A reversible cause of coma in epilepsy

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SUMMARY

A 13-year-old girl presented to our emergency department in a comatose state with history of epilepsy. Evaluation of the common causes of altered sensorium in the setting of background epilepsy turned out to be negative. Ultimately she was diagnosed to be having reversible coma due to valproate-induced hyperammonaemia.

BACKGROUND

In an emergency department, coma in a known epileptic patient throws open wide differentials, especially in a resource-limited setting. When routine evaluation including brain imaging and cerebrospinal fluid (CSF) analysis betrays the physician, drug levels and unusual metabolic causes are sought for. Valproate-induced hyperammonaemia (VIH) is a potentially reversible yet under recognised entity especially in the setting of altered sensorium in an epileptic. Our case clearly highlights the importance of prompt diagnosis and timely intervention in a case of VIH with attendant complete recovery without residual sequelae.

CASE PRESENTATION

A 13-year-old girl with recurrent seizures since 5 years of age (generalised tonic clonic and myoclonic) on irregular treatment with phenytoin (300 mg/day orally) for the last 4 years was admitted to our emergency department in a comatose state (Glasgow Coma Score of 6) with sluggishly reacting dilated pupils and mute plantar responses bilaterally without signs of meningeal irritation. Her sensorium progressively worsened over the last 48 h without any accompanying fever, seizures or other relevant systemic symptoms. She was put on mechanical ventilation on account of poor respiratory effort. She had an arterial pulse rate of 100 bpm and blood pressure was 100/60 mm Hg. She was shifted to a high-dependency unit with strict monitoring of vital parameters. On reviewing her treatment history, she was found to have received sodium valproate (1250 mg/day orally in two divided doses) from a primary physician after the last seizure 4 days back which was temporally related to her altered sensorium.

INVESTIGATIONS

Baseline haematological, renal and liver function tests, CT, Gadolinium-enhanced MRI of brain and CSF analysis were normal. Arterial blood gas analysis (ABG) on artificial ventilation showed high anion gap metabolic acidosis with a pH 7.26, PaCO₂ 34 mm Hg, bicarbonate 13 mmol/l and PaO₂ 90 mm Hg. Initial EEG showed quasi periodic large amplitude (80–120 µV) slow waves (1–2 Hz at 3–6 s interval) with diffuse background slowing (3–4 Hz;

figure 1). However, the patient's neurological status and sensorium steadily worsened. Hence, valproate-induced hyperammonaemia was suspected as a cause of persistent altered sensorium in our patient. Estimation of serum ammonia and lactate revealed hyperlactatemia (4.2 mmol/l; normal 0.5–2.2) and hyperammonaemia (243 micromol/l; normal 10–47). The serum level of Valproate was 74 mg/l (normal 60–80 mg/l).

DIFFERENTIAL DIAGNOSIS

The initial diagnostic considerations in our patient with a history of epilepsy presenting with altered sensorium were non-convulsive status epilepticus (NCSE) and acute meningoencephalitis (probably viral). However, EEG, neuroimaging studies and CSF examination were not suggestive of either of the above differentials. On further scrutinising the history, information regarding recent introduction of sodium valproate (1250 mg/day) was obtained and the patient was evaluated in lines of valproate-induced hyperammonaemia, the workup of which turned out to be positive.

TREATMENT

Our patient was treated with intravenous L-carnitine 1000 mg/day for 48 h followed by oral L-carnitine 50 mg/kg/day. She was initiated on parenteral levetiracetam 1000 mg/day for antiepileptic coverage in place of valproate and phenytoin.

OUTCOME AND FOLLOW-UP

With the initiation of the above treatment measures her sensorium started improving over the next 24 h with a concomitant reduction in the serum ammonia levels (112 mmol/l). Over the next 1 week she was weaned off artificial ventilation, associated with steady improvement of her neurological status and normalisation of serum ammonia levels, ABG parameters and EEG (figure 2). She was discharged on the seventh day in a fully conscious state without any residual neurological deficits (GCS: 15), with advice to avoid valproate and continue levetiracetam orally.

DISCUSSION

VIH with normal liver functions is a well-established cause of completely reversible coma.¹ It has to be suspected and diagnosed promptly; else the ultimate patient outcomes are dismal. Propionate, which is a metabolite of sodium valproate, decreases hepatic N-acetyl glutamate, which is an activator of carbamoyl phosphate synthetase (CPS I). CPS I is a key enzyme of the urea cycle and VIH results from a quantitative deficiency of this enzyme. Valproate also induces a decrement in hepatic carnitine levels and thereby causing reduction in acetyl CoA, in addition to inhibition of

To cite: Kesav P, VY V, Khurana D. *BMJ Case Reports* Published online: 13 December 2012
doi:10.1136/bcr-2012-007917

Figure 1 Sixteen-channel surface EEG showing quasi-periodic large amplitude (80–120 μ V) slow waves (1–2 Hz at 3–6 s interval) with diffuse background slowing (3–4 Hz).

Figure 2 Sixteen-channel surface EEG showing 9–11 Hz, 40–60 microvolts posterior dominant α rhythm with normal reactivity to eye closure.

renal glutamine synthesis.² Combination therapy with phenytoin may aggravate VIH by either inhibiting metabolism of ammonia in the liver or increasing valproate metabolites.¹ There is very little correlation if any between VIH and serum valproate levels.³ NCSE due to VIH encephalopathy is also well documented even though the mechanism is not well elucidated.⁴ Hyperammonaemia may also result from hepatic dysfunction, drugs, urea cycle defects or organic acidemia. The mechanism of altered sensorium due to hyperammonaemia is not well elucidated as of now. However, hyperammonaemia is postulated to increase the glutamine levels in astrocytes, thereby inducing osmotic fluid shift into neurons culminating in cerebral oedema and thereby altered sensorium clinically.¹ Supplementation with L-carnitine has been used widely in treating VIH.⁵

Learning points

- ▶ Valproate-induced hyperammonaemia is a relatively under-diagnosed aetiology for unexplained altered sensorium in epileptics in appropriate clinical scenario.
- ▶ Valproate-induced hyperammonaemia (VIH) may have pseudo periodic giant slow waves on EEG with diffuse background slowing.
- ▶ If promptly diagnosed complete recovery can be achieved in VIH without any residual sequelae.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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