CASE REPORT / PRIKAZ SLUČAJA

VALPROATE-INDUCED HYPERAMMONEMIC ENCEPHALOPATHY

VALPROATOM UZROKOVANA HIPERAMONEMIJSKA ENCEFALOPATIJA

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Abstract

Background: Valproate is a broad-spectrum antiepileptic drug. Valproate-induced hyperammonemic encephalopathy is an uncommon but serious adverse effect of valproate therapy.

Case presentation: We present the case of a 33-year-old woman on long-term valproate therapy who was admitted to the emergency department due to progressive impairment of consciousness. She had pharmacoresistant epilepsy and alcohol use disorder. Workup excluded structural, infectious, and psychiatric causes. Electroencephalography showed diffuse slowing of background activity consistent with generalized encephalopathy. Routine laboratory tests, including liver function, were within the normal range. Plasma ammonia was elevated. In the context of ongoing valproate use, normal liver function, and elevated ammonia, valproate-induced hyperammonemic encephalopathy was suspected. Valproate dosage was reduced and lactulose was initiated. Ammonia levels gradually decreased, accompanied by complete clinical recovery and return to baseline neurological status.

Conclusion: This case highlights that any sudden change in mental status in a patient receiving valproate should raise suspicion for valproate-induced hyperammonemic encephalopathy, enabling prompt diagnosis and timely treatment.

Keywords: encephalopathy; hyperammonemia; valproate.

Sažetak

Uvod: Valproat je antiepileptik širokog spektra. Hiperamonemijska encefalopatija rijedak je, ali ozbiljan neželjeni učinak terapije valproatom.

Prikaz slučaja: Prikazujemo slučaj 33-godišnje žene na dugotrajnoj terapiji valproatom koja je primljena na hitni bolnički prijam zbog progresivnog poremećaja svijesti. Bolovala je od farmakorezistentne epilepsije i ovisnosti o alkoholu. Dijagnostičkom obradom isključeni su strukturni, infektivni i psihijatrijski uzroci. Elektroencefalografija je pokazala difuzno usporenje moždane aktivnosti u skladu s generaliziranom encefalopatijom. Rutinski laboratorijski nalazi, uključujući funkciju jetre, bili su unutar normalnih granica. Razina amonijaka u plazmi bila je povišena. S obzirom na kontinuiranu primjenu valproata, normalnu funkciju jetre i povišeni amonijak, posumnjalo se na valproatom uzrokovanu hiperamonemijsku encefalopatiju. Doza valproata je smanjena, a uvedena je laktuloza. Vrijednosti amonijaka postupno su se snižavale, uz potpuni oporavak svijesti i povratak na početnu neurološku funkciju.

Zaključak: Ovaj slučaj naglašava da svaka nagla promjena mentalnog statusa u bolesnika na terapiji valproatom treba pobuditi sumnju na valproatom uzrokovanu hiperamonemijsku encefalopatiju, što omogućuje pravodobnu dijagnozu i liječenje.

Ključne riječi: encefalopatija; hiperamonemija; valproat.

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Introduction

Valproate is commonly prescribed for epilepsy, bipolar disorder, and various psychiatric conditions. While generally regarded as safe, valproate has been linked to several adverse effects, including hepatotoxicity, pancreatitis, thrombocytopenia, and hyperammonemia. Hyperammonemia frequently occurs during valproate therapy; however, progression to valproate-induced hyperammonemic encephalopathy (VHE) is rare but can be life-threatening (1).

The pathophysiology of VHE is not fully understood. Current evidence indicates that valproate disrupts the urea cycle by inhibiting key enzymes responsible for ammonia metabolism, leading to elevated serum ammonia levels. This accumulation of ammonia in the central nervous system increases cerebral glutamine production, causes astrocyte swelling, and results in cerebral edema, which ultimately leads to neurological dysfunction (2,3).

Hyperammonemic encephalopathy is a rare but potentially life-threatening adverse effect of valproate.

Clinical manifestations of VHE range from mild cognitive impairment and lethargy to confusion, altered mental status, vomiting, focal neurological deficits, increased seizure frequency, and, in severe cases, coma. Because these symptoms are often nonspecific and may resemble the progression of underlying neurological or psychiatric disorders, clinicians should consider VHE in any patient receiving valproate who presents with unexplained changes in mental status (1,4). We report a case of VHE in a patient receiving valproate therapy who achieved complete clinical recovery.

Altered mental status in patients receiving valproate should prompt ammonia testing.

Case presentation

A 33-year-old woman presented to our emergency department (ED) with progressive impairment of consciousness. According to family members, she became increasingly somnolent over 3 days prior to admission and was soporous on the day of presentation. There was no reported history of recent seizures, head trauma, fever, or clinical signs of infection.

She had a history of pharmacoresistant epilepsy, which was initially diagnosed as juvenile myoclonic epilepsy and was later complicated by posttraumatic structural epilepsy after traumatic brain injury. She was also receiving psychiatric care for alcohol use disorder. Her long-term antiseizure regimen consisted of valproate (500 mg in the morning and 750 mg in the evening), levetiracetam (1000 mg twice daily), and zonisamide (75 mg twice daily). Concomitant psychotropic medications included escitalopram, diazepam, mirtazapine, and quetiapine. Topiramate was not included in her treatment regimen. Given her psychiatric history, an acute psychiatric decompensation was initially considered; however, psychiatric evaluation did not support a primary psychiatric etiology.

Neurological examination revealed a quantitative disturbance of consciousness, characterized by marked somnolence, without focal neurological deficits. An urgent diagnostic workup was performed. Non-contrast brain computed tomography showed no acute intracranial pathology. Electroencephalography demonstrated diffuse slowing of background activity, predominantly in the bilateral frontotemporal regions, consistent with a generalized encephalopathic process. Routine laboratory investigations, including complete blood count, serum electrolytes, renal function tests, and inflammatory markers, were within normal limits. Liver function tests were also within the reference range (aspartate aminotransferase (AST) 32 U/L, alanine aminotransferase (ALT) 40 U/L, gamma-glutamyl transferase (GGT) 43 U/L, alkaline phosphatase (ALP) 112 U/L, and total bilirubin 12 μmol/L). Given the patient's history of chronic alcohol use, plasma ammonia levels were measured and found to be elevated (151 μmol/L; reference range 18 - 72 μmol/L). In the context of ongoing valproate therapy, normal liver function, elevated plasma ammonia, and electroencephalographic findings suggestive of metabolic encephalopathy, VHE was suspected. The patient was admitted to the neurology department for further management. Valproate dosage was reduced, but not discontinued due to pharmacoresistant epilepsy, and lactulose therapy was initiated to enhance ammonia elimination. Levocarnitine was not administered. Plasma ammonia levels gradually decreased to 73 μmol/L on hospital day 2.57 μmol/L on day 4, and 65 μmol/L on day 8, accompanied by complete clinical recovery and return to baseline neurological status. Based on the clinical presentation, exclusion of alternative etiologies, elevated plasma ammonia, and favorable response to valproate dose reduction and ammonia-lowering therapy, a diagnosis of VHE was established.

Discussion

Valproate-induced hyperammonemic encephalopathy (VHE) is a significant adverse effect of valproate therapy that may occur more often than is generally recognized. Valproate-associated hyperammonemia is thought to be uncommon but has been reported with widely varying incidence rates. Overt encephalopathy may occur with normal liver function tests and therapeutic serum valproate concentrations. Therefore, the diagnosis may be missed unless there is a high index of suspicion in patients developing an acute change in mental status during valproate therapy (1,4). The pathogenesis of VHE is not fully understood. There are several mechanisms involved and they are interrelated. Valproate may inhibit carbamoyl phosphate synthetase I and thus impair the urea cycle and reduce ammonia clearance. Other contributing factors

include the accumulation of toxic metabolites, mitochondrial dysfunction, and carnitine depletion, all of which may further promote hyperammonemia. The resulting elevation in ammonia induces neurotoxic effects, mainly through astrocytic glutamine accumulation, osmotic swelling, and cerebral edema. Electroencephalography in VHE typically shows generalized slowing or other diffuse encephalopathic patterns, consistent with a metabolic disturbance of cerebral function (1,5).

Several risk factors have been associated with VHE, including underlying urea cycle disorders, liver disease, concomitant antiepileptic therapy (particularly topiramate), fasting, poor nutritional status, and intellectual disability. Nevertheless, VHE may occur without identifiable predisposing factors and does not seem to correlate reliably with valproate dose, treatment duration, or serum drug level. This variability suggests that individual susceptibility plays an important role in its development (1,4).

Management is focused on reducing ammonia levels and withdrawal or reduction of valproate exposure. In general, valproate should be discontinued; however, dose reduction may be required in selected patients in whom seizure control must be maintained. Lactulose and levocarnitine are adjunctive therapies in common use (4,6,7). In the present case, levocarnitine was not administered because the patient demonstrated prompt clinical improvement following reduction of the valproate dose and initiation of lactulose therapy. In the absence of acute valproate overdose, hepatotoxicity, or progressive neurological deterioration, additional treatment with levocarnitine was not considered necessary.

Valproate dose reduction and lactulose therapy may be effective when valproate withdrawal is not an option.

In our patient, the diagnosis of VHE was based on subacute deterioration in consciousness, elevated plasma ammonia levels, preserved liver function, and electroencephalographic evidence of diffuse encephalopathy. The differential diagnosis was initially broadened by the patient's alcohol use disorder and psychiatric comorbidities; however, neuroimaging, laboratory evaluation, and psychiatric assessment did not support an alternative etiology. Although complete withdrawal of valproate was not feasible due to pharmacoresistant epilepsy, the time-related association between hyperammonemia, neurological deterioration, and subsequent improvement following valproate dose reduction and lactulose therapy, together with exclusion of alternative causes, strongly supports valproate as the most likely precipitating factor. Nonetheless, because valproate was reduced rather than fully discontinued, causal attribution remains partly inferential and cannot be established with absolute certainty.

Conclusion

VHE should be considered in any patient receiving valproate who presents with otherwise unexplained encephalopathy, even when liver function tests and serum valproate concentrations are within the normal range. Prompt recognition and timely intervention are essential to prevent serious neurological sequelae.

Patient confidentiality

The patient's confidentiality and anonymity were maintained throughout the preparation of this manuscript. No identifying personal information has been included.

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