The Etiologic Evaluation of Acute Pancreatitis in a General Hospital of Seoul-Gyeonggi Province in Korea

Gun Jung Youn, Woo Chul Chung, Ji Min Lee, Chang-Nyol Paik, Jung Hwan Oh and Sung Hoon Jung
Division of Gastroenterology, Department of Internal Medicine, St. Vincent Hospital, College of Medicine, The Catholic University of Korea, Suwon, Division of Gastroenterology, Department of Internal Medicine, St. Paul’s Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Background/Aims: In recent years, the incidence of acute pancreatitis (AP) has been increasing. A better understanding of the etiology is directly linked to more favorable outcomes. Unfortunately, there have been reports suggesting the variation of etiologies of AP across countries. The objective of this study was to determine the etiology of AP in a general hospital of Seoul-Gyeonggi province in Korea during the past decade.

Methods: We retrospectively reviewed the medical records of consecutive patients with AP who were admitted to St. Paul’s Hospital (Seoul, Korea) with an affiliation to the Catholic University of Korea between January 2003 and January 2013.

Results: A total of 1,110 patients were enrolled, totaling 1,833 attacks, and the most frequent cause of AP was alcohol consumption. The recurrence rate of AP was 24.5% (272/1,110), and habitual recurrence rate (more than three times) was 12.6% (140/1,110). The rate of severe AP was 4.9% (90/1,833 attacks). The frequency of an idiopathic cause of AP was 13.3%. The recurrence rate and mortality rate of idiopathic AP were 16.2% and 5.4%, respectively. In 41.7% (10/24) of cases of idiopathic AP, microlithiasis was suspected.

Conclusions: Between 2003 and 2013 in Korea, alcohol was the most frequent cause of AP in the general hospital of Seoul-Gyeonggi province of Korea. It appears that alcohol abstinence program may be necessary. Further nationwide studies would be needed to evaluate the etiologies of AP. (Korean J Gastroenterol 2017;70:190-197)

Key Words: Pancreatitis; Alcohols; Gallstone

INTRODUCTION

Acute pancreatitis (AP) is a sudden inflammatory condition of the pancreas. Although in most AP patients, conservative management usually results in clinical improvement, progression to life-threatening conditions, including multi-organ failure with significant morbidity and mortality, occurs in approximately 10% of cases. Of the various etiologies of AP, the two most common are cholelithiasis and alcohol abuse, accounting for >60% of all cases. There appears to be an increase in the annual incidence of AP in Western countries and Korea. Despite advancements in diagnostic modalities, the exact causes of AP remain unknown in up to 30% of cases, and are labeled “idiopathic acute pancreatitis.”
Effective therapy for recurrent AP involves eliminating precipitating factors. For gallstone-induced AP, stone removal is performed. For alcoholic AP, cessation of alcohol consumption effectively reduces recurrent episodes. Without appropriate correction, however, the causative factor of an initial episode of AP might lead to recurrent attacks, especially in alcoholic AP. Frequent recurrent pancreatitis could result in chronic pancreatitis with irreversible pancreatic damage. Therefore, gallstone-induced, alcohol-induced, and idiopathic AP should be treated as distinct entities. The etiologic factors of AP may affect its clinical outcome, severity, and recurrence. Better understanding of its etiology has been shown to yield more favorable outcomes, as well as developing treatment strategies and prevention of recurrent AP. Unfortunately, there seems to be various etiologies of AP depending on country.

In the past, the presence of gallstones was the major etiology of AP in Korea. To the best of our knowledge, recent data on the etiology of patients with AP in Korea are limited. Moreover, since 2003 there were no data or reports regarding the etiology of AP in Korea. It is important to recognize that the etiologies of AP change over time.

According to the data from the Korean health insurance review and assessment service, the mortality rate of AP was 3% in the 1980s, which rose to 4.4% in the early 1990s, and dropped back down to 2.1% in the late 1990s. The mortality rate has been decreasing despite the increasing percentage of severe AP (SAP). Therefore, the aim of this study was to assess the etiology and outcomes of AP in real clinical practice during a recent decade (2003-2013) in a general hospital located in Seoul-Gyeonggi province of Korea.

MATERIALS AND METHODS

1. Study population

The study was conducted at St. Vincent Hospital (Suwon, Korea) and St. Paul’s Hospital (Seoul, Korea), two hospitals affiliated with the Catholic University of Korea. We retrospectively reviewed the medical records of consecutive patients who were admitted with AP between January 2003 and January 2013. A total of 1,833 attacks in 1,110 patients were evaluated. Every patient underwent abdominal computed tomography (CT). In the event of ambiguous CT finding, ultrasonography or magnetic resonance imaging of the pancreas were performed. We excluded patients who had postoperative pancreatitis, pancreatic contamination after bowel perforation, or post-endoscopic retrograde cholangiopancreatography pancreatitis.

2. Definition

The diagnoses of acute pancreatitis and recurrent pancreatitis were most often established by the presence of two of the following three criteria: (i) abdominal pain compatible with pancreatitis; (ii) elevated serum amylase and/or lipase (>3 times the upper limit of normal); and/or (iii) characteristic features on abdominal radiological studies.

Gallstone-induced pancreatitis was diagnosed if patients had a gallstone, sludge in the gallbladder, and/or lithiasis in the common bile duct, with or without a dilated bile duct from radiologic imaging. Alcoholic pancreatitis was defined as alcohol consumption just before the development of AP. SAP was defined by the Atlanta consensus classification system and revised Atlanta classification system. The organ failure was defined as a shock (systolic pressure <90 mm Hg), pulmonary insufficiency (PaO2 ≤ 60 mm Hg), renal failure (serum creatinine >2.0 mg/dL after hydration), or gastrointestinal bleeding (>500 mL/24 hours).

The diagnosis of autoimmune pancreatitis was based on Kim’s criteria, defined as follows: (i) diffuse enlargement of the pancreas on CT and diffuse or segmental irregular narrowing of the main pancreatic duct on endoscopic retrograde cholangiopancreatography; (ii) elevated levels of serum immunoglobulin (Ig)G and/or IgG4 or detected autoantibodies; (iii) fibrosis and lymphoplasmacytic infiltration; and (iv) response to steroid therapy.

Drug-induced pancreatitis was defined by the adverse drug reaction probability scale of Naranjo. This scale system has been used to determine the likelihood of whether an adverse drug reaction is actually due to drugs, rather than other factors. Patients who had a definite or probable score (≥5 points) were included in this study. Hypertriglyceridemia was only considered as an etiology when the triglyceride level was >1,000 mg/dL and other etiologies were ruled out. Here, in idiopathic AP, we defined the elevation of serum alkaline phosphatase (ALP) and increased alanine aminotransferase (ALT) (≥3 times the upper limit of normal) as findings suggestive of microlithiasis.
3. Statistical analysis

Continuous data are expressed as the mean±standard deviation and were analyzed using an independent samples t-test or the Kruskal Wallis test. Categorical variables are expressed as quantities and were analyzed using the χ² tests or Fisher’s exact test. SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA) was used for all analyses. p-values of less than 0.05 were considered statistically significant.

4. Ethical consideration

This study was reviewed and approved by the institutional review board of the Catholic University of Korea (IRB no. VC15RISE0185) in compliance with the declaration of Helsinki.

RESULTS

A total of 1,110 patients (767 males and 343 females) were enrolled. The age ranged from 7 to 98 years. The mean age was 52.92±15.06 years in males and 56.81±17.11 years in females (p<0.001). Pancreatitis-induced mortality rate was 2.6% (29/1,110 patients), and most of the deaths occurred at the first admission (26/29, 89.7%).

1. Etiologic analysis

Alcohol consumption and gallstones were the main causes of AP (Table 1, Fig. 1). Other causes of AP included autoimmune (n=14), drug-induced (n=7), cancer-related (n=15), intraductal papillary mucinous neoplasm (IPMN) (n=8), pancreas divisum (n=5), and hypertriglyceridemia (n=4).

Alcoholic pancreatitis was observed in 59.5% (660/1,110) of cases in our study. This cause was dominant in males (528 males, 132 females). The mean age of those with this type of AP was 50.64±13.81 years in males and 55.05±17.08 years in females. Males with alcoholic pancreatitis were significantly younger than females (p<0.01).

The rate of gallstone-induced pancreatitis was 22.1% (245/1,110) (male, 154; female, 91). The mean age of those with gallstone-induced pancreatitis was 58.51±15.28 years in males and 61.21±15.70 years in females; however, this was without statistical significance (p=0.19). The rate of autoimmune pancreatitis was 1.3% (14/1,110). Most autoimmune pancreatitis (12/13) was diagnosed by typical radiologic imaging (Fig. 2A), serology, and steroid responsiveness. One patient with IgG4 related retroperitoneal fibrosis was di-

![Fig. 1. Etiology of acute pancreatitis in Korea. Alcohol consumption and gallstones are the main etiologic factors of AP. Other etiology of AP includes autoimmune (n=14), drug-induced (n=7), cancer-related (n=15), intraductal papillary mucinous neoplasm (IPMN) (n=8), pancreas divisum (n=5), and hypertriglyceridemia (n=4).](image-url)

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<th>Table 1. Etiologic Analysis of Acute Pancreatitis in Korea</th>
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Values are presented as n (%) or mean±standard deviation unless otherwise indicated.

BMI, body mass index; AP, acute pancreatitis; SAP, severe acute pancreatitis.
agnosed by a biopsy. The mean age of patients with autoimmune pancreatitis was 55.29±22.51 years. The rate of drug-induced pancreatitis was 0.6% (7/1,110) – nonsteroidal anti-inflammatory drugs (n=1), herbal medicine (n=2), sunitinib (n=1), warfarin (n=1), and azathioprine (n=2). All cases were females with a mean age of 51.29±14.42 years.

The rate of SAP was 4.9% (90/1,833 attacks). The mortality rate of SAP was 23.3% (21/90). Among those with with SAP, the causes were alcohol (n=53), gallstones (n=19), autoimmune (n=1), and idiopathic (n=17). In two cases of mortality underlying autoimmune pancreatitis, 1 case combined with retroperitoneal fibrosis (Fig. 2B) showed a refractory response to steroid therapy. It resulted in recurrent pancreatitis attacks and extrahepatic biliary obstruction. The cause of death was septic shock. The other was systemic lupus erythematosus with autoimmune pancreatitis; the cause of death...
was a fulminant pancreatitis attack with flare up of systemic lupus erythematosus activity.

2. Recurrent acute pancreatitis

The recurrent attack rates of acute pancreatitis and habitual attack (≥3 times) were 24.5% (272/1,110) and 6.6% (73/1,110), respectively. Alcohol and gallstones were the main contributing factors in both recurrent (71.7%, 195/272) and habitual pancreatitis (78.1%, 57/73). Alcohol was the dominant etiology in recurrent (62.9%, 171/272) and habitual pancreatitis (69.9%, 51/73). A male-predominant pattern was typical since they had repeated alcohol-induced AP attacks (1st: 528/660; 2nd: 110/171; 3rd or more: 47/51).

In habitual attacks, minor causes included autoimmune (n=2), IPMN (n=2), pancreas divisum (n=2), annular pancreas (n=1), and pancreatic cancer (n=1). Eight patients with habitual attack had no definite etiology.

3. Idiopathic acute pancreatitis

The rate of idiopathic cause was 13.3% (148/1,110). Among them, 24 patients (16.2%) were readmitted with idiopathic recurrent AP. The pancreatitis-induced mortality rate was 5.4% (8/148), which was higher than other causes of AP; however, statistical significance was not observed (p=0.09). A female-predominant pattern was seen in this type of AP (male, 54; female, 94). The mean age was 56.70±17.92

![Fig. 4. Unusual cause of acute pancreatitis-pancreatic AVM. (A) Acute intrapancreatic parenchymal bleeding and hematoma formation (arrow) is observed on CT coronal image. (B) In celiac artery angiography, dense stain in the pancreatic head region and early filling of the veins (double arrows) suggests pancreatic AVM. AVM, arteriovenous malformation; CT, computed tomography.](image)

![Fig. 5. Unusual cause of acute pancreatitis-pancreatic cancer. (A) Fluoroscopic image taken during ERCP shows focal segmental pancreatic duct narrowing (double arrows) in the proximal body area with post-stenotic dilatation. (B) About 3.0 cm sized ill-defined mass (arrow) of the proximal body of pancreas and pancreatic duct dilatation (arrowhead) of the tail is observed in CT axial view. ERCP, endoscopic retrograde cholangiopancreatography; CT, computed tomography.](image)
years in males and 56.86±16.42 years in females.

Thirty-one patients had findings suggestive of microlithiasis. In patients with idiopathic recurrent AP, 41.7% (10/24) had possible biliary microlithiasis. Among idiopathic habitual AP (n=8), 3 patients had findings suggestive of microlithiasis, while the remaining 5 had pancreatic calcification, which is a feature of chronic pancreatitis. One patient with microlithiasis had gallbladder sludge on magnetic resonance cholangiopancreatography upon her third admission. Another 2 patients with microlithiasis experienced no recurrence after empirical cholecystectomy.

4. Unusual causes of acute pancreatitis

Unusual causes of acute pancreatitis included cancer-related (n=15), IPMN (n=8), pancreas divisum (n=5), and hypertriglyceridemia (n=4). Minor causes included annular pancreas (n=1), anomalous pancreatico-biliary junction (n=1) (Fig. 3), arteriovenous malformation (n=1) (Fig. 4), and hypercalcemia (n=1). In cases of cancer-related acute pancreatitis, pancreatic cancer (n=11) (Fig. 5), non-Hodgkin’s lymphoma (n=1), lung cancer (n=1) (Fig. 6), gallbladder cancer (n=1), and renal cell cancer (n=1) were found.

DISCUSSION

To date and to the best of our knowledge, this is the largest study assessing the etiologies of pancreatitis in Korea, presenting real crude data in clinical practice. We performed a retrospective analysis of patients with AP during a recent decade and investigated the etiologic prevalence, frequency of SAP, pancreatitis related mortality, and clinical features of idiopathic AP. In this study, alcohol intake was the most common cause of AP, accounting for around 60% of all cases, followed by gallstone. This finding was in agreement with the findings of a recent Japanese study.

Previous studies demonstrated that the leading cause of AP was usually gallstone, followed by alcohol intake. The discrepancy could be due to differences in alcohol consumption and incidence of cholelithiasis among different countries. According to a report released by the World Health Organization, greater alcohol consumption results in negative impact on health. South Koreans drink twice as much liquor as Russians and as 4 times as much as Americans. Previous epidemiologic studies reported that the increase in alcohol consumption is usually accompanied by an increase in alcohol-related acute pancreatitis. Therefore, in most countries with high alcohol consumption levels, the prevalence and severity of alcoholic AP are likely underestimated. Furthermore, among patients with recurrent episodes or habitual attacks, alcohol consumption was the most common cause of AP. For the sake of public health and reducing social expenditures, alcohol abstinence programs should be considered for patients with alcoholic AP.

It is known that idiopathic AP is a severe disease with a high recurrence rate. Our results showed that the prevalence rate of idiopathic pancreatitis was 13.3%. Its recurrence rate was approximately 16%. Its incidence had decreased compared with previous decades in Korea, which might be attributable...
to improvements in diagnostic modalities. The result was quite similar to those reported in recent studies.\textsuperscript{12,26} Moreover, the mortality rate in patients with idiopathic AP was high, and it was thought that complete evaluations of etiologies was impossible owing to fatal conditions. Other causes of AP in this study included autoimmunity, drug use, cancer, IPMN, pancreas divisum, hypertriglyceridemia, annular pancreas, anomalous pancreaticobiliary junction, arteriovenous malformation, and hypercalcemia. Most patients with cancer-related AP had pancreatic cancer. Thus, an early extensive diagnostic evaluation appears to be necessary. In patients with an unexplained etiology of AP with old age and dilatation of the pancreatic duct, a screening for pancreatic cancer, such as magnetic resonance imaging, should be performed.\textsuperscript{27,28}

Several studies have shown that elevated ALP is a common marker for diagnosing gallstone-induced pancreatitis.\textsuperscript{16,18} Several recent reports proposed that the ALT level might be a marker for early recognition of a gallstone etiology in patients with AP.\textsuperscript{17,19,20,29} In particular, increased ALT, a marker for diagnosing gallstone-induced pancreatitis.\textsuperscript{16,18} In the current study, although imaging studies showed unequivocal findings, increased ALP and ALT levels were present in 41.7% of patients with idiopathic recurrent AP. Therefore, micro- lithiasis should be considered in patients with idiopathic recurrent AP.

This study has several limitations to consider when interpreting its results. First, its design was retrospective in nature. However, we tried to overcome this by consecutively collecting all data using the same standard approach and enrolling a large number of patients. Second, autoimmune pancreatitis was diagnosed using the Kim’s criteria,\textsuperscript{14} which were flexible and easily applicable in clinical practice. Among the diagnostic criteria, the decision of steroid responsiveness was ambiguous, and it is possible that autoimmune pancreatitis was overestimated. Third, neither a manometric evaluation of the sphincter of Oddi nor a genetic evaluation was routinely performed. Patients with sphincter of Oddi dysfunction or hereditary pancreatitis were omitted from this study. However, these disease entities are quite rare and presented as minor limitation.

In conclusion, alcohol was the most frequent cause of AP and recurrent pancreatitis in a recent decade (2003-2013) in Korea. The incidence of idiopathic AP had decreased compared with previous decades in Korea; however, it is important to recognize the severity of this disease with a relatively high mortality rate. Broader studies would be required before drawing concrete conclusions.

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