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Original Article

Etiological factors affecting the clinical features, prognosis and management of acute pancreatitis

D. Premkumar*

Professor in Surgery, Department of Surgery,Karpaga Vinayaga Institute of Medical Sciences and Research, Maduranthagam, Kanchepuram, India 603308

***Corresponding Author**
Prof. Dr. D. Premkumar, MS.PG.Dip.HM.
Professor in Surgery,
Department of Surgery,
Karpaga Vinayaga Institute of Medical Sciences and Research, Maduranthagam,
Kanchepuram, India 603308
E-mail: dr.premkumar52@gmail.com

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Pancreatic necrosis

Abstract

Aim: There are various etiological factors causing acute pancreatitis; of them to identify the most common aetiological factor affecting the severity of symptoms, complications and mortality in acute pancreatitis.

Patients and methods: The study was conducted in Sungai Petani hospital in the State of Keddah, Malaysia. A total of 64 patients were admitted with symptoms of acute pancreatitis were retrospectively studied for symptoms, investigation results and prognosis.

Results: Out of 64 patients admitted for acute pancreatitis gall stone disease was noticed in 38 patients of them Malays were 34 and others were 4.Alcohol consumption was observed in 26 patients of them 24were Indians and 2were Thai. Vomiting, jaundice, fever were more common in Malays. The symptoms are more due to gallstone induced acute pancreatitis than in alcohol induced pancreatitis. Serum enzymes like serum alanine transferase, amylase and LDH level in blood and urine amylase and diastase were elevated more commonly in Malays than in Indians. Serum albumin and PO_2 decreased in more Malays than in Indians. Both local and systemic complications were common in Malays. More Malay patients underwent surgery for gall stones.

Conclusion: The lipase/amylase ratio index, erythrocyte mean corpuscular volume, and gamma glutamyl transferase could not distinguish alcoholic from non-alcoholic acute pancreatitis. Patients with gallstone pancreatitis should have cholecystectomy, ideally during the same admission. Early imipenem- cilastatin therapy appears to significantly reduce the need for surgery and complications.

1.Introduction

Acute pancreatitis is one of the acute surgical conditions admitted which usually do not require any active surgical intervention. Acute pancreatitis is caused by variety of etiological factors like gall stone, alcohol intake, post ERCP, hyperlipidemia, mumps and other causes. The symptoms are more due to gallstone induced acute pancreatitis than in alcohol induced pancreatitis. Similarly the amlase level both in urine and blood is more pronounced in gall stone induced acute pancreatitis. The Malays and women do not consume alcohol but other ethnic population consumes alcohol in Malaysia. So the study done in Malaysia truly reflects the etiological factors and symptoms and the ethnic subpopulation. This was a retrospective study based on the clinical data collected from the hospital case records.

1.1 Objective

The Malays and women do not consume alcohol but other ethnic population consumes alcohol in Malaysia. So the study done in Malaysia truly reflects the etiological factors and severity of symptoms and the ethnic subpopulation.

2. Patients and methods

The study was conducted in Sungai Petani hospital in the State of Keddah, Malaysia. A total of 64 patients were admitted with symptoms of acute pancreatitis were retrospectively studied for symptoms, investigation results and prognosis.

2.1 Inclusion criteria

The clinical diagnosis of acute pancreatitis is based on the presence of 2 of the following 3 features: serum amylase and lipase levels elevated above 3 times the upper limit of normal; mild to severe epigastric abdominal pain (often radiating to the back); and typical imaging features as found on computed tomography or magnetic resonance imaging. Elevation of serum amylase and lipase levels to greater than 3 times the upper limit of normal in conjunction with the appropriate clinical history are mainstays in the diagnosis of acute pancreatitis.[1]

There were 39 Malay patients and 23 Indian patients and 2 Thai. There were no Chinese patients. Gall stone disease was considered when ultrasonically gall stone was demonstrated or the gall bladder showed ultrasonically demonstrable diseases. The patients presented with the common symptoms like epigastric pain, vomiting, fever with rigor, jaundice, abdominal distension and rarely of loss of appetite and shock. The diagnosis of acute pancreatitis was made on the clinical symptoms supported by laboratory investigations like serum amylase, serum lipase and serum alanine phosphate and urine amylase. For all patientsultra-sonogram was done and follows up ultra-sonogram was done to find out how many of them developed pancreatic fibrosis. CT scan was done for some patients.

3. Results

3.1 The incidence of acute pancreatitis by age and sex

Acute pancreatitis is more common in 30-39 year age group in males and 40-49 age group in females. If both sexes were included 48 patients were between 30-59 years age group. (Table 1)

3.2 The etiological factors for acute pancreatitis

Alcohol was the common etiology for Indians (20/64) and biliary disease (22/64) for Malays. The incidence of acute pancreatitis

was more common in Malays 39 and Indians 25.Out of 64 patients admitted for acute pancreatitis gall stone disease was noticed in 38 patients of them Malays were 34 and others were 4.Alcohol consumption was observed in 20 patientswere Indians. Two pediatric patients were admitted with acute pancreatitis following an attack of mumps. Post ERCP pancreatitis occurred in one female who had gall stone. (Table 2)

3.3 Clinical presentation of acute pancreatitis

Common clinical presentations were epigastric pain, vomiting50 and 45 patients. Malays had more symptoms like epigastric pain 34 whereas only 23 Indians had pain. Vomiting, jaundice, fever were more common in Malays. (Table 3)

3.4 Investigations result

Serum amlase was elevated in 39 patients and urine diastase was elevated in 39 patients. Serum enzymes like amylase and LDH and urine diastase were elevated more commonly in Malays than in Indians. The serum alanine transferase was elevated more in Malays indicating gall bladder disease. Blood urea, sugar and total WBC count were elevated in Malays. Serum albumin and PO_2 decreased in more Malays than in Indians. Bio chemical changes are more marked in Malays than in Indians. (Table 4)

3.4 Incidence of complications of acute pancreatitis

Both local and systemic complications were common in Malays. The local complications were pseudocyst of pancreas, pancreatic necrosis and systemic complications were pleural effusion, sepsis and shock. One Malay aged 43 years died due to multi organ failure. Those patients having gall stones underwent elective cholecystectomy and five patients underwent ERCP and CBD stone removal and sphicterotomy. Four patients underwent laparotomy and cystogastrostomy and removal of phlegmon and drainage of abscess. (Table 5)

Table 1: The incidence of acute pancreatitis by age and sex

Age group	0-9	10-19	20-29	**30-39**	**40-49**	**50-59**	60-69	70 above	Total
Male	1	4	3	**15**	**4**	**5**	2	1	35
Female	1	2	1	**9**	**11**	**4**	1	0	29
Total	2	6	4	**24**	**15**	**9**	3	1	64

Table 2: The etiological factors are for acute pancreatitis

Etiology	**Malay (39)**	**Indian & Thai (25)**	**Total(64)**
Alcohol	1	**20**	21
Biliary disease	**22**	4	26
Viral	1	1	2
ERCP	2	0	2
Others	1	0	1
Idiopathic	12	0	12
Total	39	25	64

Table 3: Clinical presentation of acute pancreatitis

Clinical presentation	**Malay (39)**	**Indian and Thai(25)**
Epigastric pain	**34**	**16**
Vomiting	**31**	**14**
Fever	15	5
Jaundice	11	3
Abdominal distension	12	5
Shock	2	1

Table 4: Results of Investigations

Investigations	**Malays (39)**	**Indian and Thai 25)**
Serum amylase>800U/L	31	8
Urine diastase>800U/L	30	9
Serum alanine transferase >90 U/L	18	4
Serum albumin<3.2g/l	10	2
LDH>600U/L	10	1
Serum calcium<2mmol	12	2
Blood sugar>10m.mol	10	5
Blood urea>16m.mol	4	0
PO_2<60mm/Hg	4	0
Total WBC count>15000	13	5

Table 5: Complications

Complication	**Malays (39)**	**Indians& Thai (25)**
Respiratory	5	1
Cardiovascular	2	1
Infections/Sepsis	3	1
Renal	4	1
DIVC(disseminated intravascular coagulation)	1	0
Pancreatic pseudocyst	4	3
Pancreatic necrosis	6	2
Peri-pancreatic collection	7	2
Death	1	0
Total	33	11

4. Discussion

Acute pancreatitis is a reversible inflammatory process of the pancreas. Although the disease process may be limited to pancreatic tissue, it also can involve peri-pancreatic tissues or more distant organ sites. Acute pancreatitis may occur as an isolated attack or may be recurrent. It has a variety of causes and can range in severity from mild to severe and life threatening. Some patients may require brief hospitalization, whereas others may be critically ill with multiple organ dysfunctions requiring intensive care monitoring. Mild acute pancreatitis has a very low mortality rate (less than 1 percent), whereas the death rate for severe acute pancreatitis can be 10 to 30 percent depending on the presence of sterile versus infected necrosis. Acute pancreatitis is a disorder that has numerous causes and an obscure pathogenesis.

4.1 Age

The age for the onset of acute pancreatitis varies from 30 years to 70 years. The vascultis and AIDS are the etiological factors in younger adults of 30-35 years and 40-45 years alcohol abuse and in older individuals of above 50-70 years gall bladder disease.

A recent UK study found that rates of acute pancreatitis have doubled over the past 30 years, particularly among younger age groups. Increasing alcohol consumption may be partly to blame.[2]

Age more than 70 years is an independent risk factor for mortality in patients admitted with severe acute pancreatitis. [3]

4.2 Etiology

Bile duct stones and alcohol abuse together account for about 80% of acute pancreatitis. Most episodes of biliary pancreatitis are associated with transient impaction of the stone in the ampula of Vater or the passage of stone through duodenum. Other causes of acute pancreatitis are various causes of obstruction, various toxins, drugs, metabolic abnormalities, trauma, ischemia, infection, autoimmune diseases, etc. 10% of cases no underlying cause may be identified, this is idiopathic pancreatitis. The etiology in five European countries Germany, Hungary, France, Greece, and Italy are compared. It is found that in Germany the cholilitheasis and alcohol abuse are equal in producing acute pancreatitis in Hungary and France alcohol predominate cholilitheasis, in Greece and Italy the cholilitheasis predominates. There is no statistically significant difference in mortality among different etiological group and no relation is found between mortality and age[4] In Eastern India the etiology spectrum of mild pancreatitis included the following: alcoholism (41.1%), gallstones (23.5%), trauma (17.6%), idiopathic (11.7%) and post-endoscopic retrograde cholangiopancreatography (5.8%). The causes of severe acute pancreatitis came under the following headers: trauma (27.2%), idiopathic (18.1%), gallstones (18.1%), alcoholism (18.1%) and post-endoscopic retrograde cholangiopancreatography (18.1%).[5] Corfield *et al* found that sex distribution was equal and mean age is 60 years. Gall stone were detected in 50% and alcoholics 8% and in 23% no etiological factor can be identified.[6]

4.3 Biliary Pancreatitis

The high incidence of common bile duct stones (35%) supports the hypothesis that the causative mechanism in gall stone pancreatitis is the passage of a calculus through the common channel formed by pancreatic and common bile ducts, with consequent reflux of bile or duodenal juice into thepancreatic duct.[7][8] Impaction of a stone at the ampula of Vater in 56% of necropsies showing gall stone pancreatitis lends credence to this theory and suggests that early operative intervention should be considered if this condition is suspected.

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Impaction of a stone at the ampula of Vater in 56% of necropsies showing gall stone pancreatitis lends credence to this theory and suggests that early operative intervention should be considered if this condition is suspected. Alcoholism appears to be a much commoner cause of acute pancreatitis elsewhere in Britain and abroad, although it has steadily increased over the last 30 years in Bristol.[9]

In 10% of cases is idiopathic acute pancreatitis where no underlying cause can be identified. Occult biliary microlitheasis may be the cause of two thirds of the cases of idiopathic pancreatitis. The cause of recurrent acute pancreatitis was attributed to biliary microlithiasis in 10 (13%) of 75 patients. Two additional patients developed gallstones during the follow-up period. Ten out 35 patients who were followed up developed chronic pancreatitis had biliary microlithiasis[10]; Incidence is highest in patients with small gallstones, or microlithiasis, as these stones are more likely to escape the gallbladder and transit the cystic duct to reach the common bile duct. Large stones are more likely to be retained in the gallbladder. A recent study noted that the incidence of all causes of acute pancreatitis rose between 1994 and 2001 from 33.2 cases to 43.8 cases per 100,000 adults, without a reduction of mortality rate. This increase was attributed to a rise in the incidence of gallstone pancreatitis.[11] The incidence of gallstone pancreatitis is highest among patients with small gallstones (less than 5 mm in diameter) or microlithiasis.

Bile microscopy was abnormal in 75% patients with recurrent idiopathic acute pancreatitis (RAIP). 83.3% patients with unexplained biliary pain cholesterol monohydrate crystals (CMC) and calcium bilirubinate granules (CBG)) were found in (10/12; CMC in seven, CBG in one, CMC and CBG in two) and 95.4% patients with gallstones (21/22; CMC in 12, CBG in one, CMC and CBG in eight). None of the controls without gallstone disease had CMC while three patients had low counts of CBG. Microlithiasis is a common cause for idiopathic acute pancreatitis and unexplained biliary pain. Lasting relief is obtained in most patients after treatment with UDCA, cholecystectomy or sphincterotomy.[12] Stools were screened for gall stones in 36 patients with acute pancreatitis associated with gall stones. Gall stones were found in the feces of 34 out of 36 patients with pancreatitis. These findings suggests that acute pancreatitis is associated with gall stone disease is frequently caused by transient blockage of the ampula of Vater by migrating gall stones.[5] A substantial proportion of acutepancreatitis of unclear cause may be explained by etiologiessuch as undetected microlithiasis, unrecognizeddrug-induced pancreatitis, or the controversial sphincter of Oddi dysfunction, among other possibilities.[11]

4.4 Alcoholic Pancreatitis

Alcohol is a well-known precipitant of acute pancreatitis, although the incidence of acute pancreatitis in heavy alcohol consumers is not more than 2% to 3% per year, suggesting that there are as yet undetermined environmental or genetic factors that influence the development of acute pancreatitis in this population. The incidence rate may be similar in heavy drinkers of both sexes. Acute pancreatitis incidence rates peak between ages 35 and 44 years. Furthermore, alcoholic acute pancreatitis has the highest associated risk of overall mortality, with the odds of death increased 90% as compared with biliary pancreatitis, possibly due to poor baseline nutrition.[13] Excessive alcohol use as a cause of pancreatitis is more common among men than women; the association between alcohol consumption and acute pancreatitis is complex but appears to be dose-dependent.[1] An increase in acute pancreatitis secondary to chronic alcoholism was confirmed by a study conducted by Trapnel and Duncan and steroid pancreatitis also emerged as a define entity.[14]

A retrospective cohort study conducted by Rebecca A. Noel showed an increased risk of acute pancreatitis and biliary disease observed in patients with Type 2 diabetes.[7] Pre-existing diabetes,

however, does increase the risk of death from 19 to 43%. Other etiological associations of acute pancreatitis, such as hyperlipidaemia and hyperparathyroidism, make up an expected small percentage of cases.[15]

There is no convincing evidence that pregnancy is a relevant factor. There was only one case of acute pancreatitis after ERCP, though the reported incidence is 1-2%.[16] The postoperative pancreatitis usually follows upper abdominal surgery and is a dangerous disease with a 55% chance of death.

4.5 Clinical features

Among the 64 patients 17 had fever 11 in Malays and 6 in others (Indians and Thai). Fever was considered to be significant, if the temperature was >38°C and persisted for >2 days. The fever of more than 38^0 C is not a common symptom but fever denotes the complications like pancreatic necrosis, pancreatic abscess and cholangitis. In an Indian study by Bohindar and others it was noticed 60% of the patients had fever and infected pancreatic necrosis was the cause in 18%. The mortality rate was higher in the patients who developed fever.[6]

In pediatric age group diagnosis was based most often on abnormal abdominal ultrasonography (81%) and on elevated serum amylase levels (63%). In 16% of the patients the diagnosis was based only on laparotomy. TPN was required in 28% of the patients. In 24% of the subjects a surgical intervention was indicated. Fatal outcome was described in 9.7% of the patients. Acute pancreatitis of childhood, although considered sometimes as a minor disorder, carries significant morbidity and mortality.[17]

4.6 Investigations

The single best laboratory predictor of biliary pancreatitis; a level of alanine aminotransferase more than three times the upper limit of normal has a positive predictive value of 95 percent for gallstone pancreatitis. However, the presence of normal alanine aminotransferase levels does not reliably rule out the diagnosis.[18]

The presence and degree of pancreatic necrosis (30%, 50%, or greater than 50%) was evaluated by means of bolus injection of contrast material and dynamic sequential computed tomography (CT) in patients with acute pancreatitis at initial and follow-up examinations. Pancreatic necrosis was defined as lack of enhancement of all or a portion of the gland. A CT severity index, based on a combination of peri-pancreatic inflammation, phlegmon, and degree of pancreatic necrosis as seen at initial CT study, was developed. Patients with a high CT severity index had 92% morbidity and 17% mortality; patients with a low CT severity index had 2% morbidity, and none died.[19]

Jaakkola *et al* investigated the ability of various blood markers to detect an alcoholic cause of acute pancreatis. Serum carbohydrate-deficient transferrin (CDT) was significantly correlated with reported 2 month and 7 day ethanol consumptions and was significantly higher in 42 patients with alcoholic acute pancreatitis and in 24 patients with possibly alcoholic acute pancreatitis than in 20 patients with non-alcoholic disease. At a cutoff over 17 U/L, the specificity of CDT was 100% and the sensitivity was 75% to detect an alcoholic cause of acute pancreatitis. The lipase/amylase ratio index, erythrocyte mean corpuscular volume, and gamma glutamyl transferase could not distinguish alcoholic from non-alcoholic acute pancreatitis.[21]

New developments in imaging modalities such as endoscopic ultrasonography and magnetic resonance cholangiopancreatography increase the options available to physicians for determining the cause of pancreatitis and assessing for complications.[22]

4.7 Management

Enteral nutrition is preferred to parental nutrition for improving patient outcomes. Clinical trials are ongoing to evaluate the role, selection, and timing of antibiotics in patients with infected necrosis.[23]

Antibiotic prophylaxis decreases sepsis and mortality in patients with ANP. All patients with ANP should be given prophylaxis with an antibiotic with proven efficacy in necrotic pancreatic tissue. Antibiotic prophylaxis significantly reduced sepsis by 21.1% and mortality by 12.3% compared with no prophylaxis. There was also non-significant trend towards a decrease in local pancreatic infections.[23]

Patients with acute severe biliary pancreatitis should have early endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy within 72 hours of symptom onset. Patients with gallstone pancreatitis should have cholecystectomy, ideally during the same admission.[24] Pancreatic infection is the main indication for surgery and the principal determinant of prognosis in acute necrotizing pancreatitis.A single-center randomized study compared early vs. delayed imipenem treatment for acute necrotizing pancreatitis. Early imipenem- cilastatin therapy appears to significantly reduce the need for surgery and the overall number of major organ complications in acute necrotizing pancreatitis, and reduces by half the mortality rate.[25]

Severe acute pancreatitis is frequently complicated by local and systemic infections resulting in substantial morbidity, mortality, and health care costs. Antibiotic prophylaxis may prevent some infections. Antibiotic prophylaxis decreases sepsis and mortality in patients with ANP. All patients with ANP should be given prophylaxis with an antibiotic with proven efficacy in necrotic pancreatic tissue.

Infectious complications and associated mortality are a major concern in acute pancreatitis. Enteral administration of probiotics could prevent infectious complications, but convincing evidence is scarce. In patients with predicted severe acute pancreatitis, probiotics prophylaxis with this combination of probiotics strains did not reduce the risk of infectious complications and was associated with an increased risk of mortality. Probiotics prophylaxis should therefore not be administered in this category of patients.[26]

The presence of endotoxin in blood and peritoneal fluid correlates with the severity, systemic complications, and mortality rates of acute pancreatitis. Endotoxin estimation can identify patients at risk in the early stages of acute pancreatitis.[27]

To delineate more clearly the influence of the timing of surgery in the treatment of the disease, a prospective randomized clinical study of early surgery (less than 48 hours after admission) and delayed surgery (more than 48 hours after admission) was conducted in 165 patients.

It has been observed that (1) although a gallstone initiates a bout of pancreatitis, it does not cause the progression of the disease; (2) the fate of the progression of pancreatitis is decided early by the amount of digestive enzymes being activated; (3) early removal of an impacted stone does not ameliorate the progression of pancreatitis; and (4) surgery should be performed during the initial hospital admission after the pancreatitis has subsided.[28]

The mortality reduction in the 1990s could be attributed to either a more select study sample or earlier and more selective endoscopic or surgical debridement of infected tissue, endoscopic cyst drainage, and angiographic control of gastrointestinal bleeding. Improved nutritional support by jejunal feeding, earlier use of antibiotic therapy, gut sterilization, early endoscopic retrograde cholangiopancreatography for common bile duct stones and necrosectomy for noninfected necrosis have reduced the overall mortality associated with acute pancreatitis to a mean of 5% (range, 3.8-7%) for all cases and 20% (range, 15-25%) for severe cases. However, it is clear that the greater the number of signs denoting severity of organ failure, the higher the mortality.[29]

The clinical course of 47 patients with gallstone-associated acute pancreatitis who had surgery during the same admission has been reviewed. In 37 patients, when the signs and symptoms of pancreatitis settled on conservative management, biliary tract surgery was safely performed during that admission without mortality. The 10 patients

whose clinical condition failed to settle prior to surgery had a complicated hospital stay and 50 per cent mortality. A revised prognostic factor grading system has been outlined in which the age factor is removed and serum transaminase levels are considered of prognostic significance only if it is greater than 200 u/l in the first 48 h of admission. This revised system gives a more accurate assessment of the severity of individual attacks of gallstone-associated acute pancreatitis.[30]

4.8 Prognosis

There was no significant difference concerning hospital stay, respiratory and renal insufficiency, indication for surgery, or mortality rate among the different etiological groups. However, pancreatic pseudocysts developed significantly more frequently in alcoholics than in patients with other etiologies. The increased incidence of renal insufficiency probably is related to physiological alteration with age, but the indication for dialysis did not increase. Pancreatic pseudocysts were more frequent in patients between 31 and 40 years of age, which was also the peak age group of alcoholics[31]. There has been considerable reduction in the mortality associated with acute pancreatitis over the past 20 years. The reasons are multifactorial, but recognition of severity signs, early implementation of organ-specific therapy and newer endoscopic, surgical, and angiographic therapy for infection cyst and bleeding appear to have been the major factors in reducing mortality.[29]

Retrospective analysis of the first 100 patients identified 11 objective findings which correlated with the occurrence of serious illness or death. They were, on admission, age over 55 years, blood glucose level over 200 milligrams per cent, white blood count over 16,000 per cubic millimeter, serum lactic dehydrogenase level over 350 International units per liter and serum glutamic-oxalacetic transaminase level over 250 Sigma Frankel units per cent.[32]

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