Pancreatitis Induced by Valproic Acid: Report of a Case

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Abstract A 22-year-old woman with intellectual impairment, who had been taking valproic acid continuously for 19 years since being diagnosed with epilepsy at the age of 3 years, presented to our hospital following the sudden development of epigastric pain. An abdominal computed tomography scan revealed acute exacerbation of chronic pancreatitis. Conservative treatment was initiated, despite which the pancreatitis became exacerbated, necessitating resection of the pancreatic head and duodenum. Histological examination of the resected specimens revealed a large number of pancreatic calculi in the main pancreatic duct, suggesting chronic pancreatitis with fibrosis at the periphery. The incidence of pancreatitis developing in association with valproic acid is unclear; however, only 40 such cases have been reported in the English literature. Most of the patients previously described presented with acute pancreatitis in the initial stage. However, the clinical course of our patient, with acute exacerbation following a relatively chronic course, was different from those previously described, suggesting the presence of chronic pancreatitis related to valproic acid.

Key words Pancreatitis · Valproic acid

Introduction

Drug-induced disorders may be observed in any organ or tissue. While the pancreas is no exception, because it does not contribute to drug metabolism or excretion it tends to be less often targeted as compared to the liver and kidneys. We report herein the case of a patient in whom the administration of valproic acid caused acute exacerbation of chronic pancreatitis, for which surgical treatment was required. We also review the literature on this unusual complication.

Case Report

The patient was a 22-year-old woman with intellectual impairment who had been diagnosed as having epilepsy at the age of 3 years 7 months. Since then, various anticonvulsives had been administered and there had been no signs of pancreatitis, although her mother stated that the patient had developed a dislike of meat and oily food around the age of 17 years, since when her diet had mainly consisted of vegetables.

In February 1998, she was admitted to our hospital after the sudden development of epigastric pain, vomiting, and anorexia. There was no history of alcohol-consumption or abdominal trauma, or any evidence of gallstones, hypercholesterolemia, or hyperparathyroidism. Prior to admission, her medications had consisted of 450 mg/day of zonisamide, 300 mg/day of phenytoin, 300 mg/day of carbamazepine, and 25 mg/kg/day of valproic acid. In particular, the valproic acid had been continuously taken for 19 years since the time of diagnosis when she was 3 years 7 months of age. Physically, palpation revealed a hard tumor in the right upper abdomen, over which marked pressure pain was noted. Biochemical blood examination revealed elevated serum and urinary amylase levels of 1209 IU/l and 2909 IU/l, respectively. The C-reactive protein (CRP) level was 12.9 mg/dl, suggesting an inflammatory reaction. The blood valproic acid level was 26.36 mg/ml. An abdominal computed tomography (CT) scan revealed calcification in the main pancreatic duct at the pancreatic head, peripheral pancreatic duct dilatation, and pancreatic swelling, suggesting acute exacerbation of chronic pancreatitis. The patient was fasted and gabexate mesilate was administered. Furthermore, con-
Considering the involvement of valproic acid, convulsion was controlled by discontinuing this agent and by increasing the doses of the other agents.

As the blood levels became normalized by 4 days after admission, oral ingestion was started and the patient was discharged 22 days after admission. However, the day after discharge, signs of recurrent pancreatitis became evident and she was readmitted. Abdominal CT on readmission showed an inflammatory tumor and calcification located in the main pancreatic duct at the pancreatic head. The pancreatic body was diffusely swollen and the main pancreatic duct distal to the site of calcification was dilated (Fig. 1). Blood examination revealed an increased total bilirubin level of 3.1 mg/dl and an elevated amylase level. Endoscopic retrograde cholangiopancreatography (ERCP) revealed stenosis of the lower common bile duct related to compression of the tumor at the pancreatic head. The main pancreatic duct could not be visualized due to calcification at the pancreatic head (Fig. 2).

Considering the limits of conservative treatment, the patient was fasted to allow remission of inflammation; then, in May 1998, pancreatic head and duodenal resection was performed, with preservation of the entire stomach and pyloric ring. Histologically, the resected specimens showed a large volume of pancreatic calculi in the main pancreatic duct of the pancreatic head with remarkable fibrosis around the main pancreatic duct. The pancreatic endocrine cells and acinic cells were well preserved, so no primary damage of their cells was seen. The alcoholic hyaline body was not detected. Fibrosis around the main pancreatic duct extended to the perilobar acinic space. These findings suggested that the main cause of the pancreatitis was flow disturbance of pancreatic juice due to calculi in the main pancreatic duct (Figs. 3 and 4).

The patient had an uneventful postoperative course without any complications, and was discharged 60 days after surgery. To date, convulsion control with other agents has been maintained without administering valproic acid during the 2-year postoperative follow-up. There has been no recurrence of pancreatitis. Her diet is...