Etiology of Recurrent Acute Pancreatitis: 10-year Review from a Large Tertiary Hospital

Supot Pongprasobchai, M.D., Ashari Saman, M.D.

Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

ABSTRACT

Objective: To determine the etiology of recurrent acute pancreatitis (RAP) in a single tertiary hospital in Thailand.

Methods: Medical records, imaging and endoscopic data of patients who presented with acute pancreatitis for more than once during 2005-2014 were retrospectively reviewed and analyzed.

Results: There were 66 RAP patients over the 10-year period. Majority (69.7%) were men. Mean age was 47 ± 19 years. Thirty percent smoked and 48% drank significant alcohol (defined as ethanol >80 g/day for >5 years). Liver function test, serum triglyceride and calcium were done in every case. Ultrasonography, computed tomography and endoscopic ultrasonography were performed in 54.5%, 53.0% and 33.3%, respectively. Genetic studies (*PRSS1* and *SPINK1* mutations) were performed in 9 patients (13.6%) and mutations were found for *PRSS1* in 1 and *SPINK1* in 2 patients. Alcohol was the most common etiology of RAP (40.9%), followed by biliary stone (27.3%), all of which were macrolithiasis. ICP was the third most common cause (9.1%) and hereditary pancreatitis was diagnosed in 1 patient (1.5%). Seventeen patients (25.7%) had miscellaneous etiologies and 2 (3.0%) finally had idiopathic recurrent acute pancreatitis (IRAP). More than half (61%) of patients with RAP from macrolithiasis were associated with delayed cholecystectomy after sentinel gallstone pancreatitis.

Conclusion: The most common etiologies of RAP in order were alcohol, macrolithiasis and ICP. Among RAP patients from macrolithiasis, the main cause was delayed cholecystectomy after sentinel gallstone pancreatitis.

Keywords: Etiology; recurrent acute pancreatitis; Thailand (Siriraj Med J 2017;69: 161-166)

INTRODUCTION

Recurrent acute pancreatitis (RAP) is a clinical entity characterized by recurrent episodes of acute pancreatitis.[1] RAP is a spectrum of pancreatitis lying between acute pancreatitis (AP) and chronic pancreatitis (CP). Uncontrolled or severe RAP increases the risk of developing CP according to the sentinel acute pancreatitis event (SAPE) theory.[2,3] The key message of this theory is that during episodes of AP, cytokines from the inflammatory cells will activate the pancreatic stellate cells. The activated pancreatic stellate cells have fibroblastic phenotypes and thus, are the precursor of pancreatic fibrosis. Repeat attacks of AP from any cause, alcohol consumption and smoking will accelerate this process and drive the pancreas into CP.[4] The recent mechanistic definition of CP also endorsed the SAPE theory and the importance of RAP in the development of CP.[5] From these reasons, proper searching for the etiology of RAP, treating and preventing the recurrence might retard or stop the progression to CP.[5]

There are numerous causes of RAP. Unfortunately, almost all published series of RAP focused on a subgroup of RAP, namely idiopathic recurrent acute pancreatitis (IRAP), which refers to the RAP that remains idiopathic after ruling out common causes of RAP by conventional investigations, such as blood tests, ultrasonography and computed tomography. As a result, most published series on IRAP reported microlithiasis, sphincter of Oddi

Correspondence to: Supot Pongprasobchai
E-mail: supot.pon@mahidol.ac.th
Received 21 March 2017 Revised 5 June 2017 Accepted 8 June 2017
doi:10.14456/smj.2017.33

dysfunction (SOD) and idiopathic chronic pancreatitis (ICP) as the 3 most common causes of IRAP.[6] In real life practice, we frequently see RAP from alcohol and biliary stones. This is because studies on the etiology of overall RAP are rare[7-11] despite they are very important to help diagnose, manage and set up the appropriate guideline of RAP in the future.

The aim of this study was to determine the etiology of RAP in a single tertiary hospital in Thailand.

MATERIALS AND METHODS

The present study was conducted in Siriraj Hospital, Bangkok, Thailand, under an approval from Siriraj Institutional Review Board (Si.206/2015).

Patients

We retrospectively recruited patients over 15 years old, who presented with AP and attended our hospital during 2005-2014. We selected only patients who presented with AP twice or more and the duration between the attacks was more than 3 months.[12] Data from medical records, imaging studies and endoscopic data were recorded on a standardized case record form including name, age, gender, comorbidities, current medications, alcoholic drinking, smoking, severity of RAP, number of attacks, etiology of RAP, investigations and treatments. In case there was no cause of RAP identified and the patients never had endoscopic ultrasonography (EUS) done, they were asked to undergo EUS, as recommended by some experts.[13]

Definition of the specific etiologies of RAP

Significant alcohol drinking was defined by ethanol consumption ≥80 g per day for ≥5 years.[14] Triglyceride level more than 1,000 mg/dL or high calcium level above normal were considered etiological factors. Drug-induced pancreatitis was diagnosed when the patient took the drugs that have been classified as "definite" drug-induced pancreatitis[15] and already excluded other common causes of RAP.[14] Other etiologies of AP were diagnosed using well-accepted definitions, which were reviewed elsewhere.[14]

Genetic study

Genetic study included Protease Serine 1 (*PRSS1*) mutations for hereditary pancreatitis and Serine Protease Inhibitor, Kazal type 1 (*SPINK1*) mutations for ICP. Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*) mutations for ICP were not tested due to the unavailability of this test in Thailand.

Statistical analysis

Patients' demographics were presented as number and per cent. Continuous variables were presented as mean and standard deviation. Data was analyzed using SPSS version 22.0.

RESULTS

Prevalence

Over the 10-year period, there were 1,511 patients with AP presented to our institute. Of these, 66 patients had RAP. Thus, the prevalence of RAP was 4.4% of AP patients.

Patients' demographics

Majority of the patients (69.7%) were men with a mean age of 47 ± 19 years. The average number of attacks were 2.8 times (range 2-5 times). Twenty patients (30.3%) smoked and 32 patients (48.4%) drank significant amount of alcohol. Detailed characteristics of the studied patients were given in Table 1.

Investigations of RAP

Liver function test, serum triglyceride and serum calcium level were checked in every patient. Ultrasonography, computed tomography and EUS were performed in 54.5%, 53.0% and 33.3%, respectively. Others investigations were magnetic resonance imaging/cholangiopancreatography (MRI/MRCP) and endoscopic retrograde cholangiopancreatography (ERCP). Hepatobiliary scintigraphy was performed in 1 patient to diagnose the SOD. Genetic study was performed in 9 patients (13.6%) and mutations were found for *PRSS1* in 1 patient and *SPINK1* in 2 patients (Table 2). No patient required additional EUS in this study.

Etiologies of RAP

The etiologies of RAP are shown in Table 3. Alcohol was the most common etiology of RAP (40.9%), followed by biliary stone (27.3%), all of which were macrolithiasis. ICP was the third most common cause (9.1%). Hereditary pancreatitis was diagnosed in 1 patient (1.5%). Seventeen patients (25.7%) had miscellaneous etiologies including hypertriglyceridemia, hypercalcemia, pancreas divisum, SOD type 1, intraductal papillary mucinous neoplasm, ampullary carcinoma and drugs. Two patients (3.0%) were finally defined as IRAP.

RAP from macrolithiasis

Of the 18 patients with RAP from macrolithiasis, 11 (61%) were associated with delayed or no cholecystectomy after the sentinel biliary pancreatitis and the median

duration of recurrence was 120 days (range 90-730 days). Other reasons were inadequate work-up for gallstone during the sentinel AP (4 patients, 22.2%), recurrent stone after cholecystectomy (1 patient, 5.5%) and the co-existence of other etiologies during the sentinel AP, causing overlooking of gallstones (3 patients, 16.7%).

TABLE 1. Demographic characteristics of 66 patients with recurrent acute pancreatitis.

Characteristics	Number	(%)
Gender		
Male	46	(69.7)
Female	20	(30.3)
Age (year), mean ± SD	47 ± 19	
Number of attacks, mean ± SD	2.8 ± 0.9	
Smoking	20	(30.3)
Alcohol		
≥ 80 g/day for ≥ 5 years	32	(48.4)
< 80 g/day for < 5 years	5	(7.6)
Comorbidities		
Hypertension	19	(28.7)
Diabetes	17	(25.7)
Hyperlipidemia	11	(16.7)
Cerebrovascular disease	5	(7.6)
Coronary artery disease	3	(4.5)
Others	23	(34.8)

Abbreviation: SD = standard deviation

TABLE 2. Investigations of recurrent acute pancreatitis in 66 patients.

Investigations	Number	(%)
Liver function test	66	(100)
Serum triglyceride	66	(100)
Serum calcium	66	(100)
Transabdominal ultrasonography	36	(54.5)
Computed tomography	35	(53.0)
MRI/MRCP	8	(12.1)
Endoscopic retrograde cholangiopancreatography	17	(25.8)
Endoscopic ultrasonography	22	(33.3)
Hepatobiliary scintigraphy	1	(1.5)
Genetic study (*PRSS1, SPINK1* mutations)	9	(13.6)

Abbreviations: MRI = magnetic resonance imaging; MRCP = magnetic resonance cholangiopancreatography

TABLE 3. Etiologies of recurrent acute pancreatitis in 66 patients.

Etiology	Number	(%)
Alcohol	27	(40.9)
Biliary stone	18	(27.3)
Idiopathic chronic pancreatitis	6	(9.1)
Hypertriglyceridemia	4	(6.1)
Hypercalcemia	3	(4.5)
Pancreas divisum	3	(4.5)
Sphincter of Oddi dysfunction, type 1	1	(1.5)
Intraductal papillary mucinous neoplasm	2	(3.0)
Ampullary carcinoma	2	(3.0)
Drugs	2	(3.0)
Hereditary pancreatitis	1	(1.5)
Idiopathic recurrent acute pancreatitis	2	(3.0)

DISCUSSION

Although there have been plenty of studies and systematic reviews on the etiology of AP[16], very few focused on RAP.[7-11] The prevalence of RAP had been studied in a few studies,[7-11] and the prevalence varied between 11-27%. [7-11] A recent meta-analysis of 14 studies including 8,492 patients with AP demonstrated a 22% prevalence of RAP and 10% prevalence of progression to CP.[17] The mortality rate of RAP was 6%[7], which was considerably high.

In the present study, we identified 66 RAP patients from 1,511 patients with AP (4.4%) over the 10-year period. This number was much lower than the 22% prevalence of RAP after AP by the meta-analysis.[17] This was likely because our institute is the tertiary hospital and we did not have a standard protocol for following up patients after their first attacks of AP. Thus, we likely missed many patients, who might have RAP but were not presented or referred to our hospital.

In the present study, we demonstrated the 2 most common etiologies of RAP to be alcohol (41%) and biliary macrolithiasis (27%). The frequencies of these 2 major etiologies aligned with the European study[7] (alcohol 57%, biliary stone 25%), the Japanese study[10] (alcohol 38%, biliary stone 11%) and the Chinese study[8] (alcohol 20%, biliary stone 20%), although the numbers may vary slightly. These were probably attributed to the ethnicity and alcohol drinking habits in the studied population and the aggressiveness in the search of biliary etiology. The predominant alcohol etiology of RAP in most studies,[7,8,10] including ours, paralleled with the alcohol etiology of AP in their corresponding regions.[14,18-20] However, our study and others[7,8,10] differed considerably from the Indian study, who found biliary cause in 37% and alcohol in only 6%.[9] The main reason for the predominant biliary etiology in the Indian study[9] was probably due to the performing of bile crystal analysis for microlithiasis, which was not performed in any study[7, 8, 10] including ours. As a result, microlithiasis comprised up to two-thirds of the biliary causes in their study. Another possible reason could be the less alcohol drinking habits among Indian patients, as reflected by the less commonness of alcohol etiology in the Indian studies of CP.[21-23]

Alcohol was the most common cause of RAP in most studies[7, 8, 10] including our study. The strategy to encourage patients to stop drinking is essential, but challenging. A recent randomized controlled study[24] showed that using intensive scheduled advice could reduce alcohol drinking habits and, importantly, the incidence of RAP from alcohol. Thus, abstinence is advocated to prevent RAP from alcohol.

Regarding biliary stone, all studies[7, 8, 10] including the present study similarly showed that most of RAP from biliary stones were not microlithiasis as concerned, but were macrolithiasis due to delayed cholecystectomy after the sentinel biliary pancreatitis. Recurrent biliary pancreatitis itself has morbidity and mortality, but could also lead the pancreas to CP according to the SAPE theory[4] and the new mechanistic definitions of CP.[5] Currently,

all evidence and guidelines recommend performing cholecystectomy during the index admission of biliary pancreatitis or no longer than 2 weeks after discharge.[25-31] Recent randomized controlled study also showed that interval cholecystectomy at 1 month is already too late because recurrent biliary pancreatitis occurred much more than those who had cholecystectomy during the same admission.[32] However, it has sadly been shown that only 5% of patients with biliary pancreatitis had cholecystectomy complying with the guidelines, and the median time of cholecystectomy was 40 days.[31] Thus, this problem is a challenging issue worldwide, not only in Thailand. It is our opportunity for improvement and needs to be solved systematically.

ICP was the third most common cause of RAP in the present study (9%). It differed from others[7-10], who reported IRAP as the third most common cause of RAP (10-32%). The main reason was probably the wide use of EUS in the present study, while others mainly used cross-sectional imaging studies/ERCP/MRCP[9,10], or not stated.[7,8] EUS is well established to be the most sensitive diagnostic method for early CP, over ERCP and MRCP.[33] Furthermore, EUS studies of IRAP patients identified ICP in almost half of them.[13,34,35] Thus, the authors postulate that many IRAP patients in the previous studies[7-10] might actually have ICP if EUS had been done.

Genetic study was done in a minority of patients in this study due to the cost of the test. However, *SPINK1* mutations were present in half of them, supporting the genetic roles of *SPINK1* in ICP.[36] *CFTR* mutations study was unavailable in Thailand due to the very high cost of the test. Only 1 patient had *PRSS1* mutation for hereditary pancreatitis, affirming the rarity of the disease.

Three per cent of RAP patients in the present study were finally designated as IRAP. Our result suggested that, with current dedicated investigations, true IRAP was rare.

The strengths of the present study are that it is one of a few studies on RAP. The etiologies were sought aggressively as reflected by the very small number of patients with IRAP. However, there are some limitations of our study. First, the sample size remains small even we had collected the cases over a 10-year period. Thus, multicenter study is necessary to determine the overall etiologies of RAP in Thailand. Second, we did not perform sphincter of Oddi manometry (SOM) for the diagnosis of SOD. The single case of SOD in this study had papillary stenosis or SOD type 1, which was diagnosed by clinical criteria and scintigraphy without SOM.[37] Thus, we might miss some patients with SOD, particularly the last 2 patients with IRAP. However, SOD is a very controversial cause of RAP[6,38] and SOM is a procedure at high-risk for post-procedure pancreatitis.[39,40] Even if we did perform SOM, the number of patients with SOD would be a maximum of 3 cases, since there were only 2 patients with IRAP left.

In conclusion, the most common etiologies of RAP in order were alcohol, macrolithiasis and ICP. Among patients with RAP from macrolithiasis, the common cause was delayed cholecystectomy after the sentinel biliary pancreatitis.

Conflict of interest: None

REFERENCES

1. Testoni PA. Acute recurrent pancreatitis: etiopathogenesis, diagnosis and treatment. World J Gastroenterol 2014;20:16891-901.
2. Aoun E, Slivka A, Papachristou DJ, Gleeson FC, Whitcomb DC, Papachristou GI. Rapid evolution from the first episode of acute pancreatitis to chronic pancreatitis in human subjects. JOP 2007;8:573-8.
3. Bertilsson S, Sward P, Kalaitzakis E. Factors that affect disease progression after first attack of acute pancreatitis. Clin Gastroenterol Hepatol 2015;13:1662-9 e3.
4. Schneider A, Whitcomb DC. Hereditary pancreatitis: a model for inflammatory diseases of the pancreas. Best Pract Res Clin Gastroenterol 2002;16:347-63.
5. Whitcomb DC, Frulloni L, Garg P, Greer JB, Schneider A, Yadav D, et al. Chronic pancreatitis: An international draft consensus proposal for a new mechanistic definition. Pancreatology 2016;16:218-24.
6. Steinberg WM, Chari ST, Forsmark CE, Sherman S, Reber HA, Bradley EL, 3rd, et al. Controversies in clinical pancreatology: management of acute idiopathic recurrent pancreatitis. Pancreas 2003;27:103-17.
7. Gullo L, Migliori M, Pezzilli R, Olah A, Farkas G, Levy P, et al. An update on recurrent acute pancreatitis: data from five European countries. Am J Gastroenterol 2002;97:1959-62.
8. Gao YJ, Li YQ, Wang Q, Li SL, Li GQ, Ma J, et al. Analysis of the clinical features of recurrent acute pancreatitis in China. J Gastroenterol 2006;41:681-5.
9. Sajith KG, Chacko A, Dutta AK. Recurrent acute pancreatitis: clinical profile and an approach to diagnosis. Dig Dis Sci 2010;55:3610-6.
10. Takuma K, Kamisawa T, Hara S, Tabata T, Kuruma S, Chiba K, et al. Etiology of recurrent acute pancreatitis, with special emphasis on pancreaticobiliary malformation. Adv Med Sci 2012;57:244-50.
11. Zhang W, Shan HC, Gu Y. Recurrent acute pancreatitis and its relative factors. World J Gastroenterol 2005;11:3002-4.
12. Khurana V, Ganguly I. Recurrent acute pancreatitis. JOP 2014;15:413-26.
13. Wilcox CM, Varadarajulu S, Eloubeidi M. Role of endoscopic evaluation in idiopathic pancreatitis: a systematic review. Gastrointest Endosc 2006;63:1037-45.
14. Pongprasobchai S. Appropriate seach of the etiologies of acute pancreatitis. Pancreat Disord Ther 2014;4:1000135.

15. Badalov N, Baradarian R, Iswara K, Li J, Steinberg W, Tenner S. Drug-induced acute pancreatitis: an evidence-based review. Clin Gastroenterol Hepatol 2007;5:648-61; quiz 644.
16. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology 2013;144:1252-61.
17. Sankaran SJ, Xiao AY, Wu LM, Windsor JA, Forsmark CE, Petrov MS. Frequency of progression from acute to chronic pancreatitis and risk factors: a meta-analysis. Gastroenterology 2015;149:1490-1500 e1.
18. Gullo L, Migliori M, Olah A, Farkas G, Levy P, Arvanitakis C, et al. Acute pancreatitis in five European countries: etiology and mortality. Pancreas 2002;24:223-7.
19. Hamada S, Masamune A, Kikuta K, Hirota M, Tsuji I, Shimosegawa T, et al. Nationwide epidemiological survey of acute pancreatitis in Japan. Pancreas 2014;43:1244-8.
20. Gao YJ, Li YQ, Wang Q, Li SL, Li GQ, Ma J, et al. Analysis of clinical features of acute pancreatitis in Shandong Province, China. J Gastroenterol Hepatol 2007;22:340-4.
21. Balakrishnan V, Unnikrishnan AG, Thomas V, Choudhuri G, Veeraraju P, Singh SP, et al. Chronic pancreatitis. A prospective nationwide study of 1,086 subjects from India. JOP 2008;9:593-600.
22. Rajesh G, Girish BN, Panicker S, Balakrishnan V. Time trends in the etiology of chronic pancreatitis in South India. Trop Gastroenterol 2014;35:164-7.
23. Jha AK, Goenka MK, Goenka U. Chronic pancreatitis in Eastern India: Experience from a tertiary care center. Indian J Gastroenterol 2017;36:131-136.
24. Nordback I, Pelli H, Lappalainen-Lehto R, Jarvinen S, Raty S, Sand J. The recurrence of acute alcohol-associated pancreatitis can be reduced: a randomized controlled trial. Gastroenterology 2009;136:848-55.
25. UK guidelines for the management of acute pancreatitis. Gut 2005;54 Suppl 3:iii1-9.
26. Forsmark CE, Baillie J. AGA Institute technical review on acute pancreatitis. Gastroenterology 2007;132:2022-44.
27. Pezzilli R, Uomo G, Zerbi A, Gabbrielli A, Frulloni L, De Rai P, et al. Diagnosis and treatment of acute pancreatitis: the position statement of the Italian Association for the study of the pancreas. Dig Liver Dis 2008;40:803-8.
28. Tenner S, Baillie J, DeWitt J, Vege SS, American College of Gastroenterology. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol 2013;108:1400-15; 1416.
29. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013;13:e1-15.
30. Yokoe M, Takada T, Mayumi T, Yoshida M, Isaji S, Wada K, et al. Japanese guidelines for the management of acute pancreatitis: Japanese Guidelines 2015. J Hepatobiliary Pancreat Sci 2015;22:405-32.
31. van Baal MC, Besselink MG, Bakker OJ, van Santvoort HC, Schaapherder AF, Nieuwenhuijs VB, et al. Timing of cholecystectomy after mild biliary pancreatitis: a systematic review. Ann Surg 2012;255:860-6.
32. da Costa DW, Bouwense SA, Schepers NJ, Besselink MG, van Santvoort HC, van Brunschot S, et al. Same-admission versus interval cholecystectomy for mild gallstone pancreatitis (PONCHO): a multicentre randomised controlled trial. Lancet 2015;386:1261-8.
33. Conwell DL, Lee LS, Yadav D, Longnecker DS, Miller FH, Mortele KJ, et al. American Pancreatic Association Practice Guidelines in Chronic Pancreatitis: evidence-based report on diagnostic guidelines. Pancreas 2014;43:1143-62.
34. Garg PK, Tandon RK, Madan K. Is biliary microlithiasis a significant cause of idiopathic recurrent acute pancreatitis? A long-term follow-up study. Clin Gastroenterol Hepatol 2007;5:75-9.
35. Yusoff IF, Raymond G, Sahai AV. A prospective comparison of the yield of EUS in primary vs. recurrent idiopathic acute pancreatitis. Gastrointest Endosc 2004;60:673-8.
36. Schneider A. Serine protease inhibitor Kazal type 1 mutations and pancreatitis. Gastroenterol Clin North Am 2004;33:789-806.
37. Behar J, Corazziari E, Guelrud M, Hogan W, Sherman S, Toouli J. Functional gallbladder and sphincter of oddi disorders. Gastroenterology 2006;130:1498-509.
38. Steinberg WM. Controversies in clinical pancreatology: should the sphincter of Oddi be measured in patients with idiopathic recurrent acute pancreatitis, and should sphincterotomy be performed if the pressure is high? Pancreas 2003;27:118-21.
39. Cotton PB, Garrow DA, Gallagher J, Romagnuolo J. Risk factors for complications after ERCP: a multivariate analysis of 11,497 procedures over 12 years. Gastrointest Endosc 2009;70:80-8.
40. Freeman ML, Guda NM. Prevention of post-ERCP pancreatitis: a comprehensive review. Gastrointest Endosc 2004;59:845-64.