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Valproate encephalopathy: Case series and literature review

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Abstract

Valproate encephalopathy is one of the unusual and severe but treatable side effect. This research focuses on four female patients who had valproate medication for epilepsy and developed an increased frequency of seizures, exacerbated disruption of consciousness, gastrointestinal problems, cognitive dysfunction, ataxia, and psychobehavioral abnormalities. The patient's symptoms improved over time once sodium valproate was stopped. As a result, when using sodium valproate, one should be aware of the risk of sodium valproate encephalopathy and cease using the medication right once if any of the above symptoms of unknown etiology manifest clinically. We also go over the potential pathogenesis that lead to valproate encephalopathy and the heightened risk of encephalopathy from taking antiepileptic medications together. It was stressed how crucial it is to identify, diagnose, and treat sodium valproate encephalopathy as soon as possible.

Keywords

Valproate sodium, encephalopathy, epilepsy, status epilepticus, anticonvulsants

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Introduction

Valproic acid sodium (valproate, VPA) is a commonly used drug in neurology and psychiatry, used for treating various seizures, migraines, bipolar affective disorder, and schizophrenia.[1] Its adverse effects include gastrointestinal symptoms, liver and kidney function damage, somnolence, dizziness, headache, anemia, leukopenia, weight gain, and others.[1,2] The intricate relationship between valproate and hyperammonemia has its roots in early foundational studies, with Coulter and Allen[3] illuminating a potential mechanism tying sary hyperammonemia to valproate encephalopathy. Zaccara et al.[4] further reinforced this association by delineating valproate-induced alterations in consciousness linked with hyperammonemia. Among its well-documented side effects, there lurk rare but impactful adverse reactions, with valproic acid sodium encephalopathy being an emblematic example. In the same period under consideration at our institution, out of 649 epilepsy patients who were administered valproate for their treatment, a scant four presented with symptoms of valproic acid sodium encephalopathy—translating to an incidence rate of a mere 0.61%. This figure not only underscores the rarity of this adverse event but also accentuates the imperative for heightened clinical vigilance. Through this paper, we hope to improve clinicians' understanding of valproate encephalopathy and advocate early recognition, early diagnosis, and early intervention.

Case presentation

Case 1

A 47-year-old woman was admitted to the hospital with "seizures of loss of consciousness with convulsions of the limbs for more than 35 years and reoccurrences for 15 day." She had a history of epilepsy for 35 years, during which phenytoin sodium (PHT) had been used intermittently for seizure control at a maintenance dose of 300 mg/d, with occasional seizures; 15 days prior to admission, she experienced seizures characterized by involuntary convulsions of the left upper limb, and the effect of PHT was unsatisfactory. Despite taking oral sodium valproate tablets (500 mg/d) for three consecutive days, the epilepsy symptoms have not been

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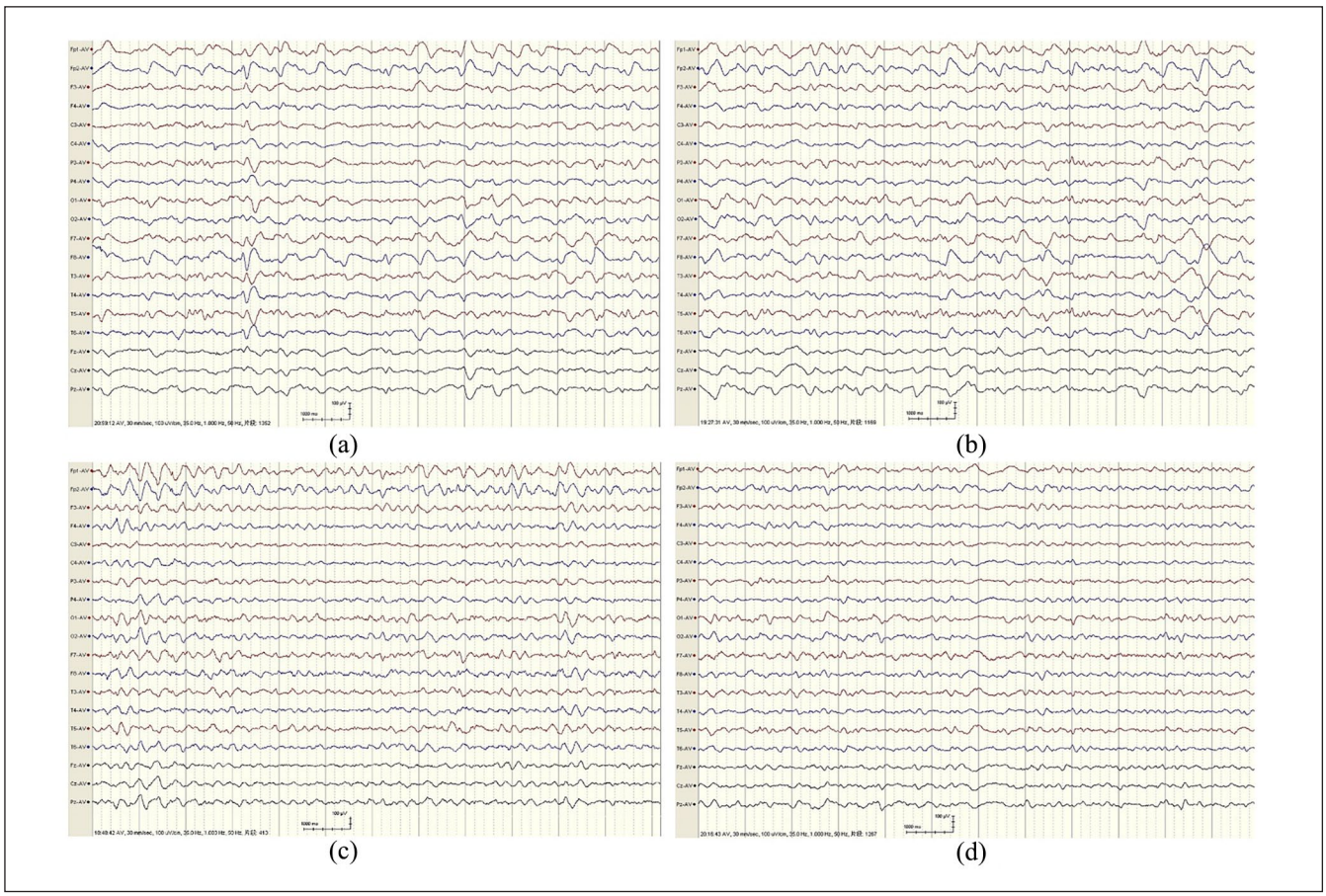

Figure 1. Patients' 24-h video EEG monitoring results. (a) Case 1: EEG monitoring results showed triphasic waves after the onset of encephalopathic symptoms. (b) Case 2: EEG monitoring results after the onset of encephalopathic symptoms showed prominent slow waves, starting from δ Predominant, synchronous occurrence of both hemispheres without epileptiform activity. (c) Case 3: EEG monitoring results after the onset of encephalopathic symptoms showed prominent slow waves to θ Predominant, synchronous occurrence of both hemispheres without epileptiform activity. (d) Case 4: after the onset of encephalopathic symptoms, EEG monitoring results showed more background slow wave activity to θ wave predominance, the synchronous occurrence of both hemispheres, and no epileptiform activity.

controlled. There were recurrent and frequent seizures, nausea, and vomiting; the seizures occurred more than 20 times a day, and in severe cases, they were accompanied by loss of consciousness and foaming at the mouth. Admission investigations: Left upper limb involuntary convulsions were seen intermittently. Laboratory tests at the time of admission showed mild elevations of alanine aminotransferase (ALT, 105 U/L, (7–40 U/L), aspartate transaminase (AST), 98 U/L (13–35 U/L), alkaline phosphatase (ALP, 325 U/L, 40–50 U/L), creatine kinase (CK, 5245 U/L, 20–140 U/L), and creatine kinase isoenzyme (CK-MB, 74 U/L, 0–24 U/L). Her total bilirubin, total protein, complete blood count, renal function test, serum electrolyte level, blood coagulation function, routine urinalysis, and chest computed tomography (CT) showed no significant abnormalities. The admission diagnosis was focal persistent status epilepticus. Recurrent seizures remained uncontrolled within 24 h of admission. The treatment plan was adjusted to intravenous pump administration (sodium valproate for injection 0.8 g, 50 ml saline; pumping rate: 3 ml/h). On the 2nd day of admission, the above epileptic symptoms included frequent seizures with frequent vomiting. On the third day after admission, the patient developed mental and behavioral abnormalities. The clinical manifestations of this patient were poor mental state and drowsiness, lethargy, and intermittent gibberish with lethargy, confusion, and ataxia. Considering drug toxicity, urgent investigation of blood ammonia, the plasma concentration of sodium valproate, blood concentration of PHT; the results of blood ammonia 115 μmol/L (18–72 μmol/L), sodium valproate blood concentration 74 μmol/ml (50–100 μg/ml); 24-h electroencephalography (EEG) results showed the emergence of tricyclic waves; Synchronization of two hemispheres (Figure 1(a)) the fourth day of hospitalization After the patient was admitted to the hospital, he was admitted to the hospital on day 4. In addition to auxiliary testing and clinical symptoms, valproate encephalopathy was suspected.

Sodium valproate use was halted, oral lactulose solution was administered for 3 days to lower blood ammonia, and symptomatic supportive therapy, including rehydration, was administered. After discontinuing valproate for 1 day, the patient's seizures and mental status gradually improved, and the symptoms of nausea and vomiting were also significantly reduced. The review of ALT, AST, ALP, CK, CK-MB valproate plasma concentration, blood ammonia, and EEG were at normal levels. In the follow-up, the patient's condition remained stable, and there is no recurrence of epilepsy at present.

Case 2

A 23-year-old female patient was admitted to the hospital with "recurrent episodes of convulsions of the limbs and loss of consciousness for 10 years, aggravated by reoccurrences for 3 d." History of epilepsy for 10 years; intermittent epileptic seizures for 10 years, manifested as episodic loss of consciousness, limb tonus, convulsions, accompanied by clenching of teeth and urinary incontinence, lasting about 30 s to 1 min before the seizure stops, with gradual awakening, an unawakened memory; previous antiepileptic drugs: carbamazepine (0.1 g, 2/day), oxcarbazepine (0.3 mg, 2/day); then, due to pregnancy, the antiepileptic medications (specific medication) were discontinued. Seizures increased in frequency following the termination of antiepileptic medications (the precise medications are unknown); 3 days ago, seizures occurred due to emotional instability. He was admitted to our hospital. She was diagnosed with status epilepticus and was admitted to our hospital. On the 1st day of admission, on the basis of the original antiepileptic regimen (carbamazepine (0.1 g, 2/day); added sodium valproate extended-release tablets 1000 mg, 2/day; on the 2nd day of admission, the patient appeared to have an increased frequency of seizures, and the patient's impaired consciousness on the third day of admission aggravated to view the patient, and was unconscious; When this patient presented with these symptoms, the clinician urgently examined blood ammonia, valproate blood concentration, liver and renal function. Long-range video EEG; results back: blood ammonia 212 μmol/L (18–72 μmol/L); valproate blood concentration: 65 μmo1/L (50–100 μg/ml); 24-h long-range video EEG: abnormal EEG with more slow wave activity in the background (Figure 1(b)) 9 aminotransferase 53 U/L (7–40 U/L), mentholatum ALT 67 UL (13–35 U/L), glutamyltransferase 48 U/L (7–45 U/L), total bilirubin 4.0 mol/L, creatine kinase CK 9880 U/L (20–140 U/L), creatine kinase isoforms CK to MB 73 UL (0–24 U/L), lactate dehydrogenase 303 U/L (7–45U/L); combined with the patient's medical history and related auxiliary examination, alert sodium valproate encephalopathy, to be discontinued sodium valproate, to lactulose oral solution, 15 m1, gastric tube injection, 3/d to reduce blood ammonia, to be rehydrated and hydrated, to promote cardiac enzyme metabolism, sodium bicarbonate tablets, 0.5 g, oral, 3/day alkalinization of the urine; discontinued on the 1st day, the patient is clear, and The patient could answer the questions correctly. Answer to the question, but the response is slow. After stopping the drug on the 5th day, the patient did not complain of special discomfort, no dizziness, headache, no impaired consciousness, and no clinical manifestations of limb twitching. Physical examination: Vital signs are stable; cardiopulmonary and abdominal examinations are normal. There was no abnormality in the advanced neurological examination; review of sodium valproate blood concentration, blood ammonia is at the normal level, and electroencephalogram is in the normal range. After discharge, the patient recovered well and took antiepileptic drugs (carbamazepine (0.1 g, 2/day) and oxcarbazepine (0.3 mg, 2/day) regularly without recurrence of seizures.

Case 3

A 26-year-old female patient was admitted to the hospital with "recurrent convulsions of the limbs with impaired consciousness for 6 years, recurrent for 7 h." Six years ago, the patient had convulsions of the limbs without any obvious cause, accompanied by loss of consciousness, double gaze, closed teeth, and foaming at the mouth, which lasted for about 1–2 min and was relieved by herself and took antiepileptic drugs (oxcarbazepine 0.3 g, 2 times/day) regularly for half a year without having a seizure. After stopping the medication, the patient had another seizure of the same nature as before and was diagnosed with "sary epilepsy" at the author's hospital and was treated with oral oxcarbazepine (0.45 g; 2 times/day) and perampanel (2 mg, once a night), but the seizure still occurred intermittently, lasting about 1–2 min each time. Seven hours before admission, the patient had a seizure, accompanied by convulsions of the limbs. Seven hours before admission, the patient's limbs twitched, accompanied by a loss of consciousness, rolling eyes, gnashing teeth, foam in mouth, and tonicity of the limbs, which lasted for about 5–6 min and then relieved and was repeated for more than 10 times, and the consciousness was not clear during the seizure period. She was admitted to the hospital with the diagnosis of symptomatic epilepsy and status epilepticus. Diazepam 10 mg IV was given as an antiepileptic treatment, but the effect was not good, and sodium valproate 0.8 g IV was added (50 ml of saline was added, and the pumping speed was 6 ml/h. Because of repeated seizures, the pumping speed was adjusted to 7 ml/h after half an hour, but the effect was not good. The pumping speed was adjusted to 8 ml/h again), and the patient was treated with joint sedation and reduction of intracranial edema. On the third day of admission, the patient was admitted to the hospital for treatment and was treated for epilepsy. On the third day of admission, the patient had frequent seizures.

The patient presented with symptoms including nausea, vomiting, a comatose state, and progressive impairment of consciousness, and was urgently examined for liver function

and blood ammonia valproate concentration, which showed that there were no obvious abnormalities in liver function, blood ammonia level was normal, and valproate concentration was 150 μg/ml (effective concentration range of 50–100 μg/ml). 24 h long long-range video EEG monitoring showed extensive slow waves, with δ and θ waves predominating (Figure 1(c)). After combining clinical symptoms and auxiliary examinations, sodium valproate encephalopathy was considered. Sodium valproate was immediately stopped, and levetiracetam 1000 mg was injected into the gastrostomy tube twice/d, and fluids were actively replenished. On the third day, after stopping sodium valproate, the patient's consciousness was better than before, and seizures were controlled. One week later, the patient's consciousness was clear, and the blood level of sodium valproate was rechecked to be 34.27 μg/ml and the EEG was rechecked to show that the background activity was normal. On the 11th day, the patient was discharged from the hospital with complete remission of symptoms. During the follow-up, the patient's condition remained stable, and there was no recurrence of epilepsy.

Case 4

A 75-year-old female patient was admitted to the hospital with "seizures with loss of consciousness, limb jerking for 6 months, and unsteady walking for 1 week." 6 months ago, the patient had a loss of consciousness with limb jerking without any triggers, starting from the right upper limb, which lasted for about a few minutes and then stopped on its own. She was admitted to the local hospital and was considered to have epilepsy, but she did not take any antiepileptic drugs (the patient did not pay attention to it). One week ago, the above epileptic symptoms recurred, and 2 days before admission, she was treated with intravenous pumping of sodium valproate 0.8 g + 50 ml saline; the pumping rate was 5 ml/h. The frequency of epileptic seizures increased compared to the previous one, and she developed mental behavioral abnormalities, which were manifested by babbling, rambling. He was characterized by babbling and ataxia. The patient was admitted to our hospital for further treatment. On the day of admission, the therapeutic team took into account the patient's medical history, the toxicity of sodium valproate, and the patient's frequent seizures after taking sodium valproate; therefore, the patient was urgently tested for blood ammonia, sodium valproate concentration, electroencephalogram, and hepatic and renal function. The results showed no abnormality of liver and kidney function, blood ammonia: 18 μmol/L, sodium valproate 132 μg/ml; 24 h long range video EEG was more slow wave activity in the background, with δ and θ waves dominant (Figure 1(d)) immediately stop using sodium valproate, adjust the antiepileptic drugs to oral levetiracetam tablets 0.5 g, 2/day; lactulose oral solution, 15 m1, 1/day; On the 5th day after stopping the use of sodium valproate, and there was no recurrence of seizures. On the 7th day of stopping the drug, the patient was clear, had no seizures, no ataxia, and was discharged from the hospital with regular levetiracetam tablets 0.5 g, 2/day. No seizures were seen during the follow-up.

Discussion

Valproate encephalopathy is a rare and severe adverse effect of VPA. It is characterized by acute or subacute progressive disorders of consciousness, focal or bilateral neurological deficits, increased seizure frequency, ataxia, asterixis, psychiatric and behavioral abnormalities, cognitive impairment, and digestive symptoms. It often presents with elevated blood ammonia levels or not.[5] At present, there is no biomarker for diagnosing sodium valproate encephalopathy, which now mainly depends on the clinical presentation of the patients taking sodium valproate. The key factor lies in changes in consciousness in the patients suffering from valproate encephalopathy, where the patient's consciousness returns upon discontinuation of sodium valproate treatment. The EEG of patients with sodium valproate encephalopathy lacks specificity, and currently, there is no universally accepted standard for EEG.[6] In this study, 24-h EEG monitoring of patients with symptoms of encephalopathy showed that case 1 presented three-phase waves, while the remaining three cases presented obvious slow waves dominated by theta waves and delta waves, which occurred synchronously in both hemispheres without epileptiform activity (Table 1) which was consistent with previous research reports. There are currently no large-scale clinical studies on sodium valproate encephalopathy. Given that this disease is rare, its early clinical manifestations are not specific, and there are currently no unified diagnostic criteria, combined with the insufficient understanding of this disease by clinicians, it is easy to miss or misdiagnose.

The four cases of sodium valproate encephalopathy collected in this paper all have varying degrees of consciousness disorders. Four cases present an increase in the frequency of seizures, two cases combined with digestive tract symptoms, two cases combined with mental and behavioral abnormalities, two cases combined with ataxia, and two cases combined with cognitive impairment (Table 2). All the above symptoms are in line with the clinical manifestations of sodium valproate encephalopathy. The occurrence of sodium valproate encephalopathy is not related to factors such as sex and age, and it often occurs in children who are also taking other Antiseizure Medication. It generally occurs a few days, weeks, or years after treatment, regardless of the dose of VPA taken.[5] Sodium valproate encephalopathy usually presents with elevated blood ammonia levels without liver function damage, but research shows that elevated blood ammonia levels are not significantly correlated with clinical symptoms, and a small portion will not present with elevated blood ammonia levels.[7] In this study, patients 1 and 2 had elevated blood ammonia levels and presented with encephalopathy symptoms, indicating valproate-induced hyperammonemia encephalopathy. Cases 3 and 4 had

Table 1. General situation and clinical data of four cases of valproate-induced hypernatremia.

Case	Age	Gender	Past medical history	Duration of epilepsy	Admission diagnosis	Previously used ASM	Use ASM after admission.	Use the dose of sodium valproate.	Clinical manifestations after VPA treatment	Time to diagnose Valproate sodium encephalopathy after VPA application (day)	Time to symptom improvement after stopping VPA (day)
1	47Y	F	Epilepsy	35Y	fSE	PHT (300 mg, 1/day)	PHT (300 mg, 1/day)	VPA (500 mg, 1/d, 3 day) was taken orally for 3 day + VPA 0.8g +50 ml normal saline was pumped intravenously. Pumping rate: 3 ml/h) for 2 day.	Drowsiness, increased frequency of seizures, nausea, and vomiting, abnormal mental behavior, ataxia	5	3
2	23Y	F	Epilepsy	10Y	SE	LTG (25 mg/d) + CBZ (0.1 g/d) + OXC (0.3 mg, 2/d)	CBZ(0.1 g/d)	VPA (1000 mg, 2/d, maintained for 3 day;	Sleepiness, increased frequency of epileptic seizures, slow response, apathetic expression	3	5
3	26Y	F	Sary epilepsy	6Y	SE	OXC (0.3 mg/d) + PER (2 mg, 1/day)	none	VPA0.8 g + 50 ml normal saline was pumped intravenously at a rate of 6–8 ml/h for 3 d);	Coma, increased frequency of epileptic seizures, nausea, and vomiting	3	8
4	75Y	F	Epilepsy	6M	SE	None	none	VPA0.8 g+50 ml normal saline was pumped intravenously at a rate of 5 ml/h for 2 day);	Increased frequency of seizures, confusion, cognitive impairment, mental behavior abnormalities, and ataxia	2	5
5											

ASM: Antiseizure Medication; CBZ: Carbamazepine; d: D/d; F: Female; fSE: Status epilepticus of focal epilepsy; H: H/h; LTG: Lamotrigine; m: Months; OXC: Oxcarbazepine; PHT: Phenytoin sodium; SE: Status epilepticus; VPA: Sodium Valproate; y: Years.

Table 2. Important auxiliary examinations of four patients with sodium valproate encephalopathy.

Case	When considering valproate encephalopathy		Long-range video EEG
	Sodium valproate blood concentration (ug/ml)	blood ammonia concentration (ug/ml)	
1	74	115	Three phases wave appears; the two hemispheres appear simultaneously.
2	65	212	The background is more slow wave activity; δ and θ waves dominate.
3	150	34	The background is a wide range of slow waves dominated by delta and theta waves.
4	132	18	The background is more slow wave activity; δ and θ waves dominate.

Note. Indicator units and normal reference ranges (sodium valproate blood concentration 50–100 μg/ml; blood ammonia 18–72 μg/ml.

normal blood ammonia levels. These two patients exhibited encephalopathy symptoms without elevated blood ammonia, which can be considered valproate encephalopathy unrelated to hyperammonemia.

The metabolic pathways of VPA are complicated. The current study primarily focuses on β-oxidation (acetylation) in the tricarboxylic acid cycle, oxidation involving cytochrome P-450 isoenzymes (p-oxidation), and glucuronidation. This complex metabolism explains the diversity of its active and non-active metabolic products. This complex metabolism explains the diversity of its active and non-active metabolic products.[8] The mechanism of onset of sodium valproate encephalopathy is still not entirely clear, and some current studies associate it with hyperammonemia.[9] VPA is believed to cause hyperammonemia by directly or indirectly inhibiting the urea cycle via its metabolic products. Carbamoyl phosphate synthetase I (CPS-I) is the rate-limiting enzyme of the urea cycle, and the direct inhibition of CPS-I by VPA is considered the primary mechanism of VPA-induced hyperammonemia.[11,11]

N-acetyl glutamate (NAG), acting as a conformational activator of CPS-I, is produced by acetyl CoA and glutamate under the regulation of N-acetyl glutamate synthase (NAGS). 4-en-VPA, a metabolite of VPA, inhibits NAGS by forming valproic CoA, which results in decreased NAG, thereby lowering ammonia metabolism and leading to elevated blood ammonia levels.[12,13] Concurrently, 4-en-VPA can elevate blood ammonia levels by stimulating glutamine synthetase, thereby enhancing the kidney's absorption of glutamine and release of ammonia.[14,15]

Furthermore, a reduction in carnitine also plays a critical role in VPA-induced hyperammonemia. VPA is a branched-chain carboxylic acid, metabolized in the liver via glucose aldehydization, mitochondrial β-oxidation, and cytoplasmic ω-oxidation. Carnitine acts as a carrier molecule, transporting VPA to the mitochondria for β-oxidation. Prolonged or high-dose VPA treatment might decrease carnitine storage in the body, leading to an increased shift from mitochondrial β-oxidation to ω-oxidation, resulting in the production and accumulation of toxic metabolites in the body.[10,12,15,16] VPA can suppress the absorption of free carnitine in the distal renal tubules and inhibit the transport of membrane carnitine receptors, thus decreasing the production of carnitine, which further inhibits carbamoyl phosphate synthetase I (CPSI), leading to a urea cycle disorder, resulting in hyperammonemia.[14,16] An increase in blood ammonia levels can enhance the activity of glutamine synthetase, leading to an increase in glutamine production in astrocytes. An increase in extracellular glutamate can lead to excitotoxic neuronal damage. The increase in intracellular production of glutamine can cause fluid to enter the astrocytes through osmosis, leading to astrocyte swelling, metabolic disturbances, increased intracranial pressure, cerebral edema, and symptoms such as coma.[16] Short-term hyperammonemia could serve as an indication of recent epileptic attacks. Following an epileptic seizure, muscle contractions can cause an increase in blood ammonia levels, which might also be associated with adjustments to antiepileptic medications after the occurrence of seizures.[17]

Some studies have found that in a small number of sodium valproate encephalopathy patients, blood ammonia levels can be within the normal range, while cerebrospinal fluid ammonia and glutamine levels are elevated.[18] For example, in cases 3 and 4, blood ammonia levels were normal, but they exhibited neurological symptoms, and in these cases, blood ammonia seems unable to explain the occurrence of encephalopathy fully. The occurrence of encephalopathy in these two patients may be related to the elevated levels of cerebrospinal fluid ammonia and glutamine. Moreover, the study by Stephens et al.[19] indicated that even at lower concentrations, ammonia can lead to coma when taking VPA, and this may be directly related to VPA's inhibition of the cortex.

In addition, the combined use of antiepileptic drugs (e.g., PHT, phenobarbital, carbamazepine, oxcarbazepine, and topiramate) is more likely to result in valproate encephalopathy. A retrospective study highlighted that among epilepsy patients taking phenobarbital, phenytoin, and carbamazepine concurrently, the average VPA concentrations decreased by 76%, 50%, and 66%, respectively.[20]

On the other hand, studies by Woo PYM and colleagues suggest that phenobarbital has a higher associated risk for valproate-induced hyperammonemic encephalopathy (VHE) compared to phenytoin.[13] Lamotrigine is a new type of antiepileptic drug that can effectively inhibit the voltage-dependent Na+ channel and reduce the frequency of abnormal brain discharge, thus achieving the purpose of relieving clinical symptoms.[21] Valproic acid can affect the activity of liver drug enzyme CYP2C19. Valproic acid inhibits the metabolism of lamotrigine by inhibiting glucosylation of lamotrigine, thereby reducing the metabolic rate of lamotrigine and increasing its blood concentration.[22,23] In cases 1–3 in this article, all had taken antiepileptic drugs in the past and did not show signs of valproate-like encephalopathy.

However, in this review of these four cases, we can find that at the same time taking valproate, case 1 combined PHT; Carbamazepine was used in case 2. Sodium valproate interacts with PHT and carbamazepine in drug metabolism, mainly due to their different effects on the hepatic cytochrome P450 (CYP) enzyme system.[20] Sodium valproate is considered to be an inhibitor of CYP enzymes, especially CYP2C9 and CYP2A6. Therefore, when sodium valproate is combined with other drugs metabolized by these enzymes, it may inhibit the metabolism of these drugs, leading to an increase in the plasma concentration of the drug.[24] PHT is a liver enzyme inducer, and it can increase liver glucosylation and the activity of the liver microsomal somatotrope P450 system, which will increase the metabolism of sodium valproate in the liver.[25,26] In turn, sodium valproate may affect the metabolism of PHT thus affecting its concentration in the body, leading to PHT poisoning.[25] On the other hand, sodium valproate may increase the total plasma concentration of PHT as well as the concentration of free PHT, which may trigger symptoms of overdose.[1,20] Carbamazepine belongs to the substrate of the CYP enzyme, and when sodium valproate is used in combination with carbamazepine, it may inhibit the activity of these enzymes, thereby slowing the drug metabolism of carbamazepine, increasing the plasma concentration of these drugs and increasing the risk of toxicity.[27] The results showed that sodium valproate inhibited the metabolic enzymes of carbamazepine so that the plasma concentration of carbamazepine increased, while the concentration of carbamazepine metabolite carbamazepine 10, 11-epoxide remained unchanged. This interaction is generally thought to be a bioconversion reaction in which sodium valproate inhibits the activity of the cyclocoxidase, thereby impeding the conversion of carbamazepine-10, 11-epoxide to carbamazepine-10, 11-trans-diol. The need for careful monitoring of drug levels and patient response when these drugs are co-administered is highlighted.[28,29] In clinical practice, this interaction requires a delicate approach to administration and monitoring designed to balance efficacy and safety.[27] Doses may need to be adjusted while closely watching for any signs of toxicity or adverse effects to optimize treatment outcomes for patients with these antiepileptic drugs.

First, In clinical practice, the primary treatment for valproic acid encephalopathy is immediate discontinuation of VPA, with most patients recovering completely 1 to several days after discontinuation. Abrupt discontinuation of VPA during treatment in patients with epilepsy often causes persistent status epilepticus; therefore, it is recommended to switch to other antiepileptic drugs that are not hepatic metabolizers, have a rapid onset of action, and do not require slow titration. Levetiracetam is generally not associated with an increased risk of valproate encephalopathy in combination with sodium valproate, and the rapid onset of action of levetiracetam stabilizes fluctuations in blood concentrations due to the reduction of sodium valproate by dosing it.[30] Second, lactulose, arginine, and L-carnitine can reduce blood ammonia levels. Lactulose is broken down into lactic acid and acetic acid by lactobacilli, anaerobes, and other bacteria in the colon, reducing colonic potential of hydrogen (PH) and making the intestinal lumen acidic, thus reducing ammonia formation and absorption in addition. Arginine can participate in the ornithine cycle so that the body's ammonia is converted to urea and excreted from the body.[1,31] L-carnitine combines with sodium valproate to alleviate the inhibitory effect on urea synthesis, thereby reducing blood ammonia concentrations.[32] Extracorporeal therapy (ECTR) may be recommended for patients presenting with severe VPA poisoning, such as cerebral edema (e.g., visual edema, focal neurologic deficits, and altered mental status), shock, and patients with VPA >1300 mg/L. Intermittent hemodialysis is the preferred option for VPA poisoning.[33,34] ECTR can be terminated when the patient's clinical improvement is evident or when the serum VPA concentration is 50–100 mg/L (350–700 μmol/L).[35] In the four cases in this article, after consideration of valproate encephalopathy, valproate was immediately discontinued in all four patients; cases 1 and 2 were treated with lactulose supplementation and rehydration therapy; cases 3 and 4 had the antiepileptic drug adjusted to levetiracetam, in addition to lactulose supplementation and rehydration therapy. All four patients had a complete remission of their clinical symptoms 3–8 days after discontinuation of the drug, and hemodialysis was not used. Our cases are consistent with a previous literature review in which 10 out of 17 patients resolved sodium valproate encephalopathy appearing.[1]

To summarize, this paper collects clinical data from four cases of valproate sodium encephalopathy and combines it with a literature review. The main clinical manifestations include varying degrees of consciousness impairment, increased seizure frequency, gastrointestinal symptoms, cognitive dysfunction, ataxia, and abnormal mental behavior. These are consistent with the clinical symptoms of valproate sodium encephalopathy reported in the past. When the abovementioned symptoms emerge clinically, the possibility of valproate sodium encephalopathy should be noted. Given the potential risks, it is imperative to avoid using multiple antiepileptic drugs in combination, especially those regimens that include multiple hepatic P450 enzyme inducers. When the

above symptoms appear clinically, the possibility of sodium valproate encephalopathy should be vigilant, and the use of sodium valproate should be stopped immediately.

The limitations of our study are that the patient sample size is relatively small, and they all come from the same department of the same hospital. It is necessary to further conduct large-scale, multi-center research on patients.

Conclusion

In clinical practice, when the use of sodium valproate increases the frequency of unexplained seizures, aggravates consciousness disorders, gastrointestinal symptoms, cognitive dysfunction, ataxia, and mental behavior abnormalities, the possibility of sodium valproate encephalopathy should be vigilant, and sodium valproate should be stopped immediately.

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Author contributions

H.H. conceived and designed the work. C.P. drafted the manuscript; Z.Z., T.L., Z.L., and M.Z. participated in the data investigation and analysis; C.Y. and Z.X. edited and revised the manuscript; all authors read and approved the final version of the manuscript.

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Ethics approval

This study was approved by the Biomedical Research Ethics Committee of the Affiliated Hospital of Zunyi Medical University (Ethics Review Approval Number: KLL-2023-248).

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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