CLINICAL CASE REPORT

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Valproic Acid–Induced Pancreatitis in a 15-Year-Old Boy With Juvenile Myoclonic Epilepsy

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Key Words: *valproic acid; acute pancreatitis; epilepsy.*

Summary. *Drug-induced acute pancreatitis is a rare condition in childhood, and information about the incidence of valproic acid–induced acute pancreatitis in the pediatric population is scarce. In this clinical case, we report a first documented pediatric case of valproic acid–induced pancreatitis in Estonia. A 15-year-old boy with juvenile myoclonic epilepsy developed acute pancreatitis after 2-month therapy with valproic acid. The symptoms of pancreatitis subsided within 1 week after the discontinuation of treatment with valproic acid. Acute pancreatitis should be suspected in any pediatric patient with gastrointestinal symptoms during valproate treatment.*

Introduction

Seizure disorder is a neurological condition with a high incidence in childhood, and valproic acid (VPA) is a widely used antiepileptic drug in the world as well as in Estonia. The side effects of this commonly well-tolerated anticonvulsant are usually benign and transient: nausea, vomiting, weight gain, dyspepsia, tremor, hair loss, etc. More serious adverse effects such as hepatotoxicity, hyperammonemic encephalopathy, coagulation disorder, and pancreatitis may occur. There are insufficient data about the incidence of these severe side effects (1). Only case reports, small series, and one review of 33 pediatric cases of VPA-induced acute pancreatitis (AP) in children are available in the literature (2, 3).

We report a case of valproate-induced pancreatitis in a 15-year-old boy with juvenile myoclonic epilepsy. This is a first documented case of VPA-induced pancreatitis in childhood in Estonia.

Case Report

The 15-year-old boy with the complaints of acute abdominal pain localized in the epigastrium was admitted to the Children's Clinic, Tartu University Hospital. Dull continuous pain radiating to the back lasted for 6 days.

Two months earlier, juvenile myoclonic epilepsy was diagnosed. The patient had complaints of jerks of the arms usually in the morning, soon after awakening. An interictal electroencephalography (EEG) awake was normal for age; there was no photosensitivity. Ictal video-EEG revealed generalized spike-slow wave paroxysms, and clinically myoclonic jerks of the arms were observed. Magnetic resonance imaging (MRI) of the brain showed no structural abnormalities. Antiepileptic treatment with VPA at a dosage of 23 mg/kg per day was tolerated well, and the patient was constantly seizure free.

On admission, the patient's condition was satisfactory; vital signs were within reference ranges. A physical examination revealed mild epigastric tenderness, normal bowel sounds, no hepatosplenomegaly, or abnormal masses felt.

There was no history of abdominal trauma and infection. The patient did not use any other regular medications except VPA.

The results of laboratory tests on admission (6 days after the onset of symptoms) were within the references ranges except for the elevated amylase and C-reactive protein levels and an increased erythrocyte sedimentation rate. The serum amylase level was 1114 U/L (reference range, 28–100 U/L); urine amylase level, 5154 U/L (reference range, 16–491 U/L); C-reactive protein, 39 mg/L (reference range, <5 mg/L); and erythrocyte sedimentation rate, 26 mm/h (reference range, <10 mm/h). The serum lipase level was not measured.

Abdominal ultrasonography revealed an enlarged hyperechogenic pancreas and a slightly dilated main pancreatic duct with a diameter of 3 mm (reference range, <2 mm).

No other known causes (infection, trauma, gallstones, etc.) of pancreatitis were documented except for the use of VPA during the last 2 months. The serum level of VPA 1 month before hospital admission was 114.4 μg/mL (therapeutic range, 50–100 μg/mL).

VPA-induced pancreatitis was suspected, and treatment with VPA was discontinued immediately. Treatment included "nothing by mouth," intravenous fluids during the admission (3 days), and antibiotic therapy with cefuroxime (7 days). Antiepileptic drug treatment was continued with topiramate.

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Two days after the discontinuation of treatment with VPA, the abdominal complaints gradually resolved, and the serum amylase level decreased to 137 U/L.

The patient remained asymptomatic during the 6-month follow-up, and the serum amylase level was in the reference range (53 U/L).

At the follow-up visit 3 years after AP, the patient receiving treatment with topiramate was seizure free; he had no gastrointestinal complaints, and the serum amylase level remained within the reference range (60 U/L).

Discussion

AP is a rare condition in childhood, and data on the incidence of AP in the pediatric population are scarce. Two latest studies have examined the incidence of AP in children: one study from the United States reported the incidence of 13.2 per 100 000 (4), and in the other from Australia, the incidence was only 3.6 per 100 000 (5). Current studies report that the incidence of AP in children has increased during the last 10 to 15 years (4–6). In our country, there are no published and known data about the incidence of childhood pancreatitis.

The diagnosis of AP is based on at least 2 of the following criteria: 1) clinical presentation showing abdominal pain or tenderness with or without distension, vomiting, diarrhea, fever, and lethargy; 2) laboratory findings showing serum and urine amylase levels elevated at least 3 times than normal or lipase upper limits; and 3) radiographic findings showing pancreatic edema and/or inflammation on abdominal ultrasonography and/or abdominal computed tomography.

Our patient met all the criteria: acute abdominal pain localized in the epigastrium radiating to the back, the amylase level in serum and urine was 10 times greater than the reference value, and an enlarged hyperechogenic pancreas on abdominal ultrasonography. It has been reported that the serum lipase level is more sensitive in diagnosing pancreatic damage than the serum amylase level (7). The amylase level may be increased in 13% of patients receiving VPA without pancreatitis (8). In our case, the serum lipase level was not measured.

The common causes of AP in childhood are abdominal trauma, viral infections, drugs, gallstones, hypercalcemia, and hyperlipidemia (9, 10). Drug-induced pancreatitis accounts for approximately 25% of AP cases in childhood (10). The most common medications are VPA (13%), prednisone (12%), and mesalamine (9%) (10).

Since the first report of VPA-associated pancreatitis by Batalden et al. in 1979 (11), several reports, usually single case studies of VPA-induced AP, have been published. In 2003, Grauso-Eby et al. published a review of 33 pediatric cases of pancreatitis due to VPA (3). Some authors suggest that the occurrence of this severe side effect due to VPA has been underestimated (2).

Pancreatitis occurs mostly during the first year with almost half of the cases being diagnosed within the first 3 months of VPA therapy, but pancreatitis can develop after years of antiepileptic treatment (12, 13). In our patient, AP occurred 2 months after the initiation of treatment with VPA, and there was no other causes of AP.

Sinclair et al. in 2004 showed that the dose, the serum VPA level, duration of treatment, generic preparation, and the use of polytherapy did not appear to be a risk factors for pancreatitis (14). Children with drug sensitivity might be at risk (12, 14). Our patient had no history of drug allergy.

The mechanism of VPA-induced pancreatitis is idiosyncratic. In 1984, it was considered that the depletion of free radical scavengers such as superoxide dismutase, catalase, and glutathione peroxidase occurs in patients receiving VPA. The excess of free radicals could result in endothelial permeability and lipid peroxidation, ultimately leading to tissue damage (15–17). Another proposed theory for VPA-induced pancreatitis involves the effect of VPA on mitochondrial β-oxidation (18, 19).

When VPA-induced AP is considered, treatment with VPA should be discontinued immediately. The time of resolution of symptoms is usually several weeks (14). Our patient had a full clinical recovery after 1 week following the discontinuation of the treatment with VPA. The reintroduction of VPA must be avoided in patients who have had VPA-associated pancreatitis due to a high risk of relapses (2, 14). The prognosis of VPA-associated AP depends on an early diagnosis and prompt discontinuation of the medication.

Conclusions

Acute pancreatitis is a severe adverse effect of treatment with valproic acid in children with epilepsy. The drug-induced pancreatitis in childhood can be underdiagnosed. Despite of the common side effects of valproic acid including abdominal pain, nausea, and vomiting, acute pancreatitis should be suspected in any pediatric patient with gastrointestinal symptoms during valproate treatment.

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Statement of Conflict of Interest

The authors state no conflict of interest.

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