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A single-centre prospective, cohort study of the natural history of acute pancreatitis

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ABSTRACT

Background: The natural history of acute pancreatitis is based on clinical studies that aim to elucidate the course of disease on the basis of predicted risk factors.
Aims: To evaluate the long-term occurrence of recurrent acute pancreatitis and chronic pancreatitis in a cohort of patients following an initial episode of acute pancreatitis.
Methods: 196 patients were enrolled consecutively and studied prospectively. Clinical characteristics, exogenously/endogenously-associated factors, and evolution to recurrent acute pancreatitis and chronic pancreatitis were analyzed.
Results: 40 patients developed recurrent acute pancreatitis 13 of whom developed chronic pancreatitis. In a univariate analysis, recurrent acute pancreatitis was associated with an idiopathic aetiology ($p < 0.001$), pancreas divisum ($p = 0.001$), and higher usage of cigarettes and alcohol ($p < 0.001$; $p = 0.023$). Chronic pancreatitis was associated with a severe first episode of acute pancreatitis ($p = 0.048$), PD ($p = 0.03$), and cigarette smoking ($p = 0.038$). By multivariate analysis, pancreas divisum was an independent risk factor for recurrent acute pancreatitis (OR 11.5, 95% CI 1.6–83.3). A severe first-episode of acute pancreatitis increased the risk of progressing to chronic pancreatitis by nine-fold.
Conclusions: Special attention should be given to patients who experience a severe first attack of acute pancreatitis as there appears to be an increased risk of developing chronic pancreatitis over the long term.

1. Introduction

The overall incidence of pancreatitis is increasing, with alcohol abuse accounting for up to one-in-eight cases of acute, and one-in-five cases of chronic pancreatitis (CP) [1]. Acute disease has also been associated with biliary gallstones, endoscopic procedures, hypertriglyceridemia, hypercalcemia, drugs, abdominal trauma, viral infections and pancreas divisum (PD) [2–6].

Disease severity is related to the extent of pancreatic cell injury and the intensity of the inflammatory response. Present understanding of the natural history of acute pancreatitis (AP) is based on clinical studies that have elucidated the possible course of the disease based on predictive risk factors like age, alcoholic aetiology, tobacco use, recurrent acute pancreatitis (RAP) and the severity of AP [7–17].

The aim of this prospective observational study is to evaluate the long-term occurrence of RAP and CP, and the presence of associated risk factors, in a cohort of patients affected by an index episode of AP admitted to a single tertiary referral centre.

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2. Materials and methods

2.1. Patient enrollment

Our study was approved by the institutional ethics committee on June 9th, 2002. All patients admitted to our department for an initial episode of AP were enrolled consecutively between July 2002 and December 2011. Informed consent regarding study procedures and data management for scientific purposes was obtained from every patient enrolled. Patients were followed prospectively for at least 12 months after the initial diagnosis of AP, and were evaluated for the subsequent development of RAP or CP according to a standard protocol approved by the institutional review board (IRB).

Exclusion criteria were: (a) lack of informed consent; (b) prior history of pancreatic disease (including previous AP episodes) and/or findings of CP; (c) follow-up period less than 12 months; (d) non-Italian ancestry (self-reported based on >4 generations of known Italian ancestry). The latter criterion reflects our intention to study a relatively homogenous population in effort to avoid genetic confounders associated with pancreatic disease.

The diagnosis of AP was established by the presence of typical abdominal pain, serum amylase and lipase levels 3-fold greater than the upper limit of normal, and/or characteristic findings on abdominal imaging by ultrasonography (US) and/or computerized tomography (CT) [18].

The aetiology of pancreatitis at hospital admission was assessed by means of clinical history, including information on current and prior daily cigarette usage, drugs and alcohol, and findings by one or more abdominal imaging techniques (trans-abdominal and/or endoscopic sonography, CT, and/or magnetic resonance imaging with or without cholangio-pancreatography). Patients with pancreatic imaging abnormalities consistent with pre-existing CP were excluded.

A dynamic contrast-enhanced abdomen CT was performed routinely in all patients using a helical CT scanner with rapid image acquisition in order to establish the severity of AP within the first 48–72 h after the onset of illness. Severe AP was defined by the presence of organ failure and/or local complications, according to the revised Atlanta classification system [18].

2.2. Protocol for patient follow-up

Following hospital discharge, patients had an outpatient medical examination every three months for the first year, and every six months thereafter. Information on recurrent pancreatitis pain episodes as well as current and/or prior consumption of cigarettes, drugs and alcohol was gathered by clinical interview. In addition, serum pancreatic enzyme and faecal elastase levels were obtained at every visit.

All follow-up patients were routinely imaged by secretin enhanced magnetic resonance cholangiopancreatography (sMRCP); endoscopic ultrasound (EUS) and CT were used in selected cases. Typically sMRCP provides a safe, non-invasive and efficient method to evaluate pancreatic ductal morphology and kinetics, together with exocrine function [19–22].

Depending on the severity of the initial episode of AP, the following imaging procedures were scheduled during follow-up: (a) all cases: sMRCP every 12 months; (b) severe AP cases: CT at 1, 3 or 6 months depending on parenchymal and/or ductal damage sequelae and patient symptoms.

Patients with additional episodes of AP and/or evolving CP during the follow-up period were scheduled for abdominal CT in addition to the routine sMRCP during the episode and referred for genetic analysis.

2.3. Genetic analysis

Clinically relevant genetic analyses were conducted in order to assess the presence of the most common CFTR gene mutations and the SPINK-1 N34S gene mutation.

Genomic DNA was extracted and purified from whole blood using a commercial kit (Generation Capture Column Kit, Gentra Systems, Minneapolis, MN, USA). All Polymerase Chain Reaction (PCR) amplification experiments were carried out in an automated PCR thermal cycler (GeneAmp PCR system 9700, Applied Biosystems, Foster City, CA, USA). Exon 3 of the SPINK-1 gene was amplified according to Teich et al. [23].

Thirty-three of the most common CFTR mutations were analyzed by multiplex DNA test for cystic fibrosis: Cystic Fibrosis v3 Genotyping Assay (Abbott Molecular, Chicago, IL, USA) per manufacturer instructions.

2.4. Definition of RAP and CP

Patients who had at least a second AP episode over the course of the study and without clinical, laboratory or morphological findings consistent with CP, were considered to have RAP.

The diagnosis of CP was established by laboratory tests (faecal elastase < 200 μg/g) [24,25] and sMRCP findings of dilatation/irregularity of the main pancreatic duct and/or side branches, pancreatic stones, according to the Cambridge classification, and parenchymal calcifications.

2.5. Statistical analysis

Data was analyzed using SPSS (version 21.0; SPSS IBM). The Yates corrected chi square test and Fisher's exact test were used to compare frequencies, as appropriate. Quantitative variables were expressed as mean and standard deviation [mean (SD)] or as median and interquartile range (IRQ). Comparisons between quantitative variables were assessed by the Wilcoxon rank-sum (Mann–Whitney) test due to their non-normal distribution. The annual rate of RAP and CP was calculated.

Variables that were statistically-significant in the univariate analysis were included in the stepwise backward logistical regression analysis, adjusted for age and gender, to identify significant independent predictors of RAP and CP. Significance testing was set at $p < 0.05$ with two-sided tails.

The cumulative incidences of RAP and CP and the overall survival after a first attack of AP were calculated using the Kaplan–Meier method.

For the multivariate analysis, we classified patients into (a) biliary aetiology (on the basis of the presence of the following criteria: positive laboratory tests for hepatic injury and/or cholestasis, associated with gallstones and/or sludge diagnosed by imaging or, in the absence of gallstones and/or sludge, with a dilated common bile duct on ultrasound), (b) alcoholic aetiology (on the basis of a present clinical history of >5 years of ethanol consumption >50 g per day), (c) other (post endoscopic retrograde cholangiopancreatography, drugs, viral infection), (d) idiopathic aetiology (an exclusion diagnosis in which none of the above etiological factors were identified).

3. Results

3.1. Study cohort and follow up

A total of 432 patients were admitted to our unit for AP, and of these, 196 were consecutively enrolled in follow-up. Of the 236 subjects who were excluded from the study, 41 did not provide