A 9-year-old male child brought to our pediatric neurology clinic with a history of drowsiness for 4 days. The child was born to the non-consanguineous couple and attained all milestones according to the age. The child had generalized tonic-clonic seizures at 6 years of age which was evaluated with magnetic resonance imaging (MRI) brain and electroencephalogram (EEG) and found normal. The child was started on VPA at10 mg/kg/day. After that, the child had two more similar events within 1 month of duration, so VPA was hiked up to 30 mg/kg/day. After that, child missed regular follow up and continued VPA with the same dosage for the past 3 years. During this period, the child did not have any other medications.

The child was admitted to our hospital with a history of drowsiness for 4 days, which was gradually increased. There was no history of fever, seizures, trauma, or other drug ingestion. On examination, the child was stupor and stable vitals; pupils were normal size and reacting to light and spasticity with brisk reflexes. Hence, a provisional diagnosis of encephalopathy was considered.

The child was evaluated with ammonia, liver function test (LFT), and serum electrolytes. Ammonia was very high (300 µmol/L; normal range 12–47 µmol/L) with normal LFT. Serum VPA levels were high (80 µg/Ml; normal 5–15 µg/mL). MRI brain showed mild atrophic changes. EEG showed encephalopathy features. These features are consistent with VHE.

The child was treated with a stoppage of VPA with IV carnitine administration followed by oral carnitine. VPA was changed to levetiracetam due to the recurrence of seizures in the hospital. The child was monitored with serial ammonia levels, which were gradually normalized. To rule out the underlying metabolic cause, tandem mass-spectroscopy was done and which was normal. The child was discharged on day 5 of admission with levetiracetam and carnitine. On follow-up, the child was asymptomatic.

## DISCUSSION

Usually, hyperammonemia due to VPA develops in children with underlying metabolic disorders [5], carnitine deficiency, or polypharmacy [3,4]. Common manifestations of VHE are disorientation, lethargy, increase in seizure frequency, unusual behavior, ataxia, and vomiting [6]. In the literature, VHE cases were reported with the above risk factors and with or without hepatic dysfunction. In this present case, we are reporting VHE with VPA monotherapy, which was rarely reported.

There are several mechanisms proposed that could have possibly been causing hyperammonemia associated with

valproate use [7,8]. Briefly, valproate is a protein-bound branched-chain fatty acid that is extensively metabolized in the liver, mainly by glucuronidation in the cytosol and beta-oxidation in the mitochondria through carnitine shuttle with only 10% being metabolized by omega-oxidation. Thus, when valproate is transported into the mitochondria in conjugation with carnitine for beta-oxidation, it interferes with the transportation of other fatty acids, which may result in attenuation of mitochondrial acetyl coenzyme A (acetyl-CoA) production through beta-oxidation of other fatty acids. Less acetyl-CoA production further leads to the decreased production of N-acetyl-glutamic acid as it is required for the allosteric activation of an enzyme of the urea cycle, carbamoyl-phosphate synthetase-1, thereby disrupting the urea cycle and leading to a rise in ammonia levels.

Another proposed mechanism is the metabolism of valproate through omega-oxidation, leading to the formation of 4-en-VPA, a toxic metabolite, which results in further impairment of carbamoyl-phosphate synthetase-1 function. When the carnitine shuttles are saturated by valproate, beta-oxidation decreases and there is a shift towards omega oxidation, leading to further build-up of the toxic metabolites, inhibiting the carbamoyl-phosphate synthetase function and attenuation of the urea cycle [7,8].

Panda *et al*. reported two cases of VHE without hepatic dysfunction with polypharmacy [3]. Rath *et al*. reported a cohort of three patients (one pediatric) who developed VHE with VPA monotherapy [2]. Vivekananda and Nayak reported a case of VHE enhanced by topiramate and phenobarbitone [3]. Vivo *et al*. reported two pediatric cases which have improved with L-carnitine administration along with stoppage of VPA [9,10]. Agrawal and Agrawal reported a similar case which was recovered with withdrawal of VPA and administration of L-carnitine [11].

A high index of suspicion is required to diagnose VHE. Behavioral changes, drowsiness may be ascribed to postictal state or non-convulsive status epilepticus. Due to these reasons, VHE may be a grossly underdiagnosed entity. The diagnosis of VHE may be overlooked when LFT is within the expected range. Withdrawal of VPA and treatment with L-carnitine will improve the condition.

## CONCLUSION

Encephalopathy is a potentially serious consequence of the use of VPA. Clinicians should consider this possible cause of changes in mental status in patients treated with VPA.

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