Current View

Endoscopic management of acute recurrent pancreatitis

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SUMMARY

The aetiology of acute pancreatitis is usually identified and treated in over 80% of the patients. However, when pancreatitis recurs, a further diagnostic work up is needed in order to discover the causative factors. A few years ago ERCP was a primary diagnostic and therapeutic tool in this field but the contribution of EUS and MRCP has changed the diagnostic algorithm of acute recurrent pancreatitis. Established (microlithiasis, neoplasms) and controversial (pancreas divisum, sphincter of Oddi dysfunction) aetiologies of acute recurrent pancreatitis may now be identified with noninvasive procedures, limiting the role of ERCP to its therapeutic arm. In this review the endoscopic management of acute pancreatitis is discussed.

Key words: Acute recurrent pancreatitis, ERCP, EUS, sMRCP.

INTRODUCTION

Acute recurrent pancreatitis is defined as more than one episode of acute pancreatitis with complete or almost complete resolution of symptoms and signs of pancreatitis between episodes. The initial workup after the first episode of acute pancreatitis (history, routine laboratory evaluation, transabdominal ultrasonography and computed tomography) reveals the aetiology in more than 80% of patients. In most of the patients pancreatitis will not recur, especially if the causative factor is removed, however about 30% of the patients may experience a recurrence.[1-3]

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Among the causes of recurrent pancreatitis, those that can be diagnosed and managed endoscopically are:

1) Gallstone disease (choledocholithiasis, microlithiasis, sludge)
2) Pancreas divisum and other congenital variants
3) Sphincter of Oddi dysfunction
4) Obstructive (ampullary lesions, pancreatic duct strictures, stones or neoplasms, mucin secreting pancreatic tumors, biliary and pancreatic parasites).

Gallstone disease

Microlithiasis refers to stones smaller than 3mm, whereas sludge comprises a suspension of precipitates (mucin, cellular debris, cholesterol monohydrate and calcium phosphate and carbonate crystals, calcium bilirubinate granules and calcium salts of fatty acids).[4] Microlithiasis and sludge may cause pancreatitis by obstructing the common channel and increasing the pancreatic intraductal pressure or, according to another hypothesis, by causing inflammation of the sphincter of Oddi as they pass through, leading eventually to stenosis and dyskinesia of the sphincter.

Bile microscopy is the gold standard technique for the diagnosis of microlithiasis. Bile is obtained from the duodenum or the common bile duct with ERCP after stimulation of the gallbladder with cholecystokinin. The sample is examined by light microscopy.[5] This technique is cumbersome and is performed in a few tertiary referral centers.[6]

Transabdominal ultrasonography could be used for the diagnosis of biliary sludge but endoscopic ultrasonography is more sensitive and most studies suggest that it could be an acceptable alternative to bile microscopy in the diagnosis of microlithiasis.[7,8] Dahan et al found that the sensitivity of EUS was 96% in contrast to 67% of the duodenal bile examination (P=0.03).[9] Similarly, Queneau et al diagnosed biliary lithiasis more often by EUS than by duodenal bile examination (36% vs 27%, P=0.03).[10] Howev-

er, Yusoff et al found lithiasis by duodenal bile apirate in 46.5% of patients with a negative EUS.[11]

Microlithiasis is an established and common cause of pancreatitis, as it occurs more frequently in patients with pancreatitis and the probability of recurrence is almost eliminated after cholecystectomy.[12-14] The prevalence of microlithiasis in patients with pancreatitis depends on the presence of gallbladder. In patients with pancreatitis and an intact gallbladder the prevalence of microlithiasis exceeds 50%, while in patients with cholecystectomy is about 10%.

Cholecystectomy is the preferable treatment in patients with microlithiasis but in poor surgical candidates endoscopic sphincterotomy or ursodeoxycholic acid are reasonable alternatives.[15,16] Ursodeoxycholic acid administration should be the last resort, since it must be prescribed for over 2 years and it is effective in cholesterol stones and crystals only.

Pancreas divisum and other congenital variants

Pancreas divisum is the most common congenital abnormality of the pancreas, occurring in up to 14% of the general population. This developmental alteration is created when the ventral and dorsal pancreas fail to fuse during the second month in utero. The ventral pancreas is drained through the major papilla, while the majority of the pancreas is drained through the minor papilla. Most of the patients with pancreas divisum are asymptomatic but about 5% may present with recurrent pancreatitis.[17]

Pancreas divisum is a controversial cause of acute recurrent pancreatitis.[18] Epidemiological evidence from autopsy and MRCP studies shows that the prevalence of pancreas divisum is the same in patients with or without pancreatitis.[19] In ERCP series, pancreas divisum is found more frequently in patients with acute recurrent pancreatitis (8-50%) in comparison with patients without pancreatitis (3-12%) but this could be attributed to the fact that endoscopists do not seek for pancreas divisum in patients without pancreatitis.[18,20] However, endoscopic treatment of pancreas divisum with minor papilla sphincterotomy or stent placement provided improvement in approximately 75% of the patients.[16,21-31] It is postulated that the orifice of the minor papilla is not large enough to accommodate the pancreatic flow and this increases the intraductal pancreatic pressure, predisposing to pancreatitis. Minor papilla sphincterotomy or stent placement relieves this hypertension and improves patients' symptoms.

The opponents of endoscopic therapy claim that the aforementioned studies are not sufficient to document a real benefit. Most of the studies have small sample size, no control group, heterogeneity and short follow up. Taking into account the natural history of acute recurrent pancreatitis, where asymptomatic intervals may be quite long, the "success" of the endoscopic therapy could be in fact a long uneventful period. Furthermore, the absence of a control group does not take into consideration the so called "placebo effect" of the endoscopic therapy. In addition, there is growing evidence that there are other factors (eg, CFTR gene mutations) which contribute to pancreatitis development in patients with pancreas divisum.[32,33] Choudari et al found CFTR mutations in 22% of patients with pancreas divisum and pancreatitis compared to 0% of patients with pancreas divisum without pancreatitis (P=0.02).[32] Accordingly, Gelrud et al found (in patients with pancreas divisum and idiopathic pancreatitis) intermediate values of nasal epithelium CFTR function between those observed in healthy controls and cystic fibrosis patients.[33]

When an endoscopist decides to treat pancreas divisum he should have in mind that the endoscopic therapy has technical difficulties and complications. The studies in favor of endoscopic treatment showed better results in patients with normal or nearly normal dorsal pancreatogram and no features of chronic pancreatitis. The presence of a Santorinocele (cystic dilatation of the distal dorsal duct) is an indication of compromised pancreatic flow and minor papilla sphincterotomy may be beneficial.[34,35] Sphincterotomy may be performed with a pull type sphincterotome or a needle knife sphincterotome over a previously placed stent.[36] Stent placement without sphincterotomy may cause chronic pancreatitis like lesions in the pancreatic duct and is not recommended.

Other congenital abnormalities of biliary and pancreatic anatomy that are associated with acute recurrent pancreatitis are choledochocele, anomalous union of the pancreatic and bile duct, duodenal duplication cyst and annular pancreas.

Choledochocele is a dilatation of the intraduodenal segment of the common bile duct. It was considered a type III choledochal cyst in the Todani classification, but recently it was decided that types II, III and V are not related to choledochal cysts.[37] When the choledochocele itself or its contents obstruct the pancreatic duct, pancreatitis may occur. Choledochocele is diagnosed by EUS, MRCP or by observation of a bulging over the papilla with a characteristic pillow sign. Unroofing the choledochocele by endoscopic sphincterotomy is the recommended treatment.[38]

Choledochocele is often associated with anomalous

union of the pancreatic and bile duct, resulting in long common channel (>15mm). Bile, stones or protein plugs may enter the pancreatic duct, increase the intraductal pressure and predispose to pancreatitis. EUS and MRCP are noninvasive procedures that can accurately diagnose congenital variants.[39,40] Endoscopic sphincterotomy may obviate future episodes of acute recurrent pancreatitis.

Duodenal duplication cyst and annular pancreas are rarely associated with acute recurrent pancreatitis. Duodenal duplication cyst may be seen as a bulging distal to the papilla and resection of its top may empty its content which is possible to obstruct the pancreatic duct. Gastrojejunostomy is advocated when the annular pancreas obstructs the duodenum.

Sphincter of Oddi dysfunction

Sphincter of Oddi dysfunction (SOD) describes a condition where stenosis or dyskinesia is present in the biliary and/or pancreatic segment of the sphincter. Similar to biliary SOD, there is a classification of pancreatic SOD with three types.[41] Type I is characterized by pancreatic type pain, elevation of serum amylase or lipase and dilation of the pancreatic duct. Type II patients have pancreatic pain and one of the two other criteria whereas type III patients have only pain. Type I is believed to be related to stenosis of the sphincter whereas type II is related to motility disorders. Most patients with acute recurrent pancreatitis are in type II category, because they do not usually have pancreatic duct dilation.[42,43] Type III is a vague disorder, with problems in the diagnosis and management.

The gold standard for the diagnosis of SOD is manometry during ERCP. Manometry is widely performed with a thin water perfused catheter, but microtransducers have also been used. Manometry has been associated with up to 25% risk of pancreatitis but it seems that it is not the procedure itself, that predisposes to pancreatitis when the biliary or pancreatic duct are cannulated but the characteristic group of patients that it is performed to. When the basal sphincter pressure is over 35-40mmHg, then SOD is diagnosed. As Varadarajulu et al showed, a negative result does not preclude SOD and in a second measurement in patients with high probability of SOD they had positive findings in 42% of patients with initially negative results.[44]

Alternative noninvasive methods to diagnose SOD and avoid the high rate of pancreatitis after manometry have been evaluated. MRCP after secretin stimulation (S-MRCP) showed encouraging results, especially in type II patients who are the principal indication for manometry.[45-49] Pancreatic SOD is diagnosed with S-MRCP when the main pancreatic duct diameter is greater than 1mm from baseline for 15 minutes after secretin stimulation. S-MRCP is not yet widely accepted as a substitute of sphincter of Oddi manometry, because negative results have also been reported, so more trials are needed.[50]

When SOD is diagnosed, many experts recommend sphincterotomy, although, similar to pancreas divisum studies, the data are not fully convincing.[51-57] Sphincterotomy without manometry is suggested for type I SOD, but manometry or S-MRCP should be performed before proceeding to sphincterotomy for type II SOD. Biliary sphincterotomy may suffice, because pancreatic sphincter pressure is also reduced,[58] but a dual complete sphincterotomy yields better results.[59] Prophylactic stent placement reduces the rate and severity of pancreatitis and it is advocated. The stent usually migrates spontaneously or is removed after 2 weeks. Patients with type III SOD are a heterogeneous group with possible hyperalgesia and motility or somatization disorders. Consequently treatment in those patients should be individualized.

Obstructive lesions

Ampullary adenomas and carcinomas, cystic tumors of the pancreas including intraductal papillary mucinous neoplasms, chronic pancreatitis and pancreatic adenocarcinoma can be diagnosed with EUS and MRCP with or without FNA. These lesions can be treated either endoscopically or surgically according to their nature.

Proposed management of acute recurrent pancreatitis

After one episode of pancreatitis the usual examinations (history, routine laboratory tests and tests for infectious and autoimmune diseases, transabdominal ultrasonography and computed tomography) reveal the aetiology in over 80% of the patients. If the pancreatitis was mild or moderate no further workup is needed but someone may consider EUS and/or MRCP, especially in patients with an intact gallbladder, where the probability of choledocholithiasis and microlithiasis is high. If the pancreatitis was severe, EUS and MRCP (S-MRCP when provided) are indicated (Fig 1).

In more than one episode of pancreatitis, EUS and S-MRCP are indicated. EUS is a reliable substitute of ERCP and can diagnose most of the causes of pancreatitis, except pancreas divisum, where further evaluation is needed.[7,8,10,11,51,60-63] EUS is also the least costly initial test for the diagnostic evaluation of patients with idiopathic pancreatitis and gallbladder in situ.[64] S-MRCP can diagnose pancreas divisum among other causes and may also suggest the presence of SOD. These procedures are not in-

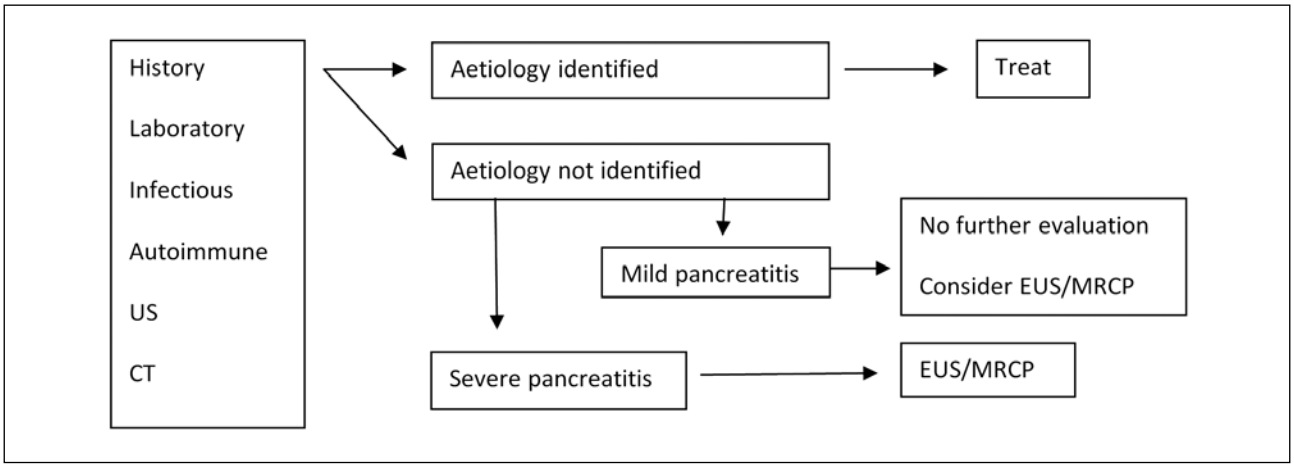

Figure 1. Proposed diagnostic algorithm after a single episode of acute pancreatitis

vasive and must be preferred instead of ERCP, which has complications. Alternatively, after two episodes of pancreatitis, empiric cholecystectomy or/and endoscopic sphincterotomy may be performed in patients with an intact gallbladder.[15]

When no other cause of pancreatitis is identified, sphincter of Oddi manometry is indicated and dual sphincterotomy should be performed if SOD is diagnosed (Fig 2).

The prevalence of the various causes of acute recurrent pancreatitis depends on the percentage of patients with an intact gallbladder. If all patients have gallbladder in situ, then the prevalence of microlithiasis would be about 50%,

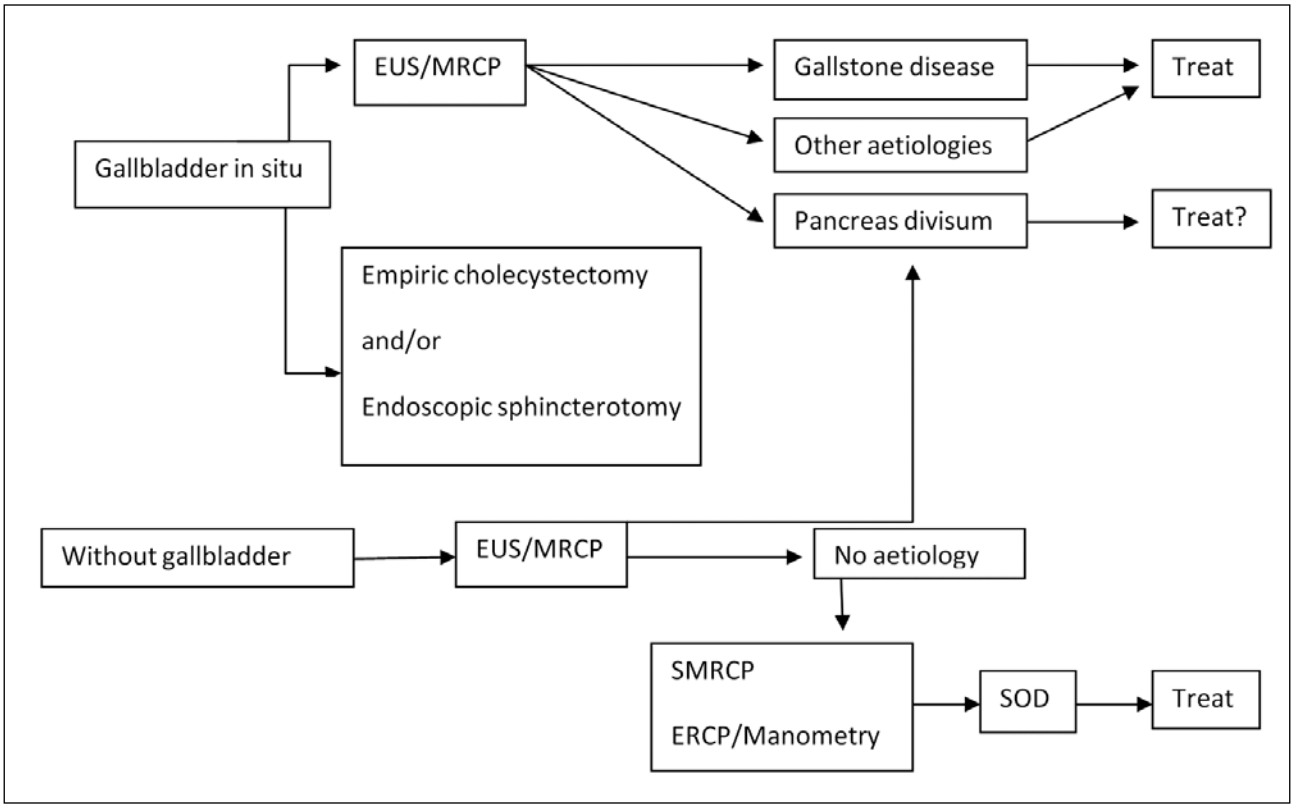

Figure 2. Proposed diagnostic algorithm in acute recurrent pancreatitis

SOD 20%, chronic pancreatitis 15%, pancreas divisum 10% and choledocholithiasis 5%.[64] In patients with cholecystectomy the probability of microlithiasis falls to 10-15% whereas the prevalence of SOD, pancreas divisum and chronic pancreatitis rises.

Endoscopists should know that most of the congenital abnormalities which are discovered during investigation (e.g. pancreas divisum), may be irrelevant. In addition, the natural history of recurrent pancreatitis is variable with episodes of usually mild severity. Before resorting to invasive procedures (ERCP, sphincter of Oddi manometry, major or minor papilla sphincterotomy) the endoscopist must review the patients' history and individualize therapy, having in mind that "first he must do no harm".

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