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Prospective evaluation of the aetiological profile of acute pancreatitis in young adult patients

Adrian Culetto[a], Barbara Bournet[a], Audrey Haennig[a], Laurent Alric[b], Jean-Marie Peron[c], Louis Buscail[a,*]

[a] Department of Gastroenterology, University Hospital Centre Rangueil-Larrey, University of Toulouse, Toulouse, France
[b] Department of Internal Medicine, University Hospital Centre Purpan, University of Toulouse, Toulouse, France
[c] Department of Gastroenterology, University Hospital Centre Purpan, University of Toulouse, Toulouse, France

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ABSTRACT

Background: The aetiologies of acute pancreatitis in young adult patients are poorly known.
Aims: To prospectively evaluate the causes of acute pancreatitis in patients aged less than 35 years.
Methods: Overall, 309 consecutive patients admitted to our centre for acute pancreatitis received first-line investigations, including medical history, standard laboratory tests, abdominal ultrasound and computed tomography. If no aetiology was found, second-line investigations were performed, including endoscopic ultrasound, magnetic-resonance cholangiopancreatography and genetic testing in cases of idiopathic pancreatitis.
Results: Overall, 66 patients aged between 16 and 35 years were included. After first-line investigations, 49% of cases of acute pancreatitis remained idiopathic. Second-line investigations reduced this rate to 21%. The frequency of aetiologies for acute pancreatitis significantly differed in adults aged ≤35 compared to those aged >35 years: biliary aetiology was less frequent (23% versus 43%, $p = 0.003$) as well as alcohol-related (8% versus 24%, $p = 0.01$); drug-induced was more common (16% versus 4%, $p = 0.0007$), as well as cannabis-related (13% versus 1%, $p < 0.0001$), or genetic (10% versus 1.5%, $p = 0.003$).
Conclusions: The aetiologies of acute pancreatitis significantly differed in adults aged less than 35 years when compared to older patients. Thus, use of medications, exposure to cannabis, and genetic mutations should be actively sought in these patients.

1. Introduction

In adults, most cases of acute pancreatitis (AP) are closely linked to gallstones and chronic alcohol consumption, accounting for 70–80% of the cases. Other aetiologies (non-alcoholic, non-biliary AP) are less frequent; among these, the proportion of idiopathic AP has declined due to advances in radiological investigations and more detailed searches for autoimmune, drug-induced, or genetic causes [1–5].

The age of patients with biliary and alcoholic AP is usually between 40 and 60 years [1–4], while genetic causes are generally diagnosed at a younger age [6]. Candidate genes and genetic-linkage studies have identified mutations or polymorphisms in the following genes: cationic trypsinogen (*PRSS1*), serine protease inhibitor Kazal type 1 (*SPINK1*), chymotrypsinogen C (*CTRC*), cystic fibrosis trans-membrane conductance regulator (*CFTR*), cathepsin B, calcium-sensing receptor, proinflammatory cytokines (tumour necrosis factor, interleukin-1 and -10, monocyte chemoattractant protein 1), claudin-2, and carboxypeptidase A1 [6–11]. Among these, *PRSS1* (gain-of-function mutations), *SPINK1*, and *CFTR* (loss-of-function mutations) have been predominantly involved in a syndrome characterised by recurrent acute and late chronic pancreatitis [10,12].

It is now recognised that autoimmune pancreatitis is a heterogeneous disorder that has significant variations in its pathophysiology and extra-pancreatic manifestations. The systemic IgG4-related sclerosing syndrome, with high levels of serum IgG4, characterises type-1 autoimmune pancreatitis. The average age at first onset of type-1 autoimmune pancreatitis is 60–65 years [13]. Conversely, type-2 autoimmune pancreatitis has a lack of IgG4-positive cells and the patients are usually younger, with an average age of 40 years at the first signs (including AP). This latter form is more

* Corresponding author at: Department of Gastroenterology, University Hospital Centre Rangueil, 1 avenue Jean Poulhès, TSA 50032, 31059 Toulouse Cedex 9, France. Tel.: +33 5 61 32 30 55; fax: +33 5 61 32 22 29.
E-mail address: Buscail.L@chu-toulouse.fr (L. Buscail).

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frequent in Western countries, while type-1 autoimmune pancreatitis is more common in Asian series.

Reports from many countries underline the alarming increase of alcohol and drug consumption in young adults, especially teenagers. We and others have previously described cases of cannabis-related AP, but their frequency could be underestimated for many reasons [5,14–19]: (i) the cases of toxic-induced AP being often difficult to prove; (ii) the difficulty in monitoring cannabinoids in the body and determining its pathophysiology as a cause of AP; (iii) the illegality of cannabis use and, consequently, patients not admitting usage.

The aim of this prospective study was to investigate the aetiological profile of AP in a population of young adults.

2. Patients and methods

2.1. Inclusion criteria and study design

All patients admitted to the emergency ward at the University Hospital Centre of Toulouse, (France) between September 2012 and December 2013 for AP were prospectively included in this study. AP was defined as an evocative painful abdominal syndrome associated with a serum-lipase level of >3 N [3,5]. Patients with acute pancreatitis that had been initially managed in another centre were excluded from the study. In the present work, we defined young adult patients as being aged between 16 and 35 years. Being aged ≥16 years is the minimum age for admission into the adult clinical department, while 35 years is the upper limit for the first symptoms of hereditary pancreatitis [6] and the lower limit for the first symptoms of alcoholic chronic pancreatitis [3].

All patients aged between 16 and 35 years were included in the aetiological investigation according to three phases (as previously described with minor corrections) [5]: (i) assessment during the acute phase of AP as a first-line investigation; (ii) second-line investigations; and (iii) follow-up of all idiopathic AP patients.

The following first-line investigations for aetiological diagnoses were performed at our centre during initial hospitalisation for AP: clinical history that included medication, pharmaceutical-drug use, toxic substances and alcohol consumption, as well as standard biology (including lipids, phosphorus, calcium), abdominal ultrasound, computerised tomographic examination (CT scan 48–72 h after admission), and investigations for infections, if there was doubt.

At this stage, the causes of AP were considered as biliary, alcoholic, with another recognised aetiology (i.e. non-alcoholic, non-biliary AP), or idiopathic. Cases of idiopathic AP were defined as AP with no cholelithiasis or choledocolithiasis at the initial examination, no chronic alcohol intake (<40 g per day), no recent serious alcohol consumption, absence of metabolic disorders, no recent consumption of toxic substances (including cocaine, cannabis, amphetamine) or medications known to induce AP (a systematic research using the http://www.mediquick.net website was performed combined with a request to the national pharmacovigilance database), no previous history of pancreatobiliary surgery, and no family history of pancreatitis or mucoviscidosis.

Second-line investigations were conducted on idiopathic AP patients as well as when non-alcoholic or non-biliary AP was not clearly proven after the first-line investigations. These investigations were performed after a minimum delay of 2 months, although this delay could be increased in cases of severe necrotic AP. In these latter cases, a subsequent CT-scan was proposed, if necessary, to verify that necrotic pancreatic and peri-pancreatic inflammatory patterns had disappeared. The second-line investigations included examination and clinical history (especially consumption of toxic substances, including cannabis), standard laboratory testing (including serum lipids, calcium, phosphorus, and parathormone), immunology (including anti-DNA and IgG4 serum levels), endoscopic ultrasound (EUS), and magnetic-resonance cholangiopancreatography (MRCP). Genetic investigations were systematically proposed at this step.

The third step of this study was to follow up all patients who presented with idiopathic AP after the first and second phases of the study. For patients aged >35 years, an aetiological diagnosis was made according to the same three phases except for genetic testing, which was proposed during the follow-up period depending on the results of the previous investigations and the context [5]. Genetic testing mutations of *PRSS1* (exons 1–3), *SPINK1* (exons 1–4), *CTRC* (exons 3, 5, 7 and 7) and intronic flanking sequences were analysed by high-resolution melting and sequencing in cases when there was an abnormal profile. Genomic rearrangements at locus 7q34 were analysed by semi-quantitative fluorescent PCR and capillary electrophoresis (at the laboratory of molecular genetic and histocompatibility, Pr C. Ferec, CHU of Brest, France) [20]. The 50 most frequent mutations and the c.1210-12T polymorphism [5] (IVS8-5T polymorphism) in the *CFTR* gene (Locus CF (7q31.2) – *ABCC7* gene) were searched for using multiplex PCR, capillary electrophoresis, and a Gene Mapper (ELUCIGENE Kit, Manchester, UK).

Written informed consent for these investigations was obtained from each patient or from their parents (for patients aged <18 years; according to the rules of the French Society of Gastroenterology [SNFGE] and Endoscopy [SFED]). Written informed consent was also obtained for the genetic analyses (one consent for *PRSS1*, *SPINK1*, and *CTRC*, and one consent for *CFTR*). The study conformed to the ethical guidelines of the 1975 declaration of Helsinki (6th revision, 2008) as reflected by the a priori approval from the institution's human research committee.

2.2. Recorded data and follow-up assessments

All standard medical data were prospectively recorded at inclusion: i.e. patient's age, gender, Ranson and Balthazar scores, clinical examinations and biological tests, local and/or general complications, aetiology after first-line investigations, time delay until a second-line investigation for patients with idiopathic AP, and results from EUS and MRCP. The follow-up included the results after surgery in cases of biliary AP and a minimum of one clinical examination every 6 months. In patients in whom AP remained idiopathic after the second phase, repeat abdominal ultrasounds (every 6 months) and a repeat EUS or MRCP, were performed if necessary.

2.3. Radiological and EUS investigations

MRCP was performed with a 1-T superconducting MR unit (Magnetom Impact; Siemens, Erlangen, Germany) using a half-Fourier single-shot turbo spin-echo (HASTE) sequence, as previously described [5,21]. EUS was performed before MRCP, as previously described [21,22], using an Olympus EUM-160 or GF-UC140T echoendoscope (Olympus, Hamburg, Germany). The EUS examination included systematic high-frequency visualisation of the gallbladder (10–12 MHz). We applied the EUS criteria as defined by others, and we met to discuss a diagnosis of lithiasis of the gallbladder and/or the common bile duct. A diagnosis of chronic pancreatitis was defined by either the presence of major criteria (hyperechoic foci with shadowing and main pancreatic-duct calculi and lobularity with honeycombing), or the association of minor criteria, such as lobularity and dilated main pancreatic ducts ≥3.5 mm in size with a hyperechoic and moniliform wall, and dilated side branches of ≥1 mm, with non-shadowing hyperechoic foci [22,23]. More