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Aetiologies of Recurrent Acute Pancreatitis: Acute or Chronic Relapsing Disease?

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The term recurrent acute pancreatitis is generally used to indicate recurrent episodes of acute pancreatitis occurring in a setting of a normal morpho-functional gland. Self-limited oedematous changes within the pancreas are the most common findings on ultrasound (US) and computerized tomography (CT) scan; bouts are generally mild to moderate, resulting in hospitalization of 3-10 days. In other cases, pancreatic-like pain associated with serum amylase and/or lipase elevation lasts only few hours and the patient recovers spontaneously, not requiring hospitalization.

However, minor ductal lesions suggesting an established chronic disease may be found in a number of cases, either on the occasion of the first episode of pancreatitis or during the follow-up; this suggests that recurrent episodes of acute pancreatitis on the one hand may complicate the course of a chronic subclinical pancreatitis and, on the other hand, may induce chronic lesions themselves as a consequence of repeated damage. Therefore, when we try to classify the aetiologies of this disease, we inevitably consider a number of factors that are also involved in the occurrence of chronic pancreatitis.

Many factors have been found to play an aetiologic role in recurrent acute pancreatitis; in fact, virtually any cause of acute pancreatitis may lead to further recurrent episodes if it is not corrected.

Patient history and conventional diagnostic tests such as blood chemistry, abdominal ultrasound, magnetic resonance cholangio-pancreatography (MRCP) and computerized tomography (CT) scan generally detect the causes of the recurrent episodes of pancreatitis in about 70% of cases. MRCP should be associated with Secretin stimulation, which permits not only a more accurate visualization of the pancreatic ductal system, but also an indirect evaluation of either the sphincter of Oddi or the excretory function of the gland [1, 2].

Further improvement in knowledge of the aetiopathogenesis is achieved by using endoscopic cholangio-pancreatography (ERCP) which visualizes the bilio-pancreatic system in detail and detects small gallstones missed at ultrasound [3, 4] and even at MRCP in a significant proportion of cases. At the same time, ERCP also permits ancillary procedures which may improve the diagnostic accuracy such as manometry of the biliary and pancreatic segments of the sphincter of Oddi and collection of stimulated bile for testing for bile crystals. ERCP is associated with a 3-5% complication rate [5, 6, 7, 8] which may rise to 30% in cases with sphincter of Oddi dysfunction [5, 9, 10, 11] so the procedure should be performed either for diagnostic purposes only in those patients in whom the aetiology of pancreatitis cannot be achieved by MRCP, eventually associated with the Secretin test, or carried out for sphincter of Oddi manometry and should be followed by immediate biliary sphincterotomy.

Established and suspected causes of recurrent acute pancreatitis can be grouped into

mechanical, inherited, metabolic, toxic, drug-induced and miscellaneous.
Metabolic well-known causes persisting over time that are able to induce recurrent episodes of acute pancreatitis are hypertriglyceridemia and hypercalcemia. The observation that antioxidant levels are depleted in patients with chronic pancreatitis who generally have a dietary history with deficiencies in the intake of selenium, vitamins A, C and E, and riboflavin, and that selenium levels were lowest during pain exacerbations [12], stimulated other investigators to study the antioxidant profile in patients with recurrent acute pancreatitis. However, the hypothesis that in some cases with unexplained recurrent pancreatitis, the acute acinar cell injury could have been the consequence of uncontrolled free radical activity was not documented, the antioxidant profiles being similar to those of the control subjects [13].
Toxic causes such as scorpion toxin, organophosphates and methylene chloride are incidental and, therefore, would be better considered as causes of acute rather than recurrent pancreatitis; alcohol consumption can cause a single episode of acute pancreatitis in case of heavy intake or induce bouts of pancreatitis overimposed on an underlying chronic damage.
Many medications have been implicated as causes of acute pancreatitis; once again however, the categorization of drugs among conditions inducing recurrent pancreatitis seems inappropriate since medications induce a single episode of acute pancreatitis and eventually further relapses if the drug is not discontinued. The drug-related risk of pancreatitis may be dose dependent or hypersensitivity-related; in most of the cases of pancreatitis however, the mechanism involved is unknown so pancreatitis is classified as idiopathic. Although there is general agreement that a number of medications are associated with acute pancreatitis, a recent review by the Midwest Multicenter Pancreatic Study Group [14] listed the following medications as having a strong association with pancreatitis and these were documented by at least one positive rechallenge: alfa-metildopa, 5-aminosalicylate, azathioprine, cimetidine, cytosine arabinoside, corticosteroids, estrogens, furosemide, isoniazid, mercaptopurine, metronidazole, pentamidine, procainamide, sulfamethazole, sulindac, tetracycline, trimethroprim/ sulfamethoxazole and valproic acid.
Among the miscellaneous causes, there are vascular disorders, tuberculosis, viral and parasitic infections, and tropical pancreatitis.
In recent years, mechanical and inherited causes have been the object of several investigations and therapeutic attempts which, for the most part, were performed endoscopically and with conflicting results. These causes will be discussed in depth in the present study.

Mechanical Causes

Mechanical factors promote recurrent episodes of pancreatitis by inducing a persistent, or more frequently, a transient obstruction to pancreatic juice flow into the duodenum, with a consequent rise in intraductal pancreatic pressure. The mechanical obstruction could also allow the bile to flow back into the main pancreatic duct with intrapancreatic activation of pancreatic zymogens; this theory has been proposed by Opie since 1901 [15] for the pathogenesis of gallstone pancreatitis.
Conditions which induce mechanical obstruction are either congenital or acquired and may be located at the level of either Vater's papilla, bilio-pancreatic junction or the main pancreatic duct.

Congenital Conditions

Pancreas divisum is the most common variant of the pancreatic ductal anatomy, occurring in from 3% up to 12% of individuals [16, 17]. When the pancreatic buds fail to fuse, the ventral and dorsal pancreatic ducts are separated in the head of the gland and the majority of pancreatic juice (80-90%) drains through the accessory duct and the minor papilla. The incapacity of the latter to

accommodate the flow of pancreatic juice when the gland is stimulated leads to a ductal hypertension which may induce either recurrent pain shortly after a meal, a persistent asymptomatic rise in serum pancreatic enzymes or acute relapsing pancreatitis in some individuals. Although one retrospective series did not show any correlation between pancreas divisum and acute recurrent pancreatitis [18], most studies demonstrate a significantly higher prevalence of this congenital variant among this patient population [16, 17, 19, 20, 21]. Dilation of the dorsal duct confirms the presence of an obstructive mechanism and favours a positive outcome after minor papilla sphincterotomy or stenting. Persistent obstruction may lead to changes of the pancreatic morphology as a consequence of the chronic obstruction.

A partial fusion between the ventral and dorsal ducts characterizes the incomplete (functional) pancreas divisum in which opacification of the dorsal duct can be accomplished through the major papilla by means of a communicating branch of the ventral duct. The ventral duct tapers before entering the dorsal duct. However, there is a narrow communication between the ducts that may be inadequate for draining the increased volume of pancreatic juice and, at times, causes obstructive pain or pancreatitis. (Figure 1).

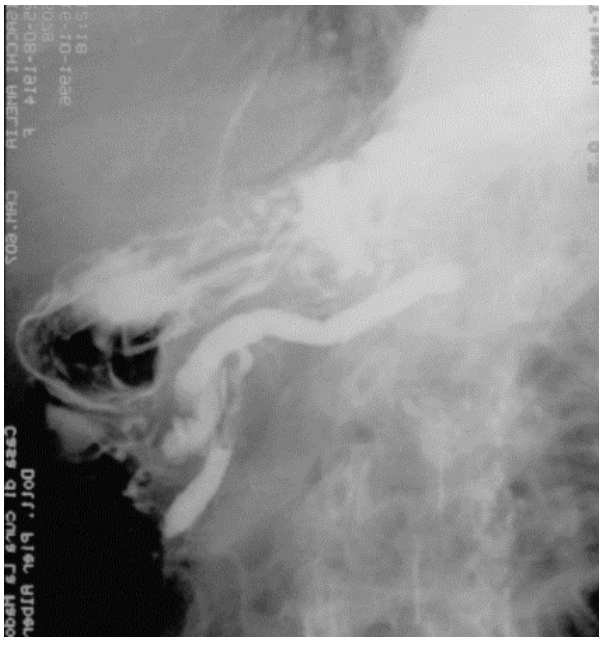

Figure 1. Incomplete pancreas divisum with ductal abnormalities suggesting a chronic obstructive pancreatitis. Both main pancreatic and dorsal ducts are irregularly dilated.

Annular pancreas is a rare variant that is often associated with duodenal or biliary obstructive symptoms, since both the duodenum and common bile duct become entrapped by the annular growth of the gland. Pancreatitis of the annulus or of the remaining pancreas may occasionally occur [22]. Opacification of the pancreatic ductal system may show a branch arising from the main pancreatic duct and curving laterally around the duodenal loop; usually the pancreatic ducts are normal [23, 24]. About one third of the patients with annular pancreas also have pancreas divisum so it is unclear whether recurrent pancreatitis depends upon the annular variant or the pancreas divisum.

A common anomalous pancreatobiliary channel which is long and devoid of sphincters which separate the biliary and pancreatic ducts, is a condition that facilitates free reflux of bile and pancreatic juice into the alternative duct. Bile entering the pancreas promotes intrapancreatic activation of zymogens and may potentially induce acute pancreatitis. The diagnosis is made easily by MRCP or ERCP. Choledochal cysts are commonly associated with such a junction.

Other anatomical variations of the pancreatic ductal system and the junction between the ventral and dorsal ducts may be seen at MRCP or ERCP and could explain the occurrence of pancreatic pain and recurrent pancreatitis resulting from the impaired outflow of the pancreatic juice into the duodenum when other causes have been excluded. The most frequent findings are loop-like or sigmoid-like configurations of the main pancreatic duct (Figures 2 and 3). However, there is no way either to prove a direct correlation between the anatomical variants and the pancreatitis or to treat them using an endoscopic approach.

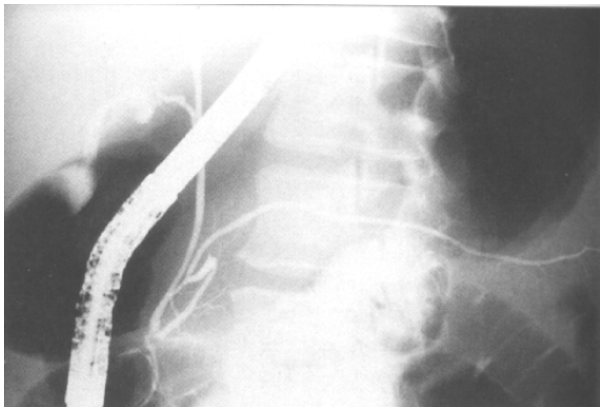

Figure 2.Sigmoid configuration of the main pancreatic duct with formation of an acute angle in correspondence with the insertion of the dorsal duct into the main duct. This anatomical configuration could induce a transient functional obstruction of the pancreatic juice outflow.

Acquired Conditions

Gallstone disease is the most common cause of recurrent acute pancreatitis in western countries. In cases of common bile duct macrolithiasis, the passage of gallstones through the ampulla of Vater is the key event in the development of pancreatitis. Pancreatitis may develop either as a consequence of an impacted stone in Vater's papilla which obstructs the main pancreatic duct, a very rare event occurring in no more than 5% of cases [25], or because of a transient papillary oedema or papillary orifice relaxation following the recent passage of stones which can obstruct the pancreatic juice flow or favour duodenopancreatic reflux, respectively. Temporary obstruction of the ampulla (due either to stone impaction or oedema) may allow bile to reflux into the pancreas, particularly if a common channel exists at the junction between the common bile duct and the main pancreatic duct; bile reflux occurs even if the pressure in the main pancreatic duct generally exceeds that in the common bile duct in normal conditions. However, the biliopancreatic junction is too short to induce a common channel situation in the majority of patients [26]; moreover, ampullary oedema would also reduce the length of the common channel required to allow biliopancreatic reflux to take place. Despite doubts about the common channel theory, in two documented studies involving patients with recent episodes of gallstone-induced acute pancreatitis who had undergone surgery, there was a much higher resting and stimulated amylase activity in the bile collected by a T-tube inserted into the common bile duct thus suggesting the occurrence of a functional channel between the two ductal systems [27, 28]. In one of these studies [27], the absence of detectable duodenal enzymes in the T-tube fluid casted doubt on the duodenopancreatic reflux theory as an aetiologic factor in acute pancreatitis.

Gallstone disease may manifest itself only by the presence of: a) very tiny stones, less than 2 mm in diameter (microlithiasis), which are seen or suspected mainly at ERCP; b) gallbladder sludge, which can generally be visualized by ultrasonography [29] or c) calcium carbonate, cholesterol monohydrate and calcium bilirubinate crystals in the bile, which can be detected only on microscopic examination of centrifuged bile aspirated from the duodenum after stimulation [30]. It is unlikely that microscopic bile crystals cause acute pancreatitis *per se*, however they could be signs that larger, undetected stones have passed through Vater's papilla. When microlithiasis or biliary sludge are seen at ERCP or ultrasonography, respectively, and when transient cholestasis occurs, eventually associated with serum alanine aminotransferase (ALT) elevation, patients are designated as having recurrent biliary

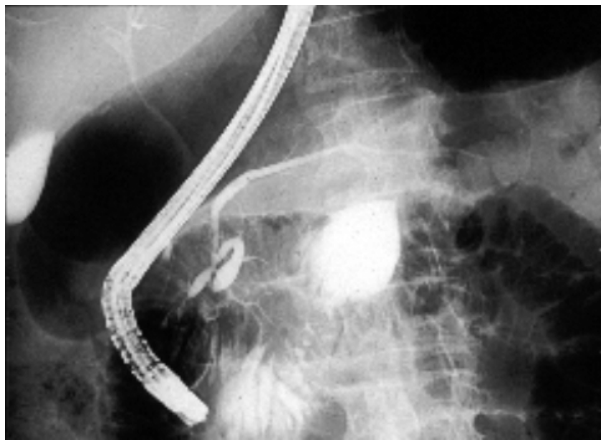

Figure 3. Sigmoid configuration of the main pancreatic duct with distal dilation of both main and dorsal ducts, suggesting the presence of an obstructive condition at the level of both major and minor papillae.

pancreatitis. In a number of patients however, US is unable to detect gallbladder stones or sludge, ERCP or MRCP indicate a normal appearance of the biliopancreatic ductal system, there are no biochemical hepatic changes accompanying pancreatitis and even the search for the bile crystals fails to achieve a diagnosis: in these cases recurrent pancreatitis is defined as idiopathic. In fact microlithiasis, although present, may be easily missed in a direct cholangiogram [31] and at US investigation even when carefully performed [32], and bile sludge is found in approximately 30% of patients [33]. Bile crystals are present intermittently in the duodenal bile [34] and are detected on microscopic examination of centrifuged bile in from 36 to 67% of patients with recurrent pancreatitis and documented gallstone disease, in prospective studies [31, 35]. Although it has been reported that the bile of control subjects contains no crystals [36, 37], the amount required to classify a specimen as a positive specimen is not standardized, so this method does not provide a definite diagnosis in all patients [34, 38]. However, the reported efficacy of either long-term ursodeoxycholic acid (UDCA) therapy, or cholecystectomy, or endoscopic biliary sphincterotomy in preventing further episodes of "idiopathic" pancreatitis in a consistent series of patients [31, 39] confirms the role played by occult gallstone disease in recurrent pancreatitis. In a recent prospective study performed by us, occult gallstone disease accounted for 55% of the cases with the so-called "idiopathic" recurrent pancreatitis [39]. Overall, documented or occult gallstone disease can be considered the most frequent aetiologic factor for recurrent acute pancreatitis; pancreatitis may occur because of either transient ampullary oedema resulting from passage of a stone, although tiny, or sphincter of Oddi dysfunction resulting from a long-standing gallstone disease. Over a 10-year period, we identified a gallstone disease by abdominal ultrasonography and/or ERCP in 72.3% of 173 patients with a history of recurrent pancreatitis [40].

Sphincter of Oddi dysfunction is the second most common cause of recurrent acute pancreatitis and is thought to be the leading cause of the idiopathic form; it may involve either the biliary [41, 42, 43], or the pancreatic segment of the sphincter of Oddi, or both [44, 45, 46, 47]. Sphincter of Oddi dysfunction, has been classified into three types on the basis of clinical and morphological parameters; such a classification can be adopted for either the biliary or pancreatic segments of the sphincter [45]. Type 1 dysfunction patients have recurrent pancreatitis or pancreatic-like pain with a mild elevation of serum pancreatic enzymes rise (less than three times the upper normal limits), together with a dilated common bile duct and/or main pancreatic duct associated with a prolonged drainage, suggesting a structural abnormality (ampullary stenosis). Type 2 patients have pancreatic-like pain associated with positive findings for one or two items from Type 1; subjects with either pancreatitis or only pancreatic-like pain are included in this group, there is probably an even distribution of patients with functional or structural sphincteric disorder; manometry indicates an elevated basal sphincter pressure in the absence of stenosis in a high percentage of patients. Type 3 patients have only pancreatic-like pain without elevation of serum pancreatic enzymes and biliopancreatic morphological abnormalities. When dilated biliary and/or pancreatic ducts are observed together, with delayed drainage, the diagnosis of Type 1 sphincter of Oddi dysfunction does not require manometric investigation for confirmation, since several studies have reported a pathological sphincter in this situation. These patients have the best results after biliary and/or pancreatic sphincterotomy. In Type 2 patients, when dilation of the ductal system or delayed drainage are documented, some sphincteric dysfunction should be present. Basal pressure is abnormally elevated in the majority of these patients [43, 45, 47] while a normal pressure profile does not exclude a transient dysfunction in the

remaining cases, so manometry does not substantially improve the diagnosis, while exposing patients to an increased risk of post-procedure pancreatitis [11, 12, 13]. In more difficult cases, in which the common bile or pancreatic ducts are not dilated, with pancreatitis (suspected Type 2 dysfunction) or with pancreatic-like pain (suspected Type 3 dysfunction), an objective diagnosis of dysfunction must rely only on manometric recording of the biliary and pancreatic segments of the sphincter of Oddi. 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 [43, 45, 48] and from 35 to 49% [13, 45] for pancreatic type dysfunction. However, in these patients a normal basal pressure does not mean the absence of a fluctuating dysfunction and excludes the sphincter as having a role in the recurrence of pancreatitis. Moreover, complications related to the procedure are not only significantly more frequent in these patients but also less acceptable than those after therapeutic ERCP. Less invasive techniques such as US- or the MRCP-Secretin test should be preferable in these cases to achieve a definite diagnosis, but, at present, results of studies carried out by using these techniques still need to be confirmed in larger series [49, 50]. Although objective evidence of sphincter of Oddi dysfunction is lacking in a number of cases, there is practical evidence that endoscopic biliary sphincterotomy causes significant relief of symptoms or complete disappearance of the disease in the majority of cases [51]. Therefore, it should be considered the first therapeutic step in the approach to recurrent idiopathic pancreatitis, instead of long-term UDCA treatment or laparoscopic cholecystectomy [39], even when manometry and US- or MRCP-Secretin test are non-diagnostic [14]. Biliary sphincterotomy appears to be effective even when abnormalities are confined to the pancreatic duct segment, since the lower basal pressure of the sphincter of Oddi also results in reduced basal pancreatic duct pressure; only in 20% of such patients does the basal pressure in the pancreatic duct segment exceed that of the common bile duct segment [52].

Persistently high pancreatic duct segment pressure may be a reason for lack of improvement after conventional sphincterotomy or sphincteroplasty [53, 54]. In such cases, pancreatic sphincterotomy should be considered after biliary sphincterotomy; however, before performing such surgery, a manometry of the pancreatic segment of the sphincter of Oddi or US- or the MRCP-Secretin test may help in decision-making.

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

The direct involvement of periampullary diverticula in the recurrence of pancreatitis is still being debated; although these diverticula are frequently found in gallstone and recurrent acute pancreatitis in middle age individuals, it has yet to be proved that they play some role in the disease process. Ampullary choledochal cysts could develop in

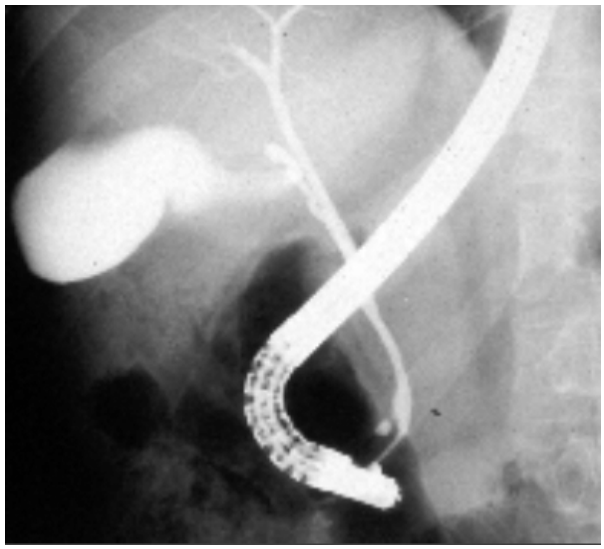

Figure 4. Pericholedochal cyst in the prepapillary region with normal biliary ERCP morphology, suggesting Type 3 dysfunction of the biliary segment of the sphincter of Oddi.

the presence of sphincter of Oddi dysfunction (Figure 4).
Benign and malignant tumors of the pancreatic ductal system or the pancreatobiliary junction present as recurrent acute pancreatitis in about 5% of cases. A neoplasm should be suspected in subjects over 45 years of age in whom either biliary or pancreatic duct dilatation, or both, are documented by non-invasive imaging.
Organic strictures involving the main pancreatic duct may be due to neoplasms or may be the consequence of a fibrotic process induced by a previous acute pancreatitis or pancreatic trauma or by a chronic disease.
Choledochocele is a cystic dilatation of the terminal segment of the pancreatobiliary ductal system which may induce recurrent pancreatitis by obstructing, in a transient manner, the pancreatic juice flow into the duodenum. A differential diagnosis must be made between choledochocele and duodenal duplication cysts since both lesions induce a similar bulging of the duodenal wall into the lumen at the level of Vater's papilla and both obstruct the pancreatic ductal system. However, duodenal duplication cysts contain Brunner's glands within the wall.
Among the cystic neoplasms, mucinous ductal ectasia is the one most frequently associated with recurrent acute pancreatitis or intermittent pancreatic-like pain. It is an intraductal premalignant lesion [55, 56, 57] characterized by dilation and filling of the pancreatic ductal system with thick mucin, leading to obstruction of the main pancreatic duct. Histologically there is the presence of a hyperplastic columnar epithelium which projects into the lumen of the ductal system and which has either a normal appearance or shows atypia or adenocarcinomatous foci. More frequently the lesion is localized in the head of the pancreas and is associated with persisting hyperamylasemia and high serum levels of CA 19-9. The diagnosis is suggested by non-invasive imaging techniques (mainly by MRCP) and can be confirmed by ERCP or endoscopic ultrasound. ERCP shows upon duodenal examination, a widely patent pancreatic orifice, eventually with mucin exuding from it; the pancreatogram shows the main pancreatic duct grossly dilated, either diffusely or segmentally [58], with a normal profile and with cystic dilatation of the side branches. In some cases ductal lesions are misdiagnosed as chronic pancreatitis.

Inherited Causes

In these patients, recurrent bouts of acute pancreatitis are superimposed on a chronic inherited condition. Although no morpho-functional abnormalities are found in most of the patients when they are investigated at the beginning of their clinical history, nevertheless the progression to a chronic pancreatic disease is reported over a period of time [59]. Inherited conditions that can induce recurrent acute pancreatitis are the Cystic Fibrosis Transmembrane Conductance Regulator-gene (CFTR-gene) and Trypsinogen-gene mutations.

CFTR-Gene Mutations

This autosomal-recessive process is the most common inherited disease of the exocrine pancreas. About 5% of the European and North American Caucasian populations carry some phenotypic CFTR-gene mutations; however, how frequently the heterozygous state is associated with any clinically manifest pancreatic disorder still remains uncertain. In fact, CFTR-gene mutations are probably underestimated [60, 61, 62, 63]. The mutated CFTR-gene protein product determines a defect of the 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 a persistent rise of intraductal pancreatic pressure. With time, this persistent condition leads to secondary ductal changes. The clinical features associated with CFTR-gene mutation phenotype are broad. Exocrine pancreatic insufficiency without inflammatory changes is the most common finding; recurrent acute pancreatitis may be the only clinical sign in a smaller number of subjects; an asymptomatic increase in serum pancreatic

amylase in the absence of morpho-functional pancreatic disorders may also be found.

Trypsinogen-Gene Mutations

Mutations of the cationic trypsinogen gene have been documented in young patients with hereditary pancreatitis [64, 65]; hereditary pancreatitis is an autosomal dominant disorder characterized by recurrent attacks of pancreatitis in childhood and frequent progression to chronic pancreatitis. Gene mutations render the pancreas unable to protect itself due to premature or excessive trypsin activation within the gland; the lack of this protective mechanism for destroying prematurely activated trypsin, which in turn promotes the digestive enzyme activation cascade, predisposes individuals to develop recurrent episodes of acute pancreatitis. Another important pathogenetic cofactor involved in the occurrence of recurrent acute pancreatitis seems to be the sphincter of Oddi dysfunction, that has been found in a number of patients with hereditary pancreatitis. The dysfunction could be the consequence of the chronic inflammation of the sphincter induced by the passage of activated trypsin through it over time in the presence of a common biliopancreatic junction [66]. In these patients sphincterotomy allowed symptom relief thus confirming a role played by the elevated intraductal pressure induced by sphincter of Oddi dysfunction or stenosis, but it did not significantly affect the progression of the recurrent acute disease to the chronic form, thereby suggesting that the underlying pathophysiological mechanism persists despite sphincterotomy. Subjects either with a history of first- or second-degree relative early-onset (<20 years) or multiple episodes of unexplained pancreatitis, or with two or more relatives with unexplained pancreatitis should look into genetic testing [14].

Conclusion

In conclusion, a careful diagnostic algorithm, cholecystectomy and eventually the resection of the biliary and/or pancreatic segment of the sphincter of Oddi identify or remove the inciting factors in about 90% of the cases of recurrent acute pancreatitis. A recent prospective long-term study by our group [39] documented that in patients with "idiopathic" recurrent pancreatitis the correct diagnosis is achieved by either diagnostic and therapeutic ERCP or UDCA oral treatment in 92.5% of the cases, so the term "idiopathic" seems in fact to be appropriate for less than 10% of the patients. In our series, occult bile stone disease and sphincter of Oddi dysfunction accounted for the majority of cases. When performed, endoscopic biliary sphincterotomy appeared to be a curative procedure *per se* in 78.6% of the patients.

Key words Cholelithiasis; Cystic Fibrosis Transmembrane Conductance Regulator; Hereditary Diseases; Oddi's Sphincter; Pancreatic Diseases: congenital; Pancreatic Ducts: abnormalities; Pancreatitis: etiology; Recurrence

Abbreviations CFTR: cystic fibrosis transmembrane conductance regulator; CT: computerized tomography; ERCP: endoscopic cholangio-pancreatography; MRCP: magnetic resonance cholangio-pancreatography; UDCA: ursodeoxycholic acid; US: ultrasound

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