

ACUTE PANCREATITIS ASSOCIATED TO THE USE OF VALPROIC ACID

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The first case of pancreatitis associated to the use of valproic acid was reported by Batalden et al in 1979¹. In Latin America, the first case of acute pancreatitis due to the use of valproic acid was reported in Brazil in 1986². The incidence of pancreatitis following the use of drugs varies between 2–15% among the general population³⁻⁵. In medical literature, by 2005, 80 cases of acute pancreatitis caused by valproic acid were reported, 33 of which were patients under the age of 18⁶. Acute pancreatitis due to valproic acid may be an idiosyncratic complication unrelated to the patient's age, the duration of the treatment and the dose of the drug⁷⁻⁹. The idiosyncratic complications associated to valproic acid may be hematological, the most common one being thrombocytopenia and hepatic complications that may lead to fulminating hepatitis and acute pancreatitis, which may become a type of hemorrhagic necrosis¹⁰⁻¹². One of the possible causes that trigger pancreatitis is the direct toxic effect produced by free radicals on the pancreas⁸. It has also been suggested that the reduction of carnitine brought about by the use of valproic acid has an important role in the damage caused to the pancreas¹³.

The diagnosis of pancreatitis is made by means of the clinical signs and symptoms, among which stand out abdominal pain localized in the epigastrium, nausea that may be attended by vomiting, abdominal distension, fever and malaise¹⁴. The determination of blood amylase and lipase levels is fundamental, as their increase helps to orient us and may confirm the clinical suspicion. Amylase levels may increase in some patients receiving valproic acid without turning into pancreatitis¹⁵. In a patient receiving valproic acid, a diagnosis of pancreatitis must be established with increased levels of pancreatic enzymes together with the presence of clinical symptoms. The increase of lipase, which is secreted only by the pancreas, is a more specific indication of pancreatic damage. Amylase may be produced by other tissues, such as the salivary glands¹⁶. The withdrawal of the drug in a child sus-

pected of having pancreatitis who is being administered valproic acid is mandatory; and once it is confirmed, the drug may not be administered again due to the high incidence of relapse leading to death¹⁷.

We alert pediatricians and neuropediatricians to consider pancreatitis when a child receiving treatment with valproic acid shows gastrointestinal symptoms, as it is a complication that may be difficult to diagnosis.

CASE

A 7-year old girl with a generalized epilepsy (*absence seizure*), being treated with valproic acid with a dose of 15 mg/kg/day, administered in two doses every twelve hours, since one year. She was brought to consult because she had abdominal pain localized in the epigastrium, medium intensity, which was not alleviated by the administration of common antispasmodic type analgesics; concomitantly she had a 38.5°C fever, for which she was hospitalized.

She was the term product of a fifth pregnancy mother resulting from a non-consanguineous relationship. The delivery was normal. Her Apgar scores were 7 at 1 minute, 9 at 5 and 10 minutes. Birth weight: 2.100 Kg (<10th percentile). Height at birth: 45 cm (< 10th percentile).

There was not family history of epilepsy, migraine or neurological disease.

On physical examination – Weight: 29Kg (90th percentile). Height: 150 cm (>97th percentile). Head circumference: 52 cm (>50th percentile).

Regular general condition, feverish, hydrated. No dysmorphic features or cutaneous blemishes were observed.

There were no cranial nerve palsies and pupils reacting equally. Deep tendon reflexes were normal. Respiratory and cardiovascular systems were normal.

The abdomen was soft and depressible, with pain upon deep palpation at the epigastrium. No masses or hepatosplenomegaly was palpable and bowel sounds were present. The remainder of the examination was normal.

PANCREATITE AGUDA ASSOCIADA AO USO DE ÁCIDO VALPROICO

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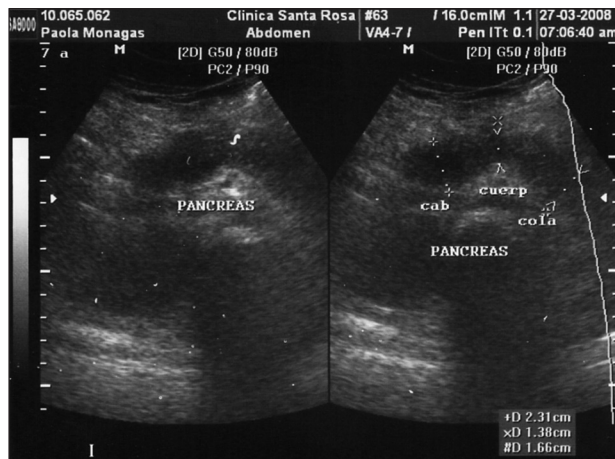


Figure. An ultrasound of pancreas in a plane transverse to a frequency of 3.5 MHz showed an enlarged pancreas with a normal morphology and measures for increased patient age.

Laboratory tests showed the following results: Hemoglobin: 13.1 g/dL; Hematocrit: 41.2%; platelets: 225,000 mm³; Leucocytes: 10,700 mm³, 65% neutrophils and 35% lymphocytes. Glucose: 109 mg/dL. Liver and kidney function tests were normal.

Valproic acid levels: 70 µg/ml (therapeutic range: 50–100 µg/ml).

The concentration of serum electrolytes was: Sodium: 148 mEq/L, Potassium: 3.58 mEq/L.

The determination of pancreatic enzymes revealed that serum amylase had increased to 400 U/L (Normal values: 20–112 U/L).

Abdominal ultrasonography revealed a morphologically normal pancreas; with considerably enlarged. There were no peripancreatic fluid collections and no biliary dilatation. The head measured 2.31 cm, the body 1.38 cm and the tail 1.66 cm, pancreatic duct with diameter 2.2 mm (Figure).

Normal pancreas size as a function of age (Ultrasound) 5 to 10 years are head in cm (1.6 ± 0.4), body (1 ± 0.3), tail (1.8 ± 0.4) on transverse scan. The normal pancreatic duct is less than 2 mm in diameter.

An EEG interictal revealed generalized spike and wave activity intermittent with a frequency of 3 Hz, bilateral and synchronous, during hyperventilation, with two seconds of duration.

An abdominal computed axial tomography (CAT) did not show cystic or tumor lesions and confirmed enlargement of the pancreas that was reported by ultrasound.

The result of an amylase determination performed 72 hours after the suspension of valproic acid was 131 U/L, and it became normal on the sixth day after the anti-epileptic drug had been suspended. The patient became asymptomatic.

Anti-epileptic therapy with lamotrigine was begun at a dose of 3 mg/kg/day, administered in two doses every 12 hours, and was tolerated satisfactorily.

The patient family gave informed consent for the publication of the case.

DISCUSSION

Valproic acid is the most widely used anti-epileptic drug in children, and it is probably the most frequent cause of drug-induced acute pancreatitis. The mechanism whereby valproic acid induces pancreatitis is unknown. Valproic acid is metabolized in the liver in the pathways of microsomal glucuronidation, mitochondrial oxidation, and by cytochrome P 450 that depend on omega oxidation, the result being at least five metabolites. Two important metabolites are: 2-valproic acid, which is the active pharmacological metabolite, and 4-valproic acid, which may be involved in toxicity¹⁸.

Several researchers have proposed that valproic acid causes a reduction of superoxide dismutase, catalase, and glutathione peroxidase, which are in charge of removing free radicals. The increase of free radicals can lead to an increase of endothelial permeability and lipid peroxidation, leading to tissue damage which in turn causes hepatotoxicity and pancreatitis¹⁹.

Abdominal pain is the most frequent symptom of acute pancreatitis, and it occurs in more than 80% of patients localized in the epigastrium, as happened with our patient. It can also be accompanied by nausea and vomiting in 70%, abdominal distension in 30%, and fever in 26% of the cases described¹⁵.

There are no reliable and sensible clinical criteria to objectively assess the gravity and the prognosis in children²⁰. The determination of the levels of lipase and the pancreatic isoenzyme amylase is essential to corroborate clinical diagnosis^{15,21}. Lipase is an enzyme that is only secreted by the pancreas, and its increase is a specific indicator of pancreatic damage¹⁶. Amylase is not an enzyme exclusive to the pancreas; other glands, such as the salivary glands, secrete it as well and may be responsible for its increase. Therefore, the determination of pancreatic and salivary amylase isoenzymes can be useful to confirm a diagnosis of pancreatitis. We did not perform the determination of either lipase or pancreatic amylase isoenzyme; nevertheless, the clinical picture, the increase of amylase to 400 U/L and echography studies, allowed us to reach a diagnosis.

Abdominal ultrasonography imaging showed the pancreas to be considerably enlarged, as has been reported by other authors²⁰.

An ultrasound is useful at the preliminary evaluation of patients suspected of having acute pancreatitis, and it must be done within the first 24 to 48 hours from the onset of the clinical symptoms. Thus, ultrasonography of the pancreatic duct is valuable in diagnosis and monitoring of pancreatitis in children²².

An abdominal CAT must be performed on every patient with serious acute pancreatitis, as it plays a very important role in the diagnosis to assess the extent of the

inflammatory process, the presence of macroscopic necrosis and the existence of pseudocysts or tumors, which were not detected in our patient.

The withdrawal of valproic acid permitted the normalization of the amylase levels and the disappearance of the clinical symptomatology, which occurred during the first week, as has been published by other authors¹⁵.

The use of valproic acid must be avoided in patients who have had acute pancreatitis associated to the use of valproic acid, due to its high relapse rate and complications¹⁷.

In conclusion, acute pancreatitis must always be considered when a child is under treatment with valproic acid. Finding pancreatic amylase and lipase isoenzymes would confirm the clinical suspicion. The suspension of the administration of valproic acid in patients who have acute pancreatitis is mandatory, and use of the acid must not be resumed once the patient has recovered.

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