

VALPROIC-INDUCED HYPERAMMONEMIC ENCEPHALOPATHY AGGRAVATED BY COMBINED USE OF TOPIRAMATE - A CASE REPORT

Ke Zhao, Dian Lv, Miao Chen & Yue Yang

Zhuji People's Hospital of Zhejiang Province, Zhuji City, China

received: 29.3.2021;

revised: 7.5.2021;

accepted: 14.5.2021

* * * * *

INTRODUCTION

Valproic-induced Hyperammonemic Encephalopathy (VHE) is a kind of neurological side effects caused by taking sodium valproate. Its clinical manifestations are atypical. It needs to be distinguished from the sedative effects of other drugs and the sequelae effect of epilepsy. One case of VHE was admitted to our department. In the course of diagnosis and treatment, it was found that the combined use of topiramate aggravated valproic-induced hyperammonemic encephalopathy. The clinical data are now reported as follows.

CASE PRESENTATION

The patient, female, 48Y, was admitted to the hospital on June 3, 2018 due to "unconsciousness and seizures of limb convulsion for 2 hours after a fall". She has a history of "hypertension" for 4 years and has been taking "Levoamlodipine Maleate Tablets 5mg qd", the left side of the body was not able to move properly and was able to limp due to a history of surgery for a left basal ganglia hematoma.

Physical examination: body temperature 36.8°C, pulse 109 beats/min, breathing 20 breaths/min, blood pressure 144/81 mmHg, clear mind, GCS 15 points, lack of articulation, equal size and equal circle of both pupils, diameter 0.3 cm, sensitive to light reflex, negative nystagmus, and the right nasolabial fold is shallow, the tongue is in the middle, the neck is soft, the left side muscle tone is moderate, the muscle strength is grade V, the right limb muscle tone is high, the right upper limb muscle strength is grade 0, and the lower limb muscle strength is grade IV, and the reflexes of both knees are symmetrical, the skin prick sensation of the limbs is symmetrical, and the bilateral babinski sign is negative.

After admission, diazepam needle micropump combined with oral sodium valproate sustained release tablets 0.5 g bid for antiepileptic treatment, no seizure occurred again. On June 5, her family members found that she was sleepy, and physical examination showed lethargy, but no attention was paid. On June 6th, the diazepam injection was stopped and the treatment with

sodium valproate tablets was continued. On June 8, the patient still needed loud call to open her eyes, the blood ammonia was 70 $\mu\text{mol/l}$ (normal blood ammonia value 0-30 $\mu\text{mol/l}$), the dose of sodium valproate sustained-release tablets was reduced and changed to 500 mg qd, and topiramate tablets 25 mg bid were added. On June 10, in the emergency department, blood ammonia was 81 $\mu\text{mol/L}$. On June 13th, the patient was lethargic, right upper limbs are inactive, and the remaining three limbs can be lifted off the bed; emergency review blood ammonia increased to 106 $\mu\text{mol/L}$, so valproic acid sustained-release tablets were discontinued, and topiramate 50 mg bid was given for anti-epileptic treatment. On June 14th, the patient's mental state improved significantly, and she was able to communicate normally, the blood ammonia was rechecked at 16 $\mu\text{mol/l}$ on June 15 and was discharged.

DISCUSSION

Sodium valproate is a broad-spectrum anti-epilepsy and treatment of mood disorders and migraine. It is widely used clinically. Laub MC et al. found that 27% of patients taking sodium valproate had elevated blood ammonia, but many of them were asymptomatic (Laub 1986). Compared with the increase in blood ammonia caused by liver disease, sodium valproate-related hyperammonia often has liver function at a normal level, suggesting that it is not caused by liver cell death and injury (McCall & Bourgeois 2004). Valproic acid is a fatty acid, most of which enters the glucuronic acid metabolic pathway and β -oxidation pathway in liver cells, and rarely undergoes ω -oxidation (Verrotti et al. 2002). Carnitine is an essential cofactor in the process of mitochondrial β -oxidation, and valproic acid consumes a large amount of carnitine when transported to the mitochondria, supplementing carnitine can correct valproic-induced hyperammonemic encephalopathy and accelerate blood ammonia metabolism (Mock & Schwetschenau 2012). However, recent literature reports that when valproic acid enters the β -oxidation pathway, valproic acid COA (hepatotoxicity product) is produced. The increase of carnitine enhances the β -oxidation pathway, which in turn increases the valproic

acid COA concentration (Verrotti et al. 2002). However the mechanism of valproic-induced hyperammonemic encephalopathy is not very clear. At present, it is mainly believed that when valproic acid metabolites enter the mitochondria, they can inhibit the production of N-acetylglutamate and the indirect effect of mitochondrial fatty acid β -oxidation pathway on cpl I (Ghodke-Puranik et al. 2013) (See mechanism diagram).

VHE is a relatively rare central nervous system adverse reaction after the use of sodium valproate (McCall & Bourgeois 2004, Yamamoto et al. 2012). The current main treatment methods: 1. Immediately stop sodium valproate or switch to other antiepileptic drugs. 2. Promote blood ammonia metabolism or speed up blood ammonia excretion (Lheureux et al. 2005, Mock & Schwetschenau 2012). The initial treatment of this patient was sodium valproate combined with diazepam, and the patient experienced a decline in consciousness. In vitro experiments confirmed that sodium valproate can inhibit the metabolism of gamma-aminobutyric acid (GABA) (Johannessen & Johannessen 2003), diazepam can enhance GABA-mediated inhibition of the central nervous system. The sedative effect of combined drug treatment was first considered, and diazepam treatment was stopped, but the state of consciousness did not improve, and further examination of blood ammonia indicated hyperammonemia. During the dressing change process, the patient's mental state and blood ammonia level still did not improve. After carefully reviewing the case and reviewing the literature, we found that the patient had a variety of antiepileptic treatment after the onset of the disease, and there was an interaction of drug treatment.

Topiramate (TPM) is a weak inducer of liver drug enzymes, and has carbonic anhydrase inhibitors. There are reports in the literature that topiramate alone can cause hyperammonemic encephalopathy (Tantikitti-chaikul et al. 2015), Noh Y et al. have found that in patients receiving VPA treatment, the prevalence of VHE is about 0.1%; combined with topiramate, the prevalence of VHE can increase about 10 times (Noh et al. 2013). Because, the metabolites of valproic acid combined with topiramate can reduce the activity of glutamine synthetase in the brain and kidney, and inhibit the conversion of glutamate to glutamine, and increase blood ammonia levels (Latour et al. 2004).

This case reminds us that because of the atypical clinical manifestations of VHE, it is easy to be mistaken for the sequelae effects of epilepsy, the sedative effect of tranquilizers, etc. In addition, it is necessary to carefully analyze the interaction between anti-epileptic drugs; when blood ammonia is found to be elevated and valproic-induced hyperammonemic encephalopathy exists, sodium valproate should be stopped in time (Raru & Zeid 2018). Moreover, in the early stage of VHE, symptoms of encephalopathy may appear first, but blood ammonia is still at a normal

level, blood ammonia should be reviewed in a short period of time to avoid misdiagnosis (Yamamoto et al. 2013, Tseng et al. 2014, Twilla & Pierce 2014).

Acknowledgments:

Ethics approval and consent to participate:

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Zhuji People's Hospital of Zhejiang Province. Patient signs informed consent.

Conflict of interest: None to declare.

Contribution of individual authors:

Ke Zhao: conceived of the study, read and approved the final manuscript.

Dian Lv & Miao Chen: participated in its design and coordination, read and approved the final manuscript.

Yue Yang: draft the manuscript, read and approved the final manuscript.

References

1. Ghodke-Puranik Y, CF Thorn, Lamba JK, Leeder JS, Song W, Birnbaum AK, et al.: Valproic acid pathway: pharmacokinetics and pharmacodynamics. *Pharmacogenet Genomics* 2013; 23:236-241. doi:10.1097/FPC.0b013e32835ea0b2
2. Johannessen CU & Johannessen SI: Valproate: past, present, and future. *CNS Drug Rev* 2003; 9:199-216. doi:10.1111/j.1527-3458.2003.tb00249.x
3. Latour P, Biraben A, Polard E, Bentué-Ferrer D, Beauplet A, Tribut O, et al.: Drug induced encephalopathy in six epileptic patients: topiramate? valproate? or both? *Hum Psychopharmacol* 2004; 19:193-203. doi:10.1002/hup.575
4. Laub MC: Hyperammonemia in valproate therapy in children and adolescents. *Nervenarzt* 1986; 57:314-318
5. Lheureux PE, Penalzoza A, Zahir S, Gris M. Science review: carnitine in the treatment of valproic acid-induced toxicity - what is the evidence? *Crit Care* 2005; 9:431-440. doi:10.1186/cc3742. Epub 2005 Jun 10
6. McCall M & Bourgeois JA: Valproic acid-induced hyperammonemia: a case report. *J Clin Psychopharmacol* 2004; 24:521-526. doi:10.1097/01.jcp.0000138768.61600.ad
7. Mock CM & Schwetschenau KH: Levocarnitine for valproic-acid-induced hyperammonemic encephalopathy. *Am J Health Syst Pharm* 2012; 69:35-39. doi:10.2146/ajhp110049
8. Noh Y, Kim DW, Chu K, Lee ST, Jung KH, Moon HJ, et al.: Topiramate increases the risk of valproic acid-induced encephalopathy. *Epilepsia* 2013; 54: e1-e4. doi: 10.1111/j.1528-1167.2012.03532.x
9. Raru Y & Zeid F: Hypoxic respiratory failure due to hyperammonemic encephalopathy induced by concurrent use of valproic acid and topiramate, a case report and review of the literature. *Respir Med Case Rep* 2018; 25:1-3. doi: 10.1016/j.rmcr.2018.05.026

10. Tantikittichaikul S, Johnson J, Laengvejkal P, DeToledo J: Topiramate-induced hyperammonemic encephalopathy in a patient with mental retardation: A case report and review of the literature. *Epilepsy Behav Case Rep* 2015; 15:84-85. doi: 10.1016/j.ebcr.2014.09.001
11. Tseng YL, Huang CR, Lin CH, Lu YT, Lu CH, Chen NC, et al.: Risk factors of hyperammonemia in patients with epilepsy under valproic acid therapy. *Medicine* 2014; 93:e66. doi:10.1097/MD.0000000000000066
12. Twilla JD & Pierce AS: Hyperammonemic Encephalopathy due to Valproic Acid and Topiramate Interaction. *Case Rep Psychiatry* 2014; 2014:410403. doi:10.1155/2014/410403
13. Verrotti A, Trotta D, Morgese G, Naqvi S, Shagufra S, Mohit A: Valproate-induced hyperammonemic encephalopathy. *Metab Brain Dis* 2002; 17:367-373. doi:10.1111/j.1600-0404.2006.00655.x
14. Yamamoto Y, Takahashi Y, Imai K, Mishima N, Yazawa R, Inoue K, et al.: Risk factors for hyperammonemia in pediatric patients with epilepsy. *Epilepsia* 2013; 54:983-989. doi:10.1111/epi.12125
15. Yamamoto Y, Takahashi Y, Suzuki E, Mishima N, Inoue K, Itoh K, et al.: Risk factors for hyperammonemia associated with valproic acid therapy in adult epilepsy patients. *Epilepsy Res* 2012; 101:202-209. doi: 10.1016/j.eplepsyres.2012.04.001

Correspondence:

Yue Yang, MD

Department of Neurology, Zhuji People's Hospital of Zhejiang Province

No. 9 Jianmin Road, Taozhu Street, Zhuji City, Zhejiang Province, 311800, China

E-mail: yangy2021cn@163.com