Valproic Acid-Induced Hyperammonemic Encephalopathy During Treatment of a Suicide Attempt in an Adolescent

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ABSTRACT

Introduction: Self-harming behaviors and suicide in adolescence represent an increasing challenge in pediatric mental health. In Argentina, suicide accounts for 13.8% of deaths among individuals aged 10 to 19 years. While treatment is predominantly psychotherapeutic, moderate to severe cases may require psychotropic medications such as mood stabilizers.

State of the art: Valproic acid, used for its action on the GABAergic system, can induce metabolic adverse effects, including hyperammonemia and encephalopathy.

Discussion: We present the case of an adolescent diagnosed with hyperammonmic encephalopathy associated with valproic acid use, with elevated plasma ammonia levels (584.4 µg/dL) and drug concentration (124 mg/L), in the absence of concomitant hepatic dysfunction. Discontinuation of valproate and initiation of levocarnitine therapy led to rapid clinical improvement and a reduction in ammonia levels. The pathophysiological mechanisms involved are discussed, including interference with mitochondrial metabolism, inhibition of the urea cycle, and the role of carnitine.

Conclusion: This case highlights the importance of clinical suspicion and metabolic monitoring in the presence of neurological symptoms in patients undergoing treatment with valproic acid.

Keywords: hyperammonemic encephalopathy, valproic acid, levocarnitine, pediatrics

Encefalopatía hiperamonémica inducida por ácido valproico durante el tratamiento de un intento de suicidio en una adolescente

RESUMEN

Introducción: las conductas autolesivas y el suicidio en la adolescencia representan un creciente desafío en salud mental pediátrica. En la Argentina, el suicidio constituye el 13,8% de las defunciones en la población de 10 a 19 años. Si bien el tratamiento de estos cuadros es predominantemente psicoterapéutico, en casos moderados a graves puede incluir psicofármacos como estabilizadores del ánimo.

Estado de arte: el ácido valproico, empleado por su acción sobre el sistema GABAérgico, puede inducir efectos adversos metabólicos, como hiperamonemia y encefalopatía.

Discusión: se presenta el caso de una adolescente con diagnóstico de encefalopatía hiperamonémica

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asociada al uso de ácido valproico, con valores plasmáticos elevados de amonio (584,4 µg/dL) y del fármaco (124 mg/L), sin disfunción hepática concomitante. La interrupción del valproato y el inicio de tratamiento con levocarnitina condujeron a una rápida mejoría clínica y reducción de la amonemia. Se discuten los mecanismos fisiopatológicos implicados, entre ellos la interferencia en el metabolismo mitocondrial, la inhibición del ciclo de la urea y el papel de la carnitina.

Conclusión: este caso enfatiza la importancia de la sospecha clínica y la monitorización metabólica ante síntomas neurológicos en pacientes bajo tratamiento con ácido valproico.

Palabras clave: encefalopatía hiperamonémica, ácido valproico, levocarnitina, pediatría.

INTRODUCTION

Self-harming behaviors and suicide in adolescence have gained increasing relevance in pediatric mental health, representing frequent reasons for consultation and, in many cases, requiring hospitalization. Suicide in this age group constitutes a significant public health problem. In Argentina, its incidence has shown an upward trend, reaching 13.8% of all deaths among adolescents aged 10-19 years[1]. Management is typically interdisciplinary and, in moderate to severe cases, may include the use of psychotropic medications, such as antipsychotics or mood stabilizers. Among the latter, valproic acid has been used due to its effects on the GABAergic system[2]. However, its use is associated with a profile of adverse effects that includes metabolic disturbances, among them hyperammonemia, which may precipitate encephalopathy. We report the case of an adolescent who developed hyperammonemic encephalopathy associated with valproic acid use, and we discuss its underlying pathophysiological mechanisms.

CASE REPORT

A 15-year-old female patient was admitted for self-harming behaviors with suicidal ideation, which had begun at age 12, including medication overdose and cutting injuries to the extremities. On examination, she was alert, awake, and oriented to time, place, and person. Weight and height were at the 50th percentile for age and sex. Physical examination revealed superficial transverse linear scars on both forearms. Due to impulsive behaviors, multiple adjustments were made to her medication regimen. Among these, risperidone was discontinued due to galactorrhea associated with elevated prolactin levels (98 ng/mL) as an adverse effect. Following a temporary discharge for reintegration into her home setting, upon returning to the inpatient unit, the patient engaged in similar superficial cutting behaviors on both forearms. Consequently, quetiapine was initiated with gradual dose escalation, along with valproic acid as a mood stabilizer (Table 1). Ten days after initiation of valproic acid, the patient was noted to be somnolent, disoriented in time and space, with incoherent speech and inappropriate laughter. She was afebrile, with isocoric and reactive pupils, motor incoordination, and preserved strength, tone, and reflexes. Laboratory tests showed: white blood cell count 3,300/mm^3, hemoglobin 13.7 g/dL, platelets 128,000/mm^3, ammonia 584.4 µg/dL (normal range 18.7-86.9 µg/dL), and valproic acid 124 mg/L (therapeutic range 50-100 mg/L). Electrolytes, renal function, and liver function tests were within normal limits. Notable findings included thrombocytopenia and hyperammonemia, associated with elevated plasma valproic acid levels from a random sample. Hyperammonemic encephalopathy secondary to valproic acid was suspected; therefore, the drug was discontinued and treatment with levocarnitine was initiated, with an intravenous loading dose of 100 mg/kg followed by maintenance doses of 15 mg/kg every 6 hours. After 36 hours, the patient showed favorable clinical evolution: she was alert, awake, with coherent speech, no significant neurological abnormalities, and a marked decrease in ammonia levels (90.5 µg/dL).

DISCUSSION

Suicide constitutes a significant public health problem. In Argentina, it accounts for 13.8% of deaths among adolescents aged 10-19 years[1]. Among the therapeutic approaches for psychiatric disorders in this age group, psychotherapy is the primary recommendation and, in some cases, is combined with psychotropic medications. Mood stabilizers include valproic acid, lithium, topiramate, and lamotrigine; however, their use is limited in the treatment of psychiatric disorders in children and adolescents. Of these, only lithium has demonstrated benefit in the treatment of bipolar disorder in adolescents aged 12 years and older, despite its multiple adverse effects[2].

Encephalopathy is a diffuse disorder of the brain that alters its structure or function, manifesting with neurological symptoms such as confusion, changes in the level of consciousness, seizures, and behavioral or movement disturbances. This condition may be acute or chronic, progressive or static, and in children its etiology includes infectious, toxic, metabolic, genetic, and ischemic causes. In the present case, the patient developed a clinical picture consistent with acute encephalopathy with a pharmacological trigger. In all patients treated with valproic acid who developed symptoms of encephalopathy, hyperammonemia has been reported, with normal liver function in most cases, regardless of dose or plasma valproic acid levels[3]. Valproic acid is a branched-chain fatty acid used as an anticonvulsant and mood stabilizer, acting by increasing

the concentration of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in the synaptic cleft. Its metabolism is predominantly hepatic, although alternative pathways include uridine diphosphate glucuronosyltransferase (UGT) and β-oxidation[4]. Among its adverse effects is hyperammonemia, defined as an elevated plasma ammonia above normal levels. Reported risk factors include concomitant administration of other medications, liver injury, and defects in carnitine metabolism[5].

Carnitine is a quaternary ammonium compound that facilitates the transport of fatty acids into the mitochondria, enabling β-oxidation and the production of adenosine triphosphate (ATP). The mechanisms underlying hyperammonemia are complex and include: (1) carnitine deficiency; (2) depletion of acetyl-CoA (due to binding of the drug to coenzyme A), resulting in decreased β-oxidation; (3) reduced generation of intermediate carbon compounds (such as β-ketoglutarate and oxaloacetate) from the tricarboxylic acid cycle (TCA), which, together with ammonia, contribute to amino acid synthesis (glutamate and aspartate, respectively); and (4) inhibition of N-acetylglutamate synthase (NAGS), which produces N-acetylglutamate (NAG), an allosteric activator of mitochondrial carbamoyl phosphate synthetase I (CPS I), a key enzyme in the urea cycle responsible for ammonia detoxification (Fig. 1)[6-9]. Ammonia, which is highly toxic, is primarily derived from amino acid metabolism. Additional mechanisms related to valproic acid or its metabolites have been proposed, although they remain incompletely understood[8,10,11]. In cases of hyperammonemic encephalopathy, initial and priority

Table 1. Patient's pharmacological regimen

Medication	Day 0	Day 1	Day 3	Day 5	Day 10	Day 12	Day13 (Event)*
Risperidone	1 mg/day	1 mg/day	1 mg/day	1 mg/day	0.5 mg/day	-	-
Quetiapine	-	25 mg/day	50 mg/day	50 mg/day	75 mg/day	75 mg/day	75 mg/day
Valproic acid	-	-	750 mg/day	1000 mg/day	1000 mg/day	750 mg/day	750 mg/day

** Event represents the episode of hyperammonemic encephalopathy*

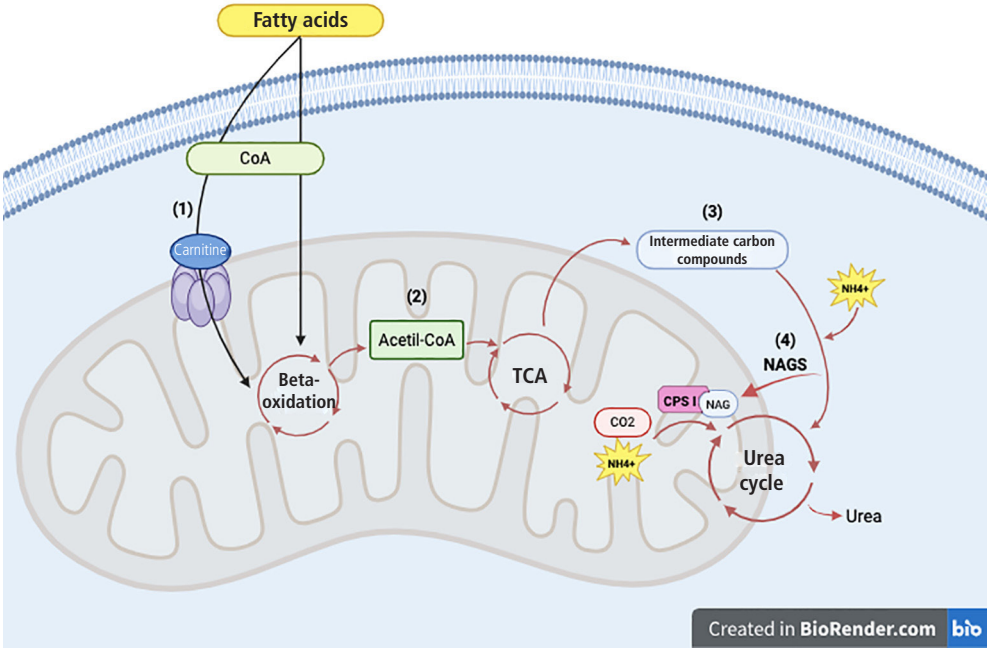

Figure 1. Simplified schematic of metabolic pathways occurring in mitochondria and the cytoplasm involved in the pathophysiology of hyperammonemia secondary to valproic acid and its metabolites (author's own work). **CoA**: coenzyme A; **TCA**: tricarboxylic acid cycle; **NAGS**: N-acetylglutamate synthase; **NAG**: N-acetylglutamate; **CPS I**: carbamoyl phosphate synthetase I; **NH_4^+**: ammonium.

management consists of discontinuation of the offending agent –in this case, valproic acid– and adjustment of protein intake, as increased protein catabolism contributes to urea cycle overload[9]. Peripheral venous access should be established to initiate parenteral hydration, and the route of administration (oral or intravenous) of specific pharmacotherapy should be determined according to the clinical status and ammonia levels. Among adjunctive measures, administration of levocarnitine is recommended, with a loading dose of 100 mg/kg followed by maintenance dosing (eg. 50 mg/kg/day in divided dosis), due to its potential role in facilitating mitochondrial fatty acid metabolism, particularly that of long-chain fatty acids[11,12]. These interventions were implemented in the patient, who showed favorable clinical evolution and continued follow-up under the Mental Health and Toxicology services.

CONCLUSION

Hyperammonemic encephalopathy induced by valproic acid, although uncommon, represents a serious complication in the pharmacological management of adolescents with psychiatric disorders. The present case highlights the importance of early recognition when neurological symptoms arise in patients receiving this drug, even in the absence of hepatic dysfunction.

Understanding the underlying pathophysiological mechanisms is essential to identify patients at higher risk and to guide timely and targeted therapeutic interventions.

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