World Journal of Gastroenterology

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DOI: 10.3748/wjg.v20.i45.16891

World J Gastroenterol 2014 December 7; 20(45): 16891-16901
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (18): Pancreatitis

Acute recurrent pancreatitis: Etiopathogenesis, diagnosis and treatment

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Received: May 15, 2014 Revised: June 19, 2014
Accepted: September 18, 2014
Published online: December 7, 2014

Abstract

Acute recurrent pancreatitis (ARP) refers to a clinical entity characterized by episodes of acute pancreatitis which occurs on more than one occasion. Recurrence of pancreatitis generally occurs in a setting of normal morpho-functional gland, however, an established chronic disease may be found either on the occasion of the first episode of pancreatitis or during the follow-up. The aetiology of ARP can be identified in the majority of patients. Most common causes include common bile duct stones or sludge and bile crystals; sphincter of oddi dysfunction; anatomical ductal variants interfering with pancreatic juice outflow; obstruction of the main pancreatic duct or pancreatico-biliary junction; genetic mutations; alcohol consumption. However, despite diagnostic technologies, the aetiology of ARP still remains unknown in up to 30% of cases: in these cases the term "idiopathic" is used. Because occult bile stone disease and sphincter of oddi dysfunction account for the majority of cases, cholecystectomy, and eventually the endoscopic biliary and/or pancreatic sphincterotomy are curative in most of cases. Endoscopic biliary sphincterotomy appeared to be a curative procedure *per se* in about 80% of patients. Ursodeoxycholic acid oral treatment alone has also been reported effective for treatment of biliary sludge. In uncertain cases toxin botulin injection may help in identifying some sphincter of oddi dysfunction, but this treatment is not widely used. In the last twenty years, pancreatic endotherapy has been proven effective in cases of recurrent pancreatitis depending on pancreatic ductal obstruction, independently from the cause of obstruction, and has been widely used instead of more aggressive approaches.

Key words: Acute recurrent pancreatitis; Chronic pancreatitis; Aetiopathogenesis; Diagnosis; Treatment

Core tip: Acute recurrent pancreatitis still represents a challenging disease. In the recent years a significant improvement has been achieved in the knowledge of aetiopathogenesis and factors involved in the occurrence of disease because of advanced diagnostic tools as magnetic resonance cholangiopancreatography with secretin test, endoscopic ultrasonography and botulin toxin injection of sphinc ter of oddi. The review reports an updated diagnostic and therapeutic flow-chart flow-chart, and recent data on clinical outcomes.

Testoni PA. Acute recurrent pancreatitis: Etiopathogenesis, diagnosis and treatment. *World J Gastroenterol* 2014; 20(45): 16891-16901 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i45/16891.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i45.16891

INTRODUCTION

Acute recurrent pancreatitis (ARP) is a clinical condition characterized by repeated episodes of acute pancreatitis; ARP is therefore diagnosed retrospectively by clinical definition after at least the second episode of acute pancreatitis. The term ARP was reported in the first Marseille classification of pancreatitis[1] which clearly distinguished

ARP from chronic pancreatitis, and then in the classification of TIGAR-O[2], so-called from the acronym of the major predisposing risk factors. However, the term was eliminated in the revised classifications of Marseille[3] and Marseille-Rome[4] because of the difficulties of distinguishing between episodes of acute pancreatitis occurring in a normal pancreas or in chronic pancreatitis.

Pancreatitis generally recurs in a normal morpho-functional gland and is characterized by self-limited edematous changes in the pancreas. Acute episodes are generally mild to moderate, requiring 3-10 d in hospital; in some cases, pancreatic-like pain, with serum amylase and/or lipase elevation, lasts only a few hours and the patient recovers without hospitalization. Minor pancreatic lesions suggesting a chronic disease may be found in some cases, either at the first episode of pancreatitis or during the follow-up. This suggests that recurrent episodes of acute pancreatitis may complicate the course of chronic subclinical pancreatitis, meaning they are the clinical expression of chronic pancreatitis diagnosed in an early phase, or otherwise they may themselves induce chronic lesions as a consequence of repeated damage. Whether or not recurring bouts of pancreatitis in a morphologically normal pancreas can lead to chronic pancreatitis is still an open question, because only few, empirical data indicate whether, how often, and in which patients recurrent pancreatitis progresses to the chronic disease.

Alcohol and, more recently, smoking have been reported as the most frequent factors associated with the progression toward chronic disease. Ammann *et al*[5,6] reported a rate of chronic pancreatitis of about 80% over a 15-year period in a series of patients with recurrent pancreatitis and alcohol consumption. Four recent studies examined the progression to chronic pancreatitis in patients with recurrent pancreatitis[7-10]; progression to chronic disease was reported in from 4.0% to 32.3% of cases. However, only the most recent study[10] simultaneously assessed alcohol consumption, smoking, bile stone disease, and unknown etiology. This study was a population-based study, carried out in a very large series of patients recruited over a ten-year period and followed up for a median of 40 mo; chronic pancreatitis was related to alcohol, other causes including smoking, unknown causes, and bile stone disease in respectively 28%, 1%, 10%, and 6% of cases. These figures confirm that, excluding cases with a history of significant alcohol consumption, there is underlying chronic pancreatic disease in about one fourth of cases of recurrent acute pancreatitis of either known or unknown etiology and it can render ineffective a therapy that removes the recognized possible causes of acute pancreatitis.

In our series of 33 patients with pancreas divisum and a history of ARP, either suffering or not from pancreatitis episodes in the year preceding enrolment in the study and followed for five years, endoscopic ultrasound findings consistent with chronic pancreatitis were seen in similar proportions of patients undergoing endoscopic therapy and in the observation group (63.2% and 57.1%, respectively). However, among patients undergoing endoscopic therapy, chronic pancreatitis findings were significantly less frequent in those whose treatment was successful. Dorsal duct dilation did not significantly affect the factors suggesting chronic pancreatitis in either group, confirming that factors other than ductal dilation may be involved in chronic disease in this category of patients.

Several factors play an etiologic role in ARP; in fact, any cause of acute pancreatitis can lead to recurrent episodes if it is not corrected. The etiology of ARP can be identified in the majority of patients and causes can be mechanical, inherited, autoimmune, metabolic, and drug-induced; parasites, vascular disorders, and toxic substances may also induce episodes of acute pancreatitis. The most common causes include common bile duct stones or sludge and bile crystals; sphincter of oddi dysfunction; anatomical variants of the pancreatic ductal system, common bile duct or pancreatico-biliary junction interfering with pancreatic juice outflow; obstruction of the main pancreatic duct or pancreatico-biliary junction; genetic mutations; alcohol consumption.

However, despite today's diagnostic technology, the etiology of ARP remains unknown in up to 30% of cases: in these cases the term "idiopathic" is used. The number of these cases diagnosed as "idiopathic", however, is decreasing as our understanding and diagnostic accuracy improve.

ETIOLOGY

Mechanical factors may induce episodes of acute pancreatitis by obstructing pancreatic juice outflow into the duodenum, with consequent intraductal hypertension, or inducing bile reflux into the main pancreatic duct, with intrapancreatic activation of zymogens (a theory proposed by Opie since 1901 for gallstone pancreatitis)[11]. Conditions that induce mechanical obstruction are either acquired or congenital and may be located at the level of the bilio-pancreatic junction, or main pancreatic duct.

Acquired conditions

Gallstone disease represents the most common condition associated with ARP in western countries. In bile duct stone disease, gallstones or bile sludge may induce acute pancreatitis either as a consequence of an impacted stone that obstructs the main pancreatic duct at the level of Vaters' papilla (a rare event), or because of transient papillary edema or papillary orifice relaxation following the passage of stones, that can obstruct the pancreatic juice flow or favor duodenopancreatic reflux, respectively. Transient ampullary obstruction may allow bile to reflux into the pancreas, even if the pressure in the main pancreatic duct in normal conditions is generally higher than in the common bile duct. Bile reflux into the pancreatic ductal system is facilitated if there is a common channel at bilio-pancreatic junction. The common channel theory, although debated, has been confirmed in two studies carried out in patients with recent episodes of gallstone-

induced acute pancreatitis who had undergone surgery; these studies documented the presence of amylase in the bile collected by a T-tube inserted into the common bile duct, suggesting there might be a functional channel between the two ductal systems[12,13].

The gallstone disease may also be manifested only by: (1) microlithiasis (stones less that 2 mm in diameter), that can be seen or suspected mainly at endoscopic ultrasound (EUS) or *endoscopic* retrograde cholangio-pancreatography (ERCP); (2) gallbladder sludge, that generally in normal conditions can only be visualized by EUS[14]; and (3) calcium carbonate, cholesterol monohydrate and calcium bilirubinate crystals, that can be detected only on microscopic examination of centrifuged bile aspirated from the duodenum or common bile duct in 36%-67% of patients[15-22]. However, microscopic bile crystals could merely indicate the presence of undetected stones, rather than cause *per se* an acute pancreatitis. In fact, either long-term ursodeoxycholic acid (UDCA) therapy, or cholecystectomy, or endoscopic biliary sphincterotomy have been found to prevent further episodes of 'idiopathic' pancreatitis in several series of patients without evidence of bile duct stones, confirming the role of occult gallstone disease in recurrent pancreatitis[23,24].

Sphincter of oddi dysfunction (SOD) is another common cause of ARP and is probably the most common cause of the idiopathic form. SOD comprises two clinical entities: (1) SO increased basal pressure, which refers to a structural alteration of the sphincter, as consequence of a long-lasting inflammatory process with subsequent fibrosis (stenosis); and (2) SO dyskinesia, referring to a transient primary motor abnormality characterized mainly by sphincter hypertone. Surgical specimens of the sphincter obtained from SOD patients show inflammation, muscular hypertrophy, and fibrosis of the Vater's ampulla in approximately 60% of patients while a primary motor disorder may occur in the remaining 40% of cases with normal histology[25]. SOD has been classified under three headings on the basis of clinical and morphological parameters[26] and may involve either the biliary or the pancreatic segment of the sphincter[27]. Type 1 dysfunction patients have acute pancreatitis (pancreatic-like pain with high serum pancreatic enzymes) together with a dilated common bile and/or main pancreatic duct and prolonged drainage, suggesting a structural abnormality (ampullary stenosis). Type Ⅱ dysfunction patients have pancreatic-like pain, associated with one or two type Ⅰ items; in this group, with either pancreatitis or only pancreatic-like pain patients with functional or structural sphincteric disorder are probably evenly distributed. Manometry shows elevated basal sphincter pressure but no stenosis in the majority of patients. Type Ⅲ dysfunction patients have only pancreatic-like pain with no rise in serum pancreatic enzymes and bilio-pancreatic morphological abnormalities. By definition, type Ⅲ SOD is not considered in case of recurrent pancreatitis.

SOD can affect either the biliary sphincter, pancreatic sphincter, or both. Judging from manometric findings from published data, SOD involves the biliary and/or pancreatic sphincter in respectively 65%-92% and 85%-100% of type Ⅰ SOD, 58%-65% and 55%-67% of type Ⅱ, and in 35%-59% and 28%-59% of type Ⅲ. In a series by Eversman *et al*[27], among 123 patients labeled as type Ⅱ, SOD was diagnosed in 65%; respectively 22%, 11%, and 32% had elevated basal sphincter pressure in the pancreatic sphincter only, biliary sphincter only, or both. However, normal basal pressure does not mean there is no fluctuating dysfunction or exclude a role of the sphincter in the recurrence of pancreatitis.

Other acquired anatomical conditions that may be associated with obstructive mechanisms are periampullary diverticula, benign and malignant tumors of the Vater's papilla or pancreatico-biliary junction, organic strictures of the main pancreatic duct, and cystic neoplasms, including mucinous ductal ectasia. Rare conditions associated with ARP are choledochocele and ampullary choledochal cysts.

There is still debate about whether periampullary diverticula are directly involved in the recurrence of pancreatitis; although these diverticula are frequently found in both gallstone and recurrent pancreatitis in middle-aged subjects, it has yet to be proved that they play any role in the occurrence of pancreatitis.

Organic strictures of the main pancreatic duct may be neoplastic or the consequence of a fibrotic process induced by a previous acute pancreatitis or pancreatic trauma, or a chronic disease. Neoplastic strictures are found to induce acute pancreatitis in about 5% of cases; among cystic neoplasms, mucinous ductal ectasia is the one most frequently associated with ARP or intermittent pancreatic-like pain.

Choledochocele is a congenital or acquired condition in which the intramural segment of the common bile duct is dilated and herniates into the duodenal lumen. Acute pancreatitis may develop when the cystic dilation or bile duct sludge or stones obstruct the pancreatic juice outflow. Endoscopically, the papilla shows a bulge into the duodenum, mainly involving the caruncula, and is soft when pressure is applied with the ERCP catheter. Ampullary choledochal cysts can develop when there is SOD.

Anatomical variants

Pancreas divisum is the most common variant of pancreatic ductal anatomy, occurring in up to 12% of individuals. Partial fusion of the ventral and dorsal ducts characterizes the incomplete (functional) pancreas divisum, in which the dorsal duct can drain through the major papilla *via* a communicating branch of the ventral duct. However, this communication is generally narrow and may be inadequate for draining the pancreatic secretion. The inability of minor papilla to accommodate the flow of pancreatic juice when the gland is stimulated leads to ductal hypertension that in some individuals may cause either recurrent pain shortly after a meal, or a persistent asymptomatic rise in serum pancreatic enzymes, or acute

relapsing pancreatitis. Persistent obstruction may lead to a chronic obstructive pancreatitis.

Although one retrospective series found no correlation between pancreas divisum and ARP[28], most studies show a significantly higher prevalence of this congenital variant in this patient population[29-33]. Dilation of the dorsal duct confirms the presence of some obstruction at the level of minor papilla and suggests a positive outcome after sphincterotomy or stenting.

Annular pancreas is a rare anatomical condition that may be associated with duodenal or biliary obstructive symptoms, as the consequence of the entrappement of both the duodenum and common bile duct by the annular growth of the gland[34-36]. About one third of patients with annular pancreas also have pancreas divisum, so it is not clear whether recurrent pancreatitis depends on the annular variant or on the pancreas divisum.

The presence of a common pancreatico-biliary channel abnormally long without sphincters separating the biliary and pancreatic ducts is a condition that facilitates free reflux of bile and pancreatic juice into the alternative duct. This abnormality of the pancreatico-biliary junction is easily diagnosed by MRCP or ERCP. Choledochal cysts are frequently associated with this kind of junction.

Other anatomical variants of the pancreatic ductal system and junction between the ventral and dorsal ducts may induce an impaired outflow of pancreatic juice into the duodenum and could explain the pancreatic pain and recurrent pancreatitis in some cases, when other causes have been excluded. The most frequent findings are a loop or sigmoid configuration of the main pancreatic duct.

Genetic causes

Genetic mutations have long been suspected as being associated with ARP and development of chronic pancreatitis over time[37]. Inherited conditions that can induce ARP are the cystic fibrosis transmembrane conductance regulator-gene (*CFTR*-gene), PRSS1-gene and SPINK1-gene mutations.

***CFTR*-gene mutations:** This condition represents the most common inherited disease of the exocrine pancreas. Some phenotypic *CFTR*-gene mutations occur in about 5% of the Caucasian European and North American populations; however the true incidence of *CFTR*-gene mutations is probably underestimated[38-41]. Mutations of *CFTR*-gene induces a defect in chloride ion transport at the level of the apical membrane-chloride channels of epithelial cells, resulting in an abnormally viscous exocrine secretion that leads to persistently high intraductal pancreatic pressure. Over time, this chronic condition leads to secondary chronic obstructive ductal changes.

There are many clinical features associated with *CFTR*-gene mutation phenotype. Exocrine pancreatic insufficiency with no inflammatory changes is the most common finding; ARP may be the only clinical sign in some patients; asymptomatic persistent pancreatic hyperenzymemia with no morpho-functional pancreatic disorders may also be found. Subjects with non-functional CFTR protein show clinical features of cystic fibrosis. Those with less severe mutations in the *CFTR* gene risk developing pancreatitis, which is estimated to be 40 to 80 times that in the general population[42]. Heterozygotes for *CFTR* mutations are generally healthy but still have a 3 to 4-fold risk over the general population for pancreatitis.

***PRSS1*-gene mutations:** Mutations in the cationic trypsinogen gene have been found in patients with hereditary pancreatitis[43,44]. In this autosomal dominant disorder the pancreas is unable to protect itself by premature or excessive trypsin activation in the gland; the lack of this protective mechanism against premature activation of trypsin predisposes individuals to recurrent bouts of pancreatitis in childhood and frequent progression to chronic pancreatitis.

Another pathogenic cofactor involved in ARP in presence of hereditary pancreatitis seems to be SOD; the dysfunction might be the consequence of the chronic inflammation of the sphincter induced by the passage of activated trypsin through it over time, in presence of a common biliopancreatic junction[45]. In these patients sphincterotomy may relieve symptoms, confirming a role of the high intraductal pressure induced by SOD or stenosis, but it does not significantly affect the progression of the acute recurrent disease to chronic pancreatitis. Patients with a history of first- or second-degree relatives with early-onset or recurrent episodes of acute pancreatitis of unknown etiology should be considered for genetic testing.

***SPINK1*-gene mutations:** Another group of mutations that predispose to pancreatitis are in the serine protease inhibitor Kazal type I gene (*SPINK1*). *SPINK1* has a protective action in the pancreas since it serves as a critical feedback inhibitor of trypsin. Therefore, in a state of retained SPINK1 protein function due to a *SPINK1* gene mutation (mostly heterozygous), the pancreas is more likely to develop pancreatitis from other genetic or environmental factors. It has been repeatedly shown that 16%-23% of patients with apparent idiopathic pancreatitis have *SPINK1* mutations, compared with only about 2% of healthy controls[46]. These mutations have been estimated to raise the risk for pancreatitis about 12-fold over the general population.

Other causes

Well-known metabolic causes persisting over time that can induce ARP are hypertriglyceridemia and hypercalcemia. There are many causes of hypercalcemia, but the majority of patients who develop ARP have hyperparathyroidism. The diagnosis may be missed if calcium levels are not measured during each attack. Hypertriglyceridemia is increasingly common in Western countries in the setting of metabolic syndrome. Typically, serum triglycerides have to exceed 1000 mg/dL to precipitate an attack

of acute pancreatitis. Control of diabetes mellitus, weight loss, and lipid-lowering agents can reduce the triglyceride levels, but non-compliance is frequent and many of these patients progress toward chronic pancreatic damage.

Low serum levels of antioxidants, as selenium, vitamins A, C and E, and riboflavin, have been found in patients with chronic pancreatitis, probably because a deficient diet. The observation that selenium levels were lowest during acute bouts of pancreatitis[47] stimulated investigators to assess the antioxidant profile also in patients with ARP; however, the hypothesis that acute cellular injury determined by an uncontrolled free radical activity may be the cause of unexplained recurrent pancreatitis in some patients was not confirmed, as the antioxidant profiles were similar to those of control subjects[48]. Excess alcohol consumption is responsible for about 30% of all cases of acute pancreatitis in the United States[49]. Alcohol-induced acute pancreatitis typically occurs in people who have consumed large amounts of alcohol for at least 5-10 years. Recurrent episodes of acute alcoholic pancreatitis typically occur in patients with existing chronic pancreatitis[50]. Alcohol intake causes a transient stimulation of exocrine pancreatic secretion by increasing the synthesis and secretion of digestive and lysosomal enzymes in pancreatic acinar cells. Alcohol also sensitizes pancreatic acinar cells to cholecystokinin and may have a direct toxic effect on the acinar cells. However, these mechanisms alone are probably not sufficient to cause acute pancreatitis. Therefore, additional genetic and environmental factors are thought to influence the development of the disease.

Smoking has long been thought to play a role in the induction of acute pancreatitis, but it was only recently that large prospective studies have proved that cigarette smoking is an independent risk factor. The duration rather than the intensity of smoking increases the risk of non-gallstone-related acute pancreatitis. The risk of pancreatitis was reduced to a level comparable to that of non-smokers only two decades after smoking cessation[51]. However, data regarding the role of smoking in recurrent pancreatitis are lacking.

Many medications have been recognized as causes of acute pancreatitis, by a dose-dependent or hypersensitivity-related mechanism. For a number of substances there is general agreement on some relation with acute pancreatitis, and a recent review by the Midwest Multicenter Pancreatic Study Group[52] listed the following as medications for which a strong association with pancreatitis is documented by at least one positive rechallenge: alpha-methyldopa, 5-aminosalicylate, azathioprine, cimetidine, cytosine arabinoside, corticosteroids, estrogens, furosemide, isoniazid, mercaptopurine, metronidazole, pentamidine, procainamide, sulfamethazole, sulindac, tetracycline, trimethroprim/sulfamethoxazole and valproic acid.

DIAGNOSIS

It is extremely important to establish the cause of episodes of acute pancreatitis because by removing it we eliminate the risk of further recurrences if there is no chronic underlying disease involved. The patient's history and standard diagnostic tests such as blood chemistry, trans-abdominal ultrasound, MRCP, and CT scan generally detect the causes of recurrent episodes in about 70% of cases. When no cause is found at the initial diagnostic work-up, these patients should have a more advanced diagnostic work-up, that includes specific pancreatic tests, genetic testing, MRCP with secretin stimulation, sphincter of oddi motility evaluation, EUS, and in selected cases ERCP. Genetic and autoimmune pancreatitis can be diagnosed by testing respectively for *CFTR* or *SPINK1/PRSS1* gene mutations and IgG 4.

MRCP with the secretin test (MRCP-S) gives details of the morphology of the pancreatico-biliary ductal system and permits indirect evaluation of sphincter of oddi motility, as an alternative to more invasive tests such as manometry. However, the secretin test is less sensitive than manometry for intermittent sphincter motility disorders like types Ⅱ and Ⅲ SOD. Injection of secretin (1 IU/kg i.v. bolus) enhances the pancreatic ductal morphology, by stimulating pancreatic secretion of water and bicarbonates, and permits an evaluation of the kinetics of the main pancreatic duct (MPD), by measuring the duct diameter as an indirect indicator of pancreatic juice outflow through the papilla of Vater. The diameter of the MPD is measured at baseline at the body of the gland, then secretin is injected. The basal MPD diameter is considered normal when it is ≤ 3 mm; changes in MPD diameter (millimeters) are then measured at 1-min intervals for 15 min. The mean of the measurements at the last three one-minute intervals (from 13 to 15 min) is taken as the final value[53]. A Δ final-basal MPD caliber > 1.0 mm is considered diagnostic for some SOD[54,55].

Three studies employed MRCP-S for the diagnosis of SOD. One found no differences in normal subjects and SOD patients[55]; another found sensitivities of 37% and 62.5% and specificities of 85% and 85% in types Ⅱ and Ⅲ SOD[56]; the third found 57.1% sensitivity and 100% specificity in idiopathic pancreatitis[57].

Sphincter of oddi manometry (SOM) is still the gold standard for the diagnosis of SOD. SOM is performed during ERCP and requires selective cannulation of the bile duct and/or pancreatic duct through the major papilla with a triple-lumen, 5 F manometry catheter. Normal basal sphincter pressure usually does not exceed 35 mmHg (mean 15 mmHg); a basal pressure higher than 40 mmHg is considered abnormal. Abnormal basal sphincter pressure may be found in one or both sphincters. Raddawi and coll[58]. reported that abnormal basal sphincter pressure was mainly confined to the pancreatic duct segment in patients with ARP and to the bile duct segment in patients with biliary-type pain and abnormal liver function tests. In patients with SO stenosis manometric recording is reproducible and does not respond to muscle relaxants. In patients with SO dyskinesia there is a variety of abnormalities of wave propagation and/or frequency; the abnormal basal sphincter pressure or motility responds to muscle relaxants, and the sphincter may give a paradoxi-

cal response to i.v. cholecystokinin (CCK).

Indications for SOM have been developed according to the modified Hogan-Geenen SOD classification system. Type I SOD does not require manometric investigation for confirmation, since a structural disorder of the sphincter (stenosis) occurs in this situation. These patients have the best outcomes after biliary and/or pancreatic sphincterotomy.

In type Ⅱ SOD with dilated ductal system, the basal sphincter pressure has been found abnormally elevated in the majority of cases[27,59,60] but a normal pressure profile does not exclude a transient dysfunction. Manometry, therefore, does not substantially improve the diagnosis, while exposing patients to an increased risk of post-procedural pancreatitis. In cases with non dilated ducts an objective diagnosis of dysfunction can be obtained only by manometric recording of the biliary and pancreatic segments of the sphincter. Unfortunately, the frequency of abnormal manometric recordings in these patients is low and varies widely, ranging in published series from 15% to 50% for biliary[27,59,60] and 35% to 49% for pancreatic-type SO dysfunction[27,61].

Although they have not been thoroughly studied, SOM results have been found to predict outcome from sphincterotomy in SOD patients, with the highest success rate in patients with type I SOD[62].

Pancreatic stent as a diagnostic test to achieve pain relief and predict the response to more definitive therapy (sphincter ablation), has been tried only limitedly. Our group has used pancreatic 5 F and 7 F stenting in some patients with recurrent pancreatitis and non-dilated ducts, with significant reductions in pancreatitis episodes; in these cases pancreatic sphincterotomy was successful[63]. Pancreatic stenting in patients with normal pancreatic ducts may cause ductal and parenchymal injury if the stent is left, even if for a short time.

Botulinum toxin (Botox) is a potent inhibitor of acetylcholine release from nerve endings. In a preliminary trial Botox injection into the SO halved the basal sphincter pressure, with an effect lasting four months, and gave symptom improvement[64]. The effect of Botox injection has been investigated only in type Ⅲ patients with manometric evidence of SOD: Botox injection has been shown to predict the patients whose symptoms were most likely to improve with endoscopic sphincterotomy in 44%-80% of cases[65].

Although further studies are still needed, Botox may serve as a diagnostic trial for symptomatic patients with uncertain or not documented SOD, with responders undergoing permanent sphincter ablation. Unfortunately, the short-lasting effect of Botox limits its indication as a trial only to patients with symptoms occurring at intervals of not more than three months.

EUS has the highest sensitivity for detecting microlithiasis and sludge, either in the gallbladder or in the common bile duct[66], pancreatic tissue fibrosis, and small ductal changes of both the main pancreatic duct and side branches. The diagnosis of biliary sludge can be very challenging, even with EUS, particularly after cholecystectomy. In some patients with recurrent pancreatitis and normal pancreas at CT scan and MRCP, EUS identifies ductal and parenchymal abnormalities, suggesting a diagnosis of chronic pancreatitis[67,68]. The frequency of the diagnosis of CP in patients with ARP, on the basis of EUS criteria, ranges from 10%-30%[69,70].

ERCP should be considered for diagnostic purposes only in selected cases of uncertain ductal morphology even at MRCP-S and should be followed by immediate biliary and/or pancreatic sphincterotomy. The procedure is associated with a 3%-5% complication rate that may reach 30% in cases with SOD. This additional work-up usually leads to the diagnosis of microlithiasis or bile sludge, SOD, pancreatic ductal abnormalities, either congenital or acquired, or anomalous pancreatico-biliary junction, early chronic pancreatitis, and genetic or autoimmune disorders. After a complete additional advanced work-up, the etiology remains unknown in no more than 10% of recurrent pancreatitis, which can then be defined as true idiopathic recurrent pancreatitis.

THERAPY

The efficacy of therapy in patients with a history of ARP depends on two main factors: whether or not the bouts of acute pancreatitis occur in a normal pancreas or in a setting of chronic pancreatitis, and whether or not a cause can be identified and removed.

Therapeutic approach to recurrent pancreatitis of biliary etiology (documented or suspected)

Laparoscopic cholecystectomy is curative when gallbladder stones or sludge are detected; however, the clinical benefit for sludge is less evident. If only sludge is present or suspected and cholecystectomy is not considered, UDCA (usually 12 mg/kg) is an acceptable alternative, if necessary combined with endoscopic biliary sphincterotomy. In these cases, long-term therapy with bile acids is required, since the drug works slowly. In previous studies[16,24,14] patients treated with UDCA had a significantly lower rate of recurrent pancreatitis (approximately 20% with therapy compared with 60% without). Unfortunately, no studies have made a head-to-head comparison of cholecystectomy, endoscopic biliary sphincterotomy, and bile acid therapy.

In patients who have already undergone cholecystectomy but present repeated attacks of pancreatitis with signs suggesting a biliary origin, even if no stones or sludge are detected, endoscopic biliary sphincterotomy is the procedure of choice. Common bile duct stones have been found in 4%-24% of patients up to 15 years after cholecystectomy. In cases with no evidence of stones, UDCA is likely to be ineffective because removing the gallbladder markedly reduces or completely eliminates the bile crystals and sludge; sludge may form in cases with SOD leading to persistent or transient bile flow obstruction. Endoscopic biliary sphincterotomy is the only effec-

tive treatment in these patients.

Therapeutic approach to recurrent pancreatitis associated with SOD

SOD is reported in about one third of cases with recurrent pancreatitis. It is still not clear whether biliary sludge or crystals, or inflammation cause sphincter malfunction, because of conflicting data and a lack of specific studies. The therapeutic approach in patients with SOD aims at reducing the resistance caused by the sphincter to the flow of bile and/or pancreatic juice. In documented SOD endoscopic sphincterotomy is currently the standard therapy. Non-invasive therapies, such as bile acids, calcium channel blockers, nitrates, and anticholinergic drugs, have proved unsuccessful in most cases and are not effective when an organic stricture involves the sphincter (type I dysfunction).

In patients with uncertain documentation of dysfunction the risks and benefits of endoscopic sphincterotomy should be carefully weighed before recommending it, because SOD patients have an ERCP-related complication rate that is markedly higher compared to patients with ductal stones.

Medical therapy of SOD has been investigated only on a small scale, by using drugs that relax smooth muscle. Sublingual nifedipine and nitrates have been found to reduce the basal sphincter pressure and achieve clinical benefit in up to 75% of patients. Drawbacks of medical therapy are the systemic side effects of the drugs, tachyphylaxis, and lack of long-term outcomes from regular therapy. Nevertheless, because of the "relative safety" of medical therapy, it should be considered in suspected type Ⅱ SOD with non-dilated ducts before considering more aggressive sphincter ablation.

Besides smooth muscle relaxants, other drugs can be used in these patients. Oral UDCA has been shown to be effective in patients with idiopathic recurrent pancreatitis, confirming the role of bile microlithiasis or sludge in SOD.

Endoscopic sphincterotomy may ablate either the biliary or the pancreatic segment of the SO, or both. In general, biliary sphincterotomy is done first and leads to clinical improvement in about 80% of cases; in case of failure, pancreatic sphincterotomy is done, preceded or not by further function testing. In some centers, biliary and pancreatic sphincterotomy are done at the same time, considering the high probability of a consensual sphincter dysfunction.

In SOD patients, endoscopic sphincterotomy is associated with a high rate of acute post-procedure pancreatitis (up to 20% of cases). To reduce such a risk, endoscopic techniques have been used (pancreatic duct stenting after biliary or pancreatic sphincterotomy and naso-pancreatic drainage after pancreatic sphincterotomy) to limit this complication.

Clinical improvement after sphincterotomy has been reported in 55%-95% of patients, depending on the type of SOD, according to the modified Hogan-Geenen classification system, and manometric recordings. Nineteen studies have been published, including up to 237 patients, with follow-up ranging from a mean of three months to five years[71,72]. Favorable outcomes are highest in type Ⅰ SOD: in these patients improvement was reported in 83%-100% of cases. In type Ⅱ SOD patients, with functional sphincter disorder, long-term symptom relief was reported in up to 79%, depending on whether manometry was abnormal (best results) or normal. In patients without documented SO abnormalities, intrasphincteric botulin toxin injection could be considered before sphincterotomy and might help identify a transient SOD undetected by functional tests[73]. Since botulin toxin induces sphincter relaxation lasting no more than three months, however, it should be use to predict those most likely to benefit from endoscopic sphincterotomy, in patients with recurrent pancreatitis with normal morpho-functional findings[74]. This approach is adopted in only a few centers.

Compared to biliary sphincterotomy alone, dual sphincterotomy has been shown to have significantly better outcomes in the majority of studies, even if in a recent study dual sphincterotomy and biliary sphincterotomy had similar effects in preventing recurrence of acute pancreatitis[75].

Endoscopic sphincterotomy may fail to achieve symptom relief in documented SOD in the following conditions: (1) biliary sphincterotomy has been inadequate or re-stenosis has occurred. Sphincterotomy should be revised; if no "cutting space" remains balloon dilation should be considered; (2) pancreatic sphincter has residual abnormal basal pressure. A persistent elevated basal pressure of the pancreatic sphincter has been reported in approximately 90% of patients with persistent pain or pancreatitis after biliary sphincterotomy. Endoscopic pancreatic sphincterotomy achieves symptomatic improvement in 60%-90% of these patients. As an alternative, if pancreatic sphincterotomy has not been done, an empirical therapeutic approach may be attempted by placing a small-caliber (5-7 F) pancreatic stent; the stent may be effective and helps to predict whether there is any persisting outflow obstruction. However, in a normal pancreas pancreatic stenting induces chronic pancreatitis-like ductal changes and should therefore be done only for a short period (no longer than three months); moreover, few published data on pancreatic stenting for SOD are available and most of them so far are disappointing; and (3) patients may fail to respond to sphincterotomy because they have chronic pancreatitis, even with an apparently normal pancreatogram. In these patients EUS may show parenchymal and ductal changes suggesting early-stage chronic pancreatitis.

The surgical approach most commonly used is transduodenal biliary sphincteroplasty with trans-ampullary septoplasty. Outcomes are similar to those of endoscopic sphincterotomy while complication rate and cost of care are higher, so the surgical approach for SOD has largely been replaced by endoscopic therapy.

Therapeutic approach to recurrent pancreatitis associated with pancreas divisum

Pancreas divisum is reported in about 20% of patients with ARP. Endoscopic and surgical therapy are comparably effective in 70%-90%[76] so endoscopic therapy is preferred in most cases. It is still not clear whether endotherapy should be considered only when there is a dilated dorsal duct and whether it can prevent the risk of progression toward chronic pancreatitis. In cases with a non-dilated dorsal duct, the MRCP-S test may help detect some minor papilla malfunction and select the therapy.

Endoscopic therapy includes minor papilla sphincterotomy or stenting, or catheter dilation. In patients with dilated dorsal duct or abnormal function test, and no ductal strictures upstream of the minor papilla, sphincterotomy is the procedure of choice. After sphincterotomy, a short-term dorsal pancreatic duct stent placement is recommended to avoid post-procedure strictures and procedure-related complications. In cases without dorsal duct dilation or abnormalities and with a normal function test, dorsal pancreatic duct short-term stenting should be considered, to identify patients who can benefit from minor papilla sphincterotomy.

If pancreatitis still recurs after sphincterotomy, pancreatic stenting may be useful, with 7 F to 10 F stents depending on the dorsal duct dilation. If ductal strictures are documented, catheter dilation followed by stenting is the therapy of choice.

Although endoscopic therapy has been proved effective in a large percentage of cases, only one randomized controlled trial examined a small number of cases: in the treatment group, 9 out of 10 patients (90%) had no further episodes of acute pancreatitis during a three-year follow-up, while 6 of 9 patients (67%) who were randomized to no treatment had at least one episode[77]. A still unsettled issue is whether a tendency towards chronic pancreatitis persists in pancreas divisum patients, even after successful treatment, and if so, why.

Therapeutic approach to recurrent pancreatitis associated with other lesions obstructing the flow of pancreatic juice

Any process preventing the free flow of pancreatic juice can lead to ARP. The lesions can be at the level of Vater's papilla or around it, or in the pancreatico-biliary ductal system. Treatment aims to relieve the obstruction and re-establish the free flow.

Ampullary adenomas and carcinomas are the commonest causes of papillary lesions and can be resected either surgically or endoscopically. Ampullary tumors generally have a more favorable outcome than pancreatic tumors. Independently from the histological diagnosis, EUS should be done to establish whether an endoscopic or surgical approach is most likely to be curative. When the lesions are confined within the muscolaris mucosae and do not involve the biliary or pancreatic duct, endoscopic resection should be preferred. The tumor can be excised en-bloc or piecemeal by snare ampullectomy. En-bloc resection should be done in cases with a lesion confined within the ampulla; in these cases there is no need to lift the mucosa by submucosal injection of saline solution, glycerol or hyaluronic acid, because this maneuver may make it more difficult to resect the lesion completely. Piecemeal resection is done when the lesion tends to extend around the papilla; in these conditions, lifting the mucosa from the submucosa permits complete and safer resection of the adenomatous tissue.

In patients with an abnormally long (> 15 mm) common pancreatico-biliary channel the sphincter does not separate the bile and pancreatic ducts so bile can flow into the pancreatic ductal system and lead to pancreatitis. Endoscopic biliary sphincter ablation avoids the bile flow into the pancreatic duct and reduces the intra-ampullary resistance to pancreatic juice flow, thus reducing the risk of recurrences of pancreatitis.

To deal with choledochocele endoscopic section by biliary sphincterotomy or needle-knife is usually effective, though a few patients require surgical sphincteroplasty. The surgical approach should be preferred for large lesions.

Segmental strictures of the main pancreatic duct are found in 5%-10% of patients with ARP[78] and may be related to chronic pancreatitis, residual scars in acute severe pancreatitis, pancreatic trauma, or neoplastic conditions. The differential diagnosis between the benign and malignant nature of the stricture is pivotal before planning treatment, which in most cases is endoscopic. EUS has swiftly became the preferred diagnostic procedure, because it offers the best sensitivity for identifying a pancreatic neoplasm for lesions 2-3 cm in diameter, and the diagnosis can be confirmed by EUS-guided fine-needle aspiration. ERCP should be done to confirm the diagnosis only in selected cases, by guide wire-guided intra-ductal brush cytology or, more recently, confocal endomicroscopy.

Endoscopic treatment should be done with curative purpose for benign lesions and palliation for malignant lesions unsuitable for curative surgery, and consists of ERCP-guided stricture dilation and stenting. Stenting of benign strictures will be planned for one or -better -two years, with three-monthly stent exchange, using progressively larger stents, to achieve lasting dilation and resolution of symptoms.

Cystic pancreatic tumors may also be associated with ARP. Serous cystadenomas are benign and can be managed conservatively. Mucinous tumors (cystadenomas and adenocarcinoma, or intraductal papillary mucinous neoplasia-IPMN) are pre-malignant or malignant, and require follow-up and surgical resection when there are worrisome features or high-risk stigmata. For IPMN involving the main pancreatic duct the risk of malignant evolution is documented, but the data are still uncertain for IPMN involving side branches. IPMN involving the main pancreatic duct more frequently causes recurrent pancreatitis, since the abnormal mucin secretion produces a dense pancreatic juice that leads to intraductal hyperten-

sion. Endoscopic biliary and pancreatic sphincterotomy facilitates the juice outflow through the papilla and may help prevent episodes of acute pancreatitis in patients in a follow-up program.

Annular pancreas is another congenital abnormality of the pancreatic ductal system seen in patients with recurrent pancreatitis. Surgical resection of the lesion is the treatment of choice in these cases.

Recurrent pancreatitis associated with the *CFTR*-gene mutation of hereditary pancreatitis may be prevented by endoscopic pancreatic sphincterotomy in selected cases with a dilated pancreatic duct; this procedure facilitates the outflow of pancreatic juice, which is particularly dense in patients with *CFTR*-gene mutations and may cause intraductal hypertension. However, as yet there are no prospective studies demonstrating that decompressive therapy can favorably alter the course of the disease.

In conclusion, a careful diagnostic algorithm serves to identify the etiology of ARP in up to 90% of cases, while in the remaining cases the cause remains unknown. The introduction into clinical practice, besides CT scans and ERCP, of genetic testing, SO manometry, MRCP and EUS with secretin, and botulin toxin injection, have markedly improved the diagnostic yield. Because occult bile stone disease and SOD account for the majority of cases, cholecystectomy, and if necessary endoscopic biliary and/or pancreatic sphincterotomy are curative in most cases of ARP. Endoscopic biliary sphincterotomy appears to be curative *per se* in about 80% of patients. Oral UDCA alone has also been reported effective for the treatment of biliary sludge and possible related SOD in some studies. In uncertain cases botulin toxin injection may help identify some cases of SOD, but this treatment is not widely used.

In the last twenty years, pancreatic endotherapy has been proved effective in cases of recurrent pancreatitis depending on pancreatic ductal obstruction, independently from the cause of obstruction, and has been widely used instead of more aggressive approaches. However, there is as yet no long-term follow-up to assess the progression of the disease, independently of the therapeutic success.

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P- Reviewer: Cerwenka HR, Marinis AD, Neri V **S- Editor**: Qi Y
L- Editor: A **E- Editor**: Wang CH

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ISSN 1007-9327