CASE REPORT

Reversible weakness and encephalopathy while on long-term valproate treatment due to carnitine deficiency

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SUMMARY

We describe a case of a 35-year-old woman who presented with bilateral leg weakness and encephalopathy while on long-term valproate therapy. She was diagnosed with valproate-induced encephalopathy due to carnitine deficiency. Clinical improvement occurred with oral carnitine supplementation. Our case report highlights the importance of considering carnitine deficiency in patients presenting with unexplained neurological signs while on long-term valproate treatment.

BACKGROUND

Valproic acid (valproate) is widely used for the management of epilepsy, neuropathic pain, migraine and bipolar disorders. However, it has well-described side effects affecting mainly the liver, pancreas and reproductive system.[1] Valproate therapy may also result in a clinically significant rise in plasma ammonia levels leading to an encephalopathy which may prove fatal.[2] Carnitine, which is an essential co-factor in fatty acid metabolism, can be depleted in those patients on long-term valproate, predisposing them to encephalopathy. As this unusual complication is reversible, early recognition and treatment may prevent life-threatening consequences.

CASE PRESENTATION

A 35-year-old woman was admitted with a 5-day history of increasing drowsiness, fatigue, personality changes, generalised weakness and deteriorating mobility. Her medical history included a 10-year history of schizo-affective disorder, lithium-induced diabetes insipidus and hypothyroidism. Her medications included sodium valproate 1 g twice daily, carbamazepine, quetiapine and lithium. On admission, the patient was drowsy, difficult to rouse (sleeping all night and in the afternoon). Her Glasgow Coma Scale (GCS) was 14/15, her abbreviated mini-mental test score was 6/10 and she was noted to be slow in her responses. Neurological examination showed reduced power in her lower limbs (3–4/5) in a pyramidal distribution, and brisk reflexes with intact sensation in all modalities. Cardiovascular, respiratory and gastrointestinal examinations were unremarkable and there were no demonstrable features of hepatic disease.

INVESTIGATIONS

Routine biochemistry was unremarkable. The patient's alanine transaminase was 7 u/L (1–15), alkaline phosphatase 61 u/L (30–130), γ-glutamyl transferase 17 u/L (<45) and bilirubin was 6 µmol/L (<21). She had normal serum B_{12} and folate levels, and normal thyroid function tests. Serum lithium levels were within the therapeutic range. Her serum ammonia was 47 µmol/L (11.2–35.4) and valproate concentrations were elevated 140 mg/L (50–100).

Brain imaging including CT and MRI did not show any haemorrhage or intracranial mass. Lumbar puncture demonstrated clear cerebrospinal fluid (white cell count $<1\times10^6$/L, protein 0.25 g/L (0.2–0.4)). EEG demonstrated mild variable slowing and irregularity of background activity (likely due to medication).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included encephalitis, Guillain-Barré syndrome and acute disseminated encephalomyelitis (ADEM), which were excluded through our investigations. In view of the raised valproate and ammonia levels, a diagnosis of valproate hyperammonaemic encephalopathy (VHE) was made at this point

TREATMENT

The dose of sodium valproate was reduced by half rather than being completely withdrawn. This was due to the complex and challenging nature of managing the patient's schizo-affective disorder. Within 3 days, there was evident clinical improvement in her mental status. The patient was able to sit and communicate with the team, and her abbreviated mental test score improved to 10/10.The serum ammonia normalised and valproate levels decreased to the therapeutic range. After 4 days she was discharged home. Results of investigations of her urea cycle were awaited.

OUTCOME AND FOLLOW-UP

Three weeks postdischarge, the patient was clinically stable in terms of mental functioning, having had no further episodes of confusion or drowsiness. However, she continued to have fatigue and walking difficulties (due to residual leg weakness). Results of her serum amino acids revealed that our patient had carnitine deficiency evident by low acylcarnitine, low free serum carnitine (14.2 µmol/L, normal range: 23–52) and low total serum carnitine (19.9 µmol/L, normal range: 27–63). She was started on oral carnitine 1 g twice daily. Within 2 weeks, her symptoms resolved completely with

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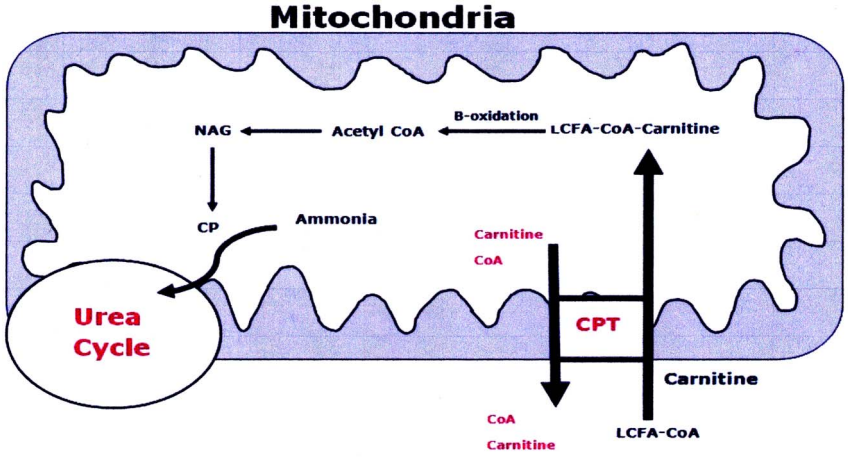

Figure 1 Carnitine and its role in long chain fatty acid oxidation and urea cycle.

Red : Depleted in presence of valproate .
Abbreviations: LCFA–Long chain fatty acid, CoA: co-enzyme A, CPT: carnitine palmitoyltransferase, NAG: N-Acetyl glutamate, CP: Carbomyl phosphate synthetase I.

normalisation of serum carnitine levels (free carnitine 25.2 µmol/L and total carnitine of 41.3 µmol/L). The sodium valproate was initially stopped completely, but due to a serious relapse of the patient's schizo-affective disorder, it was restarted and she is now well on valproate 1 g once daily and long-term carnitine supplements.

DISCUSSION

The patient's presentation was secondary to VHE complicated by a modest hyperammonaemia. Patients with VHE may present with altered GCS ranging from confusion to coma, increasing frequency of seizures, vomiting and focal neurological deficits.[2] Reported risk factors include carnitine deficiency, urea cycle disorders and polypharmacy.[3] In our patient, a urea cycle disorder was unlikely considering her age and previous good response to sodium valproate. Furthermore, she had no family history of metabolic disorders, and undetectable urinary orotic acid. An interaction between valproate and quetiapine has been suggested,[4] however, our patient had been on both for 1 year before her presentation and we felt that this was unlikely to be a factor in her case, particularly given her clinical response to carnitine.

Carnitine is an essential co-factor for the metabolism and transport of fatty acids in the mitochondria for the purpose of energy production via the Kreb's cycle.[3] Primary carnitine deficiency is a rare autosomal recessive disorder in which there is impaired carnitine transport across the plasma membrane, while secondary carnitine deficiency has been reported with hepatic and renal failure, and due to medications such as valproate.[5] This can present clinically as an encephalopathy, cardiomyopathy and myopathy.[6] Valproate depletes free carnitine in the hepatic mitochondria and carnitine palmitoyltransferase enzyme, thus affecting the metabolism of long chain fatty acids and the production of acetyl coA. This results in further deficiency of *N*-acetylglutamate, which is an activator of carbamyl phosphate synthetase I, a key enzyme in the urea cycle[7] (figure 1). The interruption of the urea cycle will result in accumulation of ammonia and subsequent encephalopathy. In the brain, the high ammonia level leads to accumulation of glutamine, cerebral oedema and astrocyte swelling, ultimately leading to cerebral atrophy.[8]

Levocarnitine supplementation has been shown to be an effective treatment for hypocarnitinaemia-induced encephalopathy in several case reports and reviews.[9–12] Hyperammonaemic coma due to pre-existing undiagnosed carnitine deficiency has been reported after 14 h of starting valproate.[13]

Two cases of valproate-induced encephalopathy were successfully corrected with levocarnitine administration, with a reduction in the dose of valproate, and clinical improvement was noticed after 10–14 days of the therapy, similar to our case.[12] A recent retrospective chart review in 38 psychiatric patients with documented hypocarnitinaemia and cognitive impairment showed that low-dose carnitine supplementation was associated with an improvement in behavioural, cognitive and motor function, with no adverse outcomes. The report also concluded that correcting carnitine deficiency either by reducing valproate dose or oral supplementation enhances recovery from encephalopathy.[14]

Learning points

- Patients presenting with neurological signs and changes in mental status suggestive of encephalopathy while on valproate therapy should be investigated for possible carnitine deficiency.
- Clinical judgement should guide the decision whether valproate should be stopped completely or continued with carnitine supplementation.
- Early recognition and appropriate correction of carnitine deficiency will enhance recovery and prevent potentially serious short-term problems and possible long-term disability.
- In populations at high risk, screening for primary carnitine deficiency prior to starting valproate should be considered.

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Competing interests None declared.

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