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Etiological diagnosis of recurrent acute pancreatitis

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Introduction

Acute pancreatitis (AP) is highly prevalent worldwide, necessitating a comprehensive approach to identify and treat underlying factors to prevent recurrence. Despite early intervention, one-third of patients experience recurrent acute pancreatitis (RAP)[1]. Many of the recognized etiological factors associated to RAP are treatable and usually present since the first episode. Identifying and addressing these factors can substantially reduce the likelihood of recurrence in a significant percentage of patients[2].

RAP is defined as two or more well-documented episodes of AP with complete resolution between episodes, lacking chronic pancreatitis (CP) morphological criteria and separated by a at least 3 months[2]. RAP is notably observed in males aged 30-40, smokers and those with excessive alcohol consumption. Additionally, is observed, albeit to a lesser extent, in patients with underlying biliary disease. Notably, RAP presents lower morbimortality when compared to individuals experiencing a single episode, likely attributed to reduced pancreatic injury resulting from acinar cell loss and fibrosis developed in previous episodes of AP[3].

Approximately 25-50% of RAP cases may progress to CP within 10 years, with various risk factors influencing this progression. Alcoholic etiology, smoking, AP severity and male sex are factors that have been associated to a higher risk of developing CP in the context of RAP[1,4].

Etiology

Various factors contribute to RAP (Table 1), including microcolelithiasis (in up to 10% of RAP)[5], alcohol abuse, tobacco use, hypertriglyceridemia, drug-induced cases, autoimmune pancreatitis and genetic mutations.

In the context of alcohol consumption, the risk of a RAP is intricately linked to factors such as the quantity of alcohol consumed, the duration of consumption, and cumulative exposure[6]. Research indicates that lithiasic disease and alcohol abuse, contribute significantly to 60-70% of RAP cases[5]. Moreover, the combined use of tobacco and alcohol exacerbates the risk of RAP, with tobacco acting synergistically and independently as a risk factor[7]. There is a positive association between smoking and non-gallstone-related pancreatitis, but not with gallstone-related pancreatitis for current smokers[8].

Hypertriglyceridemia emerges as a well-established cause of RAP, with a direct correlation between triglyceride levels and risk. The likelihood of developing acute pancreatitis in individuals with hypertriglyceridemia exceeding 1000 mg/dL is approximately 5%, escalating to 10-20% when levels surpass 2000 mg/dL[9].

Among the limited drugs implicated in RAP through clinical trials, azathioprine, 6-mercaptopurine, and didanosine have demonstrated potential roles[10].

Other diseases have been associated to an increased risk of RAP such as type 2 autoimmune pancreatitis, known as idiopathic duct-centric pancreatitis[11]; celiac disease that heightens the risk of AP by sensitizing pancreatic acinar cells to gut hormone alterations and papillary inflammation[12,13].

Genetic factors also play a pivotal role, with mutations in the PRSS1 gene (linked to hereditary CP), as well as in the SPINK1, CFTR, and CTRC genes[14], resulting in recurrent episodes of acute pancreatitis.

Additionally, various pathologies leading to pancreatic duct obstruction such as pancreaticobiliary tumors, annular pancreas, post necrosis stenosis, common bile duct cyst type 3 and intraductal papillary mucinous tumor, contribute to the occurrence of RAP[13]. Anatomical variants including pancreas divisum (PD) or sphincter of Oddi dysfunction also stand out as potential causes of RAP[15].

It is crucial to consider less common causes of RAP, such as metabolic pathologies (hyperparathyroidism or hypercalcemia), systemic diseases such as systemic lupus erythematosus or vasculitis (polyarteritis nodosa) and toxins such as pesticides[2].

Despite an adequate initial etiological study, approximately 10-30% of patients are unable to have a specific cause identified, leading to the classification of idiopathic RAP. Recent meta-analyses highlighted the efficacy of advanced diagnostic tests such as magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound (EUS) in unveiling the cause in about 50% of cases previously deemed idiopathic. Notable causes identified through these advanced diagnostic methods include microcholelithiasis, unknown underlying CP and pancreaticobiliary tumors[16].

Diagnosis

Physicians managing AP should prioritize an accurate etiological diagnosis to facilitate optimal treatment, minimize the risk of recurrent episodes, cumulative-damage, and unnecessary invasive procedures. A systematic and rational study becomes imperative in identifying the causative agent in RAP, considering the multifactorial nature of its origins (Figure 1).

For patients experiencing a first episode of AP, a thorough anamnesis and physical examination are essential. Inquiries should cover pertinent family and personal history,

including biliary disease, inflammatory bowel disease (IBD), celiac disease, familial hyperlipidemia and familial history of pancreatitis, cystic fibrosis, or pancreatic cancer. Additionally, investigations into drug use, alcohol consumption (quantity and duration) and tobacco usage are crucial, along with assessing any history of biliary colic, gastric or pancreaticobiliary surgeries.

A comprehensive blood test, encompassing parameters such as hemogram, liver function, transaminases, cholestasis, triglycerides, cholesterol, and indirect markers of alcohol consumption should be conducted. Abdominal ultrasound should be performed in all patients with AP to identificate gallstone and schedule cholecystectomy to prevent recurrent attacks and potential biliary sepsis[17,18]. In cases of poor image quality, significant inflammatory components or unidentified etiology, a repeat ultrasound after 5-7 days is recommended, given the possibility of diagnosing cholelithiasis even months after the initial AP episode[17,19].

While this initial approach can identify the etiology in up to 70-80% of cases[2,20,21], managing RAP remains a challenge due to scarce evidence, with most studies being retrospective and the absence of clinical guidelines. Despite this, it is advisable to perform advanced imaging studies (abdominal CT /MRCP/EUS) during the first AP episode. The choice of the imaging test should be based on the patient's profile, test availability and clinical suspicion. Contrast-enhanced CT is typically the initial cross-sectional imaging test, especially in situations indicating potential pancreatic neoplasia[18,19,20].

If a new episode of AP occurs, repeating the initial basic study is recommended. If not been performed during the first AP episode, an abdominal CT with contrast should be performed to rule out biliopancreatic malignancy, especially in patients with unjustified weight loss, severe abdominal pain, jaundice and recent diabetes or glycemic decompensation.

In cases where an abdominal CT scan reveals no pathology, with previous basic studies being performed at the initial AP episode, these should be cautiously examined

according to the clinical suspicion. If the blood analysis, alcohol consumption and abdominal ultrasound are normal, MRCP/EUS are recommended. EUS is especially useful in gallbladder patients, allowing evaluation of microlithiasis, biliary sludge, anatomical alterations, solid or cystic pancreatic lesions and unknown underlying CP[19,22].

EUS emerges as a precise and safe method for assessing idiopathic AP. Its accuracy in detecting microcholelithiasis and cholelithiasis, particularly when previous tests were inconclusive, highlights its diagnostic value[23]. It also allows the diagnosis of choledocholithiasis, ampullary lesions, pancreatic duct abnormalities and pancreatic cysts[2]. Given its high yield and low risk of complications, being the most sensitive technique for the diagnosis of pancreatic tumors smaller than 2 cm[24], is recommended as a primary technique for studying idiopathic RAP.

MRCP, a non-invasive technique, allows the examination of pancreatic parenchyma and biliary and pancreatic ductal anatomy. MRCP is superior to EUS in identifying biliary strictures and PD, while EUS excels in detecting choledocholithiasis, microcholelithiasis and biliary mud[25].

Intravenous secretin administration with MRCP (MRCP-S) enhances visualization of the main pancreatic duct and anomalies such as PD and incipient ductal stenosis. It outperforms conventional MRCP in diagnosing ductal anomalies in RAP patients. In addition, MCRP-S facilitates the evaluation of pancreatic exocrine function and indirect assessment of sphincter of Oddi motility. However, it is contraindicated in patients with recent AP. Integrating MRCP-S into the study of patients with RAP is recommended, but its limited availability in clinical practice should be taken into account[2,26].

Once a comprehensive assessment fails to reveal any causative agent, if no new episodes of AP occur, conservative management may be a reasonable approach. Alternatively, if recurrent episodes persist, an expanded etiological study should be undertaken considering less frequent causes. Initial basic workup should be repeated,

including immunoglobulin IgG4 and antinuclear antibody levels to rule out autoimmune pancreatitis and vasculitis, and metabolic causes should be investigated. In addition, CT or MRCP should be performed; the election of one or another depends on which first test was previously done. For suspected autoimmune pancreatitis, obtaining histological material may aid in the differential diagnosis, especially to exclude pancreatic adenocarcinoma[27].

Genetic studies play an important role particularly in young patients in whom biliary and alcoholic etiology has been reasonably ruled out. Genetic counseling and testing may be considered in young patients (< 30 years old) with recurrent episodes (>1 episode) of idiopathic acute pancreatitis especially if there is a family history of pancreatic disease[17,19]. Certain genetic mutations are prevalent among patients with RAP, and it remains unclear whether these mutations act in presence of other factors, such as PD, to modify disease severity or response to treatment. Research suggests that genetic variants within PRSS1, SPINK1, CTFR and CTRC genes are present in approximately 58% of patients with RAP classified as idiopathic[28].

Recurrent acute pancreatitis represents an important problem with respect to patient disability and health-care burden. In order to avoid new episodes of AP, the study should focus on making an accurate etiological diagnosis. For this reason, it is paramount to perform a systematic and rational study, from an initial basic study including anamnesis and physical examination, blood tests and abdominal ultrasound to advanced diagnostic tests such as EUS or MRCP. EUS is preferred in patients with gallbladder in place, because of its superior performance for small tumors and microcholelithiasis. Genetic counseling (not necessarily genetic testing) may be considered in young patients (< 30 years old) if no cause is evident and a family history of pancreatic disease is present.

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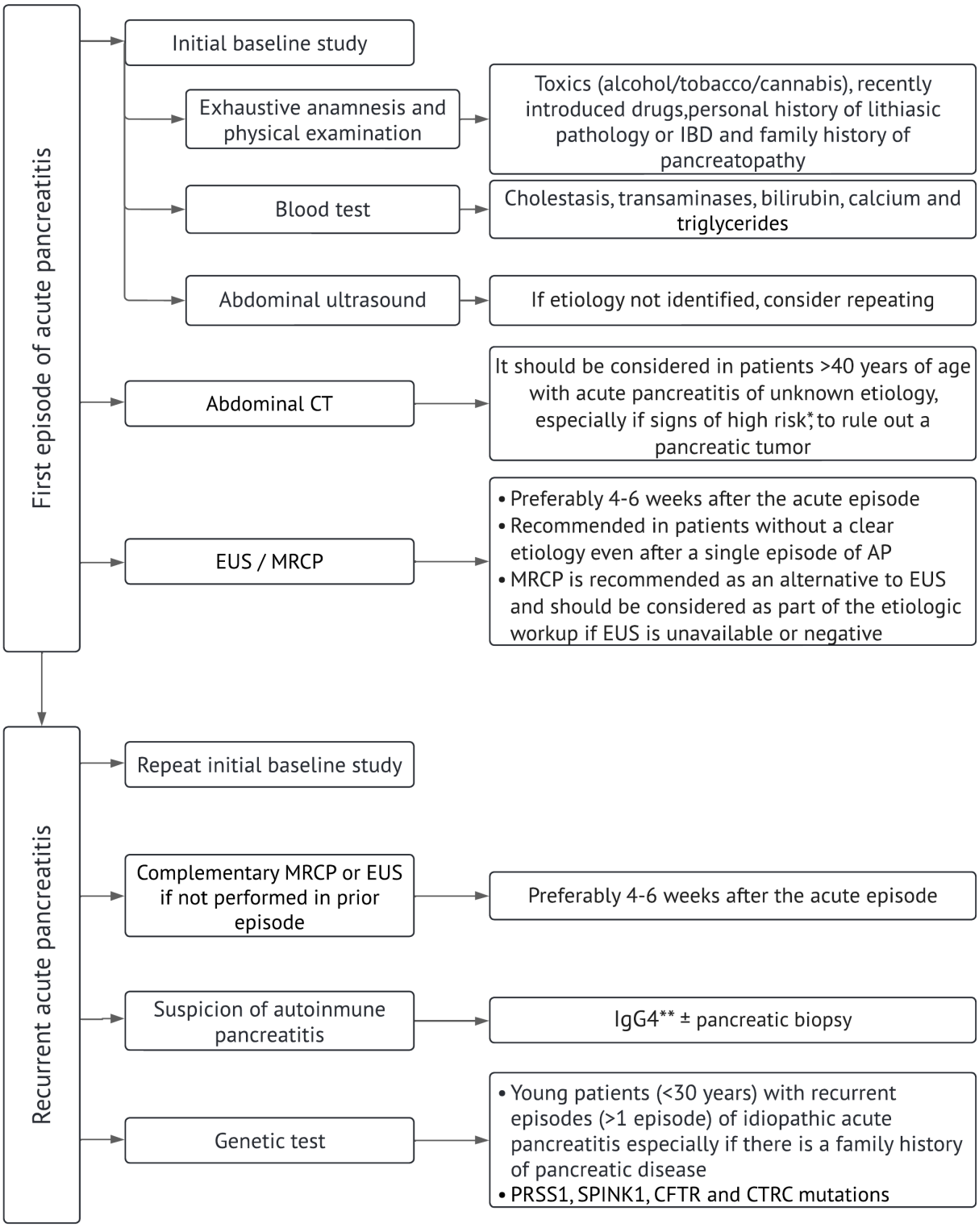

Figure 1. Recommendations for the etiological diagnosis of acute and recurrent acute pancreatitis. * Weight loss, jaundice, severe abdominal pain and new onset diabetes or glycemic decompensation. ** Serum IgG4 determination is not routinely recommended as part of the etiological study.

EC-CT: contrast-enhanced computed tomography, EUS: endoscopic ultrasound; MRCP: magnetic resonance cholangiopancreatography, IBD: inflammatory bowel disease.

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Obstructive	Biliary lithiasis, pancreatic tumors, distal cholangiocarcinoma, ampuloma, Sphincter of Oddi dysfunction, pancreas divisum*, duodenal diverticulum, duodenal stricture-obstruction, cholodochocele type IV, parasites (Ascaris lumbricoides).
Toxic	Ethanol, organophosphate poisoning, scorpion venom (only some species). Tobacco smoking is an important cofactor.
Metabolic	Hypertriglyceridemia, hypercalcemia (primary hyperparathyroidism or iatrogenic infusion)
Iatrogenic	Post ERCP (acute pancreatitis is the most frequent post ERCP complication), post PTC, post-surgical, peritoneal dialysis, renal transplantation, drugs (valproic acid, azathioprine, diclofenac, didanosine, ACE inhibitors, loop diuretics, thiazide diuretics, mesalamine, metronidazole, L-asparaginase, pentamidine, tetracycline, simvastatin).
Autoimmune	Type 1 and type 2 autoimmune pancreatitis.
Genetic	CFTR, PRSS1, SPINK1, and other genetic mutations.
Infection	Hepatotropic viruses (hepatitis A, B, E), CMV, *Cocksackie*, varicella-zoster, HSV, HIV, *Legionella*, *Mycoplasma*, *Salmonella*, *Leptospira*, *Aspergillus*, *Toxoplasma*, *Cryptosporidium*.
Others	Ischemia, vasculitis (polyarteritis nodosa, SLE), kinetic injury and other trauma (including seat belt injuries)

Table 1. Etiology of acute pancreatitis. *Controversial.

5-ASA: 5-aminosalicylic acid; ACE: angiotensin-converting enzyme; CMV: cytomegalovirus; ERCP: endoscopic retrograde cholangiopancreatography; HIV: human immunodeficiency virus; HSV: herpes simplex virus; PTC: percutaneous transhepatic cholangiography; SLE: systemic lupus erythematous.

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