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Letter to Edıtor / Editöre Mektup

Valproic Acid–Induced Hyperammonemic Encephalopathy: A Case Report

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Abstract

This article presents a case demonstrating that valproic acid, which is widely used in the treatment of bipolar disorder, can lead to hyperammonemic encephalopathy, a rare but potentially serious adverse effect.

Keywords: Hyperammonemic, Encephalopathy, Valproic Acid

Valproik Asit İlişkili Hiperamonyemik Ensefalopati: Bir Olgu Sunumu

Öz

Bu yazıda, bipolar duygudurum bozukluğu tedavisinde yaygın olarak kullanılan valproik asidin, nadir ancak potansiyel olarak ciddi bir yan etkisi olan hiperamonyemik ensefalopatiye yol açabileceğini gösteren bir olgu sunulmaktadır.

Anahtar kelimeler: Hiperammonemik, Ensefalopati, Valproik asit.

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Dear Editor,

Valproic acid is widely used in the treatment of bipolar disorder due to its mood-stabilizing and anticonvulsant properties. Although it is generally well tolerated, it can occasionally be associated with serious adverse effects. One such adverse event is hyperammonemic encephalopathy[1-3]. In this report, we present a case of valproic acid–induced hyperammonemic encephalopathy to draw clinicians' attention to this potentially life-threatening complication.

A 37-year-old male patient diagnosed with bipolar affective disorder with no history of substance, alcohol, or tobacco use and following a regular diet, was admitted to our inpatient unit with complaints of insomnia, distractibility, increased talkativeness, grandiosity, and increased activity that had started 10 days earlier. His medical history revealed that his first complaints began seven years ago, that he had been followed up in a psychiatry clinic for similar symptoms, was discharged with valproic acid treatment, and remained asymptomatic for two years. It was learned that his medication adherence had been irregular over the past five years and that he had not taken any medication for the previous two months. At admission, routine biochemical investigations showed total bilirubin: 1.56 mg/dL, direct bilirubin: 0.58 mg/dL, and AST: 47 U/L, with other parameters within normal limits. The patient was started on haloperidol 20 mg/day, biperiden 4 mg/day, and clonazepam 3 mg/day. On the third day of treatment, valproic acid 1000 mg/day was added due to a previous positive response, and valproic acid level monitoring was planned for the seventh day. During the patient's follow-up, since clonazepam had been initiated prior to valproate, no adverse effects related to clonazepam were observed other than its expected therapeutic effects. However, six days after initiating valproic acid, the patient developed bradycardia, hypertension, sedation, disorientation, and fluctuating consciousness. All medications were discontinued, and cardiology and neurology consultations were requested. No cardiac pathology was detected. Brain imaging (CT, MRI, and diffusion MRI) was normal. Electroencephalography (EEG) findings were consistent with "diffuse slowing of background rhythm without lateralization or localization."

The ammonia level was 184 µg/dL (reference range: 31–123), AST: 13.5 U/L, ALT: 12.7 U/L, total bilirubin: 0.91 mg/dL, direct bilirubin: 0.4 mg/dL, and valproic acid level: 87.4 µg/mL. Neurology consultation suggested "hyperammonemic encephalopathy," and internal medicine evaluation supported a diagnosis of "non-cirrhotic hyperammonemia." Following discontinuation of valproic acid, the patient's clinical status rapidly improved, and the control serum ammonia level decreased to 90.5 µg/dL (reference range: 31–123). Due to the rapid resolution of the clinical picture, the use of lactulose, which was recommended by internal medicine, was not deemed necessary. Carnitine supplementation was not administered. The patient's encephalopathic symptoms completely resolved. No encephalopathic symptoms were observed after the treatment was reorganized with haloperidol 7.5 mg/day, biperiden 4 mg/day, and quetiapine 100 mg/day. Once his manic symptoms stabilized, he was discharged with this regimen. During follow-up appointments, he had no complaints or findings regarding encephalopathy, and his medication adherence was good. He was followed up with haloperidol

7.5 mg, biperiden 3 mg, quetiapine 50 mg treatment.

Valproate-associated encephalopathy is a potentially life-threatening adverse effect that may develop even in patients with normal liver function[4]. Although encephalopathy often occurs within therapeutic serum valproate levels, it is typically associated with hyperammonemia[5]. The proposed mechanisms include impaired hepatic conversion of ammonia to urea or glutamine and disrupted carnitine metabolism leading to ammonia accumulation[6]. Clinically, this condition can range from asymptomatic presentation to neurological slowing, EEG abnormalities, coma, and, if untreated, death[7].

In our case, despite the therapeutic valproic acid level, the rapid onset of symptoms alongside elevated ammonia levels, and their resolution following discontinuation of valproate, are noteworthy. This clinical picture aligns with what is described in the literature as "non-cirrhotic hyperammonemic encephalopathy," which typically regresses rapidly after prompt diagnosis and discontinuation of valproate[8].

In conclusion, hyperammonemic encephalopathy should be considered in the differential diagnosis of patients receiving valproic acid who develop sudden changes in consciousness or autonomic instability. Although routine measurement of ammonia levels may not always be available due to institutional limitations, close monitoring of vital signs is crucial in patients initiated on valproic acid, and it may be essential to measure ammonia levels at the earliest sign of suggestive changes in consciousness. Early recognition and intervention are crucial for preventing serious outcomes. In future studies, it would be beneficial to investigate cases where clinical recovery is delayed despite valproic acid discontinuation, requiring lactulose or carnitine therapy. Additionally, evaluating the frequency and clinical course of cases that require the reinitiation of valproic acid due to an inadequate clinical response to alternative treatments after discontinuation could provide substantial contributions to the literature.

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REFERENCES

1. Koroglu E. Mood stabilizers. Clinical Psychiatry, 3rd ed. Esenkal Publishing, 2020: 808-10.

2. Ahmad S. Psychopharmacology. In: Sarikaya BB, Bozkurt A, eds. Kaplan & Sadock's Pocket Handbook of Clinical Psychiatry, 7th ed. Ankara: Gunes Medical Bookstores, 2023: 671-6.

3. Baddour E, Tewksbury A, Stauner N. Valproic acid-induced hyperammonemia: incidence, clinical significance, and treatment management. Ment Health Clin. 2018; 8: 73-7.

4. Carr RB, Shrewsbury K. Hyperammonemia due to valproic acid in a psychiatric setting. Am J Psychiatry. 2007; 164: 1020-7.

5. Wong YJ, Fan J, Wan A, et al. Valproic acid-associated hyperammonemia: a systematic review. J Clin Psychopharmacol. 2023; 43: 283-94.

6. Wadzinski J, Franks R, Roane D, et al. Valproate-associated hyperammonemic encephalopathy. J Am Board Fam Med. 2007; 20: 499-502.

7. Segura-Bruna N, Rodriguez-Campello A, Puente V, et al. Valproate-induced hyperammonemic encephalopathy. Acta Neurol Scand. 2006; 114: 1-7.

8. Yoo JY, Yang HS. Valproate-induced hyperammonemic encephalopathy: a case report. Brain Neurorehabil. 2013; 6: 86-9.