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Etiology of Pancreatitis and Risk Factors

Eugenia Lauret, María Rodríguez-Peláez and
Luis Rodrigo Sáez

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1. Introduction

1.1. Etiology of pancreatitis and risk factors

Acute pancreatitis (AP) is one of the most common gastrointestinal diseases requiring hospitalization worldwide, with a rising incidence ranging from 13 to 45 per 100,000 persons/year. The burden of this disease on patients and society is expected to increase even more. Chronic pancreatitis (CP) is a progressive fibro-inflammatory disorder which eventually culminates in permanent impairment of the exocrine and/or endocrine pancreatic function. Although the incidence and prevalence of CP is lower than the reported for AP, this disease significantly reduces patients' quality of life. The annual incidence of CP in industrialized countries has been estimated at 5-12 per 100,000, with a prevalence of about 50 per 100,000 persons [1].

Many conditions are known to potentially cause pancreatitis with varying degrees of certainty, and although some variations have been described between countries, most of cases are attributed to biliary stones or sludge, followed by alcohol abuse. Advances in imaging, molecular biology and genetics have broadened the list of possible etiologies, and the number of presumed idiopathic cases (10-15%) will decrease as our understanding of the disease improves [1,2].

The etiology of pancreatitis should be determined on admission or in the early course of the disease, as this allows the clinician to choose the most appropriate management strategies and therapy in acute phase, and prevent recurrence. A detailed personal history (including data such as previous acute pancreatitis or gallstone disease, alcohol abuse, drug intake, metabolic syndromes, trauma or recent invasive procedures, concomitant autoimmune diseases) and family history of pancreatic disorders can provide guidance for a first etiological approach.

Physical examination, biochemical tests (liver enzymes, calcium, triglycerides) and the appropriate performance of imaging studies will help to make a differential diagnosis among biliary, alcoholic and other causes of pancreatitis.

In this chapter, the aim will be to conduct a comprehensive and updated review of the possible causes of pancreatitis (Table 1) and associated risk factors.

2. Risk factors of pancreatitis

2.1. Age and sex

Although the incidence of AP do not differ according to sex, CP is more common among men. The risk of AP increases with age, whereas CP mainly affects middle-age individuals. Besides, age and sex distribution is different by etiology. Usually, alcohol-related pancreatitis is more common in middle-aged men. By contrast, pancreatitis in women is more frequent related to gallstones, instrumental procedures, autoimmune diseases or to be idiopathic. Geographic variations observed in age and sex distribution can be partly explained by differences in etiology [1,3].

2.2. Race

The risk of pancreatitis is 2 to 3-fold higher among the black population than the whites. Little is known about the possible reasons of this racial disparity and further studies are needed to determine whether these observed differences may be related to dietary, genetic or other factors [1,4].

2.3. Lifestyle factors

2.3.1. Diet

The role of dietary factors in the etiology of pancreatitis is unclear. The consumption of high glycemic foods has been associated with an increased risk of non-gallstone-related acute pancreatitis. By contrast, it has been suggested that vegetables and fruit consumption are associated with reduced risk for pancreatic diseases [5,6].

It also should be noted that celiac disease increases the risk of pancreatitis by approximately 3-fold. Diffuse inflammation of the duodenum and papillary stenosis may be the mechanisms involved [7].

Dietary pattern is an area for future research, with other new issues to analyze as the role of the microbiota in pancreatic diseases [8].

2.3.2. Obesity

It has been found that abdominal adiposity increases the risk and severity of AP. The overweight has similar effect for gallstone and non-gallstone-related inflammation [5,9].

2.3.3. Diabetes

Some studies found that type 2 diabetes mellitus increases the risk of AP by 1.5 to 3-fold, particularly in younger diabetic patients [10]. This risk may be attributed to diabetes itself, but also to other associated factors with this metabolic disorder (gallstones, hypertriglyceridemia) or the use of antidiabetic drugs such as dipeptidyl peptidase 4 inhibitors (sitagliptin) or glucagon-like peptide 1 agonist (exenatide) [11].

3. Etiology of pancreatitis

3.1. Obstructive disorders

Mechanical ampullary obstruction can be induced mainly by gallstone, but also for a wide variety of other disorders [1,2].

3.1.1. Gallstones

Gallstones (including microlithiasis) are the most common etiology of AP, accounting for at least 35-45% of cases. However, only 3 to 7% of patients with gallstones develop pancreatitis. The risk increases with the age, female gender and small gallstones. The rising incidence of obesity is likely to contribute to AP by promoting gallstone formation.

Proposed mechanisms in the pathogenesis of this disorder include reflux of bile into the pancreatic duct due to transient ampullary obstruction and/or secondary to edema resulting from the passage of stones. Both events may lead to increase pressure in the pancreatic duct, resulting in injury of the gland with release of pancreatic enzymes causing autodigestion and triggering AP [12].

Biliary sludge is a viscous suspension in gallbladder bile that may contain small (<5mm) stones (i.e., microlithiasis). Its formation has been associated with mechanical or functional conditions that promote bile stasis, such as distal bile duct obstruction, prolonged fasting, total parenteral nutrition or use of ceftriaxone [13]. It is commonly found up to 20-40% of patients initially diagnosed with idiopathic pancreatitis, and in the absence of any other etiology this could be considered as probable cause of the disease.

Gallstones are not recognized as etiology of CP. However, prolonged ductal obstruction may lead to development of CP.

3.1.2. Pancreatic/ampullary obstruction

Pancreatic and periampullary tumors can cause pancreatitis. The intraductal papillary mucinous neoplasm is the most commonly involved, due to obstruction of main and/or side branches of pancreatic duct by the tumor itself and/or by mucus secretion [14]. Pancreatic adenocarcinoma can also present as pancreatitis, and the acute attacks may

precede the diagnosis of overt malignancy in the gland by several months [15]. It has been estimated that approximately 5-14% of patients with benign or malignant pancreatobiliary tumors are initially diagnosed as idiopathic AP [16]. Unexplained recurrent pancreatitis from the middle age should raise the suspicion of underlying tumor, especially in patients with worrisome associated symptoms (weight loss, new-onset diabetes).

OBSTRUCTIVE

- Gallstones, microlithiasis, "biliary sludge"
- Benign and malignant strictures, ampullary or pancreatic tumors, mucin (*intraductal papillary mucinous neoplasms*)
- Anatomic variants: *Pancreas divisum, annular pancreas, choledochal cyst, choledochoceles, duodenal duplication, duodenal diverticula*
- Sphincter of Oddi dysfunction
- Parasites (*Ascaris, Anisakis*)

TOXICS

- Alcohol, Tobacco
- Organophosphorous insecticides
- Venoms (*Scorpion, spider*)
- Etricine
- Heroin, cocaine
- Drugs: *Pentamidine, Thiazide, Furosemide, Azathioprine, 6-Mercaptopurine, Sulindac, Salicylates, L-asparaginase, Valproic acid, Calcium, Estrogen, Tamoxifen, Sulfonamide, Tetracycline.*

METABOLIC. Hypertriglyceridemia, Hypercalcemia

HEREDITARY / GENETIC

- Hereditary pancreatitis
- Cystic fibrosis

TRAUMA/IATROGENIC

- Post-endoscopic retrograde cholangiopancreatography
- Transparietohepatic cholangiography
- Pancreas biopsy / Fine-needle aspiration
- Transcatheter arterial embolization for hepatocellular carcinoma
- Postoperative

INFECTIONS

- Viruses: *Mumps, Coxsackievirus, Cytomegalovirus, Varicella-zoster, Herpes simplex, EpsteinBarr, Human immunodeficiency virus, Hepatitis A, B and C*
 - Bacteria: *Mycoplasma, Mycobacterium tuberculosis, Leptospira, Legionella, Salmonella Typhi*
 - Fungi: *Aspergillus*
 - Parasites: *Toxoplasma, Cryptosporidium, Clonorchis sinensis*
-

VASCULAR DISEASE

- Hypotension/Ischemia
- Vasculitis
- Atheromatosis, emboli to pancreatic vessels
- Hypothermia
- Haemolysis

AUTOIMMUNE

MISCELLANEOUS. Celiac disease, Crohn's disease, Severe Burns, Tropical pancreatitis, Posterior Penetrating Duodenal Ulcer

IDIOPHATIC

Table 1. Etiological factors associated with acute pancreatitis.

3.1.3. *Anatomic/Functional abnormalities*

Other conditions that have been associated with obstructive pancreatitis include anatomic variants and physiologic anomalies of the pancreatic drainage that occur in 10-15 % of the population, including pancreas divisum and sphincter of Oddi dysfunction (SOD).

3.1.4. *Pancreas divisum*

It is the most common congenital malformation of the pancreas. It is due to the fusion failure between the dorsal and ventral pancreas, resulting in separate pancreatic ductal systems. It is found in approximately 7% of autopsy series. The implication of this anatomic variant as a potential cause of AP remains controversial. The proposed pathogenic mechanism is the relative obstruction to pancreatic juice flow through the minor papilla, leading to increased intraductal pressure. However, since the rate of AP in patients with pancreas divisum is similar to the general population, it has been suggested that the involvement of other factors is required to the development of the disease. In this regard, the prevalence of this malformation in patients with mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) was found to be higher than in patients with idiopathic or alcohol-related AP, or control subjects [13,17].

3.1.5. *Sphincter of Oddi dysfunction*

SOD is also a controversial cause of AP (Table 2). The involved mechanism is associated with spasm or stenosis of the sphincter muscle controlling the bile and pancreatic flow into the duodenum. Pancreatic-type SOD ranges from patients with pancreatic-type pain, raised serum amylase or lipase and pancreatic duct dilatation (Type I), to those with pancreatic-type pain and no other abnormalities (Type III). The importance of this condition as cause of recurrent AP is not clearly established, although it has been considered to cause up to one third of all cases of idiopathic pancreatitis [16].

Biliary type	Pancreatic type
<p>Type I</p> <ul style="list-style-type: none"> • Biliary-type pain • And all of the following: <ul style="list-style-type: none"> - Abnormal aminotransferases or alkaline phosphatase (>2 times normal on at least 2 occasions) - Dilated bile duct (>8 mm) 	<p>Type I</p> <ul style="list-style-type: none"> • Pancreatic-type pain • And all of the following: <ul style="list-style-type: none"> - Amylase/lipase (>1.5 times normal) - Pancreatic duct >6 mm in head or >5mm in body - Delayed drainage of contrast after ERCP (>9 minutes)
<p>Type II</p> <ul style="list-style-type: none"> • Biliary-type pain • And one of the following: <ul style="list-style-type: none"> - Abnormal aminotransferases or alkaline phosphatase (>2 times normal on at least 2 occasions) - Dilated bile duct (>8 mm) 	<p>Type II</p> <ul style="list-style-type: none"> • Pancreatic-type pain • And one or two of the following: <ul style="list-style-type: none"> - Amylase/lipase (>1.5 times normal) - Pancreatic duct >6 mm in head or >5mm in body - Delayed drainage of contrast after ERCP (>9 minutes)
<p>Type III</p> <p>Biliary-type pain only</p>	<p>Type III</p> <p>Pancreatic-type pain only</p>

Table 2. Sphincter of Oddi dysfunction. Revised Classification Milwaukee. The Rome III Consensus Statement.

3.2. Toxics

3.2.1. Alcohol

The prevalence of AP is approximately 4-fold higher among subjects who are alcohol consumers compared to nondrinkers. However, the absolute risk of developing alcohol-related pancreatitis is lower than that for chronic alcohol liver diseases and ranges from 5% to 10% for large consumers [18,19]. Alcohol intake is the single most common cause of CP, and the second after gallstones for AP being responsible for about 30-35% of cases of acute attacks.

The risk of acute alcohol-induced pancreatitis increases in a dose-dependent manner, with a threshold for CP of approximately 4-5 drinks/day. Chronic alcoholic patients eventually develop CP after 10 to 20 years of continuous alcohol abuse. The contribution of the beverage type to this risk requires further studies [19,20].

Although the exact mechanism of pancreatic injury remains unclear, alcohol may act directly on the acinar cells as a toxic by promoting the synthesis of enzymes, activation of pancreatic proteases, changes in cellular lipid metabolism, induction of oxidative stress, activation of stellate cells and/or by increasing the sensitivity of the gland to other genetic and environmental factors.

Two pathogenic theories have been described. In one, alcohol-related injury is the result of perturbations in exocrine function leading to an increase of the lithogenicity of pancreatic juice and the formation of protein plugs and stones. Atrophy and fibrosis develop as a result of the obstructive process. The other theory proposed a stepwise progression to fibrosis after recurrent attacks of AP. Inflammation and necrosis from the initial episodes

of AP lead to areas of scarring, ductal obstruction, stasis and subsequent stone formation. However, given the low rate of pancreatitis among heavy drinkers, it has been suggested that other genetic and environmental cofactors would be required for the development of alcoholic pancreatitis [19,21].

3.2.2. *Smoking*

Tobacco and alcohol are cofactors that increase the risk of pancreatitis. Furthermore, both habits often coexist and are enhanced in a dose-dependent manner. However, large studies have suggested that smoking alone is an independent risk factor for both AP and CP [22,23].

It has been reported that smoking increases by approximately 2-fold the risk of non-gallstone-related AP, but not for gallstone-related pancreatitis. This risk was higher in patients who consumed alcohol, current smokers and those with more than 20 packs-years of smoking, particularly if they met the three characteristics (relative risk, 4.12) [24].

Regarding CP, smoking alone has been attributed 25% of the risk for this disease. It has been calculated a risk more than 2-fold among subjects who smoked less than one pack/day, and more than 3-fold for those with higher consumption [25].

At this time, there is very little information about the pathogenesis of smoking-induced pancreatitis compared with those of other causes. Data from animal models suggest several potential mechanisms such as altered gene expression in the exocrine pancreas and activation of pancreatic enzymes with acinar cell damage. Nicotine has also been shown to modulate the oxidative stress and lipid peroxidation and these processes might be involved in the pathophysiology of acute and chronic pancreatitis. As is becoming evident with respect to alcohol, there may be other environmental and/or genetic factors that may promote pancreatic injury with smoking [26].

3.2.3. *Drugs*

AP due to drugs is a rare event (2%). Over one hundred of different medications have been related in the development of the disease by several mechanisms. These include immunologic reactions (azathioprine, 6-mercaptopurine, aminosalicylates, sulfonamides), a direct toxic effect (diuretics, sulfonamides), accumulation of toxic metabolites (valproic acid, didanosine, pentamidine, tetracycline), ischemia (diuretics, azathioprine), intravascular thrombosis (estrogen), and increased viscosity of pancreatic juice (diuretics and steroids). No medications are known to cause CP.

Drug-induced pancreatitis has been classified (I-IV) (Table 3) according to the number of registered cases, latency period and reaction with rechallenge: Class Ia drugs (at least 1 case report with positive rechallenge, excluding all other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs), Class Ib drugs (at least 1 case report with positive rechallenge; however, other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs were not ruled out), Class II drugs (at least 4 cases in the literature and consistent latency in $\geq 75\%$ of cases), Class III drugs (at least 2 cases in the literature with no consistent latency among cases and no rechallenge) and Class IV drugs (Not fitting into the earlier-

described classes, single case report published in medical literature, without rechallenge). Classes I and II have the greatest potential for causing AP. The time interval between beginning of the drug and the development of the disease is highly variable, depending on the substance involved and its pathogenic mechanism. Therefore, a high index of suspicion and a detailed drug history are essential for making the diagnosis [27,28].

3.2.4. Others toxics

Organophosphate pesticides, arachnids and reptiles venoms have been described to cause AP by cholinergic stimulation [2]. Cocaine consumption may cause pancreatitis by vasoconstrictor and ischemic effects [29].

Class IA

α-methyl dopa	Cytosine	Mesalamine	Simvastatin
Azodisalicylate	Arabioside	Metronidazole	Stibogluconate
Bezafibrate	Dapsone	Pentamidine	Sulfamethoxazole
Cannabis	Enalapril	Pravastatin	Sulindac
Carbimazole	Furosemide	Procainamide	Tetracycline
Codeine	Isoniazid	Pyritonol	Valproic acid

Class IB

All-trans-retinoic acid	Lamivudine	Meglumine	
Amiodarone	Losartan	Methimazole	Premarin
Azathioprine	Lynesterol/	Nelfinavir	Sulfamethazole
Clomiphene	Metho-xyethinylestradiol	Norethindronate/	Trimethoprim-
Dexamethasone	6- Mercaptopurine	mestranol	sulfamethazole
Ifosfamida		Omeprazole	

Class II

Acetaminophen	Didanosine	L-asparaginase	Propofol
Chlorthiazide	Erythromycin	Pegasparagase	Tamoxifen
Clozapine	Estrogen		

Class III

Aledronate	Cimetidine	Interferon/ribavirin	Metformin
Atorvastatin	Clarithromycin	Irbesartan	Minocycline
Carbamazepine	Cyclosporin	Isotretinoin	Mirtazapine
Captopril	Gold	Ketorolac	Naproxen
Ceftriaxone	Hydrochlorothiazide	Lisinopril	Paclitaxel
Chlorothalidone	Indomethacin	Metalozone	Prednisone
			Prednisolone

Class IV

Adrenocorticotrophic hormone	Cisplatin	Diclofenac	Fluvastatin
Ampicillin	Colchicine	Difenoxylate	Gemfibrozil

Bendroflumethiazide	Cyclophosphamide	Doxorubicin	Interleukin-2
Benzapril	Cyproheptidine	Ethacrinic acid	Ketoprofen
Betamethazone	Danazol	Famciclovir	Lovastatin
Capecytabine	Diazoxide	Finasteride	Mefanamic acid
		5-fluorouracil	Nitrofurantoin

Data modified from Badalov N et al [28].

Table 3. Summary of the medications associated with pancreatitis based on Drug Class.

3.3. Metabolic disorders

3.3.1. Hypertriglyceridemia

This type of hyperlipidemia induces AP in about 1-4% of cases, and this is an uncommon etiology of CP. The disease typically develops in patients with a history of familiar hyperlipidemia and/or an associated secondary factor as uncontrolled diabetes, alcohol consumption, hypothyroidism, nephrotic syndrome, drug intake or pregnancy. The risk is particularly increased in patients with AP not due to alcoholic or obstructive causes and with high serum triglyceride concentrations above 1000 mg/dL. Mild-to-moderate hyperlipidemia is often secondary to alcoholic AP, and should not be confused with marked hypertriglyceridemia causing AP [2].

The mechanism of hypertriglyceridemia induced pancreatitis is unclear though some authors suggest stimulation of amylase release, cell damage from free fatty acids and chylomicrons in acinar cells, and sluggish flow in the capillaries resulting in ischemic injury [13].

3.3.2. Hypercalcemia

This is a rare cause of AP and almost always happens as result of concomitant hyperparathyroidism. Pancreatitis has been reported to be related to endogenous hypercalcemia by disseminated carcinoma and after iatrogenic effect, for example with total parenteral nutrition or vitamin D poisoning. Proposed mechanisms include deposition of calcium in pancreatic duct and calcium activation of trypsinogen within the pancreatic parenchyma. Because the incidence of pancreatitis is low in patients with chronic hypercalcemia, additional factors are probable necessary to induce acute episodes [13,30].

3.4. Hereditary/genetic pancreatitis

In pancreatitis, alterations in several genes have so far been described [31].

Hereditary pancreatitis is an autosomal dominant disorder with high penetrance rates up to 80%. This disorder is associated with mutations in the trypsinogen gen *PRSS1* that promotes the premature conversion of trypsinogen to active trypsin, resulting in pancreatic autodigestion. This genetic syndrome is characterized by a strong family history of pancreatic disease, and most patients develop recurrent pancreatitis from childhood, with progressive evolution to CP and a significant increase in risk of pancreatic cancer.

Severe homozygote mutations in *CFTR* gene cause cystic fibrosis. Patients who are compound heterozygotes for mild mutations have 40 to 80-fold increased risk of developing CP compared with the general population, without presenting other manifestations of cystic fibrosis and with a normal sweat chloride test.

Mutations in the serine protease inhibitor kazal type 1 gene (*SPINK1*) and chymotrypsin C (CTRC) are associated with acute and chronic pancreatitis. Patients who have severe mutations typically develop CP in childhood. Other mutations predispose to the development, but do not necessarily cause pancreatitis.

3.5. Trauma and medical procedures

3.5.1. Blunt or penetrating trauma

Both types of injuries may cause pancreatitis in about 0.2% and 1% cases respectively, ranging from a mild contusion to a severe damage [2]. These conditions can lead to acute duct rupture and pancreatic ascites. The low rates of AP after trauma result from the retroperitoneal location of the gland. The injury healing may result in a narrowing of the main pancreatic duct, causing obstructive pancreatitis in the gland downstream from the stricture.

Rarely a posterior duodenal ulcer can penetrate into the pancreas and thereby induce AP. This complication may present as gastrointestinal bleeding.

3.5.2. Post-ERCP

The result of instrumentation of the gland as in endoscopic retrograde cholangiopancreatography (ERCP) can result in post-ERCP pancreatitis. This injury occurs in 3-5% of unselected patients and although the episodes are usually mild, up to 11% of cases the disease is severe. The risk of post-ERCP pancreatitis may be increased up to 25% in those with suspected SOD or in those with a prior history of post-ERCP pancreatitis. Other risk factors for the development of this complication include young age, female sex, repeated attempts of papilla cannulation and poor emptying of pancreatic duct after contrast injection. Proposed underlying mechanisms that may be involved in the pathogenesis of post-ERCP pancreatitis are mechanic damage from manipulation, and/or chemical, hydrostatic or thermal injury around the papillary orifice or over pancreatic duct [32,33].

3.5.3. Postoperative pancreatitis

This complication can occur after abdominal or thoracic surgery. It has been described in about 0.4-7.6% after cardiopulmonary bypass and 6% after liver transplantation. Significant risks for postoperative pancreatitis include renal insufficiency, hypotension, and infections. Intraoperative or postoperative medications may also cause pancreatitis [34,35].

Other procedures have also been described as cause of iatrogenic pancreatitis (transparietohepatic cholangiography, pancreatic biopsy/fine-needle aspiration). Pancreatitis after transarterial embolization for the treatment of hepatocellular carcinoma results from a retrograde

injection of the chemotherapeutic or embolic agents into pancreatic arteries, giving rise to ischemic pancreatitis [36].

3.6. Infectious diseases

Many infectious agents are associated with AP (Table 1), but no microorganism has ever been identified within the pancreas. Mumps and Coxsackie B virus are the most common causes of infectious pancreatitis. Other viruses (Cytomegalovirus, Herpes simplex, Varicella-zoster, Hepatitis B), bacteria (*Salmonella typhi*, *Leptospira*, *Legionella*), fungi (*Aspergillus*) and parasites (*Toxoplasma*, *Cryptosporidium*) have all been associated with AP. *Clonorchis sinensis* and *Ascaris* cause pancreatitis by invading and blocking the pancreatic duct [2,37].

AP may be caused by HIV infection or secondary to anti-retroviral treatment. In acquired immunodeficiency syndrome (AIDS), other infectious agents may cause pancreatitis including Cytomegalovirus, *Candida*, *Cryptosporidium neoformans*, *Toxoplasma gondii*, *Pneumocystis carinii* and *Mycobacterium avium* complex [38].

3.7. Vascular diseases

Pancreatic ischemia has been reported in the following circumstances: hypotension, hemorrhagic shock, vasculitis (systemic lupus erythematosus and polyarteritis nodosa), atheroembolism, hypothermia, haemolysis and emboli to pancreatic vessels. It has been described episodes of AP in long-distance runners, on an ischemic basis [2].

3.8. Autoimmune pancreatitis

Less than 5% of patients evaluated in a tertiary center with pancreatitis on admission, were diagnosed as autoimmune pancreatitis (AIP). This disease may present in a variety of ways and among patients with this disease, only 10% to 25% have features of AP or CP at the time of presentation.

AIP has distinct clinical and histological features. Two subtypes are known, the type 1 (lymphoplasmacytic sclerosing pancreatitis) is a multi-organ disease associated with IgG4, and type 2 (idiopathic duct centric pancreatitis) appears to be a pancreas-specific disorder with characteristic granulocyte-epithelial lesions [39]. Immunologic abnormalities including hypergammaglobulinemia, elevated serum IgG4 levels and the presence of autoantibodies against lactoferrin and carbonic anhydrase are important serological markers of the type 1 AIP.

Because the diagnosis can be elusive, several criteria have proposed to diagnose AIP. The most widely used in the United States are the HISORT criteria (histology, imaging, serology, other organ involvement and response to therapy) [40]. Abnormal imaging can be observed in computed tomography, magnetic resonance imaging or endoscopic ultrasound as multifocal or diffuse pancreatic-ductal narrowing, and abnormal enhancement or enlargement of the pancreas. Histologic confirmation is desirable and can be obtained by endoscopic ultrasound-guided biopsy of the pancreas. Ampullary biopsy with IgG4 immunostaining may be a safer alternative with a specificity approaching 100% but a sensitivity of about 50% [41]. AIP clearly responds to steroid therapy although spontaneous resolution without treatment has also been

described; however relapses are relatively common. In some cases, other immunosuppressive agents are necessary.

3.9. Miscellaneous conditions

3.9.1. Celiac disease

There is an increased risk of developing pancreatitis in patients with celiac disease and between 10% and 20% of newly diagnosed patients may develop pancreatic insufficiency. It has been described that celiac disease is associated with a 3-fold increased risk of development any form of pancreatitis and even higher for CP (HR: 19.8). This increased risk was only found among celiac individuals diagnosed in adulthood, and was generally noted in the first year of diagnosis especially for CP and enzyme supplementation, but remained even 5 years after [7].

Several factors might contribute to the association between celiac disease and pancreatitis [13]. The earliest proposed mechanism was malnutrition, which impairs the secretion of pancreatic enzymes and influences the composition of the bile inducing microlithiasis, thus predisposing to development of pancreatitis. Malnutrition has also been described to be associated with increased levels of pro-inflammatory cytokines as well as pancreatic acinar cell damage, ductal disruption and other structural changes, such as acinar atrophy. Other proposed mechanisms include altered levels of autoregulatory enteric hormones (cholecystokinin) and papillary stenosis resulting from localized duodenal inflammation. Another potential explanation involves immunopathogenetic mechanisms, by T helper cell class 1 (TH1) cytokine up-regulation in celiac disease through polymorphisms in tumor necrosis factor- α , a TH1 proinflammatory cytokine, which plays an important role in the pathogenesis of severe pancreatitis. Villous atrophy is associated with pancreatic insufficiency, and restored pancreatic enzyme levels are observed after introduction of a gluten-free diet.

By contrast, the relationship between autoimmune pancreatitis and celiac disease has not been demonstrated, since there is only so far a case report of this association [42].

3.9.2. Inflammatory bowel disease

Pancreatitis has been associated with inflammatory bowel disease, either secondary to the use of drugs that may potentially cause this disorder or by other mechanisms as duodenal Crohn's disease leading to pancreatic flow obstruction, or as a result of the granulomatous disease or the autoimmune process directly involving the pancreas [43].

3.10. Idiopathic pancreatitis

This condition is defined as pancreatitis with unknown etiology established after initial laboratory and imaging studies. In some patients the cause may be found after further investigations, but in others no definitive etiology is detected. These patients should be evaluated at centers of excellence focusing on pancreatic diseases. It is recommended to complete a comprehensive study, since biliary sludge/microlithiasis may be detected in up to 75% of patients with recurrent AP initially labeled as unknown origin, and it has been estimated that up to 15% of patients with benign or malignant tumors may present as apparent idiopathic

pancreatitis. Additionally, the role of genetic testing in idiopathic pancreatitis has yet to be determined, but the study of genetic abnormalities is being increasingly recognized [16,44].

4. Conclusions

Pancreatitis is a common digestive disorder with a broad spectrum of etiologies. Although most cases are secondary to biliary stones/sludge or alcohol abuse, other potential causes should be considered once the two most common etiologies have been excluded. One of the primary goals in the diagnostic process of the pancreatitis should be to reduce the rate of idiopathic pancreatitis, because the identification of the cause of the disease may help to prevent subsequent relapses when the etiological factor is eliminated.

Author details

Eugenia Lauret*, María Rodríguez-Peláez and Luis Rodrigo Sáez

*Address all correspondence to: meugelb@hotmail.com

Gastroenterology Unit, Central University Hospital of Asturias, Asturias, Spain

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