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CASE REPORT

Valproate-induced Hyperammonemic Encephalopathy

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Valproate-induced hyperammonemic encephalopathy is an unusual but serious complication that can occur in people with normal liver-associated enzyme levels, and despite normal therapeutic doses and serum levels of valproate. Here, we describe an adolescent girl suffering from absence seizures, who complained of progressive dizziness and general malaise several days after restarting valproate. She developed vomiting and decreased consciousness after 3 weeks of valproate use. She had a serum ammonia level five times higher than the upper normal limit, normal liver-associated enzymes, and a supra-therapeutic valproate level. Electroencephalography (EEG) showed continuous generalized slowing. Tandem mass spectrometry analysis revealed carnitine deficiency. Her consciousness improved after emergent hemodialysis. Her ammonia level and EEG also became normal. Possible mechanisms, risk factors and treatments of valproate-induced hyperammonemic encephalopathy are described. Physicians should consider this possibility when consciousness disturbance occurs in patients treated with valproate.

1. Introduction

Valproate is a branched-chain fatty acid that is widely used in therapy for epilepsy. Most of its side effects are mild and transient. However, several serious adverse effects can occur during valproate treatment, such as hepatotoxicity, coagulation disorders, pancreatitis, bone marrow suppression, and hyperammonemia. Valproate-induced hyperammonemic encephalopathy (VHE) is a serious disease. Valproate occasionally induces stuporous or comatose states associated with an increase in seizure frequency and electroencephalography (EEG) changes. The encephalopathy is often accompanied by hyperammonemia, without signs of hepatic failure.[1] The diagnosis of hyperammonemia is often overlooked due to an unspecific clinical presentation, and normal liver-associated enzyme levels.[2] Here we describe an adolescent girl who developed hyperammonemic encephalopathy after restarting valproate monotherapy for absence seizures. Her clinical symptoms and hyperammonemia improved rapidly after discontinuation of valproate and immediate hemodialysis.

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2. Case Report

A 14-year-old girl had absence seizures controlled with regular valproate for 2 years, at a maintenance dose of 20–23 mg/kg/day (1000 mg/day). She experienced no seizure attacks, and the drug level was within normal limits during this period. Developmental milestones and school performance were normal. However, 4 months before admission, she had discontinued the drug by herself. After stopping valproate treatment, she had poor appetite with a weight loss of about 8 kg within 3 months. She also complained of intermittent myoclonic jerks of both hands for 2 months before admission. Valproate was therefore prescribed again by another doctor, at a dose of 25 mg/kg/day (1000 mg/day), 3 weeks before admission. The patient complained of dizziness, general malaise and vomiting several days after restarting valproate treatment. She denied taking any other drugs in the previous 3 months. She visited our emergency department because of progressively worsening dizziness and general malaise. Physical examination showed a body temperature of 35.7°C, pulse rate 97/minute, respiratory rate 20/minute, and blood pressure 103/72 mmHg. Her height was 152 cm (25^{th}–50^{th} percentile) and body weight was 42 kg (25^{th} percentile). Her body mass index was 18.1 (normal range, 17.6–22.7). Neurologic examination was normal. However, she gradually became lethargic in the emergency room. Laboratory examination revealed an ammonia level of 184 μmol/L (normal range, <33 μmol/L) and valproate level of 182 μg/mL (therapeutic range 50–100 μg/mL). Serum aspartate aminotransferase was 12 IU/L and alanine aminotransferase 5 IU/L. Blood sugar, blood urea nitrogen, creatinine, and electrolytes were normal. Blood gas analysis showed pH 7.455, PCO_2 30.3 mmHg, PO_2 44.6 mmHg, and HCO_3^- 21.2 mEq/L. EEG showed continuous generalized slowing (Figure A). Brain computed tomography (CT) revealed no significant anomaly. Three hours later, the patient became irritable with incoherent and dysarthric speech, delusions and asterixis. The Glasgow Coma Scale was E4V4M6. Due to suspected VHE, we discontinued valproate therapy. Emergent hemodialysis was performed once for 3 hours. Her consciousness recovered rapidly to normal 12 hours after hemodialysis. Her EEG returned to a normal rhythm (Figure B), and her serum ammonia decreased to 1 μmmol/L, on the following day. The valproate level was 24 μg/ml 2 days after hemodialysis. Tandem mass spectrometry studies revealed carnitine deficiency (carnitine/acylcarnitine: C0=0.58, C2=0.52; normal range, C0: 1.35–3.18, C2: 1.5–5.56) before hemodialysis. After 3 months of follow-up, the patient had no cognitive impairment or neurologic sequelae. Her serum carnitine was normal, free carnitine in serum was 5.67 mg/L (normal range, 4.3–8.5 mg/L), and total carnitine in serum was 11.09 mg/L (normal range, 6.3–11.6 mg/L). Her antiepileptic treatment was changed to lamotrigine due to recurrence of absence epilepsy 2 months after discharge.

3. Discussion

The reported incidence of asymptomatic hyperammonemia in children with valproate monotherapy is 19%.[3] However, the incidence of VHE is unknown. In contrast to hyperammonemia due to advanced liver disease, patients with VHE usually have normal liver-associated enzyme levels, suggesting a mechanism other than hepatic cell injury.[4]

The clinical manifestations of VHE include an acute or subacute decreasing consciousness level that progresses from drowsiness to lethargy and coma, vomiting, dizziness, and focal neurological deficit. Low-grade fever and an increase in seizure frequency can also occur. Laboratory tests usually show normal liver function with hyperammonemia.[5] VHE can occur in people with normal dose and serum levels of valproate.[6] The main EEG findings are diffuse slowing with a predominance of rhythmical theta and delta activity, as seen in the initial EEG in our patient. Triphasic waves can occasionally be detected.[5] Our patient met all these diagnostic criteria.

The pathogenesis of VHE is incompletely understood. Valproate use can induce hyperammonemia through several mechanisms. The most important route appears to be the inhibition of hepatic mitochondrial carbamoylphosphate synthetase-I, the enzyme that begins the urea cycle. Hyperammonemia has been suggested to be the main cause of encephalopathy.[5] It is hypothesized that elevated ammonia levels could have a toxic effect on astrocytes, leading to an inhibition of their glutamate uptake and to cerebral edema. Extracellular glutamate accumulates and can cause excitotoxic neuronal injury.[1] Excessive ammonia is conjugated in the brain with alpha-ketoglutarate to form glutamate, so causing alpha-ketoglutarate depletion. Depletion of alpha-ketoglutarate in the brain produces a block in the Krebs cycle and causes cell damage and neuronal death.[7] Some data suggest that VHE may be promoted either by a pre-existing carnitine deficiency or by a deficiency induced by valproate *per se*.[8] The carnitine deficiency in our patient was likely induced by valproate.

The risk factors for valproate-associated hyperammonemia include underlying urea cycle enzyme deficiencies, underlying liver disease, long-term valproate treatment, concomitant anti-epileptic drug

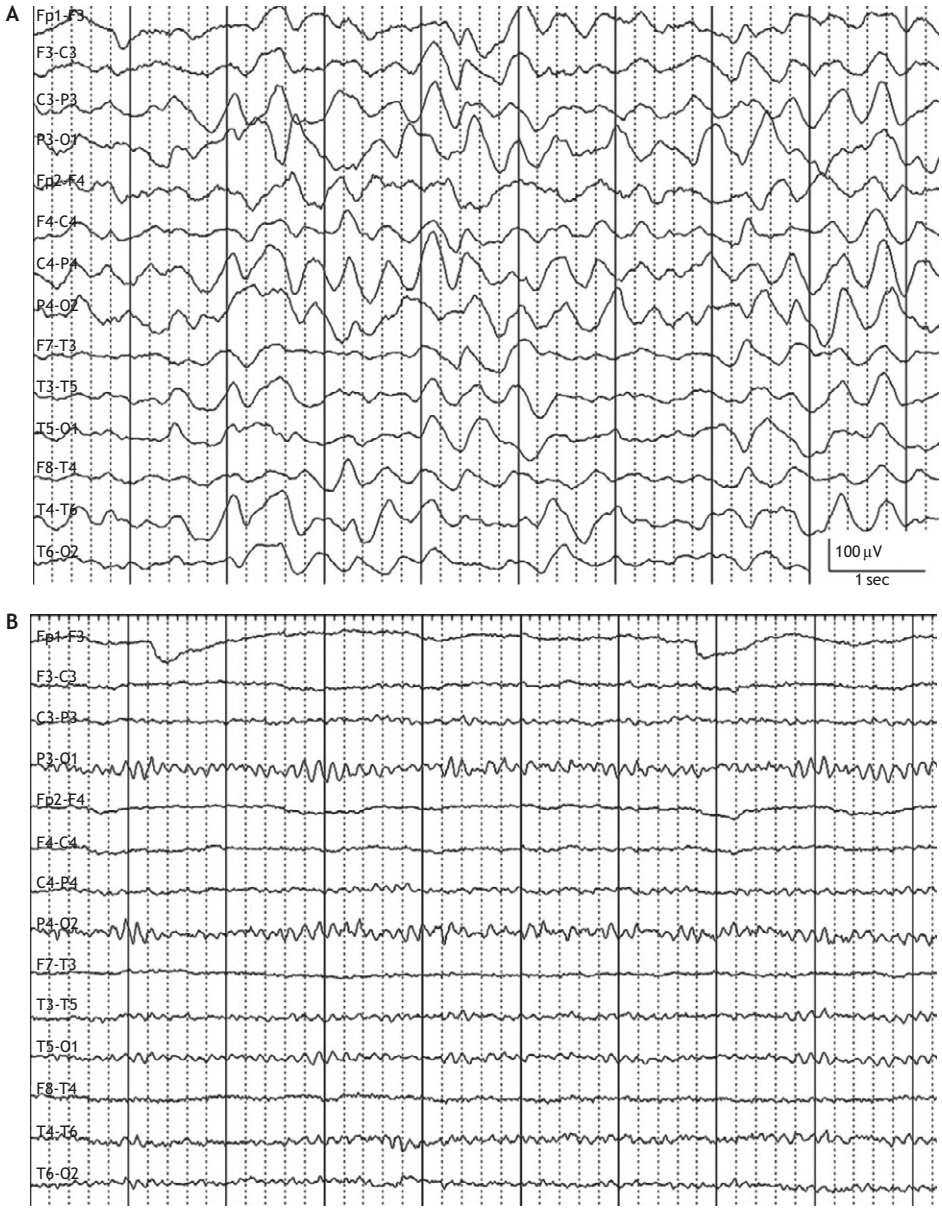

Figure (A) Awake electroencephalogram recorded on day 1, before the patient received hemodialysis. It showed diffused slow waves, consistent with diffuse cerebral dysfunction. (B) Awake electroencephalogram recorded on day 3, after hemodialysis. The slow waves had disappeared, with normal α waves in the posterior head regions. C=central, F=frontal, Fp=frontopolar, O=occipital, P=parietal, T=temporal.

therapy, particularly topiramate, or strict vegetarianism. VHE usually develops within days to weeks after initiation of valproate treatment.[1] High initial dose and catabolic state, such as infection, trauma or pregnancy, also increase the risk.[4,9] Risk factors including initiation of treatment, high initial dose and catabolic state (body weight loss and poor oral intake) might have been associated with the onset of VHE in our patient.

No relationships between daily dosages and serum concentration of valproate, hyperammonemia, and the severity of VHE have been demonstrated. In one report reviewing 15 VHE patients, the valproate level was over the therapeutic level in 40% of patients, and was within the therapeutic level in the other 60% of patients.[2] Our patient with VHE had a supra-therapeutic valproate level. VHE may be evident even in patients who have previously received valproate without experiencing any clinical or laboratory problems,[1,10] as in our patient.

The primary treatment for VHE is the withdrawal of valproate. Based on previous studies, complete recovery of consciousness generally occurs over a period of 2–14 days and the outcome is usually good after discontinuation of valproate.[3,11] Hydration, sodium phenyl acetate, and sodium benzoate may

be beneficial.[12] L-carnitine might be helpful in the prevention, as well as the treatment, of hyperammonemia caused by valproate.[4] Hemodialysis is a therapeutic option when the ammonia level is >680 μg/dL (400 μmol/L), or when there are significant clinical symptoms secondary to hyperammonemia progression.[13] It is also used in patients with toxic valproate levels. Chen et al[14] reviewed 32 patients with toxic valproate levels of whom six received hemodialysis. The half-life of valproate decreased from 2.2–4.3 hours during hemodialysis. They recommended hemodialysis as part of the management strategy in patients needing to be stabilized and with deteriorating neurologic conditions necessitating intubation. In our case, both hyperammonemia and a toxic valproate level were seen, with rapid deterioration in the level of consciousness. We regarded this condition to represent a progression of "significant clinical symptoms secondary to hyperammonemia", and we thus decided to perform immediate hemodialysis.

Two cases of VHE have been reported in Taiwan. Singh et al[15] described a 50-year-old woman taking daily carbamazepine for partial epilepsy, who developed acute confusion after initiation of valporate add-on treatment for 10 days. The patient had a mildly elevated serum ammonia level (81 μg/dL) and normal liver function. The serum levels of valporate and carbamazepine were 49.1 μg/mL and 8.6 μg/mL, respectively. This patient developed VHE while restarting valporate, with no previous record of valporate side effects. The other report described a 42-year-old woman who presented with frequent seizure attacks and lethargy at an emergency department. She had been treated with several anticonvulsants, including valproic acid and phenobarbital. She also had an elevated serum ammonia level (103 μmol/L) and normal liver function. Her valproate serum concentration was 85 μg/mL.[16] Both of these patients recovered after discontinuation of valproate.

In conclusion, VHE is a potentially serious complication of valproate treatment. Physicians should consider this possibility when consciousness disturbance occurs in patients being treated with valproate, and should monitor ammonia levels and investigate possible risk factors. Early withdrawal of valproate is necessary. In our patient, hemodialysis rapidly reduced the toxic valproate level and improved her level of consciousness and hyperammonemia.

References

1. Hamer HM, Knake S, Schomburg UA, Rosenow F. Valproate-induced hyperammonemic encephalopathy in the presence of topiramate. *Neurology* 2000;54:230–2.
2. Ott CA, Campbell N, Dworek EA. Valproic acid-induced hyperammonemia in a patient with schizoaffective disorder. *J Pharm Pract* 2007;20:82–92.
3. Iinuma K, Hayasaka K, Narisawa K, Tada K, Hori K. Hyperaminoacidemia and hyperammonemia in epileptic children treated with valproic acid. *Eur J Pediatr* 1988;148:267–9.
4. McCall M, Bourgeois JA. Valproic acid-induced hyperammonemia: a case report. *J Clin Psychopharmacol* 2004;24:521–6.
5. Segura-Bruna N, Rodriguez-Campello A, Puente V, Roquer J. Valproate-induced hyperammonemic encephalopathy. *Acta Neurol Scand* 2006;114:1–7.
6. Wadzinski J, Franks R, Roane D, Bayard M. Valproate-associated hyperammonemic encephalopathy. *J Am Board Fam Med* 2007;20:499–502.
7. Felipo V, Butterworth RF. Neurochemistry of ammonia. *Neurochem Int* 2002;41:79.
8. Lheureux PER, Penaloza A, Zahir S, Gris M. Science review: carnitine in the treatment of valproic acid-induced toxicity—What is the evidence? *Crit Care* 2005;9:431–40.
9. Rath A, Naryanan TJ, Chowdhary GV, Murthy JM. Valproate-induced hyperammonemic encephalopathy with normal liver function. *Neurol India* 2005;53:226–8.
10. Verrotti A, Trotta D, Morgese G, Chiarelli F. Valproate-induced hyperammonemic encephalopathy. *Metab Brain Dis* 2002;17;367–73.
11. Vossler DG, Wilensky AJ, Cawthon DF, et al. Serum and CSF glutamine levels in valproate-related hyperammonemia encephalopathy. *Epilepsia* 2002;43:154–9.
12. Prietsch V, Lindner M, Zschocke J, Nyhan WL, Hoffmann GF. Emergency management of inherited metabolic diseases. *J Inherit Metab Dis* 2002;25:531–46.
13. Eyer F, Felgenhauer N, Gempel K, Steimer W, Gerbitz KD, Zilker T. Acute valproate poisoning: pharmacokinetics, alteration in fatty acid metabolism, and changes during therapy. *J Clin Psychopharmacol* 2005;25:376–80.
14. Chen WT, Yen DJ, Yu HY, Liao KK. Valproate-induced encephalopathy. *Chin Med J* 2001;64:474–8.
15. Singh S, McCormick BB, Mustata S, Thompson M, Prasad GVR. Extracorporeal management of valproic acid overdose: a large regional experience. *J Nephrol* 2004;17:43–9.
16. Weng TI, Shih FY, Chen WJ. Unusual causes of hyperammonemia in the ED. *Am J Emerg Med* 2004;22:105–7.