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LETTER TO THE EDITOR

Valproic acid-induced Hyperammonemic Encephalopathy

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Dear Editor,

Valproic acid (VPA) is a generally well tolerated antiepileptic drug and mood stabilizer used in a number of neurological and psychiatric disorders, especially epilepsy and bipolar disorder. One of the side effects is asymptomatic hyperammonemia (increased blood ammonia level) with a reported incidence between 16.2 and 52.3% (1). A rare side effect is VPA-induced hyperammonemic encephalopathy (VHE). The pathogenesis of this adverse effect, which can lead to coma or even death, is still under investigation. Known risk factors for the development of VHE include deficiency of urea cycle enzymes, concomitant use of drugs such as antiepileptics and antipsychotics, and comorbid liver diseases (2).

Urea cycle enzyme deficits, liver and kidney diseases, and drugs like salicylate and VPA are among the known causes of hyperammonemia. VPA increases serum ammoniac levels by renal as well as hepatic pathways. Twenty-five percent of the rise in ammoniac levels is induced by stimulation of glutaminase activity in the renal cortex, which is reportedly related to an increased passage of glutamine through the renal mitochondrial membranes, contributing to the accumulation of ammoniac in the blood (3). The remaining larger percentage, however, is hepatogenic. VPA increases the ammoniac level directly by inhibiting carbamoyl phosphate synthetase-1, the first enzyme of the urea cycle, in the liver and indirectly by reducing carnitine. After high-dose or long-term VPA treatment, the production of toxic metabolites increases. These metabolites cause hepatotoxicity and high ammoniac levels (4).

VPA reduces the carnitine level through a number of mechanisms. Primarily, VPA binds to carnitine, forming valproylcarnitine, which is soluble in water and excreted with the urine. VPA also inhibits the tubular reabsorption of carnitine and acylcarnitine. By blocking the carnitine membrane transporter and inhibiting γ-butyrobetain hydroxylase, VPA reduces the synthesis of carnitine. Carnitine is a cofactor in the β-oxidation of fatty acids and VPA. A reduction in the carnitine biosynthesis lowers the breakdown of VPA by β-oxidation in the mitochondria and enhances the risk of the formation of toxic substances (1,4).

Hyperammonemia-related central nervous system toxicity is caused due to excessive activation of glutamate NMDA receptors and cellular edema. Ammoniac quickly crosses the blood-brain-barrier. A rise in extracellular ammoniac inhibits the entry of glutamate into the cell. Increased extracellular glutamate triggers the activity of the NMDA receptor; consequently, encephalopathy and a decrease in the seizure threshold are seen. Intracellular increase in glutamine raises intracellular osmolarity, which induces cellular edema (2,5).

This communication presents the case of a patient with polypharmacy followed with a diagnosis of mood

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disorder and epilepsy thought to have developed VHE. The patient has been informed and written consent has been received.

The 20-year-old female patient was married with 1 child, middle school graduate, not in any employment. The patient had been followed as an outpatient with complaints of unhappiness, anhedonia, and death wish, using 100 mg/day sertraline. When she expressed active suicidal ideation during control in the outpatient clinic, she was hospitalized in our clinic. It was learned that her history, in addition to depressive symptoms, included eloping, lying, stealing money, and behaviors causing harm to self and others. While the current complaints had been continuing for around 4 years, the patient had been using psychiatric treatment for the past 2 months. The patient's medical history included portal vein thrombosis, familial Mediterranean fever, homozygous methylenetetrahydrofolate reductase gene mutation, brain surgery due to fibrous dysplasia 1 year earlier, and postoperative onset of epilepsy. The patient's epilepsy was treated with levetiracetam 3,000 mg/day. The patient's full blood count, biochemical tests (alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen [BUN], creatinine, serum electrolytes, etc.), thyroid function tests, and levels of vitamin B12 and folic acid examined during hospitalization were normal. Sertraline was discontinued, as the patient did not seem to benefit from the drug. Treatment was adjusted, starting with low doses increased to 300 mg/day for venlafaxine, 3 mg/day risperidone, and 450 mg/day quetiapine. No distinct change in the patient's clinical presentation was seen. As she displayed atypical affective characteristics as well as epilepsy, the neurology department was consulted and VPA 1,000 mg/day was started. Three days after starting VPA, the patient suffered an epileptic seizure. A serum VPA level of 98 μg/mL (reference range: 50-100 μg/mL) was measured. Over the next 3 days, the patient underwent 2 more epileptic seizures. Full blood count and biochemical tests were normal. Due to the increased frequency of epileptic seizures, which in the patient's history had occurred around once every 2 months, electroencephalography (EEG) was carried out. In the EEG, it was found that the "base rhythm consisted of high-amplitude 2-Hz delta activity, with severe diffuse slowing." The EEG was interpreted as indicating encephalopathy, and the patient's ammoniac level was measured, finding a serum ammoniac level of 461 μmol/L (reference range: 18.2-72.2 μmol/L). The patient was referred to the internal medicine department for consultation. At that time, urinary incontinence and clouding of consciousness began; her pupils were dilated bilaterally. With a Glasgow Coma Scale (GKS) score of 4, the patient was moved to the Internal Medicine Intensive Care Unit. Except for levetiracetam, all medication was stopped. Hemodialysis and L-carnitine treatment were started. After the first hemodialysis, the patient's serum ammoniac level reduced to 56 μmol/L. The following day, as her serum ammoniac level was 150 μmol/L, a second hemodialysis was done. The patient, who had regained consciousness after the first hemodialysis, was evaluated with a GKS score of 15 and did not show any further symptoms. As her control serum ammoniac levels were also normal, the patient was returned to our ward after 2 hemodialyses and 3-day L-carnitine (2 g/day) treatment.

A high rate of hyperammonemia can be observed during VPA treatment. While generally asymptomatic, it has been reported that VHE can be seen in conditions of malnutrition, urea cycle disorders, carnitine deficiency, medical comorbidities, or drug interactions (5). Guide to the diagnosis of this potentially fatal picture is clinical and laboratory monitoring. Clinical signs of VHE are generally unspecific. They can arise as acute- or subacute-onset somnolence, lethargy, agitation, confusion, or coma. In addition, ataxia, emesis, subfebrile fever, focal neurological signs, and seizures can be seen. Increased seizure frequency in epileptic patients also requires considering this clinical diagnosis (6). Velioglu and Gazioglu (7) reported the case of a patient whose epileptic seizures paradoxically increased due to VHE after starting VPA; the patient went into a non-convulsive status epilepticus. One of the main laboratory signs for VHE is diffuse slowing with dominant delta and theta rhythms in the EEG (3). In our patient, too, the picture manifested itself with increased frequency of seizures, and similar EEG signs were detected. Diagnosing VHE can be difficult due to the unspecificity of symptoms and the weak correlation between occurrence of signs and dosage, blood level, and period of use of the drug (6). In most cases, no correlation was found between VPA blood level and ammoniac level, and VHE has been observed with therapeutic doses and normal blood levels of VPA (2). Two case presentations in Turkey reported VHE with the VPA blood level being in the normal range (8) or even after administering a single dose of VPA (9). In our case as well, the ammoniac level dramatically rose in the acute phase while the VPA blood level was in normal range.

Cases of VHE developing with simultaneous use of VPA and drugs like topiramate, quetiapine, or risperidone have been reported (10-12). It is known

that the concomitantly used drug competes with VPA and thus may cause an increase in the free drug level (11). It is conceivable that the development of encephalopathy in our patient was also related to an increase in the free drug level due to the concurrent use of quetiapine or risperidone, even though the blood level of VPA was normal. One study found a rate of 6.4% for hyperammonemia in patients receiving VPA monotherapy and 33.1% in combination therapy (13). The use of other antiepileptic drugs or antipsychotics combined with VPA has been reported to increase the risk of encephalopathy (13). However, with new antiepileptics, especially lamotrigine and levetiracetam, a decrease in hyperammonemia risk has been found (14). It could be assumed that the hyperammonemia in our patient might be related with the antipsychotics rather than with the levetiracetam.

The first step in treating VHE is stopping VPA. It generally takes 4-14 days for the mental state to return to normal (15). Hemodialysis has an important place in the treatment. During therapy, the serum ammoniac level needs to be monitored. In cases like ours, when the ammoniac level exceeds 680 μg/dL (400 μmol/L) or in the presence of severe clinical symptoms, aggressive interventions are recommended, especially hemodialysis (16). As well as carnitine treatment, this is also important in protection from VHE (2). In our patient, clinical signs and serum ammoniac level quickly improved after carnitine treatment and hemodialysis. The main cause for the encephalopathy may be thought to be the VPA-induced increase in ammoniac and/or carnitine deficiency. In addition, the toxicity of ammoniac seems to have increased the frequency of seizures by increasing glutamate activity. However, not having measured the blood levels of glutamate, carnitine, and VPA metabolites limits our ability to interpret the pathophysiology of our case.

To conclude, the occurrence of clinical signs like epileptic seizures, somnolence, or confusion in patients using VPA needs to alert us to the possibility of VHE. In patients treated with VPA, risk factors need to be carefully considered. Especially in cases with polypharmacy, even with normal serum VPA levels, we have to remember that the risk of hyperammonemic encephalopathy is increased. Our case may provide guidance for the management of the diagnostic and therapeutic process of the rare but important complication that is VHE.

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