A case of chronic pancreatic insufficiency due to valproic acid in a child

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Valproic acid (VPA) is a short chain fatty acid used to treat a variety of seizure disorders (1). The most common side effect is transient alopecia (2). Hepatotoxicity, ranging from asymptomatic elevation of aminotransaminase levels to fulminating hepatitis, also occurs (3). Many cases of acute pancreatitis due to VPA have been reported (2,4-23). We report a case of chronic pancreatitis with exocrine pancreatic insufficiency that appears to have been caused by VPA.
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CASE PRESENTATION
A 14-year-old white boy born at 40 weeks’ gestation developed a generalized tonic-clonic seizure disorder at two weeks of age. He had normal growth and attainment of developmental milestones but required treatment for the seizures. He responded poorly to phenobarbital, carbamazepine and phenytoin, either alone or in combination. VPA was given for the first time before the patient was five years of age but was discontinued because it was ‘not tolerated’. There was no detailed documentation of this intolerance or of other medications used. There were no biochemical data from that time. VPA was reinstituted in 1987 at age five years. The drug was tolerated well initially at 500 mg/day (with a measured drug level of 300 µmol/L, therapeutic range of 350 to 700 µmol/L, the patient’s weight was not documented). When the drug dose was increased to 1500 mg/day (no drug level available), nausea and vomiting developed, and VPA was discontinued again. Because best control of his seizures had been obtained with VPA, it was reinstituted as monotherapy in 1991 when the patient was nine years of age, and he was maintained on 1000 mg/day (27 mg/kg) without incident. The patient had demonstrated a learning disability in school, particularly in his reading skills, but was able to communicate clearly verbally. In April 1994 (at 11 years of age) he presented with complaints of gradual onset left upper quadrant pain with nausea and vomiting. He was diagnosed with viral gastroenteritis at his local emergency department. Because these symptoms persisted over several months, an abdominal ultrasound was done in August 1994, revealing an enlarged pancreas. Serum amylase or lipase levels from that time were not documented, but acute pancreatitis was diagnosed based on these radiological findings. No therapeutic intervention was undertaken, and he remained on VPA. By October 1994, the abdominal pain had resolved, but he described loose, foul-smelling stools with ‘oil in water’ suggestive of steatorrhea, having four to five such bowel movements daily. Over January and February 1995, he lost 7 kg. He was referred to the authors’ centre in March 1995; he was admitted for investigation and was tapered off the VPA. He had no history of significant abdominal trauma and no respiratory symptoms. There was no family history of pancreatitis, celiac disease or cystic fibrosis.

On admission, he weighed 37.2 kg. Physical examination was normal. The complete blood count, peripheral smear, serum B12, folic acid, amylase, total serum protein and albumin, calcium, aspartate aminotransferase, alanine aminotransferase and erythrocyte sedimentation rate were normal. Serum lipase level was not measured. Seventy-two hour fecal fat testing was markedly abnormal at 47 g/day (normal less than 5.5 g/day). The serum trypsinogen level was low at 13.1 ng/mL (normal less than 5.5 g/day). Any reduction in enzyme replacement therapy has repeatedly demonstrated steatorrhea when the patient has been off enzyme replacement (31.8 g/day to 33.5 g/day), with complete correction when on enzyme therapy (4.5 g/day). Any reduction in enzyme replacement therapy has led to loose bowel movements, typical of steatorrhea. His blood glucose level has remained within the normal range. He has never developed any respiratory symptoms.

DISCUSSION
Pancreatitis can be difficult to diagnose. In its acute form, the physician must rely on clinical suspicion with supportive biochemical and radiological evidence. It is with hindsight that we believe that this patient demonstrated acute pancreatitis in April 1994. His clinical condition was congruous with such a diagnosis (24), as was his abdominal ultrasound, although neither finding was specific. These ultrasound findings, however, are frequently found in children with acute pancreatitis (13,25). This patient’s evolution to chronic pancreatitis with pancreatic insufficiency is easier to document. He clearly had clinical steatorrhea corrected by pancreatic enzyme replacement with an atrophic gland documented radiologically by several modalities. Furthermore, the patient’s serum trypsinogen level was low, which is a relatively specific indicator of loss of exocrine pancreatic function (26-28).

Chronic pancreatitis in children is most often due to cystic fibrosis; however, up to 30% of cases may be due to drugs (2). The present patient underwent repeated tests for cystic fibrosis, and results of clinical, biochemical and genetic analyses were negative. Although the number of mutations associated with cystic fibrosis is in the hundreds, in the white population, the 10 most common mutations measured account for almost 80% of cases (The Hospital for Sick Children, Molecular Genetics Laboratory, Toronto, Ontario; personal communication). The negative result in this situation supported the other findings. He had normal calcium and lipid levels. There was no family history of chronic pancreatitis to suggest a hereditary condition. His nutritional status was adequate (demonstrated by a normal growth curve [not shown]) until the onset of symptoms. There was no evidence of biliary tract stone disease or biliary tract...
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There is only one previously reported case of chronic pancreatic insufficiency associated with VPA therapy – a 25-year-old man on combination therapy of VPA and carbamazepine for seizures related to cranial trauma (31). After 10 years of therapy, he developed abdominal pain with nausea and vomiting on a monthly basis over two to three years. He was well between episodes of pain. There was no interruption of his therapy. He then developed pancreatic calcification with pancreatic insufficiency documented by abnormal pancreaticuell test results, amino acid consumption and glucose tolerance tests.

Recent models of pancreatitis have focused on the role of oxidative stress as an etiological mechanism (17,18,32-34). It is thought that a decrease in protective antioxidants or an increase in free radicals may initiate a diversion of pancreatic enzyme activity into the pancreatic parenchyma by disruption of acinar cell exocytosis. Persistent oxidative stress may allow this process to continue until the organ is ‘burnt out’ and the patient has passed into a phase of chronic disease, with either overt or subclinical pancreatic dysfunction (32). Drugs clearly can be a source of such oxidative stress. VPA specifically has been shown to reduce free radical scavenger enzyme activity. This has been postulated as the mechanism for inducing the well described acute pancreatitis or hepatotoxicity reactions (35). Our patient was taking VPA before and throughout his probable acute pancreatitis. Because he continued to take the drug, the oxidative stress was not relieved and his clinical condition progressed to chronic pancreatitis, following the pathophysiological model proposed by Braganza (32).

Without another etiological factor identified, we believe that VPA caused this patient’s pancreatic disease, having caused acute pancreatitis, which, when continued in the face of an unrecognized association with pancreatic disease, progressed to chronic pancreatitis with exocrine pancreatic insufficiency.

REFERENCES

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