Case Report

Valproic acid intoxication imitating brain death

Abstract

The declaration of brain death requires a standardized clinical neurologic examination and, importantly, the resolution of the underlying cause. Because sedative and anesthetic agents can closely mimic brain death, intoxications must be ruled out. Aspects of brain stem function, particularly the pupillary responses to light, remain intact in most cases of poisonings. Intoxications that cause a condition that fully mimics brain death have only been described in cases of intoxications with tricyclic antidepressants and barbiturates so far.

We report the case of a 19-year-old man who presented with severe confusion and developed a deep coma over the next hours. Clinical examination revealed absence of all brain stem reflexes including missing pupillary responses to light. Blood analysis revealed a valproic acid intoxication with levels of 12 430 μmol/L (normal, 350-700 μmol/L) with concomitant severe hyperammonemia of 500 μmol/L (normal, <30 μmol/L), and treatment was initiated including the administration of L-carnitine and a continuous venovenous hemodiafiltration. Brain edema as the cause of absent brain stem reflexes was ruled out twice by computed tomography. After normalization of the serum levels, the patient had a full clinical recovery.

A 19-year-old man presented to the emergency department with severe confusion. He had a history of well-controlled epilepsy, which was treated with 1 g of valproic acid once daily. On clinical evaluation, the patient was febrile (38.3°C) with stable vital signs (heart rate, 125 beats per minute; blood pressure 148/87 mm Hg). He was sitting on his knees, whipping forward and backward. There were no signs for a convulsive status epilepticus. After he had received 2 mg of lorazepam intravenously because of severe agitation, he became unconscious, started vomiting, and required oral intubation. A computed tomography (CT) scan of the head was performed and showed no abnormalities. A CT scan of the chest revealed severe aspiration. Analysis of the cerebrospinal fluid revealed elevated lactate levels of 5.0 mmol/L (normal, <2.2 mmol/L) and glucose levels 7.5 mmol/L (normal, <4.2 mmol/L) but no cells. Laboratory examination of the blood was completely normal, whereas the valproic acid level on admission was pending.

The patient was transferred to the intensive care unit. During the following hours, he developed lactic acidosis (lactate maximal, 11.3 mmol/L) and diabetes insipidus (maximum diuresis, 900 mL/h; sodium maximum, 162 mmol/L). Consecutively, the pupils became unresponsive to light and clinical evaluation revealed absence of all brain stem reflexes. The CT scan of the head was repeated and a cerebral edema was ruled out (Fig. 1). Meanwhile, analysis of valproic acid levels was completed and revealed a value of 12430 μmol/L (therapeutic range, 350-700μmol/L). After the diagnosis of valproic acid intoxication, ammonia levels were consecutively taken and a concomitant hyperammonemia of 500μmol/L was confirmed (normal, <30 μmol/L).

We started a continuous venovenous hemodiafiltration and L-carnitine was administered. The serum levels of valproic acid and ammonia decreased rapidly (Fig. 2). Within hours, brain stem reflexes returned. The patient required sedation for 12 days due to prolonged weaning from the ventilator. After sedation was stopped, the patient awoke. Apart from a panzytopenia associated with the valproic acid overdose, his subsequent hospitalization was uneventful. He was discharged from hospital after 22 days without any complications.
neurologic sequelae. On repetitive interview he admitted that he had taken an overdose of valproic acid the night before self-admission to the hospital.

We report a patient showing clinical signs of brain death after severe valproic acid poisoning, which fully recovered after normalization of valproic acid levels. This case is interesting for 2 reasons. First, the frequency of valproic acid poisoning is likely to rise in the future because the drug is increasingly used for seizures control [1], migraine prophylaxis [2], as a mood stabilizer in bipolar disorders, and as a treatment option in chronic neuropathic pain [3]. Second, this report is the first that describes a reversible deep coma with complete loss of brain stem reflexes in the setting of acute, severe valproic acid overdose.

Coma due to valproic acid overdose is mostly attributed to the development of severe hyperammonemia and consecutive brain edema [4]. Interestingly, there was no radiologic evidence for cerebral edema in our patient. We hypothesize that the imitation of brain death must have been due to a direct toxic effect of valproic acid.

Valproic acid increases regional neuronal concentration of $\gamma$-aminobutyric acid (GABA) by inhibiting its metabolism and increasing its synthesis. After activation, the GABA receptor causes influx of chloride ions, which hyperpolarizes the cell and renders it resistant to further depolarization. Increases in GABAergic activity produce a generalized depression of the central nervous system [5].

There is a range of sedative and anesthetic agents that can mimic brain death. Nevertheless, pupillary responses to light usually remain intact [6]. Pharmacologic conditions that completely abolish all brain stem functions are rare and include tricyclic antidepressants and barbiturates poisoning [7,8]. However, no association with valproic acid overdose has been described so far, which makes this case exceptional.

Katja Auinger MD  
Véronique Müller MD  
Alain Rudiger MD  
Marco Maggiorini MD  
Medical Intensive Care Unit  
University Hospital Zurich  
Raemistrasse 100, CH 8091 Zurich, Switzerland  
E-mail address: veronique.mueller@usz.ch  
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