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Chronic Sodium Valproate Intake to Treat Epilepsy Inducing Hyperammonaemia Encephalopathy

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Abstract: Sodium valproate, frequently prescribed as an antiepileptic, can cause encephalopathy secondary to hyperammonia, even after chronic use. We report the case of a 75-year-old patient with Parkinson's disease and epilepsy presenting a coma without deficit, with a normal cerebral morphological work-up, an electroencephalogram ruling out status epilepticus, a cerebrospinal fluid culture ruling out neuromeningeal infection, and a normal metabolic work-up apart from hyperammonia explained by sodium valproate intake.

Keywords: Coma, Encephalopathy, Hyperammonaemia, Sodium Valproate,

INTRODUCTION

There are many etiologies for comas, a large proportion of which are of metabolic origin. Sodium valproate, widely prescribed to treat epilepsy, may be responsible for encephalopathy, the pathophysiological process of which lies in a defect in ammonia metabolism. This complication may occur, generally in young subjects who have just begun treatment [1] or in the context of overdose, underlying pathologies or favouring factors, but cases of chronic intake [2] and outside these situations have been described. The interest of our observation is to evoke this complication in an elderly subject chronically exposed to sodium valproate.

CASE REPORT

Mrs. A.M aged 75 years, with a history of Parkinson's disease on L-dopa, with epileptic disease treated with sodium valproate 500 mg twice daily, who presented a calm coma with a GCS of 10/15, with no motor deficit or clinical convulsion, pupils in normal position and reactive, brainstem reflexes preserved, the rest of the physical examination normal, including normal blood glucose and temperature. Etiological investigations included normal CT and MRI scans of the brain, and a lumbar puncture with bacterial culture, viral PCR and cryptococcal inks were normal, The EEG on two occasions showed neither status epilepticus nor etiological orientation with a trace of cerebral distress. The immunological, electrolyte, renal, hepatic and vitamin assays were normal, with an amoniemia assay that was elevated to 92 U/L (normal 7-55 U/L). This led to the gradual discontinuation of sodium valproate, with the concomitant onset of care-associated pneumopathy requiring mechanical ventilation under sedation, with no clinical neurological monitoring, complicated by severe acute respiratory distress syndrome and septic shock with multivisceral failure and the patient's death.

DISCUSSION

Sodium valproate is a drug frequently prescribed to a wide population, due to its multiple indications: epilepsy, psychiatric disorders, dementia syndromes, attention deficit and hyperactivity disorders in children... [1]. Its main constituent with a therapeutic effect is valproic acid, which is a branched short-chain fatty acid. Its mechanism of action is inhibition of gamma-aminobutyric acid (GABA) transaminase enzyme, thereby increasing GABA levels in the brain and blocking ion-gated voltage channels, thereby reducing the frequency of neuronal action potentials [3]. Valproic acid is metabolized in

the liver by several reactions: microsomal glucuronide conjugation inducing a toxic metabolite, mitochondrial β-oxidation resulting in a non-toxic metabolite, and cytochrome P450-dependent omega 1-2-oxidation [1]. Carnitine facilitates the transport of acid valproic into the mitochondria to promote β-oxidation [4]. Acide valproic metabolite stimulates glutaminase in the renal cortex and another one is known to indirectly inhibit the hepatic mitochondrial carbamoyl phosphate synthetase-I, the first urea cycle enzyme [1]. Ammonia crosses the blood-brain barrier, inducing glutaminergic stimulation [5], which is responsible for the clinical signs. Several precipitating factors have been described [6], the main ones being primary or secondary carnitine deficiency, urea cycle disorders, chronic liver disease, and certain drugs that either induce carnitine deficiency (antiretrovirals, chemotherapy, antibiotics, antiepileptics) [7] or interact with sodium valproate (phenytoin, aspirin) [8]. Treatment is symptomatic, with discontinuation of the drug and avoidance of a rebound in epileptic activity. Some studies have suggested the efficacy of naloxone, probably via its GABA antagonist action [9].

CONCLUSION

Metabolic coma is a frequent reason for admission to the emergency department. Elderly patients are particularly at risk, due to comorbidities, polymedication and pathophysiological changes that make them vulnerable to many of the side-effects of their own treatments.

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Conflict of interest:

The authors have no conflicts of interest to declare

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