Case: Valproat-Induced Hyperammonemic Encephalopathy

Olgu: Valproat ile İndüklenen Hiperamonemik Ensefalopati

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ABSTRACT

Valproate induced hyperammonemic encephalopathy (VHE) is a severe adverse effect of medicine. An epileptic patient with an acute hyperammonemia after the addition of valproic acid to his treatment presented with acute mental status changes consistent with encephalopathy. Notably, plasma ammonia level was 2 times of the upper limit, despite normal liver function tests. Plasma valproic acid level was in the therapeutic range. His symptoms resolved with the discontinuation of valproic acid and L-carnitine administration. We discuss this case and review the possible mechanisms of valproic acid–associated encephalopathy and the efficacy of L-carnitine.

Key Words: Valproate, hyperammonemia, carnitine, encephalopathy, transaminases, toxicity

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ÖZET

Valproat ilişkili ensefalopati, ilacın ağır bir yan etkisi olarak görülmektedir. Olgu, tedaviye valproik asit eklendikten sonra hiperamonemi ve akut ensefalopati ile uyumlu mental değişiklikle başvurmuştur. Plazma amonyak düzeyleri normal düzeyin iki katı kadar yüksek iken, karaciğer fonksiyon testleri normaldi. Plazma valproik asit düzeyi normal sınırlardaydı. Valproat kesilip, L-karnitin eklendikten sonra semptomları düzeldi. Bu olguyla birlikte, hiperamonemi ve ensefalopatinin olası mekanizmaları ve bu hastalarda L-karnitin tedavisinin etkinliği tartışılmıştır.

Anahtar Sözcükler: Valproat, hiperamonemi, karnitin, ensefalopati, transaminazlar, toksisite

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INTRODUCTION

VPA is commonly prescribed for the treatment of seizure disorders and various other neurological and psychiatric conditions. While VPA usage and related issues increase, numerous drug interactions and toxicities are reported. Severe toxicities include hepatic damage, pancreatitis, teratogenicity, bone marrow supression, coagulation disorders and hyperammonemic encephalopathy (1). Under VPA treatment over a few months, asymptomatic hyperammonaemia occurs in 16,2-52,3% of patients in the literature (2). Valproate induced hyperammonemic encephalopathy (VHE) is characterized by an acute onset of impaired consciousness, focal neurologic symptoms and increased seizure frequency (1,3). Different mechanisms have been implicated in VHE. The pathogenesis is not still completely understood (4). The inhibition of the activity of carbamoyl-phosphate synthetase I (CPS-I) is thought to be the reason of hyperammonemia and due to hypermmonemia N-methyl-D-aspartate (NMDA) receptors' excessive activation is thougt to be the reason of encephalopathy (3) . VHE is usually seen in association with a normal liver function (3). Carnitine has been recommended as an antidote for acute valproic acid overdose (5). Also prophylactic carnitine supplementation has been recommended during a VPA therapy for the prevention of hepatotoxicity in high-risk pediatric patients (6,7). Plasma carnitine levels were found to be decreased, reversible after the VPA discontinuation (4).

Herein, we report a case of VHE with normal liver functions, who has no history of an underlying liver disease, and who was succesfully treated with L-carnitene.

CASE REPORT

A 8-year-old boy was admitted to our emergency department with a decreased level of consciousness and vomiting for 7 days. Glasgow Coma Scale score was 14/15, and his vital signs were stable. According to his family, he had been confused and mumbling incoherently in the previous week. He complained of lethargy and weakness. He had epilepsy and had been successfully treated with oxcarbazepine for the past 4 years and with the extended-release divalproex for the past one month.

In the emergency department, he had a variable level of consciousness. He was unable to recognize recent events. The brain computed tomography scan showed a right cerebral hemisphere edema. Further laboratory studies included normal complete blood cell count, normal electrolytes and bicarbonate (22 mEq/L) levels. Blood glucose was 90 mg/dL. Renal function values were normal. Plasma ammonia level was 195 umol/L (N:14-73 umol/L); VPA level was 75 µg/L (N:50-100 µg/L); and aspartate aminotransferase and alanine aminotransferase were normal at 16 IU/L and 12 IU/L, respectively. Electroencephalogram (EEG) showed poorly formed, diffuse slow background activity. Spike and slow waves and sharp transients were seen on the right frontocentral region. The patient was diagnosed with hyperammonemic encephalopathy secondary to VPA. VPA was discontinued and substituted with levetiracetam. L-carnitine was also supplemented through 100 mg/kg IV. No advers effects occured.

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By day 4, the patient was less confused. Ammonia level dropped to 66 umol/L (14-73 umol/L). On day 5, his mental status continued to improve. Seven days after admission, the patient returned to his baseline mental status. On day 7, an electroencephalogram revelaed normal background activity.

DISCUSSION

Valproate induced hyperammonemic encephalopathy is rare, but potentially life-threatening adverse events are associated with VPA therapy. The clinical presentation of VHE is variable and includes impaired consciousness, irritability, drowsiness, confusion, lethargy and coma (4). Our patient presented with decreased conciousness. At the follow up, ammonia levels decresed in correlation with his clinical improvement.

Although the exact incidence of VHE is unknown, it is rare in adults (7). The symptoms develop in days, or months or years after the initiation of VPA **(**7). Its pathogenesis is not completely understood but it is suspected that hyperammonemia appears to be the main cause of encephalopathy. Ammonia is thought to increase extracellular glutamate concentrations which result in the excessive activation of NMDA receptors (3). Hyperammonemia may be due to the inhibition of activity CPS-1, the first enzymatic reaction in the urea cycle, or the inhibition of N-acetylglutamate synthase (NAGS) activity, which is an obligatory activator CPS-1, by valproyl-CoA (3,8). Also, VPA stimulates glutaminase in renal cortex and incresases glutamine uptake and ammonia release (8).

VPA leads to the carnitine deficiency by several mechanisms (7). VPA combines with carnitine to be excreted in urine. VPA reduces tubular reabsorption and the edogenous synthesis of carnitine, decreases the transport of extracellular carnitine. VPA metabolites combine with mitochondrial CoA-SH; free mitochondrial carnitine stores cannot be restored from acylcarnitine. VPA is a branched chain fatty acid and metabolized by in the mitochondria of hepatocytes. And carnitine has a part in β-oxidation of VPA. Carnitine supplementation in VHE increases β-oxidation of VPA (7). The net effect of carnitine depletion is the interference with mitochondrial synthesis and energy production. There are many reports that points carnitine efficiacy in VPA induced hyperammonemia and VHE. In a study; plasma carnitine levels were found to be negatively correlated with ammonia levels in 60 epileptic children who had been treated with VPA for at least 1 year and ammonia levels decreased after the L-carnitine supplementation (9). However Hantson et al. reported a patient, dignosed as VHE, treated with L- carnitine, whose plasma ammonia level decreased within 4 days, but who had remained in coma for 3 weeks (10). And Blackford et al. found normal carnitine levels in a patient who developed hyperammonemic encephalopathy with VPA. They emphasized the discrepancies between serum and tissue/ muscle concentrations of carnitine (11). Gomceli et al. evaluated seven adult patients who were diagnosed as VHE. One of their patients had had carnitine deficiency, had been treated with carnitine. However, they had not found significant differences in clinical improvement, EEG findings and recovery duration between carnitine deficiency patient and the others (12). Our case was also treated succesfully with L-carnitene. His ammonia level fell to normal levels and his conciousness became normal after L-carnitene ingestion. Also EEG findings are not spesific for VHE, but was used for monitoring recovery (3).

Arginine, furosemide, mannitol, carglumic acid, lactulose, neomycin, protein restriction, hemodialysis are used for the treatment of hyperammonaemia in patients with VHE in previous reports (3,13). Underlying urea cycle enzyme deficiencies creates predispositions for VHE (14). Concominant antiepileptic poly-therapy; phenobarbital, phenytoin, carbamazepine and topiramate, may exacerbate VHE (14). Our patient had been using oxcarbazepine for four years and the co-administration of valproate and oxcarbazepine was thought to be a major risk factor. However Cheng et al. evaulated 21 VHE patients in China. They found that no plasma ammonia concentrations directly correlate with the daily dosage and plasma concentrations of VPA, duration of VPA treatment, polytherapy, age or gender (3). And they emphasized that the symptoms of VHE had developed within 2 months of starting VPA (3). Nevertheless Rousseau et al. showed hyperammonemia in 25,4% patients who had used VPA for very long durations (2). Underlying liver disease, co-medication with other drugs such as salicylates, disorders associated with reduced albumin synthesis may be the other risk factors (4).

Physicians are reminded of the risk for hyperammonemia with VPA and the need for proper laboratory monitoring of these patients. In the cases of encephalopathy caused by VPA, prompt determination of the ammonia level and withdrawal of VPA treatment should be considered, and the appropriate measures including liver-associated enzymes and monitoring of valproate levels had to be taken. With immediate intervention and supportive care, including L-carnitine treatment, mental-status changes and risk of permanent brain damage can be minimized. We recommend the administration of L-carnitine for patients with VHE.

Conflict of interest

No conflict of interest was declared by the authors

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