ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at:www.ijmacr.com

Volume – 8, Issue – 5, October - 2025, Page No.: 50 – 53

Ageing, Valproate and Altered Sensorium-Unmasking A Treatable Encephalopathy Induced By Valproate-A Case Series

[1]Dr. Pazhaniyandi Pillai K., Department of Neurology, Tirunelveli Medical College

[2]Prof. Dr. Sriramakrishnan V., Department of Neurology, Tirunelveli Medical College

Corresponding Author: Dr. Pazhaniyandi Pillai.K, Department of Neurology, Tirunelveli Medical College

How to citation this article: Dr. Pazhaniyandi Pillai K., Prof. Dr. Sriramakrishnan V., "Ageing, Valproate and Altered Sensorium-Unmasking A Treatable Encephalopathy Induced By Valproate-A Case Series", IJMACR- October - 2025, Volume – 8, Issue - 5, P. No. 50 – 53.

Type of Publication: Case Series

Conflicts of Interest: Nil

Abstract

Background: Valproate (VPA) is an antiepileptic drug with broad spectrum of efficacy. Although usually well-tolerated, it may have side-effects of which encephalopathy is one of the most serious.

Objective: To describe the clinical characteristics of valproate encephalopathy (VE) in four older patients with VPA for various indications.

Design: Case Series.

Patients: Four patients with underlying migraine or symptomatic seizure disorder.

Results: VE was characterised by decline in conscious level and (in some cases) increase in frequency of movement disorders. Four patients had elevated ammonia levels. EEG showed generalised slowness in activity, in some cases accompanied by additional epileptic discharges. The condition was reversible in four patients after VPA discontinuation. **Conclusions**: older people may be at particular risk of VE because of co-morbid pathology, age-related metabolic changes and co-medication.

Keywords: Ageing, Valproate, Encephalopathy, Hyperammonemia, Complications of Seizures

Introduction

Sodium valproate is a commonly prescribed antiepileptic and mood-stabilizing agent. Despite its widespread use and efficacy, it is associated with various adverse effects, including hepatotoxicity, thrombocytopenia, and, rarely, hyperammonemic encephalopathy. In older patients with epilepsy, sodium valproate (VPA) is sometimes regarded as the antiepileptic drug of first choice because of its good tolerability and cardiovascular safety. Valproate induced encephalopathy can occur with or without liver dysfunction and may present with nonspecific symptoms such as confusion, lethargy, and tremors. Recognizing this is crucial, especially in long-term users, as timely discontinuation of the drug can reverse the condition. In

adult epileptology, VPA-induced encephalopathy is regarded as a rare complication with incidence of 0.5% to 2.52% per year in long-term users, however it is underreported in acute settings with scarce data regarding the incidence rates. Here, we describe four patients who developed signs and symptoms suggestive of encephalopathy during initial VPA treatment.

Case Reports

Case 1

A 90-year-old male on sodium valproate for over a month presented with acute onset confusion, slowness with increased reaction time and gait ataxia. Investigations revealed elevated ammonia (53.6 µmol/L) with a subtherapeutic valproate level (18.3 µg/mL) and normal liver function. Discontinuation of valproate led to clinical improvement within 48 hours.

Case 2

A 52-year-old male on valproate therapy for a duration of four weeks initiated for seizure disorder presented with mild behavioural abnormality, confusion, slowness of activity and prolonged reaction time. His valproate level was 25.2 µg/mL, and ammonia was 45.8 µmol/L. Liver function tests were normal. Symptoms resolved after stopping valproate and initiating lactulose.

Case 3

A 52-year-old man on VPA for seizure disorder presented with progressive disorientation and behavioral changes. Serum ammonia was 45.8 µmol/L; valproate levels were within normal limits. Her mental status improved over four days after stopping valproate.

Case 4

A middle-aged patient on valproate as an antiseizure medication for hemorrhagic stroke presented with confusion, slowness of activity, altered behaviour, gait ataxia and tremors. Serum ammonia was elevated (53.6 µmol/L) with normal liver function. Valproate was withdrawn, and lactulose was given, resulting in symptom resolution.

Review of Literature

Valproate-induced hyperammonemic encephalopathy (VHE) has been described since the 1980s, with multiple mechanisms proposed. The most accepted mechanism involves valproate's inhibition of carbamoyl phosphate synthetase I, leading to impaired ammonia detoxification. This enzyme is situated in the mitochondrial matrix of hepatocytes and genetic variants and polymorphisms exists in CPS I which leads to its deficiency and thereby increased propensity to develop hyperammonemia when exposed to catabolic stress, high protein load and medications like valproate.

CPS I enzyme is ATP dependent. Valproate induced mitochondrial dysfunction reduces ATP availability further compromising CPS I activity.

Lam (2023) emphasized the potential for subclinical hyperammonemia to progress to encephalopathy even without elevated valproate levels [1]. Chopra et al. (2012) highlighted that VHE can present with altered sensorium, vomiting, and ataxia, and is more common in patients receiving polytherapy or with underlying urea cycle enzyme deficiencies [2]. Segura-Bruna et al. (2006) described astrocyte swelling and cerebral edema on MR imaging in patients with VHE as a result of hyperammonemia [3]. Recent studies by Loser et al. (2023) reported VHE in status epilepticus patients, emphasizing that hyperammonemia may not be present in all cases [4]. Dinçer et al. (2018) reported that up to 51% of psychiatric patients on valproate exhibited elevated ammonia, and those with polypharmacy and CPS polymorphism (underdiagnosed) were at greater risk[5].

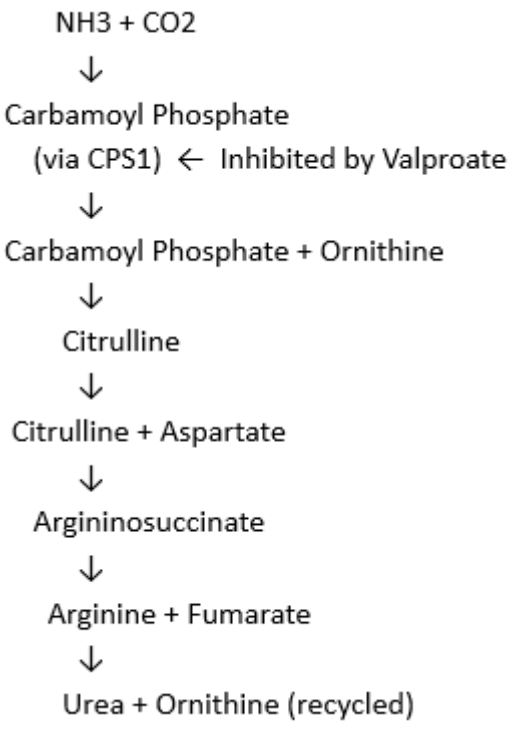
Discussion

Valproate-induced encephalopathy may present subtly with symptoms such as fatigue, restlessness, and confusion. Biochemically, valproate disrupts the urea cycle—a hepatic mitochondrial pathway essential for detoxifying ammonia into urea. This disruption is primarily due to:

- Inhibition of carbamoyl phosphate synthetase I (CPS1)
- the rate-limiting enzyme of the urea cycle.
- Carnitine depletion – impairing mitochondrial fatty acid metabolism.

These effects collectively impair ammonia clearance, leading to hyperammonemia, astrocytic dysfunction, cerebral edema, and encephalopathy.

Urea Cycle Flowchart with Valproate Action Site



Valproate inhibits CPS1, impairing the first and critical step of ammonia detoxification, leading to elevated ammonia levels.

Why Even Subtherapeutic Valproate Levels Can Cause Encephalopathy ?

Importantly, encephalopathy can occur even at subtherapeutic valproate levels. This paradox arises because:

- The toxicity is not dose-dependent but rather idiosyncratic, particularly in individuals with:
- Underlying urea cycle enzyme defects (even partial or latent)
- Age-related mitochondrial inefficiency
- Carnitine deficiency
- Polytherapy with other antiepileptics
- Inhibition of CPS1 and carnitine depletion can occur at low serum drug levels, particularly in the elderly where drug metabolism and clearance are altered due to hepatic and renal senescence.
- Additionally, age-related blood-brain barrier permeability allows even small amounts of ammonia to exert significant CNS effects.

Thus, therapeutic or subtherapeutic drug levels do not preclude toxicity.

Clinical Relevance

This condition is particularly under recognized in the elderly, where acute neuropsychiatric changes may be misattributed to:

- Stroke
- Dementia
- Drug side effects unrelated to valproate.

The cases presented illustrate that elevated serum ammonia, even with normal liver function and subtherapeutic valproate levels, can be clinically significant.

Early identification and treatment—via discontinuation of valproate, ammonia-lowering therapy (lactulose, L-carnitine), and supportive care—can reverse the

condition. In severe cases, carglumic acid may be considered.

Conclusion

Clinicians should maintain a high index of suspicion for VHE in patients on valproate therapy who present with unexplained encephalopathy especially in elderly. Early identification and treatment are crucial. Serum ammonia should be routinely checked in symptomatic patients regardless of valproate level or liver functions. The difficult differential diagnosis suggests that this entity is probably under-recognised, especially in patients with preexisting neurological disorders like dementia. Patients with age-related metabolic changes, cognitive decline and other disturbances of brain function (e.g. vascular leukoencephalopathy) may be at particular risk of VE. Judicious use of valproate, regular monitoring for cognitive changes and a low threshold for checking serum ammonia levels in elderly patients may mitigate the risk of this potentially reversible encephalopathy.

References

1. Lam CW. Valproate-induced hyperammonemic encephalopathy: A brief review. J Neurol Sci. 2023;451:120661.
2. Chopra A, Kolla BP, Mansukhani MP, Netzel P, Frye MA. Valproate-induced hyperammonemic encephalopathy: an update. Curr Neurol Neurosci Rep. 2012;12(6):583-591.
3. Segura-Bruna N, Rodriguez-Campello A, Puente V, Roquer J. Valproate-induced hyperammonemic encephalopathy. Acta Neurol Scand. 2006;114(1):1-7.
4. Loser W, Fauser S, Schulze-Bonhage A. Hyperammonemia in patients with status epilepticus receiving valproate: Incidence and clinical significance. Epilepsia. 2023;64(1):102-109.
5. Dinçer Y, Canan F, Ataoglu A. Hyperammonemia in psychiatric inpatients receiving valproate: a clinical study. Psychiatry Clin Neurosci. 2018;72(7):538-544.