Valproate-induced Hyperammonemonia Manifested with Delirium

A 50-year-old female patient was diagnosed with bipolar I disorder. Her first depressive episode was in her teens, and first manic episode at 45 years of age. She was admitted to acute psychiatric ward for a manic episode presenting herself with mood liability, talkativeness, violence, and grandiose delusions. The results of initial laboratory examinations were all within normal limits.

On admission day one, the patient received daily valproic acid (VPA) 1,000 mg, lorazepam 2 mg, and flurazepam 30 mg. VPA was uptitrated to 1,300 mg/day on day four in addition to her daily clotiapine 40 mg and chlorpromazine 50 mg while her behaviors became more disturbing. With increased VPA dosage to 1,500 mg/day, her elated mood and grandiosity were gradually improved, but she started to develop confusion, disorganized behaviors, and aggravated daytime somnolence. Chlorpromazine was discontinued on day 14 and changed to olanzapine 5 mg/day. The laboratory data on day 19 demonstrated to have normal serum liver enzymes but elevated serum VPA level (124.1 mcg/mL) and hyperammonemia (111.3 mcmol/L). VPA dosage was reduced from 1,500 to 1,300 mg/day. But her consciousness fluctuation and disorientation were worsened with increasing serum VPA level (126.7 mcg/mL) and hyperammonemia (434.9 mcmol/L). VPA was totally discontinued on day 22, and she received emergency fluid resuscitation. She received lactulose to eliminate the hyperammonemia.

After VPA discontinuation, the patient’s disorientation was gradually recovered with olanzapine 10 mg/day alone. Serum ammonia returned to normal range on day 25, and she became oriented and regained clear consciousness one week later. Four weeks after VPA discontinuation, she was eventually discharged home under olanzapine 20 mg/day. Figure 1 shows the temporal relationship of her clinical symptoms, laboratory findings, and VPA dosage.

Comment

Valproate-induced hyperammonemonic encephalopathy is the most probable diagnosis in our patient. VPA is a common mood stabilizer treating mood disorders. Its common side effects include elevations of serum liver enzymes, as well as adverse effects in hematopoietic and digestive systems. Delirium has been associated with VPA in scarce clinical reports [1].

Temporal relationship between drug and confusion was obvious in the clinical course of our patient (Figure 1). Hyperammonemia and normal liver enzymes were noted throughout delirium in this patient. Hyperammonemonic encephalopathy is a rare, but serious drug-related adverse effect induced by the use of valproate, sometimes with concomitant use of other antiepileptic drugs [1]. In a previous review of 30 (16 female, 14 male) psychiatric patients who developed hyperammonemonic encephalopathy, the patients’ mean VPA dosage (1,336 ± 575 mg) and mean serum VPA level (91 ± 23 mcg/mL) are not extremely high in psychiatric treatment setting [2]. In the literature, no correlation has been found between the development of hyperammonemonic encephalopathy and serum VPA levels [2]. The mean serum ammonia level

Figure 1. Temporal relationship of delirium with serum valproate, ammonia, and liver enzyme levels.

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is 174 ± 184 mcMol/L, and the duration of recovery from hyperammonemic encephalopathy has been ranged from 1 to 30 days [3]. Pathophysiologically, the metabolism of VPA in mitochondria leads to the formation of valproyl-CoA, which can inhibit N-acetyl glutamate, resulting in accumulating serum ammonia [4]. Hyperammonemia increases serum glutamine level and impairs glutamate transporter, eventually leading to the swelling of astrocytes and brain edema [4]. Although our report is limited by being a single case report, we suggest that hyperammonemic encephalopathy is induced by valproate.

In summary, hyperammonemic encephalopathy with delirium can occur in valproate-induced patients, although it is rarely seen in clinical practice. Even in patients without liver function impairment or previous exposure history of valproate, we suggest that hyperammonemic encephalopathy should be routinely considered in the list of differential diagnoses once delirium (or the acute confusional state) is observed clinically (This case report was approved by the institution review board of Taoyuan Psychiatric Center for publication [No. R20190328, approved on April 2, 2019]. The IRB agreed to waive the patient consent form).

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Conflicts of Interest
There are no conflicts of interest.

References

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