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Case Report

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Valproate-Induced Hyperammonemic Encephalopathy in a Child with Down Syndrome Despite Therapeutic Serum Valproate Levels: A Case Report

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ABSTRACT

Background: Valproate is a broad-spectrum antiseizure medication widely used in pediatric epilepsy. Hyperammonemia and hyperammonemic encephalopathy are recognized adverse effects and may occur despite therapeutic valproate concentrations and normal liver function tests. Down syndrome is associated with mitochondrial dysfunction, but whether it confers additional susceptibility to valproate-induced hyperammonemic encephalopathy is unknown.

Case Presentation: An 8-year-old boy with Down syndrome and epilepsy secondary to a remote left middle cerebral artery infarction presented with recurrent difficult-to-control seizures, including daily myoclonic seizures, drop attacks, and generalized tonic-clonic seizures. Valproate was initiated at 15 mg/kg/day. Four days later, he developed progressive encephalopathy requiring pediatric intensive care admission. Laboratory evaluation demonstrated severe hyperammonemia (750 $\mu\text{mol/L}$) despite therapeutic serum valproate concentration and normal liver function tests. Valproate was discontinued and intravenous sodium benzoate/sodium phenylacetate therapy was initiated. Ammonia levels normalized over approximately 48 hours with complete neurological recovery.

Conclusion: This case highlights the rapid onset of severe valproate-induced hyperammonemic encephalopathy despite a therapeutic serum valproate concentration and normal liver function tests. It raises, but does not establish, the possibility that underlying mitochondrial dysfunction in Down syndrome may modify susceptibility.

Keywords: Valproate; Hyperammonemic encephalopathy; Down syndrome; Epilepsy; Pediatric neurology.

INTRODUCTION

Valproate is a broad-spectrum antiseizure medication widely used in pediatric neurology. Hyperammonemia and hyperammonemic encephalopathy are recognized adverse effects and may occur despite therapeutic valproate concentrations and normal liver function tests [1–3]. Down syndrome is associated with mitochondrial dysfunction, oxidative stress, and impaired bioenergetic reserve [4–6]. Whether these abnormalities increase susceptibility to valproate-induced hyperammonemic encephalopathy has not been established.

CASE PRESENTATION

An 8-year-old boy with Down syndrome and epilepsy secondary to a remote perinatal left middle cerebral artery infarction presented with recurrent seizures. His seizure types included daily myoclonic seizures, drop attacks, and generalized tonic-clonic seizures. Valproate was initiated at 15 mg/kg/day because of difficult-to-control epilepsy.

Four days later, he developed progressive drowsiness and deterioration of consciousness. EEG demonstrated frequent multifocal epileptiform discharges with generalized frontal polyspike activity consistent with epileptic encephalopathy. MRI revealed left frontoparietal encephalomalacia and gliosis.

Plasma ammonia was markedly elevated at 750 $\mu\text{mol/L}$ despite therapeutic serum valproate levels and normal liver function tests. Valproate was discontinued and intravenous sodium benzoate/sodium phenylacetate (Ammonul®) therapy was initiated. Ammonia levels progressively normalized over approximately 48 hours with complete neurological recovery.

DISCUSSION

Valproate-induced hyperammonemic encephalopathy (VHE) is an uncommon but potentially life-threatening adverse reaction. It may develop with normal liver function and valproate concentrations within the therapeutic range, making diagnosis dependent on clinical suspicion and ammonia measurement [1–3]. In this child, the temporal relationship to valproate initiation, severe hyperammonemia, preserved liver function, and recovery after drug withdrawal and ammonia-lowering treatment support VHE. The coexistence of Down syndrome is clinically noteworthy, but a causal increase in VHE risk cannot be inferred from a single case.

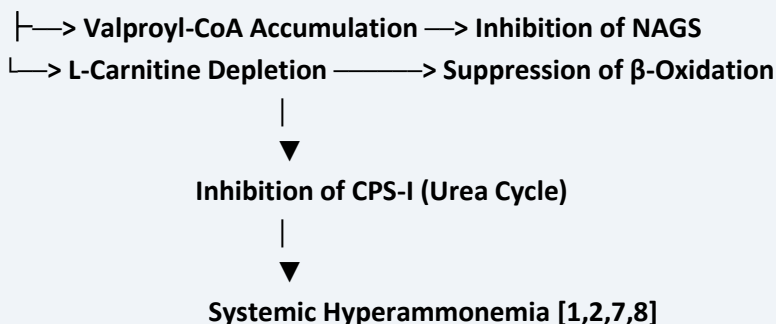
Mechanisms of Valproate-Induced Hyperammonemia

The pathophysiology of VHE is multifactorial. Valproate metabolism can reduce N-acetylglutamate availability and thereby impair activation of carbamoyl phosphate synthetase I, the first mitochondrial enzyme of the urea cycle. Valproate can also shift fatty-acid metabolism away from mitochondrial β -oxidation, further compromising ammonia detoxification [1,2,7].

Valproate may also lower free carnitine through formation and urinary excretion of valproylcarnitine and reduced renal reabsorption. Carnitine depletion limits transport of long-chain fatty acids into mitochondria and favors ω -oxidation, producing metabolites that can further inhibit the urea cycle. Increased renal ammonia production has also been proposed [2,7,8]. These mechanisms help explain why ammonia elevation may not correlate closely with the serum valproate concentration.

Pathophysiological Cascade of Valproate Toxicity

Valproate Therapy



Susceptibility in Down Syndrome: Mitochondrial & Metabolic Vulnerability

Down syndrome is associated with well-described abnormalities of mitochondrial structure and function, including altered oxidative phosphorylation, reduced ATP production, abnormal mitochondrial dynamics, and increased oxidative stress [4–6]. Overexpression of chromosome 21 genes, including SOD1, may contribute to redox imbalance; however, the magnitude and clinical consequences vary among individuals [4,6].

Reported abnormalities include [4–6]:

- **Structural Mitochondrial Abnormalities:** Disrupted cristae architecture and decreased mitochondrial membrane potential in neural and hepatic tissues.
- **Decreased Baseline ATP Synthesis:** Impaired Complex I and Complex IV activity of the electron transport chain.
- **Reduced Metabolic Reserve:** Compromised capacity to handle exogenous metabolic stressors or hepatotoxic drugs.

Valproate itself can impair mitochondrial fatty-acid metabolism. It is therefore biologically plausible that pre-existing mitochondrial dysfunction could reduce metabolic reserve during valproate exposure [4–8]. Nevertheless, published evidence does not establish that children with Down syndrome have a higher incidence of VHE than other children. The present case should be interpreted as a hypothesis-generating observation rather than proof of a syndrome-specific risk.

Evidence Limitations and Clinical Implications

Epilepsy is common in Down syndrome and shows an age-related bimodal pattern, with epileptic spasms prominent in infancy and myoclonic epilepsy associated with Alzheimer disease in later adulthood [9,10]. Antiseizure treatment should be individualized according to seizure type, age, comorbidities, and adverse-effect profile [9,10].

Direct evidence linking Down syndrome to an increased risk of VHE is currently insufficient.

- The mitochondrial phenotype of Down syndrome provides biological plausibility, but the available literature does not support claims of higher rates of valproate-related carnitine depletion, hyperammonemia, or diagnostic delay specifically in this population [4–6].
- Accordingly, the clinical message from this case is not that valproate is contraindicated in Down syndrome. Rather, any patient receiving valproate who develops unexplained drowsiness, vomiting, cognitive or behavioral change, ataxia, or worsening seizures should undergo prompt ammonia measurement, even when liver function and valproate levels are normal [1–3].
- Management begins with immediate discontinuation of valproate and supportive care. Levocarnitine may be considered, particularly when carnitine deficiency, hepatotoxicity, or severe toxicity is suspected, although high-quality efficacy data remain limited [7,8].
- For severe hyperammonemia, early metabolic consultation and ammonia-lowering therapy should follow age-appropriate hyperammonemia guidance [11]. In this case, intravenous sodium benzoate/sodium phenylacetate was associated with rapid biochemical and neurological recovery.

CONCLUSION

This case demonstrates that severe VHE can occur rapidly after valproate initiation despite therapeutic serum concentrations and normal liver function tests. Down syndrome-related mitochondrial dysfunction offers a plausible context, but a syndrome-specific excess risk remains unproven. Clinicians should maintain a low threshold for ammonia testing in any valproate-treated child with acute neurological or behavioral deterioration, promptly discontinue valproate when VHE is suspected, and initiate appropriate metabolic treatment [1–3,11].

ETHICS STATEMENT

Written informed consent for publication was obtained from the patient's parent/legal guardian.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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