REVIEW ARTICLE

Recurrent acute pancreatitis: a diagnostic and a therapeutic dilemma

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AP (Acute Pancreatitis), RAP (Recurrent Acute Pancreatitis), CP (Chronic Pancreatitis), SOD (Sphincter of Oddie Dysfunction), SOM (Sphincter of Oddi Manometry), PD (Pancreatic Divisum), AIP (Auto Immune Pancreatitis)

Abstract

Although uncommon, surgeons and physicians are sometimes confronted with patients who presents with recurrent episodes of acute pancreatitis. When two or more episodes of acute pancreatitis occur without an identifiable cause, it is referred to as Recurrent Acute Pancreatitis (RAP). In such patients, selecting the most appropriate management strategy continue to pose a challenge due to multiple aetiological factors, associated conditions, microanatomical and pathological processes and complex immunological mechanisms of this condition.

The identifiable causes of RAP such as bile duct stones, biliary sludge or crystals, Sphincter of Oddi Dysfunction (SOD), pancreatic duct obstructions due to benign and malignant neoplasms, genetic mutations, Pancreatic Divisum (PD), metabolic disorders, alcohol consumption and smoking may be identified in some patients. There are several other rare conditions which may be associated with RAP. However, in about 30%, no cause/s can be identified. Diagnosis is further complicated by the fact that, although the gland may appear morphologically normal following the initial episode of Acute Pancreatitis (AP), in some patients, evidence of Chronic Pancreatitis (CP) may manifest later. Furthermore, there is an ongoing debate as to whether, recurrent bouts of pancreatitis following the first; the Sentinel Acute Pancreatitis episode in patients who are 'immunologically' predisposed may lead to Chronic Pancreatitis. In such patients who subsequently develop acute episodes, i.e., Acute on Chronic Pancreatitis will further complicate recognition of aetiological factors of RAP.

The recognition of possible causes, associated factors, and understanding of pathological progressions are therefore important in the management of such patients. Detailed clinical assessment and clinical reasoning, standard haematological and biochemical workup and basic and advanced imaging studies will help identify patients who can be selected for specific invasive and medical therapy to prevent acute episodes.

This brief review is a clinical update to guide clinicians, the best way forward in the management of RAP.

Introduction

Recurrent Acute Pancreatitis (RAP) is often defined as a clinical entity when two or more episodes of acute pancreatitis occur without an identifiable cause, and when such episodes occur in a space more than 3 months between two episodes, in a setting of a 'structurally normal' gland self-limiting oedematous changes (1,17).

Despite recent understanding of pathophysiology and pathogenesis of acute pancreatitis, management of this clinical entity continues to pose a challenge. The objective of this brief review is to provide a clinical update of the way forward in the management of RAP.

Causative factors can be identified in many such patients. In clinical practice, stones, biliary sludge or crystals in the bile duct, dysfunction of the Sphincter of Oddi (SOD), pancreatic duct obstruction due to benign or malignant neoplasms, genetic mutations, Pancreatic Divisum (PD), alcohol consumption and smoking may be identified. However, approximately in 30% of patients, the aetiology of RAP continues to be elusive and the phrase, “idiopathic” is used.

It must be reiterated that, although the gland may appear morphologically normal after such an episode, in a proportion, evidence of Chronic Pancreatitis (CP) may subsequently manifest. This is because of the diagnostic difficulties of early chronic pancreatitis that may arise even

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with the best technology. However, if the evidence of early CP is identified, then, the title, recurrent acute pancreatitis (RAP) may be revised to Acute on Chronic Pancreatitis, that is, Acute Pancreatitis in a setting of early Chronic Pancreatitis. However, there is an ongoing debate, whether episodes of acute pancreatitis eventually lead to chronic pancreatitis in some patients who are 'immunologically' predisposed.

The descriptive term sentinel acute pancreatitis is used by some for the initial event. In susceptible individuals, the microanatomic changes, and immunological changes will continue following the oedematous phase resulting in persistent changes that predisposes to RAP. (2,3)

Therefore, it is important to identify patients who can be selected for specific invasive or medical treatment to prevent further acute episodes following the sentinel AP event.

Management of RAP therefore requires identification of possible causes, associated issues, and ongoing pathological derangements. Detailed clinical assessment, standard hematological and biochemical workup and basic and advanced imaging will help identify such aetologically important factors in approximately 70% of the patients

Alcohol consumption and smoking are recognized as predisposing/causative factors. There is evidence that RAP typically occurs in patients who continued to be heavy drinkers (>5 drinks per day). Furthermore, cessation of alcohol reduces further attacks and progression. Smoking is recognized as an independent risk factor for AP, RAP and CP. The effect is shown to be dose dependent and worsened with drinking (4,5).

Gallstones is identified as the most common condition associated with RAP (6,7). In the absence of easily identifiable bile duct stones, Gallstone disease may present only with microlithiasis (stones less than two mm in diameter), gallbladder sludge or bile crystals. Technological advancements and standardization of interpretation of Endoscopic Ultrasound have refined the diagnosis of microlithiasis and biliary sludge and is considered superior to Computerized Axial Tomography and Magnetic Resonance Cholangio-Pancreatography (MRCP) (17). Bile Microscopy identifies Biliary Crystals. However, microlithiasis have not shown a clear relationship as a causative factor (8,9).

Sphincter of Oddi Dysfunction (SOD) is recognized as a cause of RAP especially in young females who present with biliary type pain where no apparent cause is found. SOD comprises two clinical entities: one related to a functional disorder; referred to as Sphincter of Oddi Dyskinesia where the clinical features are brought on by episodes of transient sphincter hypertonia. Fibrosis due to ongoing chronic inflammatory process resulting in stenosis of the orifice of the ampulla of vator is the other entity which may produce similar symptoms.

In the clinical context, SOD is classified into three types.

Type I patients present with pancreatic type pain with high serum pancreatic enzymes and/or elevated liver enzymes and a dilated common bile duct and/or main pancreatic duct: a demonstratable structural problem.

Type II patients have pancreatic type pain, associated with at least one of the type I features. In these patients, the manometry may indicate elevated basal sphincter pressures. However, no stenosis may be demonstrable in most of them.

Type III have only pancreatic type pain but no elevation of pancreatic enzymes, normal biochemistry, and normal imaging. Type III patients are generally not considered for Recurrent Acute Pancreatitis (10,11)

Sphincter of Oddi Manometry (SOM) remains the gold standard investigation for the diagnosis of SOD. Manometry is performed during Endoscopic Retrograde Cholangio Pancreatogrm (ERCP) during which, selective cannulation is done through the major papilla with a catheter. Normal basal sphincter pressure is less than 35 mmHg (mean 15 mmHg) and a level more than 40 mmHg is considered abnormal. An alternative to manometry is MRCP with the secretin test (MRCP-S).

Pancreatitis susceptibility gene variants (PRSS1, SPINK1, and CFTR mutations) have been identified in some patients with RAP. The PRSS1, SPINK1, CFTR, and/or CTRC variants have been identified in 58% of patients of idiopathic RAP patients, in one study (12).

Auto Immune Pancreatitis (AIP) is described as a rare cause of Recurrent Acute Pancreatitis especially in younger patients. Some of these patients may have inflammatory bowel disease. (13)

There are several other rare conditions. Early malignancies that may occlude the pancreatic duct can induce acute pancreatitis. One such lesion is mucinous ductal neoplasm which is not infrequently associated with RAP. Other benign conditions that are implicated in RAP are Periampullary Diverticula, Pancreatic Divisum, Choledochocele and presence of abnormally long common channel.

Periampullary Diverticula are frequently found in patients with gall stones and RAP. However, their role in the occurrence of pancreatitis is debatable.

Pancreas Divisum is identified in some patients with recurrent 'pancreatic type' pain. Pancreatic Divisum is a developmental abnormality where the dorsal and ventral ducts are partially fused. In some such patients the dorsal duct drains through the major papilla through the communicating branch which joins ventral duct and dorsal duct. In many, this communication branch is thin and not well developed. Therefore, the passage may be inadequate for draining of pancreatic fluid when the pancreas is stimulated during meals. Studies show a prevalence of PD in patients with RAP. If dilation of the dorsal duct is found in such patients, this may also indicate an obstruction at the minor papilla orifice. (14,15)

Choledochocele is a condition where the intramural segment of the common bile duct is dilated and protrudes into duodenum. It is postulated that biliary sludge or small stones may get lodged in this dilated segment, occlude the flow of bile and pancreatic juice, and initiate pancreatitis. SOD may be considered as a cause of ampullary choledochal cysts.

Annular pancreas is a rare anatomical condition. The duodenum and the bile duct may get entrapped by the annular growth of the pancreas and in about 1/3 of such patients there is an 'entrapment' of duodenum and common bile duct by the annular growth of the gland. About one third of patients with annular pancreas may also have Pancreas Divisum. However, the relationship between PD and Annular Pancreas with RAP is far from clear.

An abnormally long common channel may facilitate reflux of bile into the pancreatic duct. This abnormality is easily diagnosed by MRCP or ERCP. Choledochal cysts are not infrequently associated with this anomaly.

Hypertriglyceridemia and hypercalcemia can cause RAP. Most patients with hypercalcemia may have Hyperparathyroidism. Unless serum calcium levels are performed during an acute episode, the diagnosis of hyperparathyroidism may be missed.

Serum triglycerides over 1000 mg/dL may be needed to precipitate an episode of acute pancreatitis. This is rare.

So how do we select patients with RAP who may be helped by specific intervention procedures or therapy? Choices include Cholecystectomy, Biliary or Selective Pancreatic Sphnicterotomy, Minor Papilla Sphincterotomy or Gallstone Dissolution Therapy. However, the impact of Biliary and Pancreatic Sphincterotomy on the Natural History of RAP is still unclear. Although the role of Biliary Sphincterotomy in the setting of Biliary Pancreatitis is well defined, the benefit of empiric biliary sphincterotomy for RAP is still unproven.

Nevertheless, because of high association between SOD and RAP, some endoscopists perform Biliary Sphincterotomy or Selective Pancreatic Sphincterotomy.

If a biliary aetiology is suspected with the presence of abnormal liver function tests (LFT) within 24 to 48 hours of the onset of AP, and it is suspected to be due to microlithiasis, many centres recommend cholecystectomy and/or ERCP with biliary sphincterotomy to prevent further attacks.

It is recommended that Biliary and Pancreatic Sphincterotomy must be performed in centres with experience and expertise to minimize the risk of post ERCP Pancreatitis. A high prevalence of post ERCP pancreatitis is observed in patients with RAP.

If the gallbladder appears normal on EUS and liver biochemistry is repeatedly within normal limits, empiric cholecystectomy may be avoided. (17)

Apart from total abstinence of alcohol and tobacco, reducing weight and control of serum triglycerides, other medical therapies such as Ursodeoxycholic acid, and Antioxidants are also shown to be effective in the treatment of RAP. However, there is no convincing data to support medical therapy for RAP. (18,19)

References

1. Al-Haddad M, Wallace MB. Diagnostic approach to patients with acute idiopathic and recurrent pancreatitis, what should be done? World J Gastroenterol. 2008; 14:1007–1010.

2. Whitcomb DC. Genetic risk factors for pancreatic disorders. Gastroenterology. 2013; 144:1292–1302.

3. Yadav D, Whitcomb DC. The role of alcohol and smoking in pancreatitis. Nat Rev Gastroenterol Hepatol. 2010; 7:131–145.

4. Coté GA, Yadav D, Slivka A, et al. Alcohol and smoking as risk factors in an epidemiology study of patients with chronic pancreatitis. Clin Gastroenterol Hepatol. 2011; 9:266–273.

5. Yadav D, Hawes RH, Brand RE, et al. Alcohol consumption, cigarette smoking, and the risk of recurrent

acute and chronic pancreatitis. Arch Intern Med. 2009; 169:1035–1045.

6. Ros E, Navarro S, Bru C, Garcia-Pugés A, Valderrama R. Occult microlithiasis in 'idiopathic' acute pancreatitis: prevention of relapses by cholecystectomy or ursodeoxycholic acid therapy. Gastroenterology. 1991; 101:1701–1709.[PubMed][Google Scholar]

7. Testoni PA, Caporuscio S, Bagnolo F, Lella F. Idiopathic recurrent pancreatitis: long-term results after ERCP, endoscopic sphincterotomy, or ursodeoxycholic acid treatment. Am J Gastroenterol. 2000;95:1702–1707[PubMed][Google Scholar]

8. Ros E, Navarro S, Bru C, et al. Occult microlithiasis in 'idiopathic' acute pancreatitis: prevention of relapses by cholecystectomy or ursodeoxycholic acid therapy. Gastroenterology. 1991; 101:1701–1709.

9. Kaw M, Brodmerkel G J Jr. ERCP, biliary crystal analysis, and sphincter of Oddi manometry in idiopathic recurrent pancreatitis. Gastrointest Endosc. 2002; 55:157–162.

10. Coyle WJ, Pineau BC, Tarnasky PR, et al. Evaluation of unexplained acute and acute recurrent pancreatitis using endoscopic retrograde cholangiopancreatography, sphincter of Oddi manometry and endoscopic ultrasound. Endoscopy. 2002; 34:617–623.

11. Toouli J, Roberts-Thomson IC, Dent J, et al. Sphincter of Oddi motility disorders in patients with idiopathic recurrent pancreatitis. Br J Surg. 1985; 72:859–863.

12. Jalaly NY, Moran RA, Fargahi F, et al. An evaluation of factors associated with pathogenic PRSS1, SPINK1, CTFR, and/or CTRC genetic variants in patients with idiopathic pancreatitis. Am J Gastroenterol. 2017;112: 1320–1329.

13. Hart PA, Zen Y, Chari ST. Recent advances in autoimmune pancreatitis. Gastroenterology. 2015; 149:39–51.

14. Borak GD, Romagnuolo J, Alsolaiman M, et al. Long-term clinical outcomes after endoscopic minor papilla therapy in symptomatic patients with pancreas divisum. Pancreas. 2009; 38:903–906.

15. Chacko LN, Chen YK, Shah RJ. Clinical outcomes and non-endoscopic interventions after minor papilla endotherapy in patients with symptomatic pancreas divisum. Gastrointest Endosc. 2008;68: 667–673.

16. Coté GA, Imperiale TF, Schmidt SE, et al. Similar efficacies of biliary, with or without pancreatic, sphincterotomy in treatment of idiopathic recurrent acute pancreatitis. Gastroenterology. 2012; 143:1502–1509

17. Nalini M Guda, Venkata Muddana, D N Reddy, D C Whitcomb, Markus M. Lerch, J. Shawn Mallery, Martin L. Freeman et al. Conference report. Recurrent Acute Pancreatitis. International State-of-the-Science Conference with Recommendations. Pancreas. Volume 47, Number 6, July 2018

18. Testoni PA, Caporuscio S, Bagnolo F, et al. Idiopathic recurrent pancreatitis: long-term results after ERCP, endoscopic sphincterotomy, or ursodeoxycholic acid treatment. Am J Gastroenterol. 2000;95: 1702–1707.

19. Saraswat VA, Sharma BC, Agarwal DK, et al. Biliary microlithiasis in patients with idiopathic acute pancreatitis and unexplained biliary pain: response to therapy. J Gastroenterol Hepatol. 2004;19: 1206–1211.