Is Biliary Microlithiasis a Significant Cause of Idiopathic Recurrent Acute Pancreatitis? A Long-term Follow-up Study

PRAMOD KUMAR GARG, RAKESH KUMAR TANDON, and KAUSHAL MADAN

Department of Gastroenterology, All India Institute of Medical Sciences, New Delhi, India

Background & Aims: **The cause of recurrent acute pancreatitis (RAP) is not known in 10%–30% of patients. The aim of the present study was to determine the cause of idiopathic RAP in a long-term follow-up study.** ***Methods:*** **All consecutive patients with idiopathic RAP underwent detailed evaluations and investigations to find out the cause. The pancreatitis was considered to be idiopathic when no cause could be found after standard investigations that included serum biochemistry, transabdominal ultrasonography, and computerized tomography scan of the abdomen. The detailed work-up included repeat serum biochemistry and transabdominal ultrasonography, an endoscopic retrograde cholangiopancreatography, duodenal bile microscopy to diagnose biliary microlithiasis, and endoscopic ultrasonography.** ***Results:*** **Seventy-five patients were studied from June 1995 to May 2003. Their mean age was 31.9 years and 80% were male. The mean number of attacks of acute pancreatitis was 4.82 (range, 2–10). The cause of RAP was attributed to biliary microlithiasis in only 10 (13%) of 75 patients. Two additional patients developed gallstones during the follow-up period. Thirty-five (47%) patients developed chronic pancreatitis during the follow-up period. Ten of these 35 patients with chronic pancreatitis had biliary microlithiasis; 8 of these 10 patients had undergone cholecystectomy/endoscopic sphincterotomy yet continued to have recurrent pancreatitis and developed chronic pancreatitis. Miscellaneous causes were found in 10 (13%) patients. No cause was found in the remaining 18 (24%) patients.** ***Conclusions:*** **Microlithiasis was not a significant cause of idiopathic RAP in our patients. About one half of the patients with RAP developed chronic pancreatitis during the follow-up period.**

Acute pancreatitis (AP) is associated with considerable morbidity and mortality. The cause of AP is evident in 70%–90% of patients and the most common causes of AP are gallstones and alcohol.[1–3] However, 10%–30% of patients are labeled as having idiopathic pancreatitis after the initial evaluation and diagnostic work-up.[1–4] Patients with 2 or more attacks of AP are labeled as having recurrent acute pancreatitis (RAP). Determining the cause is of particular importance in patients with idiopathic recurrent acute pancreatitis (IRAP) to prevent further attacks by specific treatment of the cause. Extensive evaluation of patients with IRAP may reveal causes such as biliary microlithiasis, biliopancreatic ductal abnormalities, sphincter of Oddi dysfunction (SOD), occult tumors, and early chronic pancreatitis (CP).[5–8] Of these, the most common cause is said to be occult biliary microlithiasis in up to 73% of patients with IRAP.[9,10] The relative significance of the various causes, however, has varied considerably across different studies and there have been contradictory reports about the role of each of these causes in IRAP. For example, a few studies have not shown microlithiasis as a significant cause of IRAP whereas others have not shown SOD to be an important cause of IRAP.[11–13] One important limitation of most of the previous studies has been the lack of long-term follow-up evaluation and the patients were evaluated at a single point of time. Many patients with CP do not show evidence of CP initially and may present with recurrent pancreatitis.[5,14] These patients may masquerade as having IRAP until they develop overt features of CP, underscoring the importance of long-term follow-up evaluation.

The objective of the present prospective study was to determine the cause of idiopathic recurrent acute pancreatitis with timed re-evaluations over a long follow-up period.

Methods

All patients presenting with a history of acute pancreatitis from June 1995 to May 2003 were included in the study. These patients were either attending the pancreas clinic or were admitted to the gastroenterology ward of the All India Institute of Medical Sciences in New Delhi. The diagnosis of acute pancreatitis was made in the presence of suggestive clinical features, increased serum amylase and/or lipase (>2 times the upper limit of normal) levels, and evidence of pancreatitis on ultrasonography (USG) and/or computerized tomography (CT) of the abdomen. Pancreatitis was considered to be idiopathic when no definite cause for it could be detected, such as gallstones, alcoholism, hyperlipidemia, hypercalcemia, drugs known to cause acute pancreatitis, and viral infection after clinical evaluation and appropriate investigations. Acute pancreatitis was considered to be a result of alcohol if the patient was consuming more than 40 g of alcohol per day for more than 5 years.

Patients with IRAP with at least 2 or more attacks of AP formed the study group and were subjected to a detailed work-up to determine the cause of IRAP. The work-up for the cause was directed to find out the presence of biliary microli-

Abbreviations used in this paper: AP, acute pancreatitis; CBD, common bile duct; CP, chronic pancreatitis; CT, computerized tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; IRAP, idiopathic recurrent acute pancreatitis; RAP, recurrent acute pancreatitis; SOD, sphincter of Oddi; USG, ultrasonography.

1542-3565/07/$32.00
doi:10.1016/j.cgh.2006.06.023

thiasis, common bile duct (CBD) stones, SOD, biliopancreatic ductal abnormalities, occult tumor, and early CP.

All the study patients underwent detailed clinical evaluation and investigations. The investigations for idiopathic pancreatitis were divided into phase 1 and phase 2 tests (Table 1). Phase 1 tests included serum biochemistry (sugar, urea, creatinine, sodium, potassium, bilirubin, alkaline phosphatase, aspartate and alanine aminotransferases, amylase, calcium, cholesterol, and triglyceride levels), repeat transabdominal USG, and a contrast-enhanced CT scan of the abdomen. Tests of calcium and triglyceride levels were repeated in the quiescent stage and during an attack of acute pancreatitis to rule out hypercalcemia and hypertriglyceridemia as the cause of idiopathic pancreatitis. Phase 1 tests were performed at the initial evaluation.

Real-time transabdominal USG was performed in a fasting state using a 3.5-MHz curved probe in the supine and left lateral decubitus positions. The gallbladder, CBD, and pancreas were imaged with special attention. The diagnosis of gallstones was made if there were movable intraluminal echogenic foci casting acoustic shadows. The diagnosis of biliary sludge was made if there were low-amplitude echoes in the gallbladder without shadowing and that layered in the dependent part of the gallbladder.

In the phase 2 tests, an endoscopic retrograde cholangiopancreatography (ERCP), bile microscopy, and an endoscopic ultrasonography (EUS) were performed. Phase 2 tests were performed if the cause was not found after phase 1 tests. The phase 2 tests were performed within 3 months of inclusion in the study.

Endoscopic Retrograde Cholangiopancreatography

ERCP was performed to look for stones in the CBD, ascariasis, SOD, small tumors, biliopancreatic ductal abnormalities such as pancreas divisum and choledochal cyst, and changes suggestive of CP. The diagnosis of types 1 and 2 SOD was made according to the standard criteria.[13] The diagnosis of CP on ERCP was made according to the Cambridge classification.[15] ERCP was performed at the initial presentation or during the follow-up evaluation of the patients.

Table 1. Phase-Wise Investigations Performed to Determine the Cause of RAP

Phase 1 investigations (at initial evaluation)
Repeat serum biochemistry
Serum lipid profile
Serum calcium
Liver function tests
Transabdominal ultrasonography
CT scan of the abdomen
Phase 2 investigations (≤3 mo)
ERCP
Bile microscopy for biliary crystals
EUS
Investigations during re-evaluation in the follow-up period
Repeat serum biochemistry
Repeat transabdominal ultrasonography
Repeat CT scan

Bile Microscopy

The diagnosis of biliary microlithiasis was made if biliary crystals were found in the bile. Bile microscopy was performed to look for the presence of biliary crystals (ie, cholesterol monohydrate crystals, calcium bilirubinate granules, and calcium carbonate microspheroliths). Duodenal bile was obtained for microscopy as described previously from our center.[16] Briefly, a tube was placed in the duodenum, an amino acid solution was infused rapidly to make the gallbladder contract, and then the duodenal bile was collected. The bile thus collected was centrifuged and examined under a polarizing microscope.[16] The presence of more than 3 crystals per slide was taken as positive for biliary crystals.

Endoscopic Ultrasonography

EUS was performed using a radial scanning echoendoscope (Olympus Medical Systems Corp., Tokyo, Japan). Particular attention was paid to look for the presence of gallbladder stones including microliths (<3 mm in diameter), biliary sludge, CBD stones, small periampullary tumors, and evidence of early CP. The diagnosis of early CP was made if 3 or more of the following features were present: (1) heterogenous pancreatic echotexture, (2) hyperechoic foci, (3) multiple hypoechoic areas, (4) a honeycombing pattern, (5) a dilated pancreatic duct, (6) irregular main pancreatic duct with hyperechoic walls, and (7) intraductal echoes suggestive of calculi or protein plugs.[17] EUS was performed in patients who were included in the later part of study from July 2000 to May 2003.

Re-Evaluation During the Follow-Up Period

All the patients were followed-up regularly, usually at 3- to 6-month intervals or earlier if they had recurrence of pain. Patients were re-evaluated at 6-month intervals with repeat serum biochemistry and USG. A CT scan was repeated at an interval of 1–2 years if the initial CT scan was normal and the patient continued to have recurrent attacks of pancreatitis.

Statistical Analysis

Kaplan–Meier analysis was performed to depict the time from the onset of disease to the development of CP for the patients with RAP. Cox proportional regression analysis was performed to find out the significance of different variables that could influence the development of CP among patients with RAP. The variables included were age at onset, sex, number of attacks of pancreatitis, cause, presence of diabetes, and family history of diabetes.

All the patients were included in the study after providing an informed written consent. The study was performed in accordance with the humane and ethical principles of research set forth in the Helsinki guidelines.

Results

There were a total of 75 patients with IRAP who were included in the present study. The mean age of these patients was 31.9 years (range, 14–67 y); 60 (80%) were male and 15 were female. The mean duration of disease was 30.42 months (standard deviation, 27.52 mo) and the mean number of attacks of pancreatitis was 4.82 (range, 2–10). The attacks of pancreatitis were mild in 60 patients, although one of the attacks was severe in 15 patients. The mean follow-up period was 17.63 months