

Non-Hyperammonemic valproate encephalopathy

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ABSTRACT

A 21-year-old male known case of primary hypothyroidism, Seizure disorder sequelae of an old trauma receiving sodium valproate, clobazam and phenobarbitone for control of Generalized tonic clonic seizures reported to neurology OPD with history of altered sensorium and gait unsteadiness for 1 week with history of hike in valproate dose 2 weeks before. On examination he was drowsy. Neurological examination was unremarkable except for gait unsteadiness and ataxia. Patient was admitted and evaluated for acute worsening. All (the) biochemical parameters including complete blood count, liver function tests, kidney function tests, routine urine examination, arterial blood gas analysis, blood and urine culture tests were normal. CSF analysis was also normal. Repeat MRI brain was also done which depicted all old changes with no fresh changes which will account for worsening of his sensorium. EEG was suggestive of diffuse encephalopathy. Thyroid function tests were also normal. Valproate encephalopathy was suspected and Valproate was empirically stopped and he was put on levetiracetam and phenytoin. His sensorium improved rapidly after stoppage of valproate with normalization of EEG. Serum valproate Levels were high with serum ammonia levels were in the normal range. We made the inference of nonhyperammonemic valproate encephalopathy. This case highlights the existence of non-hyperammonemic valproate induced encephalopathy, suggesting mechanisms other than hyperammonemia responsible for this encephalopathy.

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Introduction

Valproic acid is a versatile drug that has demonstrated efficacy against primary generalized tonic-clonic, absence, and myoclonic seizures as well as in different non-epileptic conditions such as migraine and bipolar disorders. Other than common side effects like tremor, weight gain, abnormalities of hair, Valproic acid is also known to cause rare side effects such as encephalopathy. In most of the cases it is associated with hyperammonemia. The reported incidence of asymptomatic hyperammonemia in children is 20% and found to be symptomatic in 5% of cases.¹

Rarely this valproate induced encephalopathy may not be associated with hyperammonemia and other mechanism might be responsible for this side effect.

We encountered a case of valproate-induced encephalopathy where we did not find hyperammonemia further strengthening this fact.

Case report

A 21-year-old male non-hypertensive, non-diabetic, right handed, known case of primary hypothyroidism on levothyroxine 200 µg daily, seizure disorder with MRI documented bifrontal gliosis sequelae of an old trauma receiving sodium valproate 200 mg twice a day, clobazam 10 mg bd and phenobarbitone 60 mg bd for control of Generalized tonic clonic seizures and was on follow up in neurology department SMHS Srinagar.

Patient reported to neurology outpatient with history of altered sensorium and gait unsteadiness for 1 Week with history of increase in valproate dose to 400 mg BD 2 weeks back by some personal physician.

There was no history of yellowish discoloration of urine or eyes. He did not complain of fever, headache, vomiting, and stiffness in the neck or any exacerbation of seizure.

On examination he was drowsy, disoriented providing inappropriate answers to questions. His pulse 86 beats per minute regular. BP was 100/70 mmHg. The respiratory rate was found to be 16 breaths per minute

Plantars were bilaterally downwards with no focal neurological deficit. He was drowsy and over next 2 days he remained stuporous. The meningeal signs were absent. Examination of cranial nerves and motor system was normal. Deep tendon jerks were elicited in all 4 limbs. Plantar reflex was bilaterally flexor. Abdominal reflexes were present in all quadrants. Examination of sensory system was normal.

Other systemic examination was unremarkable.

Patient was admitted and evaluated in ward for acute worsening.

Following biochemical parameters were analysed and found to

Complete blood count, Liver function tests, kidney function tests, blood sugar, Routine urine examination was normal, Arterial blood gas analysis, Blood and urine culture tests were normal. ECG and chest X-ray were normal. CSF analysis was also normal.



Fig. 1: EEG done after admission during drowsy state showed a marked diffuse background slowing intermixed with 2-2.5 Hz of high-amplitude slow waves, occurring synchronously over both hemispheres, which did not change after injection of IV diazepam.

Naranjo Adverse Drug Reaction (ADR) Probability Score was 9

Repeat NCCT head was normal except for previous bifrontal-gliosis, Repeat MRI brain Bifrontal gliosis, ventriculomegaly

EEG showed diffuse slow wave suggesting diffuse encephalopathy

Thyroid function tests were also normal. Vitamin D levels were normal, Coagulogram was also normal. USG abdomen and Echocardiography was also normal

His serum ammonia levels and serum valproate levels were sent with suspicion of valproate toxicity. Patient's sensorium was progressively deteriorating with no improvement despite starting him on broad spectrum antibiotics and no apparent cause of encephalopathy.

Valproate was stopped, suspecting it induced encephalopathy and patient was put on levetiracetam 500 mg bd and phenytoin 100 mg tid. His sensorium improved rapidly after stoppage of valproate with normalization of EEG.

Patient was discharged in satisfactory condition, and remained stable on follow-up visits to date without any recurrence of seizures or altered sensorium.

Serum ammonia and valproate levels were received retrospectively after the patient improved. Serum valproate levels were high with serum ammonia levels in the normal range.

We made the inference of nonhyperammonemic valproate encephalopathy. This case highlights the existence of non-hyperammonemic valproate induced encephalopathy, suggesting mechanisms other than hyperammonemia responsible for this encephalopathy.

Discussion

Encephalopathy is an uncommon adverse effect of sodium valproate. The clinical presentation of valproate-induced encephalopathy can be varied and includes irritability, agitation, drowsiness, and coma and occasionally these patients may have paradoxical seizures.^{2,3} The other symptoms include loss of appetite, nausea and vomiting.⁴

Our patient presented with increasing drowsiness and disorientation without any localizing signs or focal neurodeficit or convulsive seizure. EEG during drowsy state showed a marked diffuse background slowing intermixed with 2-2.5 Hz of high-amplitude slow waves, which occurred synchronously over both hemispheres without any epileptiform activity without any response to IV diazepam, suggesting generalized encephalopathy and excluding non-convulsive status epilepticus. Relevant laboratory investigations excluded any metabolic cause of encephalopathy. CSF was also normal.

After exclusion of all these common causes we thought it to be a case of valproate induced encephalopathy as there was a temporal relation with hike in valproate dose and Naranjo adverse drug score was also suggestive, and this was confirmed when the clinical condition improved after stoppage of valproate with normalization of EEG.

In most of the cases valproate-induced encephalopathy, as reported in the literature, is associated with hyperammonemia. Hyperammonemia is more common in children¹ and develops within days to weeks of initiation of treatment.² underlying urea cycle enzyme deficiencies may predispose to valproate-induced hyperammonemia.⁵ The risk factors included high initial dose¹, long-term valproate therapy², and long-term valproate therapy with concomitant topiramate.²



Fig. 2: Electroencephalogram appears almost completely normal, with well-developed α -waves in the posterior head regions(arrows).

The pathogenesis of valproate-induced encephalopathy is unclear. Decreased levels of consciousness could be due to hyperammonemia, but could be related to other compounds including toxic metabolites of sodium valproate or other organic acids. The presence of the latter may explain encephalopathy in cases with normal ammonia. Patients with valproate-induced encephalopathy typically have a substantial elevation in serum ammonia; at least two fold the upper normal limit.^{9,10} However, a few patients, including the present one, who exhibited a typical valproate-induced encephalopathy, revealed normal or slightly elevated ammonia levels.^{11,14} In these cases, serum ammonia seemed unable to fully explain the encephalopathic effect of Valproic acid. Based on this finding, valproate-induced encephalopathy has been considered as multifactorial rather than secondary to hyperammonemia only. In fact, using a model of ammonium-induced coma, Stephens et al showed in the presence of sodium valproate, a lower concentration of ammonia produced coma.¹² Thus, Valproic acid might have a dual effect on encephalopathy- beside a hyperammonemic effect, it might also cause a direct cortical depression to enhance encephalopathy associated with specific ammonia levels.¹² However, it has recently been suggested that brain ammonia concentrations may remain high despite normal serum levels.⁶ Hyperammonemia is believed to produce encephalopathy through inhibition of glutamate uptake by astrocytes. This leads to potential glutamate mediated excitotoxic neuronal injury, cerebral edema, and, possibly, seizures.⁷ Our patient did not show any hyperammonemia, and hence, as discussed above, mechanisms other than hyperammonemia may be involved in this case.

In patients with non-hyperammonemic valproate induced encephalopathy, early diagnosis and prompt discontinuation of sodium valproate is always associated with subsidence of

clinical manifestations.^{9,10,13} Nevertheless, the following pitfalls might lead to a delayed diagnosis or misdiagnosis. First, most cases had a non-toxic serum valproate concentration.^{9,10,13} Measurement of serum valproate level is not helpful in establishing the diagnosis. Second, symptoms of encephalopathy could be mistaken for a postictal confusional state. In our patient, the diagnosis was helpfully made by characteristic EEG findings, which usually encompassed a diffuse background slowing intermixed with high-amplitude slow waves or triphasic waves, especially when there were clinical symptoms and signs indicating an encephalopathy.^{2,9}

In conclusion, the diagnosis of valproate-induced encephalopathy should be suspected in any patient on valproate therapy with altered sensorium. Patients taking Valproic acid may have mild to marked encephalopathic signs that can progress to lethargy and stupor. Early recognition of subtle cognitive and behavioral changes can lead to therapeutic interventions to avoid this progression. Response to therapy is rewarding. Valproate-induced encephalopathy has no correlation with the amount of the valproate dosage and its serum level. Temporal relation after the administration of valproate and reversibility of state of consciousness following its withdrawal establish the diagnosis.

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