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TOPIC HIGHLIGHT

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Sphincter of Oddi dysfunction and bile duct microlithiasis in acute idiopathic pancreatitis

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Abstract

Although there are numerous causes of acute pancreatitis, an etiology cannot always be found. Two potential etiologies, microlithiasis and sphincter of Oddi dysfunction, are discussed in this review. Gallbladder microlithiasis, missed on transcutaneous ultrasound, is reported as the cause of idiopathic acute pancreatitis in a wide frequency range of 6%-80%. The best diagnostic technique for gallbladder microlithiasis is endoscopic ultrasound although biliary crystal analysis and empiric cholecystectomy remain as reasonable options. In contrast, in patients who are post-cholecystectomy, bile duct microlithiasis does not appear to have a role in the pathogenesis of acute pancreatitis. Sphincter of Oddi dysfunction is present in 30%-65% of patients with idiopathic acute recurrent pancreatitis in whom other diagnoses have been excluded. It is unclear if this sphincter dysfunction was the original etiology of the first episode of pancreatitis although it appears to have a causative role in recurring episodes since sphincter ablation decreases the frequency of recurrent attacks. Unfortunately, this conclusion is primarily based on small retrospective case series; larger prospective studies of the outcome of pancreatic sphincterotomy for SOD-associated acute pancreatitis are sorely needed. Another problem with this diagnosis and its treatment is the concern over potential procedure related complications from endoscopic retrograde cholangiopancreatography (ERCP), manometry and pancreatic sphincterotomy. For these reasons, patients should have recurrent acute pancreatitis, not a single episode, and have a careful informed consent before assessment of the sphincter of Oddi is undertaken.

Key words: Sphincter of Oddi dysfunction; Microlithiasis; Idiopathic pancreatitis

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INTRODUCTION

Sphincter of dysfunction (SOD) is a benign, noncalculous obstructive disorder that occurs at the level of the sphincter of Oddi (SO) (Figure 1). The pathogenesis of SOD relates either to passive obstruction at the SO caused by fibrosis and/or inflammation or to active obstruction caused by sphincter muscle spasm. These two mechanisms of functional obstruction at the SO are not mutually exclusive.

SOD is a possible cause of three clinical conditions: (1) persistent or recurrent biliary pain following cholecystectomy in the absence of structural abnormalities, (2) acute idiopathic pancreatitis, and (3) biliary pain in patients with intact gallbladders but without cholelithiasis (the least studied and most controversial clinical association). SOD also has been described in patients who have had liver transplantation, have the acquired immunodeficiency syndrome, and have hyperlipidemia. This manuscript will discuss only the association of SOD with acute idiopathic pancreatitis (AIP).

Microlithiasis is another possible cause of acute idiopathic pancreatitis. This is best studied in patients with intact gallbladders, and is felt to be one of the most common causes of AIP. Although it seems intuitive that microlithiasis may also occur *de novo* in the bile duct in patients with prior cholecystectomy, this entity is not well described.

MICROLITHIASIS AS A POTENTIAL CAUSE OF ACUTE IDIOPATHIC PANCREATITIS

Gallbladder in situ

Microlithiasis has been defined as tiny stones (1-2 mm) that are missed on imaging studies. In contrast, biliary sludge is a collection of crystals (seen only by microscopic

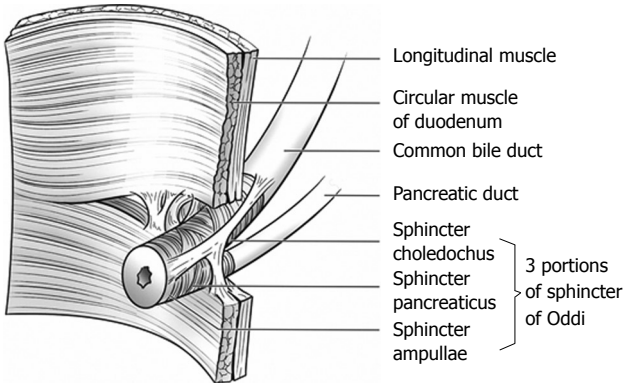

Figure 1 Sphincter of Oddi anatomy.

exam), glycoproteins, protein, cellular debris and mucin. In practice, since biliary sludge may contain microlithiasis these two terms have been used interchangeably[1]. In patients with intact gallbladders, it has been estimated that up to 60%-80% of acute idiopathic pancreatitis may be due to microlithiasis[2-4]. Other centers have found a much lower incidence of 6%-8% of "missed gallbladder disease" in AIP patients[5].

For AIP patients with an intact gallbladder and a normal transcutaneous gallbladder ultrasound, several diagnostic and therapeutic options exist. First is empiric cholecystectomy. This is still commonly practiced and is not unreasonable if the incidence of "missed stones or sludge" is common in your area. Alternatively, duodenal aspiration of bile after CCK stimulation can be utilized for diagnostic confirmation. The sensitivity of this procedure is 66%[6,7]. Direct common bile duct aspiration at ERCP has also been performed although requires CCK administration to ensure collection of gallbladder bile[8]. Technical problems with crystal analysis have limited its popularity for the confirmation of microlithiasis despite its long history of use. Endoscopic ultrasound has become a popular alternative for further diagnostic testing due to its higher sensitivity for microlithiasis and sludge[9]. (Table 1) EUS also has the advantage of evaluating several alternative causes for AIP including pancreas divisum, neoplasms, and undiagnosed chronic pancreatitis[10].

Therapy for microlithiasis/sludge is generally laparoscopic cholecystectomy although endoscopic biliary sphincterotomy in the poor operative candidate[11] or long-term treatment with ursodeoxycholic acid[3] are alternatives.

Post cholecystectomy

Bile duct stones that present within 2 years of cholecystectomy are usually stones that originated in the gallbladder that were missed at the time of surgery. If they present more than 2 years after cholecystectomy, they are de novo bile duct stones. Both types can be missed on traditional imaging tests and may be small stones or "microlithiasis". Endoscopic ultrasound is the most sensitive test to detect bile duct stones and appears more cost effective and sensitive than MRCP[12]. Bile obtained from the common bile duct at ERCP for crystal analysis in patients who have had prior cholecystectomy does not have diagnostic value in AIP patients[13]. Bile crystals are rare in patients with manometrically proven sphincter of Oddi dysfunction (SOD)[14]. The fact that empiric biliary sphincterotomy benefits less AIP patients compared to dual or pancreatic sphincterotomy also suggests that biliary sludge/microlithiasis is not a likely cause of AIP in patients post cholecystectomy. Indeed the benefit of biliary sphincterotomy alone in AIP patients has been attributed to a decrease of pancreatic sphincter pressure that may occur after bilary sphincterotomy[15] rather than a treatment for microlithiasis.

Table 1 Diagnostic yield of EUS in acute idiopathic pancreatitis[10]

EUS finding	No cholecystectomy (%) (n=246)	Post-cholecystectomy (%) (n = 124)
Stones (GB or BD)	7	3
GB Sludge	11	-
Pancreas division	5	11
IPMN/neoplasm	2.8	4.8
Chronic pancreatitis (≥ 5 criteria)	31	27
Other	4.8	4.8

SPHINCTER OF ODDI DYSFUNCTION IN AIP

Several studies have demonstrated a high frequency (30%-65%) of sphincter hypertension in patients with acute idiopathic pancreatitis, and a 50% to 87% frequency in those with chronic pancreatitis. Elevated pancreatic sphincter pressure in humans has been shown to correlate to increased intrapancreatic ductal pressure presumably playing a role in the pathogenesis of pancreatitis[16]. Whether this pancreatic duct obstruction causes the initial injury or is the result of prior pancreatic inflammation is unknown. Elevated pancreatic basal SO pressure and concomitant elevated PD pressure also occurs in patients with pain only and no prior evidence of pancreatitis arguing that it is not the sole determinant of pancreatitis. However, since pancreatic sphincter ablation does decrease future attacks of pancreatitis (although studies are primarily retrospective and uncontrolled), it appears that pancreatic SOD plays a role in the pathogenesis of recurrent attacks even if it was not the original cause.

A classification system similar to the three types of suspected biliary SOD has been proposed for possible pancreatic SOD[17]. In the contemporary proposed system, pancreatic type I patients have pancreatic-type pain, a serum amylase or lipase level of 1.1 times normal on one occasion, and pancreatic duct dilation (> 6 mm in the head and > 5 mm in the body); pancreatic type Ⅱ patients have pain and one of the preceding criteria; type Ⅲ patients have pancreatic-type pain only. This classification system is not widely utilized for several reasons: (1) Few patients with type I pancreatic SOD are reported, the vast majority of AIP patients have normal pancreatic duct caliber, (2) AIP patients would fit into the pancreatic type Ⅱ category and are the primary patients of interest, and (3) Pancreatic type pain only is not sufficiently specific to be a widely accepted diagnosis.

The gold standard for making the diagnosis of SOD

is SO manometry during ERCP. Water perfused catheters are the most commonly utilized systems although microtransducer manometry is also reported[18]. Although some experts have argued for attention to abnormalities of sphincter manometry other than baseline sphincter pressure, such as phasic wave frequency and propagation direction, only basal pressures are widely used clinically. Abnormal basal sphincter pressures are usually concordant for the pancreatic and bile ducts but may occur in only one portion of the sphincter. It has been shown that increased basal sphincter pressure is more likely to be confined to the pancreas in patients with pancreatitis and more likely confined to the bile duct in persons with elevated levels of serum liver enzymes[19].

PANCREATIC SOD TREATMENT CHOICES

Medical therapy with sphincter relaxing medications has been used in biliary SOD although data is sparse supporting their benefit. There are no trials of medical therapy in the treatment of AIP, although intravenous gabexate[20] and somatostatin[21] given during pancreatic SOM have been shown to either alter phasic wave frequency or lower pancreatic basal sphincter pressure. Endoscopic injection of botulinum toxin in patients with AIP is reported to decrease pancreatitis episodes in 80% of patients[22] although the benefit is not prolonged and there is concern about possible long-term side effects.

Endoscopic sphinctertomy results in clinical benefit for pancreatic SOD in AIP patients although the studies are mostly small case series[13,23,24]. There continues to be disagreement about the type and method of sphincterotomy. Some experts continue to perform biliary sphincterotomy alone as a first line treatment[25]. It is known that this will decrease pancreatic sphincter pressure in some patients and is thought to be a safer first line therapy. It is also a treatment for possible biliary microlithiasis. Other experts direct their endoscopic treatment to the pancreatic sphincter alone when the indication is IAP and pancreatic SOD[17]. This avoids unnecessary biliary sphincterotomy although a small one likely occurs during septotomy. Other experts advocate dual complete sphincterotomies[26]. Current literature supports temporary pancreatic stenting in all of these patients to lower their risk of procedure-induced pancreatitis. There is also some evidence suggesting a lower rate of subsequent pancreatic orifice stenosis and procedure-induced pancreatitis if the pancreatic sphincterotomy is performed with a needle knife over a pancreatic stent instead of a traction type sphincterotome[27].

Surgical sphincteroplasty has also been performed for pancreatic SOD in AIP patients[28]. Although clinical response was reported in 58% of AIP patients in this case series, it is unlikely that the more aggressive surgical approach is warranted unless endoscopic therapy is not feasible due to altered anatomy or in other unusual circumstances.

TREATMENT OUTCOMES IN IAP

There are few prospective data and only one controlled trial that address the outcome of endoscopic therapy in patients with IAP. The controlled trial used serial pancreatic stents over 9 mo *vs* serial ERCP without stent insertion and was performed in patients without sphincter hypertension so it is uncertain if the results pertain to the AIP patients with documented pancreatic SOD. The rate of recurrent pancreatitis was reduced from 53% to 11% over the 3-year study period in the stented group[29]. This positive result in manometrically normal AIP patients highlights our lack of understanding of the sensitivity and specificity of SOM.

Several case series report excellent response to biliary sphincterotomy alone[30,31] although Guelrud in an abstract found that patients who underwent dual sphincterotomy fared better (86%) than those treated by biliary sphincterotomy alone (28%)[32]. Most experts believe that treatment of the pancreatic sphincter should occur at the initial therapy although strong evidence is lacking. However, it seems rational to first incise the sphincter that correlates with the presentation of the patient, meaning that pancreatic or dual sphincterotomy should be considered the treatment of choice for AIP patients with documented pancreatic SOD. A rational approach to an AIP patient is to perform EUS to rule out other potential causes of pancreatitis and to proceed to ERCP with manometry if the patient is anxious for treatment and understands that treatment success occurs in only 60%-80% of patients and that the treatment is not without complications[33]. Some experts would limit ERCP with manometry and possible pancreatic sphincterotomy to patients with recurrent AIP since some patients may have only one attack or have attacks separated by many years.

Skeptics continue to point out that there are many problems with endoscopic therapy for AIP[34]. First, there is a variable natural history of AIP patients making it difficult to assess treatment outcome. It is clear that some patients may go years between attacks of pancreatitis making long-term follow up mandatory. Second, endoscopic therapy is not without risks even with prophylactic pancreatic duct stent placement. A prospective randomized controlled trial is needed.

CONCLUSION

Two potential causes of acute idiopathic pancreatitis are microlithiasis and sphincter of Oddi dysfunction. Microlithiasis is common in patients with an intact gallbladder and acute idiopathic pancreatitis although the reported incidence varies widely. It is best detected by endoscopic ultrasound although empiric cholecystectomy remains a reasonable choice, especially in high incidence centers. Microlithiasis has not been found to be associated with acute idiopathic pancreatitis in post-cholecystectomy patients.

Sphincter of Oddi dysfunction is also common in patients with acute recurrent idiopathic pancreatitis. It remains unclear if SOD is the initial cause of the pancreatitis or is due to prior attacks. Irregardless, sphincter ablation decreases the frequency of subsequent attacks although this conclusion is based on the few available studies that are retrospective and small. Despite

this lack of data, it is reasonable to pursue ERCP with manometry and possible pancreatic sphincterotomy in patients with frequent recurrent attacks since there are no other treatment options. However, a careful discussion with the patient of the risks versus benefits of pancreatitic sphincterotomy in acute recurrent pancreatitis is required.

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